Antibiotic therapy in the emergency room: just adapted or optimal?

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Abstract

Introduction: An inadequate antibiotics' prescription was found to be associated with worse prognosis in some infections. Emergency departments (ED) are pivotal for the initial prescription of antibiotics. However, its appropriateness and consequences have been rarely assessed.

Methods: A retrospective, monocentric study included patients who consulted to the ED of our center and who were hospitalized with an advocated diagnosis of infection. Initial antibiotic therapy was graded as optimal, adapted, or inadequate. If reevaluation of this therapy was performed at day 2 (D2), the appropriateness of antibiotic therapy was again graded. The primary endpoint was the onset of an unfavorable event (i.e., death, transfer to intensive care unit, or re-hospitalization). Prognosis factors associated with survival without unfavorable event were assessed by multivariate analysis.

Results: We included 484 patients. Respiratory (153, 40.4%), urinary-tract (83, 21.9%), and abdominal (76, 20.1%) infections were mostly diagnosed after reevaluation. Optimal, adapted, and inadequate initial prescriptions concerned respectively 328 (67.8%), 110 (22.7%) and 46 (9.5%) patients. Compared to an optimal prescription, an initial adapted prescription was associated with a poorer prognosis (HR = 1.95, CI95% [1.18-3.22]; p = 0.01). The reevaluation was performed in 436 (90.1%) patients. After reevaluation, optimal, adapted, and inadequate prescriptions concerned 326 (74.8%), 64 (14.7%), and 46 (10.5%) patients. After reevaluation, compared with optimal prescriptions, an inadequate prescription was associated with unfavorable events (HR = 3.52, CI95% [1.42-8.72]; p = 0.003).

Conclusion: The appropriateness of both initial and D2 antibiotic therapies are associated with a better prognosis.

Introduction

Antibiotics represent a drug class with a high prescription volume in medical care. Some antibiotics, such as amoxicillin-clavulanic acid, are part of the most prescribed molecules in France, whether in ambulatory medicine or at hospital [1]. The rationale use of antibiotics seems a primordial goal to achieve to prevent the risk of multiresistant bacteria [2].

In addition, it has been showed that an inadequate antibiotic therapy could be associated with a poorer prognosis. This has been particularly studied in pulmonary infections. Indeed, some studies have found that the survival rate was improved and the length of stay was shortened in patients with an initial adapted antibiotic prescription [3, 4].

Emergency Departments (ED) have a crucial importance for the good use of antibiotics, first because ED is a main way of admission to the hospital, especially in case of infection. Indeed, between half and two-third of patients with a diagnosis of sepsis (whatever its origin) are hospitalized via the ED where the initial antibiotic therapy is prescribed [5–8]. Secondly, these infections are heterogeneous, even though urinary tract infections (UTI) and pulmonary infections are overrepresented [9]. Such a heterogeneity also

translates into a wide range of therapeutic prescriptions, also linked to the diversity in the profiles of the medical staff working in ED.

Several studies focused on antibiotics prescription in ED [3, 4, 10, 11]. Even though many of these studies reported that a non-adapted antibiotic therapy was not rare, very few could assess the impact of non-adapted antibiotic therapy on the prognosis of the patients. Only two studies on bacteriemia concluded that a non-adapted antibiotic prescribed at ED was associated with a higher mortality [10, 11].

We thus conducted a study which aimed at assessing the impact on prognosis of an inadequate antibiotic therapy prescribed at ED in patients hospitalized subsequently for infections.

Methods

Study and participants

An observational retrospective study was conducted in the University Hospital of Dijon, France, from November 2019, the 1st, to January 2020, 31st (before the COVID-19 epidemics started in France). All patients more than 18 years old, referred to the ED, and who were thereafter hospitalized with a prescription of antibiotics initiated in the ED, were eligible. Patients were not included if they were hospitalized in another center, if they were directly transferred from the ED to an intensive care unit (ICU), if they died in the ED, if they were prescribed antibiotics in a prophylactic approach, or if an infectious diagnosis was not clearly advocated in the ED.

Data collection

For each included patient, the following data were collected from the computerized medical records: its demographic characteristics (including age, gender, Body Mass Index (BMI)), its underlying conditions (in particular hypertension, cardiovascular disease, chronic kidney failure, chronic pulmonary disease, diabetes, immunosuppression), its life habits (autonomy, smoking, alcohol consumption) and the duration of hospitalization.

The clinical data at the ED were collected in a standardized manner, in particular the quick Sequential Organ Failure Assessment (qSOFA) score [12]. Biological data, especially blood leucocytes, neutrophils count, C-reactive protein (CRP), procalcitonin (PCT), creatinine, Glomerular Filtration Rate (GFR) and liver enzymes, were also collected. The microbiological and radiological exams performed in the ED or during the hospitalization were also collected.

Data on the antibiotic therapy initiated in the ED were collected. For each antibiotic therapy prescribed at ED, it was also assessed if a reevaluation at D2 was performed, and the new antibiotic therapy was collected if any. The following data were recorded for each antibiotic therapy: type of antibiotics (or molecules), doses, way of administration and proposed duration (only for antibiotic therapy prescribed after the reevaluation).

Definitions

The main infectious diagnosis advocated by the ED physician was systematically collected for all the patients included. Then, whether reassessed and modified, or confirmed by the ward physician at D2 following the reevaluation, the final infectious diagnosis called “retained diagnosis” was also recorded, whether based on suspected or documented infection.

A suspected infection was defined as clinical and/or biological and/or radiological arguments for infection, but without microbiological documentation. A documented infection was an infection with a microbiological documentation in coherence with the clinical presentation.

Antibiotic therapy initiated at the ED was assessed and graded into three categories, according to a pre-established algorithm, as optimal, adapted, or inadequate. An optimal antibiotic therapy was defined as a prescription which fully followed the French guidelines in terms of recommended molecule(s), dose(s), and way of administration, according to the type and the severity of the disease and the characteristics of the patient (e.g., kidney or liver failure, if any). An antibiotic therapy was defined as adapted if the prescribed molecule was active but not the recommended one as the first line antibiotic, or if the molecule or the dose or the way of administration were not the one recommended. An antibiotic prescription was characterized as inadequate in all other situations, in particular if the molecule was not active for the type of infection treated. The term of non-optimal antibiotic therapy included the adapted and inadequate categories. In case of difficulties to grade antibiotic therapy with the algorithms, the prescriptions were graded by 2 infectious diseases specialists.

If the initial antibiotic therapy was reevaluated at D2 by the physician in charge of the patient at this time, the antibiotics’ prescription was again graded (as above, except that the proposed duration also intervenes at this time to distinguish optimal from non-optimal therapy) according to the retained diagnosis. Antibiotic de-escalation was defined as a prescription of an antibiotic therapy with a reduced spectrum which included the suspected or documented bacteria.

Outcomes

The primary endpoint was the onset of an “unfavorable event”, defined by at least one of the following: death, transfer to ICU during the hospitalization, new hospitalization within 30 days for the same reason. The primary outcome was the association between the onset of unfavorable events and the adequation of antibiotic therapy in the ED.

Secondary outcomes were defined: the association between the prognosis and the adequation of antibiotic therapy after reevaluation at D2 and according to different subgroups (as type of infection), the description of the population, the description of the antibiotic prescription in the ED, the description of antibiotic prescription after the reevaluation at D2.

Statistical analysis

A univariate analysis was first performed with a Cox model to assess the factors significantly associated with the primary endpoint. Survival without unfavorable event in the different categories of prescriptions' adequation was compared by Kaplan-Meier curves using log rank test.

Then, a multivariate Cox model was performed on complete data, first including all baseline variables which were clinically relevant or associated with the primary outcome with a p value < 0.2. A step by step descending model was used. Hazard Ratios (HR) with 95% interval confidence (95%CI) were calculated.

Sensitivity analyses were also performed by using Cox model in patients with a final diagnosis of bacterial infection, in patients with a pulmonary infection, in patients with UTI, and in patients with abdominal infection.

Statistical analyses were performed using IBM SPSS Statistics version 25. For all analyses, a p value <.05 was considered as significant.

Results

Population

During the study period, there were 4251 admissions at the ED. Among these patients, 605 (14.2%) received antibiotics, and 484 were finally included in the study (**Figure 1)**.

Two-hundred and fifty-five (52.7%) patients were men and median age was 79.9 years (extremes 18-105 years) (**Table 1**). The most frequent underlying conditions were chronic cardiovascular diseases (250, 51.7%), high blood pressure (240, 49.6%), dementia (131, 27.1%), and diabetes mellitus (111, 22.9%). One hundred patients (20.7%) were immunocompromised.

Clinical presentation in the ED

Respiratory symptoms were the most frequent cause of consultation to the ED (150, 31.0%), before abdominal symptoms (110, 22.7%) or "isolated" fever (49, 10.1%) (**Table 2**). Most of the patients had a baseline qSOFA < 2 (409, 84.5%), whereas a septic shock was diagnosed in 11 (2.3%) patients.

Blood cultures and urine analysis were performed in the ED in 372 (76.9%) and 259 (53.5%) patients, respectively. Most of the blood cultures were negative (324 patients, 87.1%). Among the 48 positive ones, Escherichia coli (19, 39.6%), other Enterobacteriaceae (15, 31.3%), Staphylococcus aureus (9, 18.8%) and anaerobic bacteria (5, 10.4%) were the most frequently observed pathogens. Out of the 92 (35.5%) positive urine analyses, Escherichia coli (61, 66.3%), other Enterobacteriaceae (20, 21.7%), Pseudomonas aeruginosa (8, 8.7%) and Enterococci (7, 7.6%) were the most frequently observed pathogens.

Antibiotics prescribed in the ED

Among the 484 treated patients, antibiotic therapy was most often prescribed as monotherapy (324, 66.9%). Third generation cephalosporin (244, 50.4%), amoxicillin-clavulanic acid (167, 34.5%),

metronidazole (88, 18.2%) and spiramycine (47, 9.7%), were the most often prescribed antibiotics. The antibiotic therapy in the ED was graded as optimal in 328 (67.8%), as adapted in 110 (22.7%) and as inadequate in 46 (9.5%).

The main reasons justifying that the antibiotic therapy was just considered as adapted at ED were mainly a too wide spectrum (45, 40.9%), a non-adapted dose (33, 30.0%), and a non-adaptation to the clinical severity (14, 12.7%). The main reasons justifying that the antibiotic therapy was inadequate at ED were an absence of indication to treat with antibiotics (24, 52.1%) and a prescribed antibiotic which was not active for the type of infection (11, 23.9%).

Non-optimal antibiotic therapy was prescribed in 51 (33.3%) patients with lung infection, in 29 (34.9%) patients with UTI, in 13 (17.1%) patients with abdominal infections and in 9 (39.1%) patients with cutaneous infections.

Primary outcome

The primary endpoint was reached for 74 (15.3%) patients: 38 deaths (7.9%), 22 transfers to ICU (4.6%) and 14 new hospitalizations within 30 days after discharge (2.8%).

Compared to an optimal antibiotic therapy, an adapted antibiotic therapy at ED was significatively associated with unfavorable outcome (HR = 1.95, Confidence Interval (CI) 95% (CI95%) [1.18-3.22]; p = 0.01). On contrary, no significant association was found with an inadequate antibiotic therapy (HR = 0.58, CI95% [0.21-1.61]; p = 0.29) (**Figure 2**).

This significant association between an adapted (compared to an optimal) antibiotic therapy in the ED and an unfavorable event was also found when considering only patients with a bacterial infection (HR = 2.16, CI95% [1.25-3.75]; p = 0.006) and those with a pulmonary infection (HR = 2.96, CI95% [1.25-7.03]; p = 0.01).

Factors associated with the main outcome in the univariate and multivariate analyses are summarized in **Table 3**. The candidates as adjustment variables for the multivariate model were cardiovascular diseases, chronic respiratory failure, diabetes mellitus, autonomy of the patient, community infection, qSOFA, septic shock, haemoglobin, CRP, creatinine, adequation of antibiotics' prescription at ED, type of infection, bacterial infection, adequation of antibiotics' prescription after the reevaluation.

Reevaluation of antibiotic therapy at D2

At D2, 358 patients (74%) were still hospitalized, whereas 103 (21.2%) have been discharged and 23 (4.8%) underwent an unfavorable event (14 deaths, 4 transfer to ICU, 5 discharges followed by re-hospitalization for the same infection).

The reevaluation of antibiotic therapy at D2 was performed in 436 patients (90.1%). Three-hundred and twenty-three of 358 patients (90.2%) still hospitalized at D2 underwent the reevaluation. Among the 103

patients discharged at D2, most of them (101, 98.1%) underwent a reevaluation before they were discharged.

The infectious diagnosis was modified between the ED and D2 for 56 patients (11.6%). Most of the diagnoses' modifications concerned pulmonary infections at ED (24, 42.9%) and UTI at ED (15, 26.8%).

Only 26 (6.0%) had their initial antibiotic therapy unchanged. The antibiotic therapy was stopped in 106 patients (24.3%). The reasons of discontinuation were no retained diagnosis of bacterial infection (84, 79.2%), complete duration of antibiotic therapy (17, 16.1%) and comfort care only (5, 4.7%). The antibiotic therapy was de-escalated in 150 patients (34.4%), had its administration way or dosage modified in 113 (25.9%), or was escalated in 41 (9.4%).

Out of the 330 (75.7%) patients still on antibiotic therapy following reevaluation, monotherapy was used in 278 (84.2%) patients. Amoxicillin-clavulanic acid (148, 44.8%), third generation cephalosporins (69, 20.9%), amoxicillin (42, 12.7%) and metronidazole (26, 7.9%) were the antibiotics the most often prescribed.

Among the 436 patients who underwent the reevaluation at D2, the antibiotic therapy was graded as optimal in 326 (74.8%) patients, including 104 (31.9%) with justified antibiotic therapy discontinuation. Antibiotic therapy was graded as adapted in 64 (14.7%) and as inadequate in 46 (10.5%).

The main reasons justifying that the antibiotic therapy was just considered as adapted after reevaluation were mainly a not-adapted proposed duration (28, 43.8%), a too wide spectrum (22, 34.4%), and the use of an antibiotic not recommended by the guidelines (7, 10.9%). The main reasons justifying that the antibiotic therapy was inadequate after reevaluation were mainly an absence of indication (24, 54.2%) and a not-adapted molecule (12, 26.1%).

Compared to an optimal antibiotic therapy, an inadequate prescription after reevaluation was significantly associated with an unfavorable outcome: HR = 3.52, CI95% [1.42-8.72]; p = 0.003.

Discussion

The first main point of this study is that 14.2% (605 of 4251 patients) of the patients admitted in the ED are hospitalized with antibiotics. This proportion is similar to those found in the 2000s studies which is between 10 and 20% according to the center [13, 14]. This confirms that the antibiotics' prescription remains an important part of the patients' management at ED.

The second main point is that the proportion of optimal antibiotic therapy at ED in this study represents two-third of our patients, which means that the initial antibiotic therapy may be upgraded/improved in nearly one third of the cases, as previously reported in an Australian study [15]. In other studies [3, 9], the rate of non-optimal antibiotic therapies at ED was even higher (between 40 and 60%). It could be argued that considering only the initial diagnosis to grade the adequacy of the antibiotic therapy as we did in our

study may explain such a difference. However, since our proportion of modified diagnoses following the reevaluation was low (11.6%), this could not be the only explanation.

The third main point is that the need for optimal antibiotic therapy is highlighted by its association with a better prognosis. This was true not only for all the patients, but also when considering only those with bacterial infection, or those with pulmonary infections. To our knowledge, this is the first study which shows that an optimal antibiotic therapy prescribed at the ED is associated with a better prognosis for the patients whatever the type of infection. A few previous studies linked the prognosis and the adaptation of antibiotics' prescription, but only for bacteriemia [10] and for community-acquired pneumonia [3, 4]. This association between an adapted prescription and the prognosis may be strong especially since our study found other prognosis factors (as qSOFA, high level of CRP and the onset of a septic shock) which are known in the literature for having an important impact on the onset of unfavorable events.

In this study, the reasons of non-optimal antibiotic therapies at ED were a too wider spectrum and a non-adaptation to kidney function (in particular failure). However, these two reasons may have not the same impact on the patient. Indeed, a wider spectrum could mainly lead to the selection of bacterial resistances and the emergence of multiresistant bacteria with a collective impact. On the opposite, the non-adaptation to kidney function may be associated with a lower efficacy or with an increased risk for side effects. Besides, the adaptation of antibiotics' doses is often discussed at the acute phase, especially in case of acute kidney failure linked to the sepsis. In this context, avoiding underdosing seems to be the most important.

The fourth main point is that the reevaluation at D2, as recommended by the guidelines, was performed in most of the patients (nearly 90%). This proportion is higher than in other studies, especially for bacteriemia [11]. This is encouraging in the era of an antibiotics proper use, especially since this reevaluation leads in our study to a global improvement of antibiotic prescription. The reevaluation is pivotal since it allows stopping inadequate antibiotic therapies. Indeed, one quarter of reevaluations resulted in discontinuation of antibiotics, particularly after reaching the conclusion that there was no ongoing bacterial infection. It thus allowed to increase the proportion of optimal therapy from 67.8% to 74.8%, a rate close to that reported in other studies [3, 15].

Finally, surprisingly, an adapted prescription after reevaluation was not significatively associated with the onset of unfavorable events whereas an initial adapted prescription was associated with a poorer prognosis. This difference highlights a gap between the consequences of an adapted prescription at ED and after reevaluation. Indeed, an initial adapted prescription at ED may have an individual impact, particularly on the prognosis. On contrary, an adapted prescription after reevaluation may rather have a collective impact. This could be explained by a gradation in this category mostly because of too long duration of antibiotic therapy. This overtreatment may not be the cause of unfavorable event but could lead to antimicrobial resistance and side effects. On contrary, the prescriptions at ED graded as adapted were mostly classified in this group because of non-adaptation to the severity or a too wider spectrum which could lead to a worse prognosis.

Despite these interesting results, our study has some limitations. Firstly, the monocentric character of this study could lead to bias by the differences of clinical practices between the different physicians, even though the guidelines were the same for all. Then, because of its retrospective character, the side-effects linked to the antibiotic therapy could not be thoroughly collected, potentially impacting on some results such as the absence of association between an adapted antibiotic therapy after reevaluation and the prognosis. It could indeed be speculated that some optimal therapies could not be initiated or had to be stopped because of contra-indications or side-effects leading to evolve towards a therapy just adapted. In some cases, the diagnosis of bacterial infection was not certain, in particular in respiratory infections, even though the main respiratory viruses were systematically searched in case of respiratory infection suspicion. Last, because of the small number of patients in some type of infections, in-depth analyses according to the types of infections were not always possible, except for pneumonias, UTI and abdominal infections.

To conclude, our results show that an optimal antibiotic therapy is prescribed at the ED for most of the patients. This proportion is also increased with the reevaluation. However, a significant part of antibiotic therapies after reevaluation remains graded as inadequate. Increasing the proportion of optimal prescriptions represents an important objective, especially since this study shows that an adapted prescription at the ED and an inadequate prescription after reevaluation is associated with a poorer prognosis. According to our results, even though the initial antibiotic therapy prescribed in the ED may be reevaluated later on, its appropriateness is crucial, not only by limiting the risk of emergence of antimicrobial therapy at the collective level, but also and mainly because associated with a better clinical prognosis at the individual level. To decrease the part of inadequate antibiotic therapy after reevaluation, physicians' formation must be reinforced, maybe with antimicrobial stewardship. Besides, it may be interesting to implement another reevaluation of the antibiotics' prescription before the end of the treatment.

Declarations

ETHICAL APPROVAL

This study complies with French (Loi Informatique et Liberté n°78-17 du 6 janvier 1978) [16] and European (GRPD EU 2016/679) regulations on data protection and patient information (Commitment of compliance MR004 n°2210228 of 3 December 2018) [17].

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

COMPETING INTERESTS

None to declare.

FUNDING

None to declare.

AUTHORS' CONTRIBUTIONS

Conceptualization: Moretto F., Piroth L.; Methodology: Moretto F., Piroth L.; Data collection: Moretto F.; Writing: Moretto F., Piroth L.; Reviewing: Catherine F., Martha B., Sixt T., Chavanet P., Blot M., Ray P.

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Tables

Table 1: Characteristics of the population

	Overall (n=484)
Median age (minimal-maximal), years	79.9 (18-105)
Men, n (%)	255 (52.7)
Underlying conditions, n (%)	
High blood pressure	240 (49.6)
Chronic heart failure	67 (13.8)
Chronic cardiac diseases	250 (51.7)
Stroke	58 (12)
Dementia	131 (27.1)
Other chronic neurological diseases[1]	30 (6.2)
Chronic kidney failure[2]	82 (16.9)
COPD	65 (13.4)
Chronic respiratory failure	28 (5.8)
Diabetes mellitus	111 (22.9)
Neoplasia	60 (12.4)
Hemopathy	28 (5.8)
Other chronic diseases[3]	119 (24.6)
Immunodepression, n (%)	100 (20.7)
Drug related[4]	93 (19.2)
Not drug related[5]	52 (10.7)
Place of life, n (%)	
Home	390 (80.6)
Retirement home	79 (16.3)
Other	15 (3.1)
Autonomy at home[6]**, n (%)**	241 (49.8)

COPD: Chronic Obstructive Pulmonary Disease

[1] Other chronic neurological disease: epilepsy (13), Parkinson disease (10), Lewy body disease (2), multiple sclerosis (1), Charcot-Marie-Tooth disease (1), myasthenia gravis (1), multifocal myelitis (1), spina bifida (1)

[2] Chronic kidney failure defined for a Glomerular Filtration Rate less than 60 mL/min/1.73m²

[3] Other chronic diseases: chronic inflammatory disease (rheumatological diseases, chronic bowel diseases, vascularitis) (29), cirrhosis (5)

[4] Drug-related immunosuppression: chemotherapy (27), corticoids (10), immunosuppressive drugs (13), immunotherapy (2)

[5] Not-drug related immunosuppression: neoplasia (40), hemopathy (23), rheumatological disease (12), cirrhosis (5)

[6] Patients considered not autonomous at home if they need external help for at least two activities of ADL scale

Table 2: Clinical presentation of the patients at the ED

	Overall (n=484)
Cause of consultation to the ED, n (%)	
Respiratory symptoms	150 (31)
Abdominal symptoms	110 (22.7)
Fever	49 (10.1)
Fall	44 (9.1)
General state impairment	39 (8.1)
Urinary tract infection symptoms	21 (4.3)
Malaise	17 (3.5)
Cutaneous infection symptoms	11 (2.3)
ENT symptoms	11 (2.3)
Other reason[1]	32 (6.6)
Quick SOFA, n (%)	
0-1	409 (84.5)
2	63 (13)
3	12 (2.5)
Septic shock, n (%)	11 (2.3)
Median (min-max) biological variables at admission	
Leucocytes, G/L*	11.9 (0.2-75.4)
Neutrophils cells G/L*	9.4 (0.07-35.04)
Lymphocytes, G/L*	0.99 (0.05-59.71)
CRP, mg/L*	91.2 (2.9-475)
PCT, pg/mL*	0.41 (0.02-70.8)
Creatinine, µmol/L*	82 (14-657)
GFR, mL/min/1,73m²*	69 (6-167)
ASAT, UI/L*	26 (7-1523)
ALAT, UI/L*	25 (6-1113)
Advocated diagnosis at the ED, n (%)	
Pulmonary infections	224 (46.3)
Urinary tract infections	94 (19.4)

Abdominal infections	87 (18.0)
Cutaneous infections	36 (7.4)
Other infections[2]	43 (8.9)
Retained diagnosis after reevaluation at D2	
Type of infection, n (%)	
Pulmonary infections	379
Urinary tract infections	153 (40.4)
Abdominal infections	83 (21.9)
Cutaneous infections	76 (20.1)
Other infections[3]	23 (6.1)
Microbiological documented infection, n (%)	122 (32.2)

*When available

[1] Cardiac symptoms, neurological symptoms, pain, osteoarticular symptoms

[2] Ear-Nose-Throat (ENT) infections (15, 3.1%), immunodepression-linked infection (8, 1.7%), central nervous system infections (8, 1.7%), cardiovascular infection (5, 1%), septic shock (4, 0.8%), unknown infections (e.g., hesitation between urinary and lung origin) (2, 0.4%), osteoarticular infection (1, 0.2%).

[3] Cardiovascular infection (24, 6.3%), ENT infections (13, 3.4%), immunodepression-linked infection (2, 0.5%), central nervous system infections (2, 0.5%), septic shock (1, 0.25%), unknown infections (1, 0.25%), osteoarticular infection (1, 0.25%).

Table 3: Factors associated with unfavorable events

	Patients at D0 (n = 484)[1]		Patients at D2 (n = 436)[2]	
	Univariate analysis HR (CI95%)	Multivariate analysis HR (CI95%)	Univariate analysis HR (CI95%)	Multivariate analysis HR (CI95%)
Chronic cardiac disease	0.64 (0.40-1.01) p = 0.05	0.62 (0.38-1.00) p = 0.048	NS	NS
Chronic respiratory failure	2.29 (1.17-4.46) p = 0.02	2.75 (1.35-5.59) p = 0.005	2.81 (1.28-6.13) p = 0.01	2.40 (1.08-5.32) p = 0.03
Diabetes mellitus	0.52 (0.28-0.97) p = 0.04	NS	NS	NS
Autonomous patient	0.63 (0.38-1.04) p = 0.07	NS	NS	NS
qSOFA at admission (per +1 increment)	1.86 (1.42-2.44) p < .001	1.77 (1.33-2.35) p < .001	1.54 (1.06-2.25) p = 0.03	NS
Septic shock at admission	3.91 (1.42-10.79) p = 0.009	NS	NS	NS
Hemoglobin at D0 (per +1 g/dL increment)	0.9 (0.81-1.00) p = 0.05	0.86 (0.77-0.96) p = 0.007	NS	NS

CRP at D0 (per +100 mg/L increment)	1. (1.00-1.49) p = 0.04	NS	NS	NS
Creatinine at D0 (per +10 µmol/L increment)	1. (1.00-1.04) p = 0.05	NS	NS	NS
Adapted antibiotic therapy at D0 (compared with optimal therapy)	1.95 (1.18-3.22) p = 0.01	2.29 (1.35-3.91) p = 0.002	NA	NA
Inadequate antibiotic therapy after reevaluation at D2 (compared with optimal therapy)	NA	NA	3.52 (1.42-8.72) p = 0.003	4.05 (1.55-10.55) p = 0.004

HR : Hazard ratio ; CI95% : Confidence Interval 95% ; NS : non-significant; NA : non applicable

[1] Analyses at D0: univariate and multivariate Cox models performed with the antibiotic therapy prescription at ED

[2] Analysis at D2: multivariate Cox model performed with antibiotic therapy prescription after reevaluation

Figures

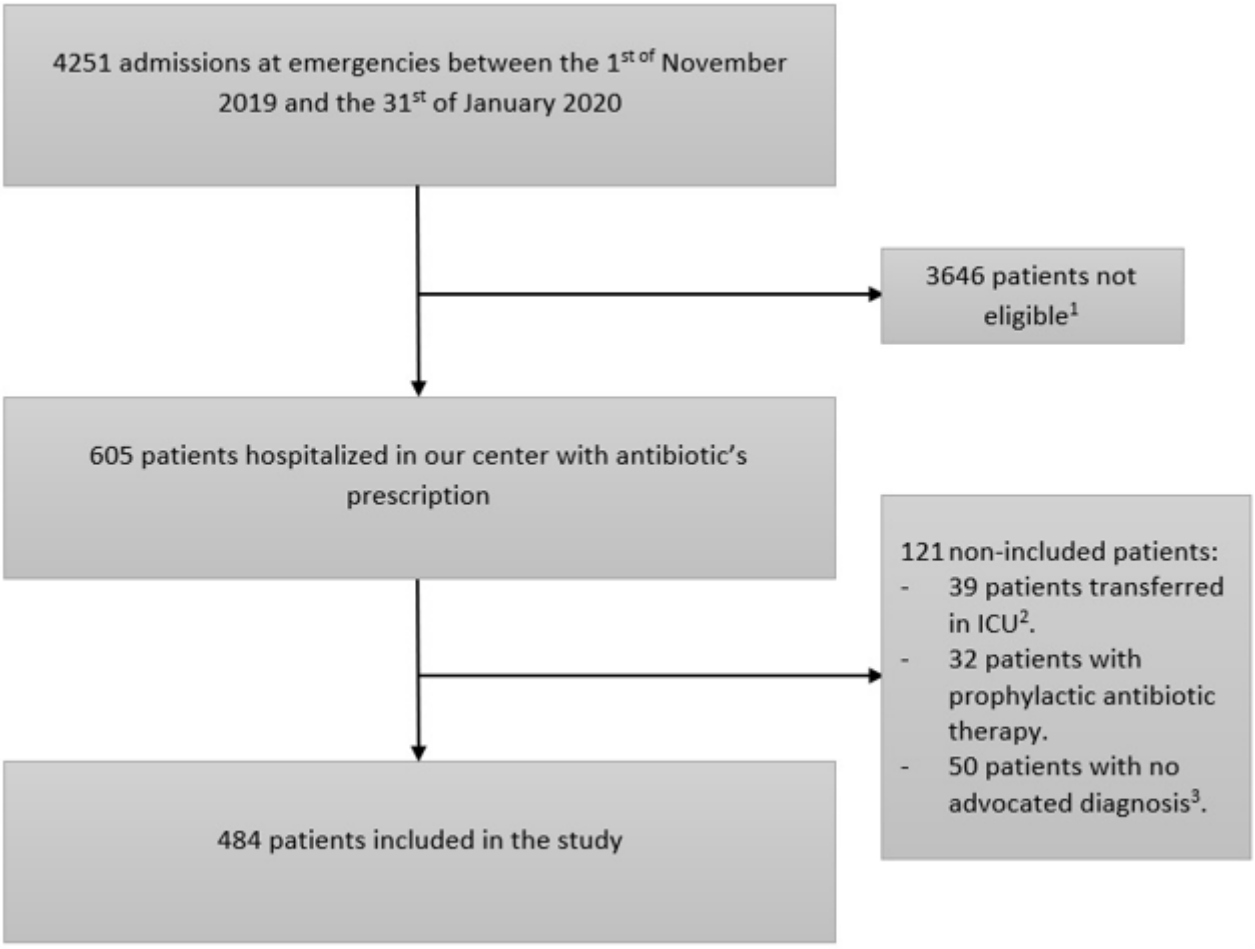

Figure 1

Flow-chart of the study

[1] Not eligible: patients not hospitalized or/and without antibiotic prescription at ED or/and hospitalized in another center

[2] Non-inclusion if the patient was transferred in ICU directly from ED

[3] No advocated diagnosis: non-inclusion if the diagnosis at ED was not clearly mentioned in medical records

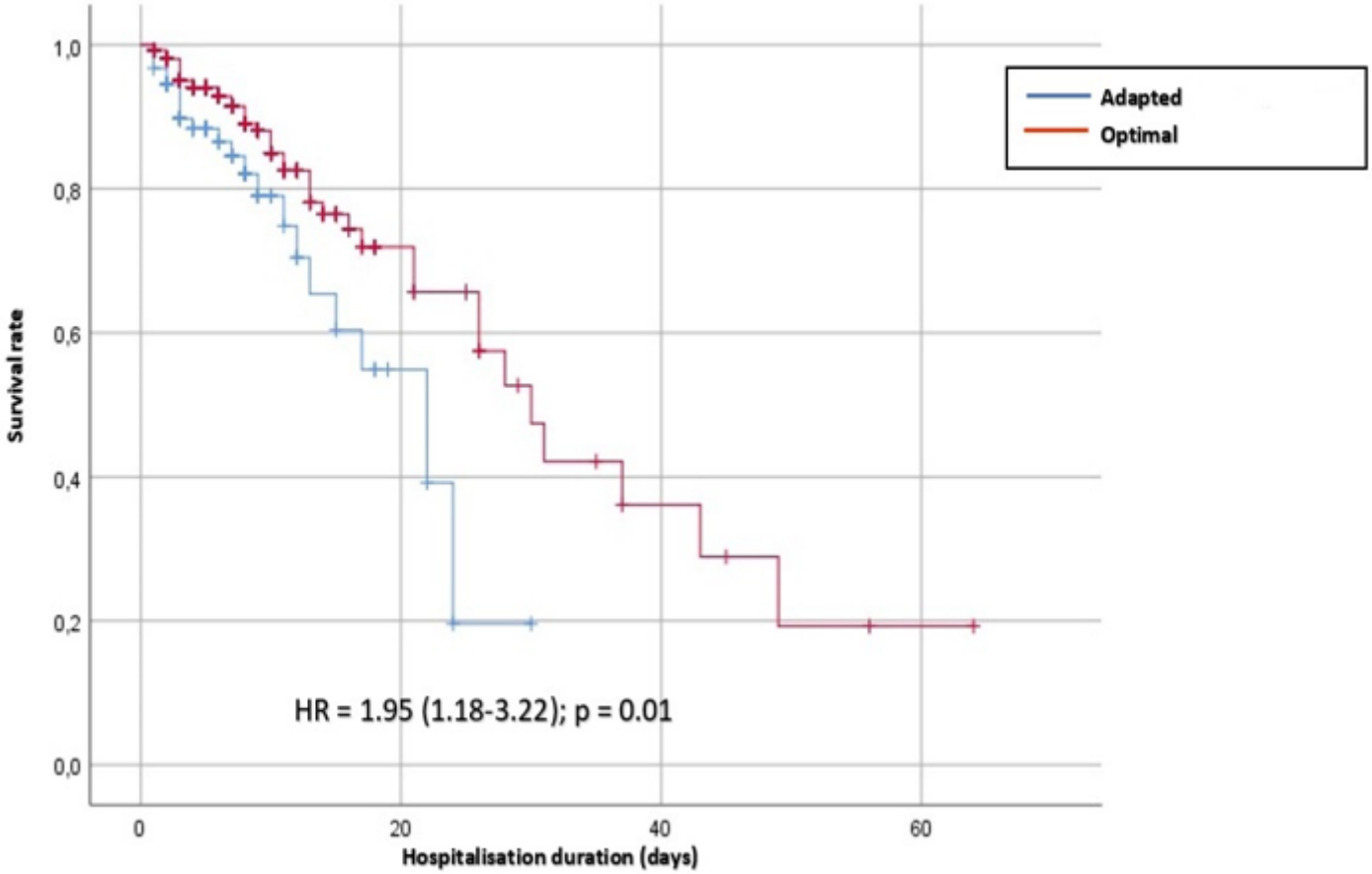

Figure 2

Survival rate curves according to the adaptation of the antibiotic therapy at ED

These curves represent the survival rate without unfavorable event (defined as death or transfer to intensive care unit or re-hospitalization) over the time according to the adequation of the antibiotic therapy prescribed at the ED: either optimal or adapted.