Adequacy of Antimicrobial Empirical Treatment for Sepsis in the Emergency Department of a Large University Hospital

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Abstract: *Purpose*: This retrospective study analyzes the adequacy of the empirical antimicrobial treatment for sepsis at the emergency department according to the results of the microbiological isolations and describes the associations between microbiological variables and mortality. Values for several clinical and microbiological variables were prospectively collected for a total of 101 patients. Cases of inadequate antimicrobial treatment as defined in the text were further studied.

Results: Fifty-two patients had microbiological confirmation of infection (51.4%), constituting 62 different isolates. *Escherichia coli* represented half of the cases. One third of the microbiological isolates were not adequately covered by initially chosen treatment, mostly due to microbiological resistances. Having a respiratory source was the only variable associated to inadequate coverage (p=0.05). Lack of adequate empirical microbiological coverage was not associated with mortality (p=0.16). In a multivariate test, "respiratory source" (OR=46.6 [2.2-972; 95%CI] and "severity" (OR=42.5 [1.2-1456; 95%CI] remained significantly associated to mortality.

Conclusions: Lack of empirical coverage for microbiological agents in sepsis is not uncommon. Institutional efforts are needed to improve the empirical use of antimicrobials for sepsis in the Emergency Department.

Keywords: Sepsis, Antimicrobial, Empirical treatment, Microbiological isolation, Mortality, Emergency Department.

1. INTRODUCTION

Sepsis is a leading cause of in-hospital death [1]. We have previously demonstrated that actions implemented in the Emergency Department (ED) can improve the medical care of patients with sepsis [2,3].

Antimicrobial therapy is one of the milestones of sepsis therapy. A recent study of patients with septic shock showed that the delay in antimicrobial administration after the onset of hypotension was associated with decreasing survival rates [4]. It may seem straightforward that selecting an adequate empirical antibiotic therapy will decrease the mortality rate of patients admitted with sepsis to the ED. Yet, to our knowledge no previous studies have been specifically designed to validate this hypothesis. During the last years, conflicting reports regarding the frequency of inadequate antimicrobial treatment and its effect on the outcome of critically ill patients have been published [5-17].

The main objective of this retrospective study was to analyze the adequacy of empirical coverage for microbiological isolations of patients presenting with sepsis at the ED of a large teaching Hospital. A secondary objective was to evaluate the association of clinical and microbiological variables with mortality.

2. MATERIALS AND METHODOLOGY

2.1. Study Setting and Population

We gathered data from patients consecutively coming to our ED along two separate "2-month" periods of time belonging to 2004-2005 and 2007. These two periods were chosen for a comparison among them to evaluate if the 2004 surviving sepsis campaign guidelines had been implemented in this setting [18]. Our institution is a large (1.700 beds) tertiary-care university teaching hospital with a large catchment area of 720.000 people drawn from the south-eastern sector of the city and province of Madrid, Spain.

For clinical research purposes, the definition of "inadequate" antimicrobial treatment of infection included, as described elsewhere, the microbiological documentation of an infection that was not being effectively treated at the time of its identification, the absence of antimicrobial agents directed against a specific class of microorganisms (*e.g.*, for fungal infections) or the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant [19].

Patients were included whenever physicians from the General Internal Medicine Section of the ED had made the diagnosis of sepsis, severe sepsis, or septic shock for them at any point of their stay in our Department. Furthermore, a 6-

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1876-5424/09

hour minimum stay at our ED was required; thus, patients with an "earlier than 6-hour" admission to the Intensive Care Unit (ICU) or those who had died shortly after their arrival were excluded. We thought that this requested issue would allow direct comparisons with the results from other studies under the same conditions [20].

Physicians on duty at the observation units were contacted at least 3 times a day for cases report. Additionally, the software used by the Admission Office of our hospital was consulted to identify all those patients admitted with diagnoses related to sepsis that might not have been detected by other means. ICU admissions coming from the ED during that period were also checked. The competent Hospital Authority approved the collection and statistical analysis of the original data. Patients, or a relative in case of inability on behalf of the patient, gave oral consent for data prospective collection.

2.2. Study Design

Data were obtained both from written medical charts and from electronic applications for Hematology, Biochemistry and Microbiology Laboratories of the Hospital. They included age, sex, pre-existing conditions predisposing to infection and Acute Physiology and Chronic Health Evaluation (APACHE II) score, calculated with the worst values of the first 6 hours since presentation at the ED [21]; number of failing organs, as defined in previously published guidelines, as well as "severity" following universal definitions of sepsis stages [22, 23] (Tables **1** and **2**). Definite source of infection according to final diagnosis and results of cultures from blood, urine and other biological samples were recorded. The pattern of use of antimicrobials was analyzed, especially regarding the appropriateness of the empirical coverage of those microbiological agents lately identified. The final diagnosis, length of hospital stay and the outcome of every patient were surveyed.

2.3. Data Analysis

All tests for significance and resulting P values were 2-sided, with a level of significance set at 0.05. Fisher's exact test and the X^2 test were used for categorical variables. For continuous variables, the Kolmogorov-Smirnov test served to identify those variables with a normal distribution, for which the T test for independent samples was used. The Mann-Whitney U test was used as a nonparametric test for variables that did not follow a normal distribution. A model of backward logistic regression was designed to evaluate those variables significantly associated with mortality. Statistical calculations were done using the SPSS version 15.0 software package (LEAD Technologies, Inc, USA).

3. RESULTS

The database comprised 101 cases (data are referred to the total cohort). Mean age was 71.2±18.4 years old, with a male to female ratio of 6:4. Fifty percent of the patients had no predisposing conditions that could put them at risk to develop sepsis. The average APACHE II score was 17.0±6.7. According to the stage of severity, 46% had sepsis syndrome, 28% severe sepsis and 26% septic shock. Sources of infection were urinary tract (45%), lung (25%), abdominal cavity (17%) and skin (13%).

Blood cultures were drawn in 76% and the positivity rate was 45% of this subgroup. Fifty-two patients had a microbiological confirmation of an infection (51.4% of the whole). In 49 patients, no isolates were identified: in 14 cases no samples at all were sent for culture and in 35 cases, cultures yielded no positive results.

A total of 62 different isolates were identified (Fig. **1**). *Escherichia coli* (*E. coli*) represented half of the isolates, mostly from urinary or abdominal sources. Simultaneous growth of two agents took place in 10 patients. No single variable was associated to simultaneous growth. In 18 cases the infective agent was identified only in a biological sample other than blood, more commonly in urine (n=10).

Three quarters of the 101 patients initially received one antimicrobial drug and another quarter received two. Third-generation cephalosporins were the most frequently used ones (32%), followed by amoxicillin-clavulanate (16%) and quinolones (15%). Clinical profiles of those cases in which physicians initially chose a combination of antibiotics are

Table 1. Criteria for Acute Organ Failure

- Need for vasoactive drugs
- Severe hypoxia (pO2/FiO2 < 200), or need for mechanical ventilation
- Platelet count < 100.000/mm^3, or baseline platelet count/2
- Creatinine > 2 mg/dl or baseline creatinine x 2. Or urine output < 0.5 ml/kg/h for more than two hours
- Bilirrubine > 2 mg/dl or baseline bilirrubine x 2
- Glasgow Coma Score < 15 points

Table 2. Definitions in Sepsis

Sepsis	=	SIRS* due to proved or suspected infection.
Severe sepsis	=	sepsis plus acute failure of one or more organs, or impaired perfusion (hyperlactacidaemia) or hypotension (transient o persistent).
Septic shock	=	Hypotension unresponsive to fluid therapy, needing vasoactive drugs.

*SIRS denotes "Systemic Inflammatory Response Syndrome".

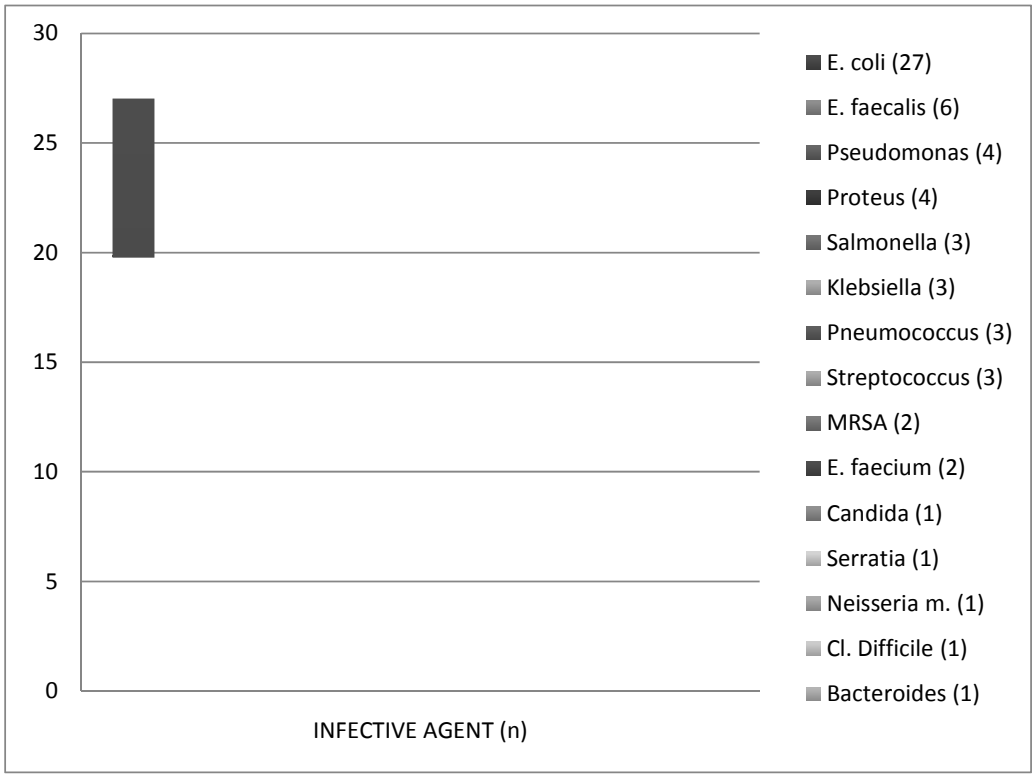

Fig. (1). Definite identification of infective agents.

Table 3. Clinical Profile of Cases Where a Combination of Antimicrobials was Used

Case	Age	Source of Infection	Agents Isolated	Drugs Used at Presentation	Survive
1	82	Abdominal	None	Ciprofloxacin Metronidazol	Yes
2	74	Respiratory	None	Imipenem Tobramycin	No
3	87	Respiratory	None	Ceftazidime Clyndamicin	Yes
4	66	Skin	Pseudomonas aeruginosa	Ceftriaxone Clyndamicin	Yes
5	90	Abdominal	Escherichia coli	Ampicillin Gentamycin Metronidazole	Yes
6	74	Abdominal	Escherichia coli	Imipenem Tobramycin	Yes
7	36	Skin	Streptococcus viridans	Imipenem Metronidazole	Yes
8	76	Urinary	Salmonella spp. Enterococcus faecalis	Ceftriaxone Gentamycin	Yes
9	81	Skin	None	Piperacillin/tazobactam Ciprofloxacin	No
10	85	Intestinal	Clostridium difficile	Vancomycin Metronidazole	No
11	76	Respiratory	None	Ceftriaxone Levofloxacin	Yes
12	34	Respiratory	None	Ceftriaxone Clyndamicin	Yes

(Table 3). Contd.....

Case	Age	Source of Infection	Agents Isolated	Drugs Used at Presentation	Survive
13	34	Respiratory	None	Vancomycin Gentamycin	Yes
14	66	Respiratory	None	Aztreonam Azithromycin	No
15	94	Skin	Pseudomonas aeruginosa	Ceftriaxone Clyndamicin	No
16	92	Respiratory	None	Ceftriaxone Levofloxacin	Yes
17	42	Respiratory	Streptococcus pneumoniae	Ceftriaxone Levofloxacin	Yes
18	28	Skin	Streptococcus viridans	Cloxacillin Amikacin	Yes
19	75	Skin	*Escherichia coli* Proteus mirabilis	Ceftriaxone Metronidazole	Yes
20	81	Urinary	None	Imipenem Vancomycin	No
21	88	Urinary	*Escherichia coli*	Amoxicillin/clavulanate Gentamycin	Yes
22	98	Abdominal	Klebsiella pneumoniae	Ciprofloxacin Metronidazole	Yes

Table 4. Patients with Infections without a Correct Empirical Antibiotic Coverage at Presentation

Age	Previous Conditions	Suspected Source	Agent	Resistant Agent?	Drugs Used at Presentation	"Avoidable Mistake?"	Survive?
93	Home. Skin ulcers	Respiratory	Enterococcus faecalis	No	Ceftriaxone	Yes	Yes
61	"Double J" catheter	Urinary	Enterococcus faecalis	No	Ceftriaxone	Yes	Yes
66	Nosocomial. Skin ulcers	Skin	Pseudomonas aeruginosa	No	Ceftriaxone	Yes	Yes
82	None	Urinary	MRSA	No	Ceftriaxone	No	Yes
83	Uremia	Urinary	MRSA	No	Ceftriaxone	No	No
76	None	Urinary	Candida albicans	No	Ciprofloxacin	Yes (hifae in urinalysis)	Yes
79	Liver disease. Skin ulcers	Respiratory	Enterococcus faecalis Streptococcus viridans	No	Ceftriaxone	Yes	No
74	None	Urinary	*Escherichia coli*	Yes	Amoxicillin/clavulanate	No	Yes
86	Urolithiasis	Urinary	*Escherichia coli*	Yes	Piperacillin/tazobactam	No	No
51	None	Intestinal	Steptococcus pneumoniae	No	Ciprofloxacin	No	Yes
51	Skin ulcers. Cancer. Nosocomial	Respiratory	Pseudomonas aeruginosa	No	Ceftriaxone	Yes	Yes
94	Legs ischaemia and ulcers. Nosocomial	Skin	Pseudomonas aeruginosa	No	Ceftriaxone plus clindamycin	Yes	No
59	Diabetes mellitus	Urinary	*Escherichia coli*	Yes	Amoxicillin/clavulanate	No	Yes
73	Bronchial aspiration	Respiratory	Klebsiella pneumoniae Enterococcus faecium	No	Ceftriaxone	Yes	Yes
53	Cancer. Nosocomial	Cholangitis	Pseudomonas aeruginosa Enterococcus faecium	No	Imipenem	No	No

MRSA: Methicillin-resistant Staphylococcus aureus.

"Avoidable mistake" denotes cases where previous clinical background or suspected source should have prompted the use of a more aggressive pattern of antimicrobials. However, *e.g.*, unexpected resistances, routine coverage of MRSA pneumonia in a non-institutionalized patient or a mistake in identifying source of infection were not classified as "preventable".

previous conditions of the patient also appear as powerful factors with effect on survival.

Even more interesting can be the finding that, in our study, barely half of the failures of prescription could have been prevented with protocols: no protocol would have helped adequately treat the other half. Choosing a wider antibiotic coverage in the most seriously ill patients could decrease mortality, but it might as well have a deleterious influence on later emergences of antimicrobial resistances.

5. CONCLUSION

Many questions regarding the impact of infection caused by antimicrobial-resistant pathogens on the mortality of patients with sepsis still need to be clarified. This study highlights the importance of identifying pitfalls in the empirical use of antimicrobials; otherwise, the remaining "bundle" measures included in universal guidelines may lose effectiveness in achieving lower mortality rates for patients with sepsis.

ABBREVIATIONS

ED = Emergency Department

ICU = Intensive Care Unit

E. coli = *Escherichia coli*

CONFLICT OF INTEREST

This paper was conducted without institutional funding or financial support from the pharmaceutical industry. No other potential conflict of interest is disclosed.

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Received: April 26, 2009 Revised: June 11, 2009 Accepted: June 11, 2009