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Bacterial ecology and effects of initial empiric antimicrobial treatment in severe trauma patients

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Guillaume FAIVRE

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**“ Bacterial ecology and effects of initial empiric antimicrobial
treatment in severe trauma patients ”**

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Écologie bactérienne et effets de l'antibiothérapie initiale empirique chez les patients traumatisés sévères

Introduction : Les infections nosocomiales et la résistance aux antibiotiques sont des préoccupations majeures en réanimation. Les patients traumatisés sévères sont fréquemment exposés aux antibiotiques selon plusieurs indications. L'effet d'une antibiothérapie empirique initiale (ATEI) sur l'écologie bactérienne chez les patients traumatisés sévères n'a jamais été étudié. Le but de cette étude était de décrire l'écologie bactérienne précoce (depuis l'admission au 5^e jour inclus) et tardive (depuis le 6^e jour) des traumatisés sévères et d'évaluer l'effet d'une ATEI sur l'émergence de résistances dans cette population.

Méthodes : Tous les dossiers des patients traumatisés admis dans un centre de traumatologie de niveau 1 entre janvier 2010 et décembre 2015 ont été examinés. Les patients présentant un Injury Severity Score (ISS) > 16 et une durée de séjour en réanimation > 10j ont été inclus. Outre les caractéristiques démographiques et de sévérité principales, les informations sur l'ATEI et l'antibiothérapie secondaire ont été rapportées. Pour chaque patient, tous les échantillons bactériologiques (avec le site et le jour de réalisation) précoces (≤ 5 ans) et tardifs (> 5 jours), de l'admission à la sortie de réanimation, ont été collectés ainsi que la souche bactérienne mise en évidence et son profil de résistance.

Résultats : 507 patients (ISS médian de 29 [IQR, 22-34]) ont été inclus : 114 (22%) n'ont pas reçu d'ATEI (groupe pas-ATEI), 95 (19%) ont reçu une ATEI courte ≤ 3 jours (groupe ATEI-courte), 298 (59%) ont reçu une ATEI > 3 jours (groupe ATEI-longue).

Dans l'ensemble de la cohorte, l'écologie précoce était dominée par *Staphylococcus aureus* (SA), les bactéries résidant dans le nasopharynx (RNP) et les entérobactéries du groupe 0-1 (29% des patients, 13% et 10%). Les entérobactéries du groupe 3 et *Pseudomonas aeruginosa* (PA) ont été trouvées respectivement chez 11% et 6% des patients.

L'écologie tardive était dominée par les entérobactéries du groupe 3 (22% des patients), les entérobactéries du groupe 0-1 (17%) et les SA (20%). Les entérobactéries du groupe 2, PA et *Acinetobacter* ont été trouvées chez respectivement 10%, 11% et 5% des patients. Aucune différence au niveau de l'écologie n'a été trouvée selon l'ATEI.

Les résistances sont plus nombreuses pour l'écologie tardive ; des entérobactéries avec céphalosporinase hyperproduite (HCASE) étaient présentes chez 19% des patients, des entérobactéries à β -lactamase à spectre étendu (BLSE) chez 4%, des PA résistants chez moins de 4% et des SA résistants à la méthicilline dans moins de 1% des cas.

Aucune différence n'a été constatée en ce qui concerne l'émergence d'une résistance selon l'ATEI.

Conclusion : Ce travail a permis de décrire l'écologie bactérienne précoce et tardive d'une population spécifique de traumatismes sévères. Dans cette population, l'émergence de la résistance est dominée par les HCASE et aucune influence de l'ATEI n'a été montrée.

Bacterial ecology and effects of initial empiric antimicrobial treatment in severe trauma patients (abstract)

Introduction: Nosocomial infections and antimicrobial resistance are major concerns for intensive care unit (ICU) caregivers. Trauma population is specially underwent to an precocious antimicrobial (AT) exposure for several indications. The effect of an initial empiric AT (IEAT) on the bacterial ecology in severe trauma patients has never been studied. The aim of this study was to describe the early (from admission to day 5) and late (since day 6) bacterial ecology of severe trauma patients and to assess the effect of an IEAT on the emergence of resistance in this population.

Methods: All trauma patients admitted in a Level 1 trauma centre between January 2010 and December 2015, has been screened. Patients with an Injury Severity Score (ISS) >16 and a trauma ICU length of stay > 10 were included. In addition to mains demographic and severity characteristics, details on IEAT and secondary AT have been reported. Finally, for each patient, all early (\leq day 5) and late ($>$ day 5) bacteriological sample, from admission to ICU discharge, were recorded as well as sample timing, sample site, bacterial strain and antimicrobial resistance.

Results: 507 patients, of median ISS of 29 [IQR, 22-34], were included: 114 (22%) did not received IEAT (No-IEAT group), 95 (19%) received a short IEAT \leq 3 days (Short-IEAT group), 298 (59%) received a long IEAT $>$ 3 days (Long-IEAT group). In the entire cohort, early ecology was dominated by *Staphylococcus aureus* (SA), bacteria resident within the nasopharynx (RNP) and Group 0-1 Enterobacteria (29% of patients, 13% and 10%). Group 3 Enterobacteria and *Pseudomonas aeruginosa* (PA) were found in 11% and 6% of patients respectively. Late ecology was dominated by Group 3 Enterobacteria (22% of patients), Group 0-1 Enterobacteria (17%) and SA (20%). Group 2 Enterobacteria, PA and *Acinetobacter* were found in 10%, 11% and 5% of patients respectively. No difference of ecology repartition was found according to IEAT management. Resistance emerged essentially during the late period; Hypercephalosporinase enterobacteria (HCASE) were present in 19% of patients, extended spectrum betalactamase (ESBL) enterobacteria in 4%, resistant PA in less than 4% and methicillin resistant SA in less than 1%. No difference was found regarding emergence of resistance according to the IEAT management.

Conclusion: This work had permit to describe clearly the early and late bacterial ecology of a specific severe trauma population. In this population, resistance emergence is dominated by HCASE and no influence of IEAT has been revealed.

BACTERIAL ECOLOGY AND EFFECTS OF INITIAL EMPIRIC ANTIMICROBIAL TREATMENT IN SEVERE TRAUMA PATIENTS

INTRODUCTION

Nosocomial infections and antimicrobial resistances are major concerns for health care professionals, especially in intensive care unit (ICU) setting (1,2). Many specific conditions of critically injured patients increase the risk of infection (3,4); open fractures, pulmonary aspirations, abdominal trauma, invasive procedures, profound physiological dysfunction altering the pharmacokinetics of the antimicrobials (5,6), trauma-induced immunoparalysis (7,8), and immune response to surgery (9). In ICUs, where severe infections are frequent, antimicrobial strategy need an accurate empiric cover without antibiotic overuse. A delayed or inadequate antimicrobial therapy is indeed well known to be associated with mortality in the critically ill (10–12). In the other hand, antimicrobial treatment (AT) overuse leads to both selection pressure (13) and colonization pressure (14) which are reputed to be significant risk factors for acquisition of multidrug resistant (MDR) bacteria, which is another cause of elevated mortality, worst outcome and increased cost (15,16). To control these different risks, two strategies could be proposed: antimicrobial stewardship and surveillance (17). If the interest of an antimicrobial stewardship program in the setting of trauma has already been reported in the literature (17–20), the impact of the empiric antimicrobial therapies on the bacterial ecology of severe trauma population has never been studied to the best of our knowledge. A best knowledge of the bacterial ecology of trauma patients could probably help to optimize the management of infections by reducing the use of broad-spectrum antibiotics and the occurrence of bacterial resistance.

The aim of this study was to describe the bacterial ecology of severe trauma patients in early and late phase of management. A second objective was to assess the effects of an initial empiric antimicrobial therapy (IEAT) on the emergence of bacterial resistance in this population.

METHODS

Study design and patients

The hospital chart of the trauma ICU of Lapeyronie University Hospital, Montpellier, France (Level I Regional Trauma Centre) were retrospectively studied from January 2010 to December 2015. All consecutive patients directly admitted from the trauma scene with a strong suspicion of severe trauma during pre-hospital assessment according to French guidelines were screened (21), and those with an Injury Severity Score (ISS) > 15 associated with an ICU length of stay > 10 days were included.

Exclusion criteria were as follows: (1) previous admission to another hospital; (2) age < 18 years, (3) data missing from the medical report. Because of its retrospective and observational nature, the need for written consent for present study was not required by our institutional ethical committee.

Antimicrobial management

In our trauma ICU, IEAT was prescribed according the French and international recommendations; (1) early aspiration pneumonia suspicion in severe comatose patient (i.e., severe trauma brain injury, sedated patient), (2) open fractures or large soft tissues wounds, (3) severe facial trauma or oro-pharyngeal mucosal injury, (4) penetrating cranio-cerebral or trunk trauma, cranio-cerebral wound, (5) hollow viscous injury or perforation with peritonitis (22–27). The antimicrobial drugs and the treatment duration followed our chart protocol in agreement with the international recommendations. Following the protocols, Amoxi-clav was administrated 2g three times a day, gentamicin 3-5 mg/kg once a day, cefotaxime 2g three time a day. Piperacillin-tazobactam was administrated 12 to 16g a day by continuous infusion. Imipenem was prescribed 1g three time a day for and meropenem 2g three times a day.

Data collection

Age, sex, mechanism of injuries, vasopressor use, initial transfusion management, and mechanical ventilation requirements were extracted from the medical records. The ISS, Abbreviated Injury Scale (AIS) by body area, , and the new Simplified

Acute Physiology score (SAPS II) were calculated for each patient (28,29). For each patient, all bacteriological sample from admission ICU to discharge were recorded: (1) sample timing, (2) sample site, (3) bacterial strain and (4) antimicrobial resistance. Rectal and nasopharyngeal bacterial carriage samples were systematically collected on admission then once a week. The following samples were drawn only in case of suspected infection: urine analysis, respiratory samples (broncho-alveolar lavage or tracheal aspirate), blood streams, bone or soft tissues biopsies and peritoneal fluid analysis. Finally, main details on antimicrobial therapy during hospitalization were especially collected: (1) timing of initiation, (2) treatment duration, (3) drugs administrated.

Study definitions

Three groups were firstly defined according to the administration of an IEAT: patients who had an IEAT started at admission and stopped after 72 hours were classified in the Short-IEAT group; patients who had an IEAT started at admission and discontinued after more than 72 hours of treatment were included in the Long-IEAT group; whereas patients who did not have any AT belonged to the No-IEAT group. Furthermore, an AT administrated 48 hours or more after the end of the IEAT was noted as a secondary AT.

Ecology obtained on different samples was classified as follow: “early” if the sample was drawn between admission and day 5, and “late” if the sample was drawn after day 6.

Bacterial strains were classified as follows: (1) resident within the nasopharynx (RNP): *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, (2) group 0-1 Enterobacteria, (3) group 2 Enterobacteria, (4) group 3 Enterobacteria, from the international classification of Enterobacteria, (5) *Pseudomonas aeruginosa* (PA), (6) *Staphylococcus aureus* (SA), (7) Coagulase Negative Staphylococcus (CNS) and (8) *Acinetobacter* (AB).

Antimicrobial resistance was encoded as follows: (1) third generation cephalosporin resistance (3GC-R) for Enterobacteria species, including hypercephalosporinase (HCASE) and extended spectrum betalactamase (ESBL), other Enterobacteria was considered as 3GC sensible (3GC-S); (2) methicillin-resistant SA

(MRSA) and methicillin-sensitive SA (MSSA), (3) PA species resistant to meropenem (MeroR) and/or to piperacillin-tazobactam (PipTazR) and/or to ceftazidim (CeftaR) and savage PA. Resistance was defined by the presence of (1) a 3GC-R for enterobacteria species, (2) SAMR for SA and (3) MeroR and/or CeftazR and/or PiperTazR for PA.

Statistical Analysis

The demographic data of the patients, main characteristics on admission and during hospitalization were compared according to the IEAT strategy using univariate analysis. Bacterial strains, strains profile and sample site were specifically analysed. The main endpoint - criterion was the occurrence of resistance during the early and late period compared between groups. Continuous data were expressed as means (standard deviation [SD]) when normally distributed, or medians [interquartile range (IQR)] when non-normally distributed-. Comparisons between these groups were performed using the ANOVA or the Kruskal-Wallis test as appropriate. Categorical data were expressed as number (percentage) and compared using χ^2 test. Statistical analysis was performed using XLSTAT Pro 5.7.2 (Addinsoft, New York, NY). $P \leq 0.05$ indicated significance.

RESULTS

Patient characteristics

A total of 1873 consecutive severe trauma patients were admitted to our trauma centre between January 2010 and December 2015. Following a first analysis, 1366 patients were excluded from the study; (1) 475 transfers from another institution, (2) 127 with an age younger than 18 years old, (3) 387 with an ISS lower than 16, (4) 331 with an ICU stay lower than 10 days, and (5) 46 with an incomplete medical record (Fig 1). Of 507 remaining patients, 396 (78%) were male, mean age was 43 years (SD 19.7), median ISS was 29 (IQR, 22–34), median SPAS II was 35 (IQR, 25–47). Two-hundred and sixty-six patients (52%) had a head AIS ≥ 3 , 232 (46%) had a chest AIS ≥ 3 and, 224 (44%) had an extremity AIS ≥ 3 . Motor vehicle, bicycle accidents and fall were the main mechanisms of injury. A total of 448 (88%) patients required during hospitalization a mechanical ventilation (median duration of 10.0 days [IQR, 4.5–18 days]) and 391

(77%) required a vasoactive drug (median duration of 2.8 days [IQR, 0.5–6.0 days]). Among the study population, 114 patients (22%) did not have any IEAT (No-IEAT group), 95 patients (19%) had a short IEAT (Short-IEAT group) and 298 (59%) had a long IEAT (Long-IEAT group). The characteristics of the study population are summarized in the table 1.

Antimicrobial management

Among the 393 patients who had an IEAT, 24 patients had a short IEAT but were analysed in the Long-IEAT group because another AT had been started less than 48 hours the discontinuation of the IEAT. All these patients were initially treated with amoxi-clav up to 48 hours, then had been treated with cefotaxime (18 patients), Piperacillin-Tazobactam (3 patients) or carbapenem (3 patients).

Most of patient who had an IEAT, were treated with amoxi-clav. 84 patients (88%) in the Short-IEAT group and 226 patients (75%) in the Long-IEAT group ($p=0.01$). In the Long-IEAT group, the number of patients treated with cefotaxime and piperacillin-tazobactam were 44 (15%) and 19 (6%) respectively, whereas they were 7 patients (7%) and 1 patient (1%) in the Short-IEAT group respectively ($P=0.05$ and $P=0.04$). An aminoglycoside was associated in about 50% of cases (no difference between groups). The median duration of antimicrobial treatment was 2.5 days [IQR, 2_3] in Short-IEAT group versus 6 days [IQR, 5_7] in Long-IEAT group ($p=0.001$).

A half of patients received a secondary AT ($P=0.34$), regardless of the IEAT duration. The secondary AT were mainly: 3GC, 21 patients (37%) in the No-IEAT group, 16 patients (37%) in the Short-IEAT group, 56 patients (35%) in the Long-IEAT group ($P=0.94$) and piperacillin-tazobactam, 22 patients (39%), 17 patients (40%) and 64 patients (40%) respectively ($P=0.98$). An aminoglycoside or a fluoroquinolone were associated in around 50% of patients, regardless of the different groups ($P=0.76$). Secondary AT duration did not significantly differ between the three different groups: 7 days [IQR, 6_9], 7 days [IQR, 7_8] and 8 days [IQR, 7_12] respectively ($P=0.24$). Finally, in the Long-IEAT group only, 25 patients (5%) had another AT. Details of initial and secondary antimicrobial treatment are reported in Table 2.

Groups comparison

Three groups differed from their mean age (50.3 years (20.7) in the No-IEAT group, 42.3 years (19.6) in the Short-IEAT group and 41.6 (18.7) in the long-IEAT group, $P=0.001$), their mechanism of injury ($P=0.001$) and their injury severity (median ISS 25 [IQR, 17_33] in the No-IEAT group, 29 [IQR, 22_34] in the Short-IEAT group and 29 [IQR, 24_36] in the long-IEAT group, $P= 0.001$). Massive transfusion requirement (6 patients (39%) in the No-IEAT group, 8 patients (67%) in the Short-IEAT group and 48 (57%) in the long-IEAT group, $P=0.005$) was also different between the three groups.

There was a significantly longer ICU length of stay in the Long-IEAT group versus the No-IEAT group and the Short-IEAT group: 18.3 days [IQR, 12_32] vs 13.8 days [IQR, 9_23.4] in and 13 days [IQR, 9_23] respectively ($P<0.001$), a longer hospitalization length of stay (29 days [IQR, 19_45] vs 21 days [IQR, 13.2_34] and 23 days [IQR, 16_39] respectively, $P<0.001$), more days of vasopressor support (3.3 days [IQR, 1.5_6.5] vs 1.7 days [IQR, 0_5] and 2.3 days [IQR, 0.3_5] respectively, $P<0.001$), more days of mechanical ventilation (11 days [IQR, 6.8_20.3] vs 6.1 days [IQR, 0_16.8] and 6.5 days [IQR, 2.8_13.5] respectively, $P<0.001$) and a higher IGS2 (37 [IQR, 27_49] vs 32 [IQR, 20.5_4] and 33 [IQR, 24_47] respectively, $P= 0.001$).

Ecology of the total study population

42% of the early bacterial ecology was mainly constituted by SA (146 patients, 29%), RNP bacteria (65 patients, 13%), and Group 0-1 Enterobacteria (50 patients, 10%). Group 3 Enterobacteria and PA were found in 57 patients (11%) and 30 patients (6%) respectively, and CSN and AB were found in 16 and 10 patients (3% and 2% respectively).

The late bacterial ecology was predominantly constituted by Group 3 Enterobacteria (109 patients, 22%), Group 0-1 Enterobacteria (86 patients, 17%) and SA (99 patients, 20%). Group 2 Enterobacteria, CSN, PA and AB were found in 50 patients (10%), 64 patients (13%), 58 patients (11%) and 25 patients (5%) respectively. These bacterial ecologies are illustrated in figure 2.

Effect of an IEAT on the bacterial ecology distribution

Early and late bacterial ecology distributions in relation to IEAT management are reported in figure 3. No influence of the IEAT, be it short or long, was found because no statistically difference was found between the three groups.

Occurrence of bacterial resistance and potential effect of an IEAT

The proportion of patient infected or carrier of an Enterobacteria 3GC-R have increased significantly between the early and the late period: 51 patients (10%) had an Enterobacteria 3GC-R during the early period (4% of ESBL and 6% of HCASE) versus 72 patients (23%) during the late period (4% of ESBL and 19% of HCASE), $P < 0.001$. There was no difference between the proportion of early and late Enterobacteria 3GC-R regarding the administration of an IEAT. The proportions of patient with an HCASE Enterobacteria in the late period were 21% (20 patients), 20% (60 patients) and 16% (18 patients) ($P=0.66$) in the Short-IEAT group, the Long-IEAT group and the No-IEAT group. The proportions of patient with an ESBL Enterobacteria in the late period were 4% (4 patients), 4% (12 patients) and 4% (5 patients) ($P=0.66$) in the Short-IEAT group, the Long-IEAT group and the No-IEAT group; (Fig 4).

On the overall 507 patients, 14 patients had a PA with at least one acquired bacterial resistance: 3 patients during the early period and 11 in the late. PA resistance was as follow: 7 patients presented with a MeroR PA, one patient had a PiperTazR PA, 2 patients had a CeftazR and PiperTazR PA, and 4 patients had a PiperTazR, CeftazR and MeroR PA (Table 3). During the late period, the probability of PA resistance for each drug of interest was as follow: PiperTazR, 0.8%; CeftazR, 0.8%; MeroR, 1.8%. PA resistance was not associated with the administration of an IEAT, whatever its duration: 1% in the Short-IEAT group, 3% in the Long-IEAT group versus the 0% in the No-IEAT group, ($P= 0.09$) (Fig 5).

Finally, MRSA was implicated in infection or carriage in 6 patients, or 1% of the whole cohort. All MRSA have been highlighted during the early period and none during the late period. The occurrence of colonization or infection with MRSA was not associated with the duration or use of an IEAT; 0 patients (0%) in the No-IEAT group, 1

patient (1%) in the Short-IEAT group and 3 patients (1%) in the Long-IEAT group (P=0.66) (Fig 6).

DISCUSSION

Present study is one of the first works to describe the early and late bacterial ecology of a large cohort of severe trauma patients (ISS \geq 16), hospitalized for 10 days or more in ICU. In this series of 507 patients, median ISS 29 [IQR 22_34], 114 patients (22%) did not received IEAT, 95 patients (19%) received a short IEAT and 298 patients (59%) received a long IEAT. The early bacterial ecology (\leq 5 days) mainly included in this specific population MSSA, wild type Enterobacteria and RNP bacteria. The late bacterial ecology (\geq 6 days) involved in contrast a non-negligible number of Enterobacteria, mainly group 3 (21%), among them almost 20% of derepressed AmpC mutant), followed by SA (20%), SCN (13%) and PA (11%). Despite an important use of IEAT (more than three-quarter of patients), IEAT did not appear to influence the late bacterial ecology or to favour the emergence of bacterial resistance.

During the first days in ICU, the influence of MSSA, other RNP bacteria and susceptible group 0-1 and 2 Enterobacteria during the first days of ICU stay remains a major issue in severely ill patients (30,31). Indeed, in our work, these strains represented 42% of the early ecology. Even so, group 3 Enterobacteria represented 11% and PA 6% of the early ecology, which is comparable to others medical ICU. Usually, in France, 3GC-R Enterobacteria occurrence in ICU is about 10 - 20% (32,33). In our cohort, 3GC-R Enterobacteria represented 10% in the early period. MRSA prevalence in the early bacterial ecology was less than 1% as usual in commentary infection setting in France (33). Likewise, occurrence of MRSA in our cohort was also 1% in the early period. Finally, an empiric AT on admission, based on amoxi-clav would be associated with more than 80% of success, and the association with an aminoglycoside provide a safety strategy, so that a group 3 Enterobacteria should not be missed.

Change in the bacterial ecology of critically ill patients was also largely described after the first week of management; classically a raising of PA, Enterobacteria (mainly Group 3) and NCS is observed, as a persistence of SA. The nosocomial infection

surveillance of French ICU network (REA-RAISIN) reported for example a prevalence of PA, SA, NCS and Enterobacteria of 20%, 13%, 12% and 20% respectively (33). One of the main differences with our cohort of patients is the incidence of PA (11%), slightly lower than other series, and the higher incidence of SA (20%). We found the same occurrence of group 3 Enterobacteria (21%). The lower rate of PA, in the early and late bacterial ecology of our series, should be due to a lower prevalence of risk factor for pseudomonas infection, as immunodepression or chronic respiratory failure, in our cohort of severe trauma patient (34). The other Gram negative non-fermenting bacteria are also under represented in our cohort for the same reasons and because of geographical setting. Indeed, a recent cohort study of 227 patients admitted in a 10-bed Trauma ICU in South Africa has reported a distribution of the late bacterial ecology similar to the one we describe except for a higher prevalence of *Acinetobacter* spp (AB) (17). However, South Africa is a country that has reported an outbreak of AB (35). AB represented only 5% of the late ecology of our study. In our study, occurrence of bacterial resistance seemed to be lower than in the literature, owing the lack of available evidence. Campbell et al, reported in a recent study among 2,699 trauma patients admitted to U.S. hospitals, that 913 (33.8%) patient experienced ≥ 1 infection event, of which 245 (26.8%) had a MDR Gram negative strain implicated, favoured by longer hospitalization and greater injury severity (36). Regarding resistance in the late ecology, ESBL Enterobacteria prevalence was in the same range than in the community and lower than in hospital setting (32,37). Regarding PA, resistance remained rare: PiperTazR was 1%; CeftazR was 0.8%; MeroR, was 1.8%. We did not find any MDR or XDR PA. HCASE was an important resistance issue in our population, because it was found in 19% during the late period, which is a higher rate than the non-trauma ICU population (around 12%) (33). In case of nosocomial infection, an empiric AT based on piperacillin-tazobactam or cefepime in association with amikacin seem to be safe and permit to spear carbapenem.

In the trauma population, late bacterial ecology is quite unknown and seems to be different from these of medical or chirurgial ICU patients. However, in this injured specific population, a strong relation between trauma and severe immunomodulation, mixing hyperinflammation and immunosuppression, is well known in the literature and favourite infectious complications during the severe trauma patient ICU stay.

Among the main findings, our study supports that the IEAT would not have of substantial influence on the late bacterial ecology or the emergence of bacterial

resistance. The effect of the AT on the emergence of bacterial resistance remains debated. Some studies support an association between antibiotic use and bacterial ecology changes or occurrence of resistance (13,38). In a population of severe trauma patients, Guidry et al. have thus demonstrated a substantial effect on the development of de novo emergence of resistance after an antimicrobial treatment (38). Other authors have in contrast reported no effect of systematic empiric treatment on the bacterial ecology, despite broad-spectrum antibiotic treatment such as imipenem (39). Our study did not observe a significant difference of resistance occurrence between the different IEAT group, in particularly regarding the late HCASE occurrence; 16% in the No-IEAT group, 21% in the Short-IEAT group and 20% in the Long-IEAT group ($P=0.66$) and 19% in the total population. Besides the selection pressure related to antibiotic use, patient-to-patient transmission is also recognising as a prominent mechanism for the emergence of antibiotic-resistance in ICU settings (14,40). This mechanism could be evocated in our study. Indeed, HCASE Enterobacteria prevalence was high in the late ecology and no specific hygienic rules are recommended in our hospital, except in case of ESBL or carbapenemase Enterobacteria, MRSA, MDR PA carriage or infection.

Our study suffered from some limitation because of its retrospective design. In another hand, the power of this study resides in the high specificity of the population and the exhaustivity of the data collections because all samples of each patient were collected and treated for the statistical analysis.

CONCLUSION

In conclusion, this work had permit to clearly describe the early and late bacterial ecology of a severe trauma population. In this population, HCASE is the main resistance mechanism which represent 20% in the late ecology. No influence of IEAT has been revealed.

TABLE 1- Characteristics of patients according to the initial antibiotic management

	No-IEAT	Short-IEAT	Long-IEAT	Total	P value
No. of patients	N = 114	N = 95	N = 298	N = 507	
Main characteristics					
Age (y)	50.3 (20.7)	42.3 (19.6)	41.6 (18.7)	43 (19.7)	0.001†
Male, n (%)	83 (73%)	75 (79%)	238 (80%)	396 (78%)	0.29*
Mechanism of injury, n (%)					0.001*
Motor Vehicle Crash	53 (46%)	51 (54%)	178 (60%)	282 (56%)	
Bicycle	22 (19%)	17 (18%)	42 (14%)	81 (16%)	
Pedestrian	3 (3%)	9 (9%)	17 (6%)	29 (6%)	
Fall	32 (28%)	15 (16%)	37 (12%)	84 (17%)	
Assault	4 (4%)	3 (3%)	24 (8%)	31 (6%)	
Injury severity					
ISS	25 [17-33]	29 [22-34]	29 [24-36]	29 [22-34]	0.001†
Severe anatomic injuries, n (%)					
Head AIS ≥ 3	45 (39%)	48 (51%)	173 (58%)	266 (52%)	0.003*
Chest AIS ≥ 3	68 (60%)	45 (47%)	119 (40%)	232 (46%)	0.001*
Abdominal AIS ≥ 3	25 (22%)	19 (20%)	95 (32%)	139 (27%)	0.026*
Extremity AIS ≥ 3	31(27%)	56 (59%)	134 (46%)	224 (44%)	<0.001*
Initial Transfusion Management					
Requirement in the first 24 hours					
Number of RBC (units)	0 [0-3]	2 [0-6]	2 [0-6]	2 [0-5]	< 0.001†
Number of FFP (units)	0 [0-2]	1 [0-4]	0 [0-6]	0 [0-4]	< 0.001†
Massive transfusion, n (%)	6 (39%)	8 (67%)	48 (57%)	62 (55%)	0.005*
Global severity					
IGS2	32 [20.5-41]	33 [24-47]	37 [27-49]	35 [[25-47]	0.001†
Mechanical ventilation days °	6.1 [0-16.8]	6.5 [2.8-13.5]	11 [6.8-20.3]	10 [4.5-18]	< 0.001†
Vasopressor use days	1.7 [0-5]	2.3 [0.3-5]	3.3 [1.5-6.5]	2.8 [0.5-6]	< 0.001†
ICU days	13.8 [9-23.4]	13 [9-23]	18.3 [12-32]	16 [10-28]	< 0.001†
Hospital days	21 [13.2-34]	23 [16-39]	29 [19-45]	25 [17-42]	< 0.001†

Data are expressed as median [IQR] or mean ± SD or as number of patients (percentage) as appropriate.

* Chi-square test.

† ANOVA or KW test.

ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; RBC, red blood cells; FFP, fresh frozen plasma. Massive transfusion, ≥10 CGR during first 24 hours.

° Mechanical ventilation was considered if the patient was ventilated for at least 24 hours, excluding in the operating room.

TABLE 2- Antimicrobial therapy characteristics

	No-IEAT	Short-IEAT	Long-IEAT	P value
IEAT				
Total patients, n (%)	114	95	298	
Amoxi-clav, n (%)	-	84 (88%)	226 (75%)	0,01*
Clindamycine, n (%)	-	1 (1%)	0 (0%)	0,08*
3GC, n (%)	-	7 (7%)	44 (15%)	0,05*
Piper-Taz, n (%)	-	1 (1%)	19 (6%)	0,04*
Carbapenem, n (%)	-	0 (0%)	4 (1%)	0,26*
Other, n (%)	-	2 (2%)	5 (2%)	0,78*
Aminoglycoside in association, n (%)	-	47 (50%)	147 (49%)	0,98*
Médian Length, (days)	-	2,5 [2-3]	6 [5-7]	0,001†
Secondary antibiotic				
Total of patients, n (%)	57 (50%)	43 (45%)	160 (54%)	0,34*
Amoxi-clav, n (%)	8 (14%)	3 (7%)	13 (8%)	0,36*
3GC, n (%)	21 (37%)	16 (37%)	56 (35%)	0,94*
Piper-Taz, n (%)	22 (39%)	17 (40%)	64 (40%)	0,98*
Carbapenem, n (%)	2 (4%)	2 (5%)	16 (10%)	0,20*
Other, n (%)	3 (5,3%)	5 (12%)	11 (7%)	0,45*
Association, n (%)	28 (49%)	24 (56%)	80 (50%)	0,76*
Médian length of treatment, (days)	7 [6-9]	7 [7-8]	8 [7-12]	0,24†
Médian day of introduction	6 [5-8]	7 [6-10]	8 [6-10]	0,24†

Data are expressed as median [IQR] or mean \pm SD or as number of patients (percentage) as appropriate.

* Chi-square test.

† ANOVA ou KW test.

IEAT : initial empirical antimicrobial treatment ; No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group

Amoxi-clav : amoxicilline and clavulanic acid association ; 3GC : third generation cephalosporin ; Piper-Taz : piperacilline and Tazobactam association.

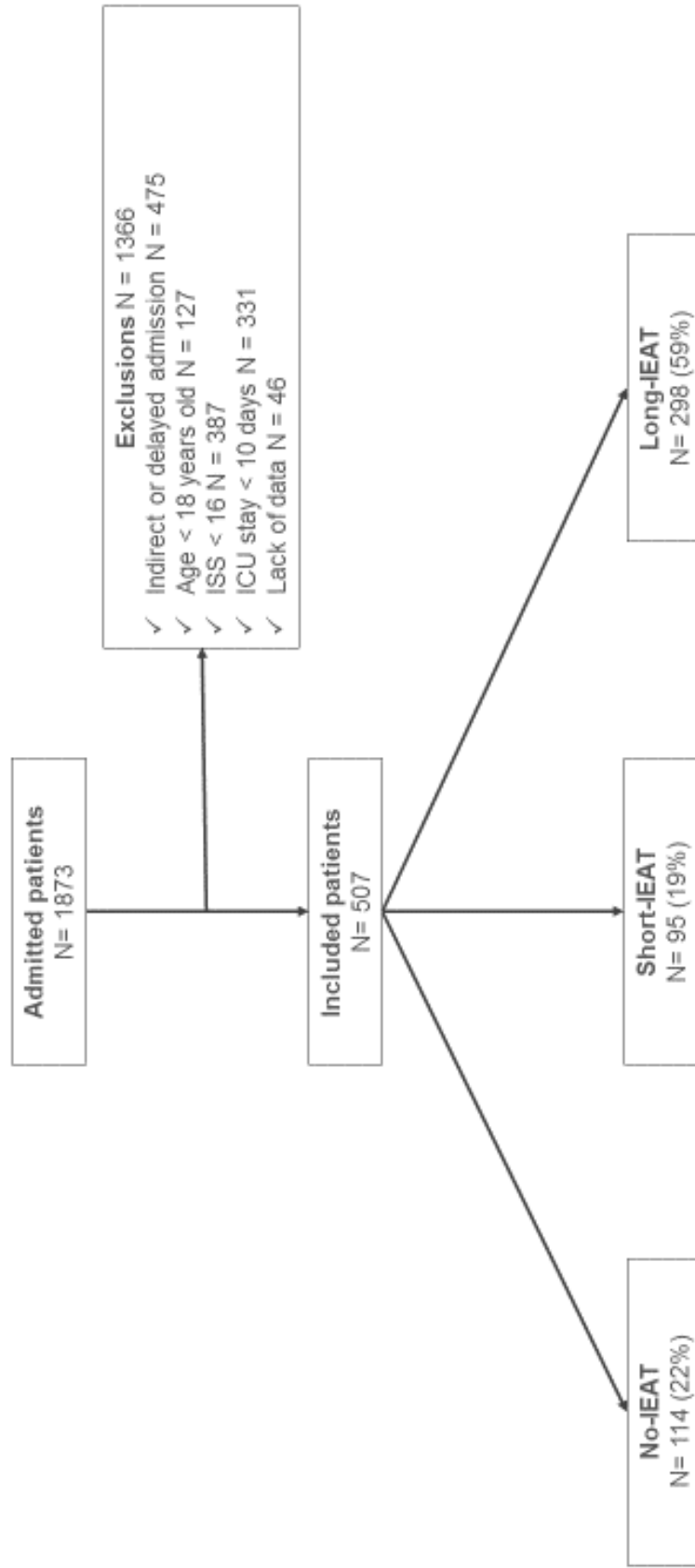
TABLE 3- Number and Resistance profile of *Pseudomonas aeruginosa*

	No IEAT N = 114		Short IEAT N = 95		Long IEAT N= 298	
	Early	Late	Early	Late	Early	Late
Savage PA	8	7	6	12	10	30
PiperTaz R alone	0	0	0	0	1	0
CeftazR alone	0	0	0	0	0	0
MeroR alone	0	0	0	1	0	6
PiperTazR and CeftazR	0	0	0	0	0	2
PiperTaz CeftazR and MeroR	0	0	0	0	2	2

Savage PA: Savage *Pseudomonas aeruginosa*; MeroR PA: *Pseudomonas aeruginosa* resistant to meropenem; PiperTazR PA: *Pseudomonas aeruginosa* resistant to piper-tazo; CeftazR PA: *Pseudomonas aeruginosa* resistant to Ceftazidim

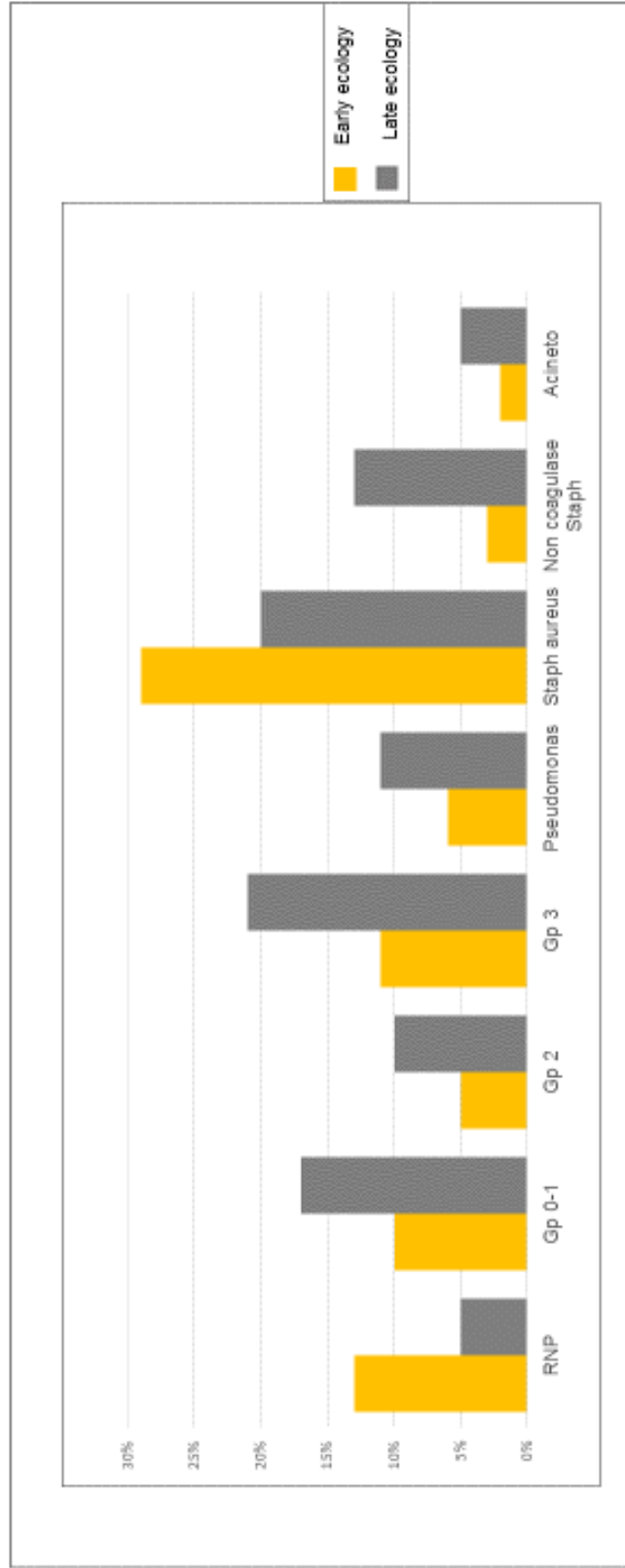
No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group

Figure 1 : Flow Chart



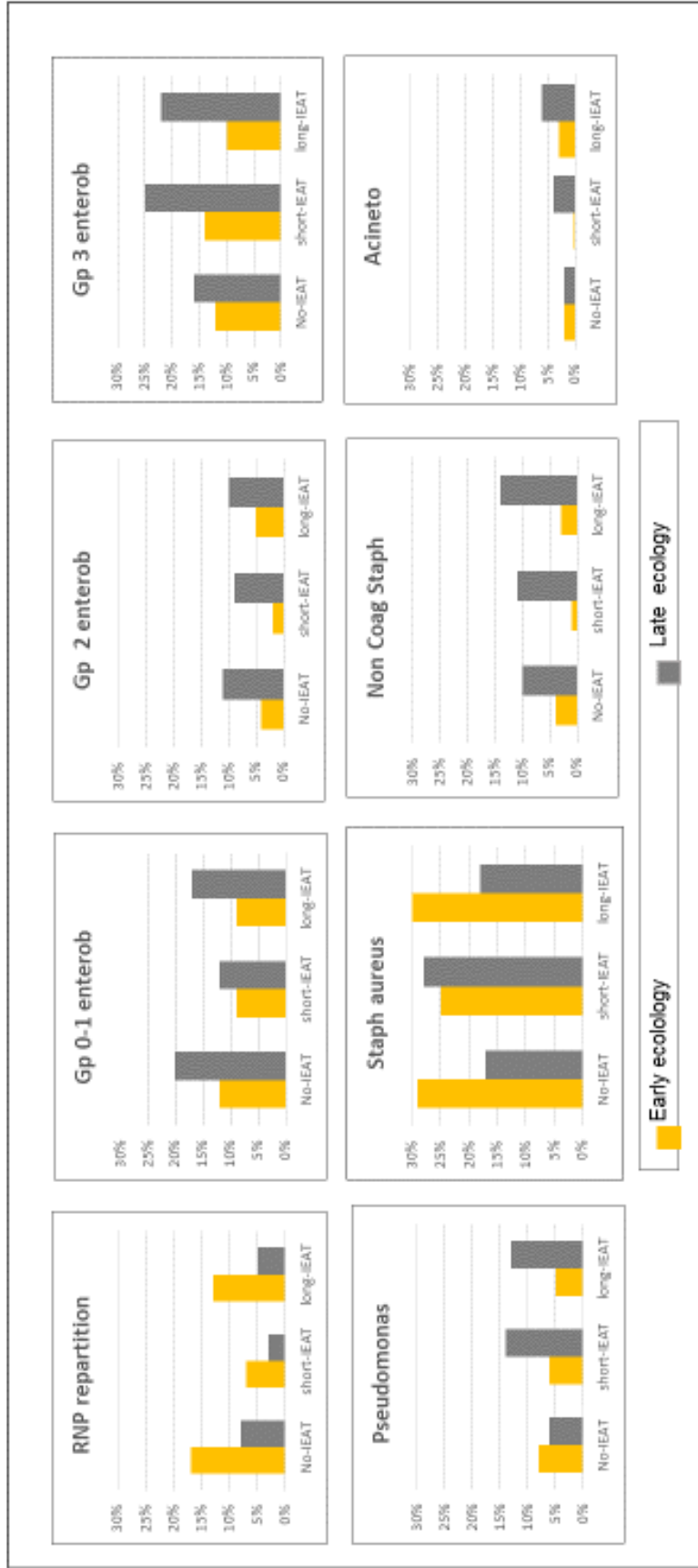
No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group.

Figure 2 - Global ecology of the total population



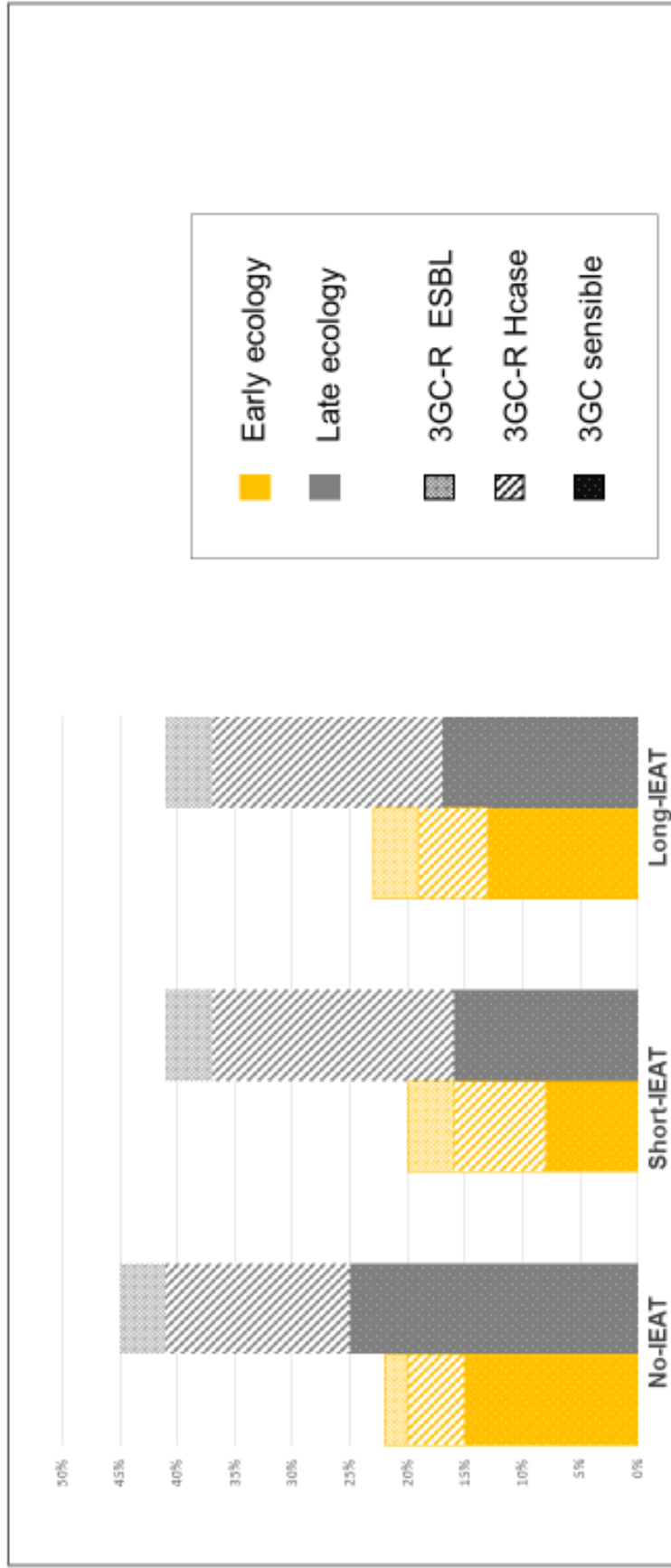
RNP: resident within the nasopharynx; Gp 0-1: group 0 and 1 enterobacteriae; Gp 2: group 2 enterobacteriae; Gp 3: group 3 enterobacteriae; Pseudomonas: *pseudomonas aeruginosa*; Staph aureus: *staphylococcus aureus*; Non Coagulase Staph: *non coagulase staphylococcus*; Acinetobacter spp: *acinetobacter spp*

Figure 3 - Ecology repartition according to IEAT management



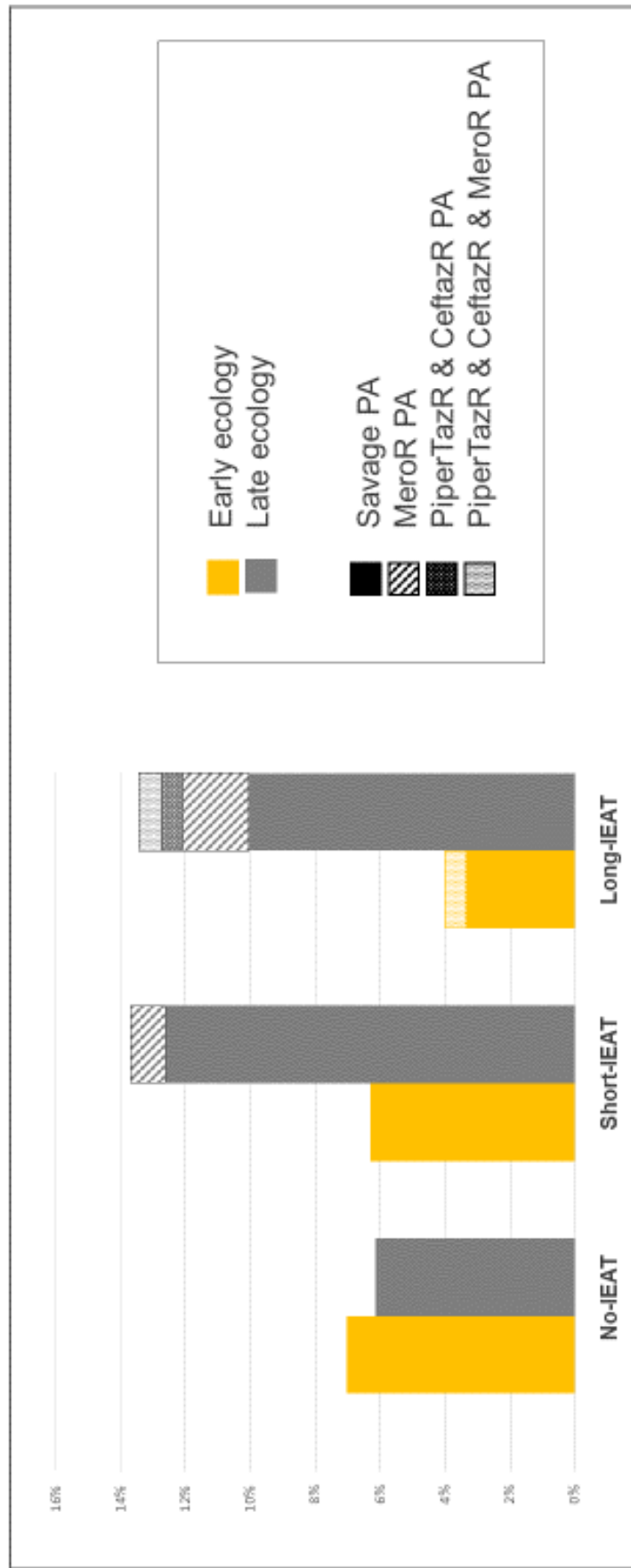
RNP : resident within the nasopharynx; Gp 0-1 enterob : group 0 and 1 enterobacteriae; Gp 2 enterob : group 2 enterobacteriae; Gp 3 enterob : group 3 enterobacteriae; Pseudomonas: *Pseudomonas aeruginosa*; Staph aureus: *staphylococcus aureus*; Non Coag Staph: *non coagulase staphylococcus*; Acineto: *acinetobacter spp*;
 No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group.

Figure 4 - 3GC resistance according to the IEAT management



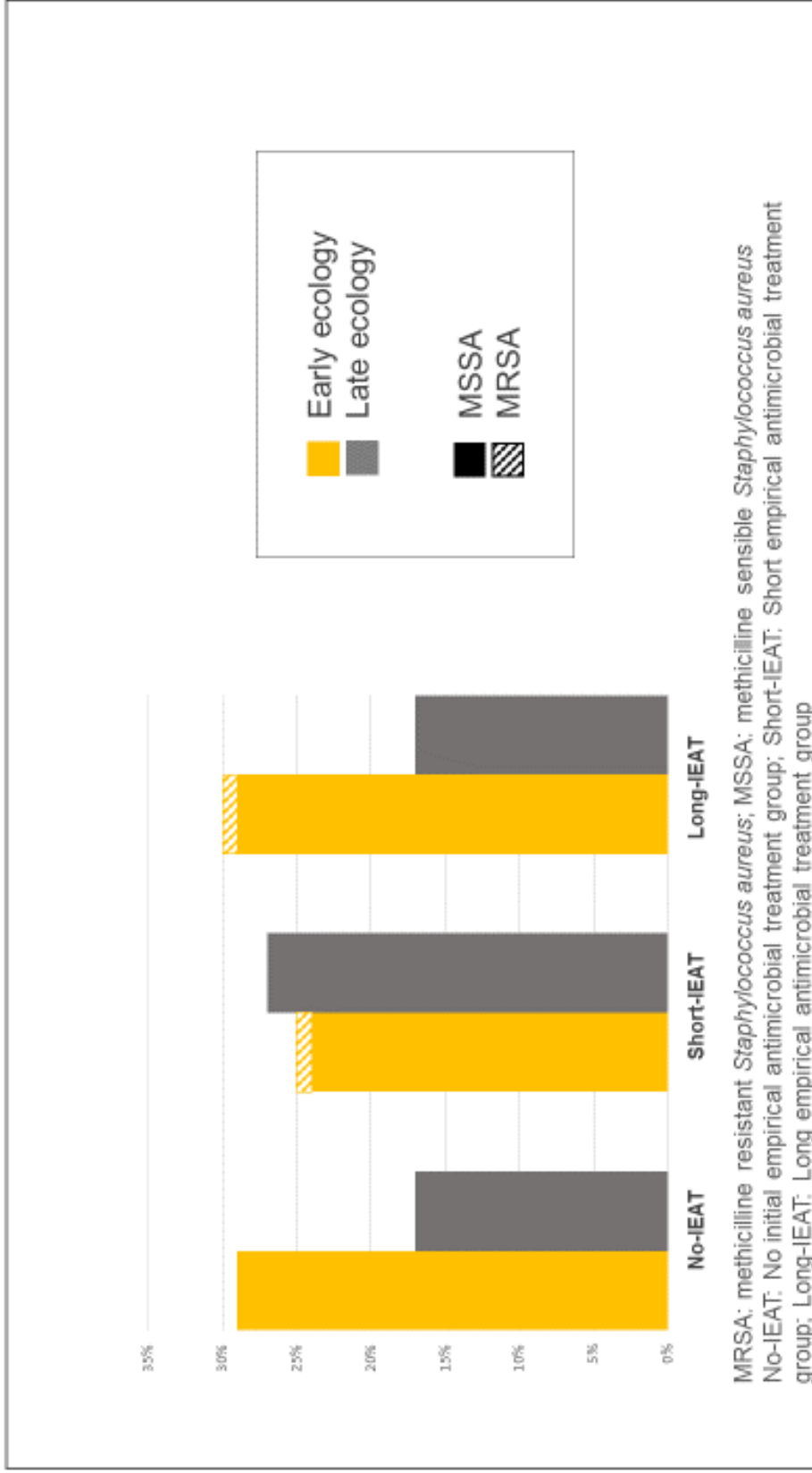
3GC-R ESBL: strains 3GCR resistant by Extended Spectrum Betalactamase; 3GC-R Hcse: strains 3GCR resistant by Hypercephalosporinase; 3GC sensitive: strains 3GCsensible
 No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group

Figure 5 - *Pseudomonas aeruginosa* resistance repartition according to IEAT management



Savage PA: Savage *Pseudomonas aeruginosa*; MeroR PA: *Pseudomonas aeruginosa* resistant to meropenem; PiperTazR PA: *Pseudomonas aeruginosa* resistant to piper-tazo; CeftazR PA: *Pseudomonas aeruginosa* resistant to Ceftazidim
 No-IEAT: No initial empirical antimicrobial treatment group; Short-IEAT: Short empirical antimicrobial treatment group; Long-IEAT: Long empirical antimicrobial treatment group

Figure 6 – *Staphylococcus aureus* resistance according to IEAT management



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SERMENT

- En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Être suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.
- Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.
- Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.
- Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.
- Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Écologie bactérienne et effets de l'antibiothérapie initiale empirique chez les patients traumatisés sévères

Introduction : Les infections nosocomiales et la résistance aux antibiotiques sont des préoccupations majeures en réanimation. Les patients traumatisés sévères sont fréquemment exposés aux antibiotiques selon plusieurs indications. L'effet d'une antibiothérapie empirique initiale (ATEI) sur l'écologie bactérienne chez les patients traumatisés sévères n'a jamais été étudié. Le but de cette étude était de décrire l'écologie bactérienne précoce (depuis l'admission au 5^e jour inclus) et tardive (depuis le 6^e jour) des traumatisés sévères et d'évaluer l'effet d'une ATEI sur l'émergence de résistances dans cette population.

Méthodes : Tous les dossiers des patients traumatisés admis dans un centre de traumatologie de niveau 1 entre janvier 2010 et décembre 2015 ont été examinés. Les patients présentant un Injury Severity Score (ISS) > 16 et une durée de séjour en réanimation > 10j ont été inclus. Outre les caractéristiques démographiques et de sévérité principales, les informations sur l'ATEI et l'antibiothérapie secondaire ont été rapportées. Pour chaque patient, tous les échantillons bactériologiques (avec le site et le jour de réalisation) précoces (≤ 5 ans) et tardifs (> 5 jours), de l'admission à la sortie de réanimation, ont été collectés ainsi que la souche bactérienne mise en évidence et son profil de résistance.

Résultats : 507 patients (ISS médian de 29 [IQR, 22-34]) ont été inclus : 114 (22%) n'ont pas reçu d'ATEI (groupe pas-ATEI), 95 (19%) ont reçu une ATEI courte ≤ 3 jours (groupe ATEI-courte), 298 (59%) ont reçu une ATEI > 3 jours (groupe ATEI-longue).

Dans l'ensemble de la cohorte, l'écologie précoce était dominée par *Staphylococcus aureus* (SA), les bactéries résidant dans le nasopharynx (RNP) et les entérobactéries du groupe 0-1 (29% des patients, 13% et 10%). Les entérobactéries du groupe 3 et *Pseudomonas aeruginosa* (PA) ont été trouvées respectivement chez 11% et 6% des patients.

L'écologie tardive était dominée par les entérobactéries du groupe 3 (22% des patients), les entérobactéries du groupe 0-1 (17%) et les SA (20%). Les entérobactéries du groupe 2, PA et *Acinetobacter* ont été trouvées chez respectivement 10%, 11% et 5% des patients. Aucune différence au niveau de l'écologie n'a été trouvée selon l'ATEI.

Les résistances sont plus nombreuses pour l'écologie tardive ; des entérobactéries avec céphalosporinase hyperproduite (HCASE) étaient présentes chez 19% des patients, des entérobactéries à β -lactamase à spectre étendu (BLSE) chez 4%, des PA résistants chez moins de 4% et des SA résistants à la méthicilline dans moins de 1% des cas.

Aucune différence n'a été constatée en ce qui concerne l'émergence d'une résistance selon l'ATEI.

Conclusion : Ce travail a permis de décrire l'écologie bactérienne précoce et tardive d'une population spécifique de traumatismes sévères. Dans cette population, l'émergence de la résistance est dominée par les HCASE et aucune influence de l'ATEI n'a été montrée

Mots-clés : traumatisés sévères, réanimation, antibiothérapie, bactéries multi-résistantes, résistances bactériennes, écologie bactérienne.