INCREMENT-SOT PROJECT
An International Consortium for the clinical study of bloodstream infections caused by multidrug-resistant *Enterobacteriaceae* in Solid Organ Transplantation

Supporting Institutions

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Spanish Network for Research in Infectious Diseases

ESGICH ESCMID STUDY GROUP FOR INFECTIONS IN COMPROMISED HOSTS
European Society of Clinical Microbiology and Infectious Diseases

ESGBIS ESCMID STUDY GROUP FOR BLOODSTREAM INFECTIONS AND SEPSIS
European Society of Clinical Microbiology and Infectious Diseases

Promoter Investigators

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Assistant Scientific Committee

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PROJECT TITLE

Impact of specific antimicrobials and MIC values on the outcome of bloodstream infections due to ESBL- or carbapenemase-producing *Enterobacteriaceae* in Solid Organ Transplantation: an observational multinational study.

PERSONNEL AND CO-INVESTIGATORS

A total of 58 centres belonging to 18 countries across the world have accepted to participate in this project. Herein the list of participating centres:

Promoter Institutions

Country	Number	Institution	Town	Investigator
Spain	1	Reina Sofía Univ. Hospitall /IMIBIC/UCO, Cordoba	Córdoba	Dr. Julián Torre-Cisneros
				Dr. Elena Perez-Nadales
	2	Virgen Macarena University Hospital, Seville	Seville	Dr. Jesús Rodríguez-Baño
				Dr. Álvaro Pascual
				Dr. Belén Gutiérrez Gutiérrez
	3	12 Octubre University Hospital, Madrid	Madrid	Dr. José María Aguado
				Dr. Jaime Lora-Tamayo

Scientific Committee

Country		Institution	Town	Investigator
Republic of Singapore	4	Singapore General Hospital	Singapore	Dr. Tan Ban Hock
Australia	5	St Vincent's Hospital	Sydney	Dr. Debbie Marriott
Brazil	*6*	Faculdade de Medicina da Universidade de São Paulo	São Paulo	Dr. Edson Abdala
Chile	7	Pontifical Catholic University of Chile	Santiago	Dr. Ricardo Rabagliati
Germany	8	Albert-Ludwigs-University	Freiburg	Dr. Winfried Kern
Italy	*9*	University of Insubria. Clinica Malattie Infettive. Ospedale Di Circolo	Varese	Dr. Paolo Grossi
Spain	10	Bellvitge University Hospital	Barcelona	Dr. Jordi Carratala
	11	Marqués de Valdecilla University Hospital	Cantabria	Dr. Luis Martinez Martinez and Dr. M. Carmen fariñas
	12	Virgen del Rocío University Hospital	Seville	Dr. Elisa Cordero
Switzerland	13	University Hospital and University of Lausanne	Lausanne	Dr. Oriol Manuel
Turkey	14	Dept. of Infectious Diseases Hacettepe University School of Medicine Sihhiye	Ankara	Dr. Murat Akova
USA	15	Northwestern University Feinberg School of Medicine	Chicago	Dr. Michael Ison
	16	Hospital of the University of Pennsylvania	Philadelphia	Dr. Emily Blumberg

Participating Institutions

Country	Number	Institution	Town	Investigator
Australia	17	The Westmead Hospital, Sydney	Sydney	Dr. Sharon Chen
Belgium	18	Erasme University Hospital, Brussels	Brussels	Dr. Julien Coussement and Dr. Magali Dodémont
Brazil	19	Instituto Dante Pazzanese de Cardiologia	Vila Mariana, São Paulo	Dr. Cely Saad Abboud
	20	Faculdade de Medicina da Universidade Federal de Minas Gerais	Santa Efigenia, Belo Horizonte	Dr. Wanessa Trindade Clemente
	21	Faculdade de Medicina da Universidade Federal do Ceará	Rodolfo Teófilo, Fortaleza	Dr. Evelyne Santana Girão

	22	Instituto do Coração do Hospital das Clíncas da Faculdade de Medicina da Universidade de São Paulo	São Paulo	Dr. Tânia Mara Varejão Strabelli
	23	Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro	Rio de Janeiro	Dr. Guilherme Santoro Lopes
	24	Hospital de Clínicas de Porto Alegre	Porto Alegre	Dr. Alexandre Prehn Zavascki
Canada	25	University of Alberta	Edmonton	Dr. Carlos Cervera
Germany	26	Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne	Cologne	Dr. Axel Hamprecht
Israel	27	Rambam Health Care Campus	Haifa, 3109601	Dr. Mical Paul
Italy	28	Università di Bologna	Bologna	Dr. Pierluigi Viale
	29	Azienda Ospedaliera Universitaria Integrata di Verona	Verona	Dr. Ercole Concia and Dr. Fabio Soldani
	30	AO Ospedale Papa Giovanni XXIII	Bergamo	Dr. Marco Rizzi
	31	Università Cattolica Sacro Cuore	Milan	Dr. Mario Tumbarello
	32	ISMETT-UPMC	Palermo	Dr. Alessandra Mularoni
	33	Fondazione IRCCS Policlinico San Matteo	Pavia	Dr. Elena Maria Seminari
Malta	34	Mater Dei Hospital	Msida	Dr. Nina Nina Nestorova
South Africa	35	Wits Donald Gordon Medical Centre; Wits School of Pathology, Faculty of Health Sciences, University of the Witwatersrand	Johannesburg	Dr. Warren Lowman
Spain	36	Hospital Ramón y Cajal	Madrid	Dr. Jesús Fortún and Dr. Pilar Martín
	37	Hospital Clínico Lozano Blesa	Zaragoza	Dr. Jose Ramón Paño and Dr. Pilar Luque Gómez
	38	Hospital La Paz	Madrid	Dr. María Belén Loeches
	39	Hospital clínic de Barcelona	Barcelona	Dr. Marta Bodro
	40	Hospital Universitario A Coruña	Coruña	Dr. Germán Bou
Sweden	41	Akademiska Hospital	Uppsala	Dr. Britt Marie Eriksson
Switzerland	42-47	Swiss Transplant Cohort Study (STCS). University Hospitals of Basel, Bern, Geneva, Lausanne, Zurich and St Gallen, Switzerland	Basel, Bern, Geneva, Lausanne, Zurich and St Gallen	Dr. Christian van Delden
Turkey	48	Yildirim Beyazit University, Ankara Ataturk T&R Hospital	Ankara	Dr. Zeliha Koçak Tufan
	49	Akdemiz University, Antalya	Antalya	Dr. Filiz Gunseren
	50	Başkent University School Of Medicine	Ankara	Dr. Hande Arslan
	51	Uludag University	Bursa	Dr. Esra Kazak
Ukraine	52	National Medical Academy of Postgraduate Study	Kyiv	Prof.Dmytro Kyryk
UK	53	University Hospital Birmingham NHS Trust	Birmingham, UK	Dr. Miruna David
USA	54	University of Alabama at Birmingham	Birmingham, USA	Dr. John Baddley
	55	Icahn School of Medicine at Mount Sinai	New York	Dr. Shirish Huprikar and Dr. Gopi Patel
	56	Ohio State University	Columbus, Ohio	Dr. Nicole Theodoropoulos
	57	University of Washington	Seattle	Dr. Erika Lease
	58	Johns Hopkins University	Baltimore	Dr. Seema Metha

INTRODUCTION

Bloodstream infections (BSI) are a major cause of mortality in solid-organ (SOT) transplant recipients. Mortality can reach 50% when bacteremia is accompanied with septic shock.

In recent years, infections due to extended-spectrum beta-lactamases (ESBL) and carbapenemase-producing *Enterobacteriaceae* have emerged as a global threat in SOT. Renal transplant recipients seem to be at higher risk of infections with ESBL-producing *E. coli*, especially in cases of simultaneous pancreas transplantation, previous use of antibiotics, post-transplant dialysis and post-transplant urinary tract infections. Most BSIs in renal transplant patients are due to urinary tract infections. Infections due to carbapenemase-producing *K. pneumoniae* are frequent in liver and intestinal transplantation. The main sources of the infections are intra-abdominal collections and the biliary tract.

The incidence of EBSL- and carbapenemase-producing Enterobacteriaceae BSI after SOT increases proportionally with the prevalence of bowel colonization. Treatment of invasive infections caused by these organisms is difficult because agents showing *in vitro* activity are limited and there are scarce clinical studies reporting on their efficacy, particularly in the SOT population.

Regarding ESBL-producers, carbapenems are considered the drugs of choice for invasive/severe infections. As a consequence, carbapenems are being increasingly used, which may facilitate the spread of carbapenemase-producing organisms. Thus, seeking for alternatives to carbapenems for infections caused by ESBL-producers is a priority. Preliminary results from the previous INCREMENT study in non-transplant patients and a meta-analysis suggested that β-lactams/β-lactamase inhibitors are a good alternative, mainly for susceptible *E. coli* causing urinary or biliary tract BSI. However, it would be important to confirm these results in SOT patients and evaluate whether such observation expand to other *Enterobacteriaceae* and sites of infection and if these recommendations can be extended to patients with underlying immunosuppression. Also, breakpoints for susceptibility to cephalosporins have been changed according to PK/PD data and some case series showing that some ESBL producers are susceptible to these drugs, thus clinical data supporting the efficient use of cephalosporins for susceptible isolates according to new breakpoints in SOT would be needed. Similarly, more clinical data on the efficacy of fluoroquinolones for infections caused by ESBL-producers (which are frequently resistant or present decreased susceptibility to these drugs) are awaited. Finally, published experience with other drugs is also scarce.

Regarding carbapenemase-producing organisms, similar questions arise. Depending on the specific carbapenemase that is expressed, isolates may show low MICs to carbapenems (even in the range of susceptibility) and the efficacy of carbapenems for invasive infections caused by such isolates,

alone or in combinations, is controversial. Other antibiotics are being used for the treatment of these infections. Recent data suggest that combination therapy including one carbapenem plus one or two other active drugs may be superior to monotherapy. Whether these data would apply for different carbapenemases, MICs of carbapenems, etc., in the particular setting of SOT is not known. Available clinical data from non-transplant patients is limited by sample size, lack of control groups, appropriate control for confounders and the unicenter nature of the studies conducted so far.

Another aspect of interest is the safety of antibiotics used for treatment of these infections in SOT patients. Because these patients frequently receive other drugs and may have impairment of liver or renal function, evaluation of the safety of antibiotics is particularly relevant in this population.

In order to compile further clinical evidence, larger, multinational studies are needed. A reasonable starting point would be the organization of an international consortium. This project aims to both address some of the clinical and scientific questions outlined above and to build an international network of contacts among experts in the field of transplant infections and bacterial resistances. We expect that creation of such a consortium will stimulate international cooperation for development of further projects and ideas in the transplant setting, including randomised control trials.

OBJECTIVES

Main objective: to observationally assess the efficacy and safety of different antimicrobials in BSI due to ESBL or carbapenemase-producing *Enterobacteriaceae* in SOT.

Secondary objectives:

1. To evaluate the efficacy and safety of different antibiotics used for the treatment of infections caused by ESBL- and carbapenemase-producing *Enterobacteriaceae* in the SOT population.
2. To compare the efficacy of different antimicrobials between SOT and non-SOT patients (using matched controls from the “non-transplant” INCREMENT cohort).
3. To create a microbiological collection of ESBL- and carbapenemase-producing *Enterobacteriaceae* isolated from the SOT population. (PENDING ON RESULTS FROM FEASIBILITY TEST)
4. To provide data on specific MICs for each antimicrobial evaluated (PENDING ON RESULTS FROM THE FEASABILITY TEST).
5. To provide data on the prevalence of specific mechanisms of resistance and their clinical impact in the particular setting of SOT (PENDING ON RESULTS FROM THE FEASABILITY TEST)
6. To organise an international consortium capable of developing high quality prospective cohort studies and randomised clinical trials in the area of MDR and XDR *Enterobacteriaceae* in SOT.

Specific hypothesis and objectives

Bacteremic infections due to ESBL-producing *Enterobacteriaceae* in SOT:

- (A1) β-lactam/β-lactam inhibitors are as effective as the carbapenems in the empiric and definitive therapy, irrespective of the empirical therapy, severity of infection, source and species.
    - Objective: to demonstrate that β-lactam/β-lactam inhibitors are not associated with worse cure rate and mortality than carbapenems after controlling for potential confounders, including transplantation, both for empirical and definitive therapies.
- (A2) Definitive therapy with fluoroquinolones is as effective as definitive therapy with carbapenems, provided that the organism is susceptible to both types of antibiotics according to current endpoint criteria (EUCAST/CLSI), irrespective of empirical therapy, severity of infection, transplantation status, source and species.
    - Objective: to demonstrate that definitive therapy with fluoroquinolones is not associated with worse cure rate and mortality than definitive therapy with carbapenems, after controlling for potential confounders, including transplantation and considering both the dose and type of infusion (continuous/intermittent) and the use of single vs combined carbapenems.
- (A3) Empirical therapy with active cephalosporins in monotherapy according to current EUCAST and CLSI breakpoints is associated with worse outcome than empirical therapy with carbapenems, except for urinary tract infections.
    - Objective: to demonstrate that empirical therapy with cephalosporins in monotherapy is associated with worse cure rate and mortality in infections, other than the urinary tract ones, than carbapenems, after controlling for potential confounders, including transplantation,
- (A4) Empirical therapy with active aminoglycosides plus cephalosporins or fluoroquinolones is as effective as carbapenem monotherapy in urinary tract infections.
    - Objective: to demonstrate that the association of active aminoglycosides with cephalosporins or fluoroquinolones is not associated with worse cure rate and mortality than carbapenems after controlling for potential confounders, including transplantation.

- (A5) Combination therapy is not superior to monotherapy and is associated with increased renal and/or liver toxicity
    - Objective: to demonstrate that combination of empirical and definitive therapy is not associated with better cure rate than monotherapy after controlling for potential confounders, including transplantation, and is associated with increased toxicity.

- (A6) For tigecycline, colistin and fosfomycin, no hypothesis. The objective is to provide adjusted estimations of their association with outcome variables in comparison with carbapenem monotherapy according to the clinical situation and infection.

Bacteremic infections due to carbapenemase-producing *Enterobacteriaceae*:

- (B1) Combined empirical and definitive therapies are associated with better outcome than monotherapy with carbapenem, colistin or tigecycline even though they may be associated with increased adverse events.
    - Objective: to demonstrate that combination therapy is associated with worse cure rate and mortality than monotherapy after controlling for potential confounders, including transplantation.
    - Objective: to comparatively evaluate the extent of renal and liver toxicity for combination therapy vs monotherapy.
- (B2) Carbapenems are more effective for infections caused by isolates with low MICs than for infections, other than the urinary tract ones, caused by isolates with higher MICs.
    - Objective: to show that carbapenems are associated with worse cure rate and mortality when used in infections, other than the urinary tract ones, caused by isolates showing MIC >2 µg/mL for imipenem or meropenem as compared to infections caused by isolates with lower MICs, after controlling for potential confounders and considering both the dose and type of infusion (continuous/intermittent) and the use of single vs combined carbapenems.
- (B3) Tigecycline is more effective that carbapenems for infections , other than the urinary tract ones, caused by isolates with a high level of resistance to carbapenems.
    - Objective: to show that carbapenems are associated with worse cure rate and mortality than tigecycline when used in infections, other than the urinary tract ones, caused by isolates with MICs >32 µg/mL for imipenem or meropenem, after controlling for potential confounders as transplantation.
- (B4) β lactam/avibactam is more effective that carbapenems or tigecycline for infections others than the urinary tract ones caused by isolates with high level of resistance to carbapenems.
    - Objective: to show that carbapenems and tigecycline are associated with worse cure rate and mortality than β lactam/avibactam when used in infections other than the urinary tract ones, after controlling for potential confounders, including transplantation.
- (B5) Colistin is more effective when used in optimized dose.
    - Objective: to show that colistin used at a dose >6 million IU per day is associated with improved outcomes in comparison with a lower dose, after controlling for potential confounders, including transplantation.

METHODS

Study design: multicentre, international retrospective cohort study.

Sites: multiple expert investigators from different countries will be invited. Criteria for participation will include accessibility to a database with the required data or ability to retrospectively collect the data in a timely manner.

Inclusion criteria:

- Solid Organ Transplant patients, including multivisceral transplantation and transplant in HIV-infected recipients.
- Episodes of clinically significant monomicrobial BSI due to cephalosporin-resistant *Enterobacteriaceae* (CRE), specifically ESBL or carbapenemase-producing *Enterobacteriaceae*, including community and nosocomial ones.
    - For cephalosporin resistance, a susceptibility phenotype based in a microdilution antibiogram is sufficient.
    - For ESBL-producers:

      THREE POSSIBILITIES, PENDING ON RESULTS FROM THE FEASABILITY TEST AND APPLICATION FOR FUNDING:

        1. Antimicrobial susceptibility profile
        2. At least one phenotypic confirmation test according to current endpoints (i.e. CLSI, EUCAST).
        3. PCR-based characterization
    - For carbapenemase-producers:

      TWO POSSIBILITIES, PENDING ON RESULTS FROM THE FEASABILITY TEST AND APPLICATION FOR FUNDING:

        1. Characterization of carbapenemase production by these isolates must be based on PCR analysis. Determination of carbapenemase production based on antimicrobial susceptibility profile and phenotypic tests alone will not be acceptable (see below).

        2. Participating Centers may provide bacterial isolates and microbiological tests may be centralized in a Microbiology Reference Laboratory.
- Subsequent episodes in a patient caused by the same microorganism may be included if the interval between them is >3 months.
- No age limits.

Exclusion criteria:

- Polymicrobial or non-clinically significant episodes. Episodes in which a potential contaminant (e.g., coagulase-negative staphylococci) is isolated only in one set of blood cultures and there is not a typical source of infection for that kind of organism (e.g. catheter-related) that can be included.
- Unavailability of key data (such cases should be counted to analyse a potential selection bias).
- Episodes occurring before January 2004.

Procedure

The participant centres will be requested to include:

- Previously published cases: all these cases should be included if possible. The fact that the case was previously published should be specified in the database.
- Additionally, participants will be requested to include consecutive episodes detected by reviewing their databases (clinical, infection control or microbiological records) from January 2004 to December 2014, according to the following criteria:
    - For ESBL producers: Consecutive cases for which the enzyme was characterised at least to group level by PCR (it is, CTX-M, SHV, TEM) should be prioritised despite the date of diagnosis. If PCR-characterisation was not performed, cases in which ESBL-production was identified using a standard phenotypic method may be included.
      PENDING ON RESULTS FROM THE FEASABILITY TEST.
    - For carbapenemase-producers: only cases in which the carbapenemase was characterised by PCR should be included.
      PENDING ON RESULTS FROM THE FEASABILITY TEST.

Overall, to avoid selection biases, consecutive cases according to previous criteria should be included.

Variables

A common, online database has been designed. Access to this database will be restricted to authorized researchers by use of an individual user name and password.

Main outcome variables: Cure rate at day 14 and all-cause mortality until day 30. For safety issues, frequency and types of renal and liver toxicity.

Secondary outcome variables: Mortality at 72 hours, 7, 14 and 90 days, clinical improvement at 72 hours, clinical cure at day 28. Renal and liver toxicity and other serious adverse events.

Explanatory variables:

- Demographics

- Use of antibiotics within 30 days before the BSI.
- Severity of chronic underlying conditions: McCabe and Charlson index
- Acute severity of underlying disease: Pitt score during the day before BSI.
- Type of acquisition
- Source of BSI
- Severity of SIRS at presentation
- Microorganism, MICs, clinical category (Susceptible, Intermediate, Resistant), guideline (CLSI or EUCAST), mechanisms of resistance if studied.
- Empirical therapy
- Definitive therapy
- Bacteremia Source Control: drainage within the first four days, removal of prosthetic material, removal of infected catheter, etc.
- Renal function when bacteremia occurred (Creatinine clearance).
- Selective Intestinal Decontamination (SID) during the previous 12 months and type of SID (drugs used).
- Variables related with transplantation:
    - Type of SOT
    - Day after transplantation
    - Acute rejection within 30 days before the BSI
    - Leukopenia (number of lymphocytes, lymphocyte subpopulations, immunoglobulins and complement).
    - Basal immunosuppression
    - Induction of immunosuppression
    - Prophylaxis with TMP/SMX within 30 days before the BSI
    - Surgical reoperation.
    - Urinary catheter.
    - Urinary stenosis (renal)
    - Biliary stenosis (liver)
    - Traqueal stenosis (lung)
    - Post-transplant dialysis within 30 days before the BSI
    - CMV replication within 30 days before the BSI
    - CMV disease within 30 days before the BSI
    - Mechanical ventilation
    - Other underlining condition

Definitions

- Clinically significant bacteremia: bacteremia that occurs in a patient who fulfils criteria for systemic inflammatory response (see below, sepsis criteria).
- Charlson index: punctuation is automatically calculated by filling the data in the database. Alternatively, if Pitt score was previously calculated, it may be added directly to the database. For all diseases, a medical diagnosis in chart is enough. Additionally, the following criteria should be used: 1,Diabetes mellitus: antidiabetic therapy (oral or insulin); 2, Chronic pulmonary disease: any disease leading to chronic respiratory insufficiency; 3,Myocardial infarction: EKG evidence; 4, Congestive heart failure: NYHA grade II or higher; 5, Peripheral arterial disease: when causing skin ulcer or the need for revascularization or amputation; 6. Dementia: if significantly limiting independence for basic activities; 7,Connective tissue disease: if requiring immunosuppressive therapy, 8.Liver disease: chronic hepatitis, significant liver fibrosis or cirrhosis; 9,Kidney disease: creatinine clearance <30 ml/min or the need for chromic dialysis; 10 Any tumour: any malignancy requiring chemotherapy and/or radiotherapy or palliative care.
- McCabe classification (modified). This is a classification for the chronic underlying condition (not the acute condition): non-fatal underlying disease (no underlying disease or related death is expected to occur in the next 5 years), ultimately fatal underlying disease (related death is expected to occur in the next 5 years), or rapidly fatal disease (related death is expected to occur in the next year).
- Pitt score: punctuation is automatically calculated by filling the data in the database, which should be retrospectively collected in the 24 hours prior to diagnosis of bacteremia. Alternatively, if Pitt score had been calculated previously, it can be directly added.
- SIRS severity
    - Sepsis: at least 2 of the following: temperature >38ºC or <36ºC, respiratory rate >20 or PaCO2 <32 mmHg, heart rate >90, altered mental status, systolic blood pressure <90 mmHg, leukocyte count >12.000/mm3 or <4,000/mm3 or immature forms >10%.
    - Severe sepsis: sepsis plus one of the following: hypotension (systolic BP <90 mmHg, median BP <70 mmHg, decrease in median BO >40 mmGh), organ dysfunction (respiratory, renal, liver, neurologic, hematologic), or hyperlactatemia (> 3 mmol/L)
    - Septic shock: sustained hypotension not responding to fluid support therapy and requiring inotropic support.
- Acquisition. Nosocomial if infection signs/symptoms started >48 hours after hospital admission or in less than 48 hours after hospital discharge. Otherwise, the case should be considered community-onset.
    - If community-onset, the episode is considered healthcare-associated if fulfilling any of the following criteria in the previous 3 months: hospitalization in acute care center, any kind of dialysis, surgery, specialized home care, attention at day-hospital, any kind

of invasive procedure (endoscopy, urinary or vascular catheterization, etc.) or long-term care facility resident.

- Source: CDC definitions for nosocomial infections will be used as a reference; however, clinical and microbiological criteria as evaluated by the investigators may be used for interpretation. A source does not need to be microbiologically confirmed if enough clinical criteria are present.
- Empirical therapy: administered before susceptibility report is available.
- Definitive therapy: administered once the susceptibility report is available. If empirical therapy was continued, it is not necessary to fill in the definitive therapy data.
- Outcome definitions:
    - Improvement: partial control or resolution of signs and symptoms related to the infection, or resolution but antibiotic therapy is still necessary.
    - Non-improvement or deterioration: clinical situation qualified as similar or worse in comparison to that at the point of diagnosis of bacteremia.
    - Cure: resolution of all signs and symptoms related to the infection, and antibiotic therapy is no longer necessary.
    - Dead: death of the patient for whatever the reason.
    - Renal toxicity: development of acute kidney injury according to RIFLE criteria (Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative workgroup: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The second international consensus conference of the acute dialysis quality initiative (ADQI) group. Crit Care 2004, 8:R204 - R212.
    - Liver toxicity: Patients will be considered to have hepatotoxicity when they presented alanine transaminase, aspartate aminotransferase or bilirubin elevations of more than two times the upper limit of the normal range. Toxicity is considered severe when symptomatic elevations are more than three times or asymptomatic elevations are more than five times the normal levels.
    - Severe adverse event (SAD): Any event that becomes fatal or life-threatening, produces a significant or persistent alteration (according to the Principal Investigator), requires patient hospitalization or prolongation of an existing hospitalization, produces a congenital anomaly or results in overdose of the drugs included in this stud. Any toxicity of grade 4 will be considered a SAD (*National Cancer Institute Common Toxicity Criteria* Version 3.0).

Quality of data

Data will be approved and signed by the responsible investigator in each center. All data will be centrally reviewed; queries will be sent for missing data as well as data showing inconsistencies or

discrepancies. Data will be analysed per center; those centers showing significant differences with the average will be requested to review their data.

Statistical Analysis Plan

- Cases that occurred in transplant patients (Transplant-INCREMENT cohort) will be controlled with cases in non-transplant patients selected from the INCREMENT cohort. Two control groups will be defined according to the following criteria:
    - Clinical variables: age, source of BSI, severity of SIRS (septic shock), acquisition
    - Propensity score to receive a particular treatment.

- Subcohorts with patients treated with the treatments to be compared will be selected.
- Empirical and definitive therapy will be analysed separately; active/inactive empirical therapy will be a potential confounder when analysing definitive therapy and vice versa.
- To be assigned to specific treatment arms, patients must have received drugs according to the following specific criteria: Empirical therapy: patients received the drug in monotherapy (except if combination is considered) within 24 hours of the blood culture being drawn and prior to availability of antibiogram results. The antibiotic must have been administered for at least 48 hours, with the single exception of patients who died before 48 hours, who will be included if death occurred after 1 complete day of therapy with the assigned regimen (and will be otherwise excluded). Definitive therapy: the drug was administered in monotherapy (except if combination is considered) once susceptibility data was available When more than one drug was used, only drugs that were administered for at least half the duration of the definitive therapy will be included in this study.
- A propensity score to receive the two treatment types under comparison will be calculated by obtaining a non-parsimonious multivariate model by logistic regression in which the outcome variable will be the treatment type. The explanatory variables will include age, gender, center, type of ward, acquisition, Charlson index, Pitt score, severity of SIRS and source.
- After univariate analysis, multivariate analysis to investigate the adjusted association of treatment type and transplantation with the main and secondary outcome variables will be performed by using logistic regression (for clinical response at day 14) and by Cox regression for mortality. If time until death is unavailable, logistic regression will be used for 30-day mortality. Logistic regression will also be used for 72-hour and 30-day clinical response. The propensity score will be added in all cases; also, Charlson score, Pitt score, severity of SIRS, source and transplant-related variables will be added. Finally, interaction between treatment type and source classified as urinary tract and others will be included.

ETHICAL ISSUES

This is a retrospective, non-intervention study. The main ethical issue to consider regards protection of patients' data. In the database, patient personal data will be unlinked from any personal data that may identify the patient, ensuring confidentiality is preserved. Additionally, access to the database will only be allowed by use of an individual access password.

The project will be submitted for qualification by the Spanish Medicines Agency (AEMPS) as post-authorization study (EPA-OD) and will be evaluated by the Reina Sofía University Hospital Institutional Review Board together with a specific request to waive the need to obtain written informed consent for the retrospective cohort. Local policies should be followed at each centre.

The study will be registered in ClinicalTrials.gov.

FUNDING

The study is supported by Plan Nacional de I+D+i 2008-2011 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD06/0008 and RD12/0015) - co-financed by European Development Regional Fund "A way to achieve Europe" ERDF. REIPI provides funding for development of the online database and server. Staff hired with REIPI funding dedicated to different research projects included in the REIPI Research Program will be dedicated part-time to the project. There is no other funding.

PUBLICATION, AUTHORSHIP, AND DATABASE RIGHTS/SECURITY POLICY

- Consortium. Each centre or research group may include up to 3 investigators in the Consortium (plus one member of the Assistant Scientific Committee in the case of the three Promoter Centers). One of them will be designated as principal investigator from their centre.
- The Scientific Committee will advise Promoter Investigators on the scientific content and objectives of this project. It will also be asked to provide a list of potential participating centers from their geographical area.
- Publication policy. The promoter group will decide the publication and authorship policy with the advice of the Scientific Committee. Any participating center may propose additional analysis and publications beyond those included in the objectives of this project, which will be submitted to approval by the Promoter group, with the advice of the Scientific Committee.
- Authorship. To be author, authorship criteria established by medical journals must be fulfilled. In general terms, manuscripts will be authored by writer, promoters and assistant scientific committee and one author per centre according to the number of cases included in the article provided they fulfil authorship criteria; if a limited number of authors is allowed, all other

authors will be included in a list in the Acknowledgement section as “Other authors”. All other participants in the study will be listed in the Acknowledgement section as “Other participants”. Alternatively, group authorship may be considered.

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