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Retrospective observational study to assess the clinical management and outcomes of hospitalised patients with complicated urinary tract infection in countries with high prevalence of multidrug resistant Gram-negative bacteria (RESCUING)

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ABSTRACT

Introduction: The emergence of multidrug resistant (MDR) Gram-negative bacteria (GNB), including carbapenemase-producing strains, has become a major therapeutic challenge. These MDR isolates are often involved in complicated urinary tract infection (cUTI), and are associated with poor clinical outcomes. The study has been designed to gain insight into the epidemiology, clinical management, outcome and healthcare cost of patients with cUTI, especially in countries with high prevalence of MDR GNB.

Methods and analysis: This multinational and multicentre observational, retrospective study will identify cases from 1 January 2013 to 31 December 2014 in order to collect data on patients with cUTI as a cause of hospital admission, and patients who develop cUTI during their hospital stay. The primary end point will be treatment failure defined as the presence of any of the following criteria: (1) signs or symptoms of cUTI present at diagnosis that have not improved by days 5–7 with appropriate antibiotic therapy, (2) new cUTI-related symptoms that have developed within 30 days of diagnosis, (3) urine culture taken within 30 days of diagnosis, either during or after completion of therapy, that grows $\geq 10^4$ colony-forming unit/mL of the original pathogen and (4) death irrespective of cause within 30 days of the cUTI diagnosis.

Sample size: 1000 patients afford a power of 0.83 ($\alpha=0.05$) to detect an absolute difference of 10% in the treatment failure rate between MDR bacteria and other pathogens. This should allow for the introduction of about 20 independent risk factors (or their interaction) in a logistic regression model looking at risk factors for failure.

Ethics and dissemination: Approval will be sought from all relevant Research Ethics Committees. Publication of this study will be considered as a joint publication by

Strengths and limitations of this study

- The study has been designed by a multinational team. The team members have worked collaboratively to determine the data to be collected. The multinational team approach to the design of the study and data set has made the study more likely to succeed in collecting data in a number of different countries than if it had been designed for just one country.
- The study will increase knowledge of the clinical picture, epidemiology and outcomes of hospitalised patients with complicated urinary tract infection (cUTI) caused by multidrug resistant Gram-negative bacteria. The identification of modifiable risk factors might lead to suggestion of changes in practice that could reduce the incidence of cUTI.
- The study also aims to calculate costs relating to cUTI which are currently unknown.
- The retrospective nature of the study design means that it is only possible to collect information that is still available on paper or electronically. Inevitably, some information may have been lost or has never been recorded.
- The study is also reliant on proper documentation of signs and symptoms of urinary tract infections and outcome data for up to 2 months subsequent to discharge; however, this is not always available in some sites.

the participating investigator leads, and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE).

Trial registration number: NCT02641015; Pre-results.

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INTRODUCTION

Bacterial resistance to antimicrobial agents has been identified in the European Union and many other countries as a major public health problem.[1–4] Prompt action is a clear priority nationally and internationally. Most disturbing is the rapid emergence and dissemination of resistance to third generation cephalosporins in *Escherichia coli* and *Klebsiella pneumoniae*, primarily due to the production of extended spectrum β-lactamases, which are frequently seen in association with resistance to other classes of antibiotics.[3 5 6] These multidrug resistant (MDR) isolates[7] are particularly prevalent in hospital practice, and are associated with increased morbidity and mortality in infections such as complicated urinary tract infections (cUTIs) and healthcare-associated infections (HAIs).[8–12] Patients with MDR *E. coli* or *K. pneumoniae* are frequently treated with carbapenems. However, there is an increasing number of MDR isolates that are also carbapenemase producers. Therefore, for an increasing number of patients with life-threatening infections due to *E. coli* and *K. pneumoniae* there are few therapeutic options.[13] As well as a rapid increase in the prevalence of MDR *E. coli* and *K. pneumoniae*, there has been a rise in the prevalence of MDR *Pseudomonas aeruginosa*, with more than three-quarters of European countries reporting MDR rates of >10% in invasive isolates.[3 4]

Urinary tract infections (UTIs) are highly prevalent worldwide. In patients with cUTI these are frequently caused by MDR Gram-negative bacteria (GNB).[14 15] Currently, there is a lack of information about the burden of this disease. Reports from the USA show that in early 2000 this disease accounted for more than 100 000 hospital admissions annually, often as a result of pyelonephritis.[16] Data from Europe are limited, although the last point prevalence survey of European acute care hospitals demonstrated that the prevalence of HAIs was 6%. This represents ∼80 000 patients on any given day in European acute care hospitals. Of these, UTI was the third most common infection (19%). *Enterobacteriaceae* were the most frequently isolated micro-organisms in UTI. Overall, *Enterobacteriaceae* prevalence resistant to third-generation cephalosporins in the study was 33.4%, and 7.3% to carbapenems.[17] Additionally, the presentation of patients with cUTI is changing over time; patients are older, with a high prevalence of chronic renal failure and other chronic diseases, instrumentation of the urinary tract and polypharmacy. Therefore, there is a need for contemporary data on the management, response to treatment and outcome of patients with cUTI against a background of increasing antibiotic resistance and significant changes in patients' characteristics.

RATIONALE

Considering the lack of contemporary data on hospitalised patients with cUTI, increasing the knowledge can be useful for improving clinical management, and also for formulating research questions.

This study will especially focus on (1) patients at high risk of infections caused by MDR pathogens, (2) the clinical management during hospitalisation, (3) the impact of inappropriate empirical antibiotic treatment, (4) the risk factors for adverse outcomes, particularly those that could be modifiable and (5) the costs of cUTI for healthcare systems.

Primary objective

To determine the outcome of hospitalised patients with cUTI and identify the risk factors associated with treatment failure.

Secondary objectives

1. To identify clinical characteristics and demographic factors of hospitalised patients with cUTI.
2. To identify the main causative MDR GNB, and their most frequent resistance profiles.
3. To define risk factors associated with cUTI caused by MDR GNB.
4. To describe clinical management of hospitalised patients with cUTI.
5. To determine the modifiable risk factors associated with early treatment failure in patients with cUTI.
6. To determine length of hospital stay in patients with cUTI.
7. To determine duration of antibiotic therapy (intravenous, intramuscular and oral) in patients with cUTI.
8. To determine mortality rate of hospitalised patients with cUTI.
9. To estimate the cost per case of cUTI measured by length of hospital stay, intensive care unit requirements, medications, tests and need for urological intervention and haemodialysis.
10. To estimate the total national cost of illness due to cUTI in participating countries.
11. To help identify patient types, and potential clinical trial sites for future phase 2 or 3 clinical trials in cUTI.

METHODS AND ANALYSIS
Study design

A multinational and multicentre retrospective, observational cohort study which will involve the collection of data on hospitalised patients from 1 January 2013 to 31 December 2014.

Study population

Data will be collected on patients who had a diagnosis of cUTI as the primary cause of hospitalisation, and patients hospitalised for another reason but who developed cUTI during their hospitalisation.

Setting

The study will be conducted in Bulgaria, Greece, Hungary, Israel, Italy, Romania, Spain and Turkey.

The number of sites per country will be identified via the Clinical Trial Network (CLIN-NET), and be included in the study.

Selection of cases

Patients will be identified by searching for any of the following International Classification of Diseases (ICD)-9 Clinical Modification (CM) or ICD-10 CM Codes[18] [19] at discharge on the hospital administration system:

ICD-9 CM Codes: 590.1, 590.10, 590.11, 590.2, 590.8, 590.80, 590.9, 595.0, 595.89, 595.9, 599.0;

ICD-10 CM Codes: N10, N12, N13.6, N15.1, N15.9, N30.0, N30.8, N30.9, N39.0.

In order to avoid selection bias, all consecutive patients who have ICD-9 or ICD-10 CM codes will be reviewed at each site. All patients who meet the inclusion criteria will be selected for data collection.

Inclusion criteria

1. The following criteria, which have been adapted from Food and Drug Administration (FDA) guidance on cUTIs: Developing Drugs for Treatment. Guidance for Industry;[20] European Medicines Agency (EMA) guidelines on the evaluation of medicinal products indicated for treatment of bacterial infections;[21] and clinical practice guidelines for the evaluation and management of chronic kidney disease[22] must be met to qualify for enrolment into this study: patients with UTI and at least one of the following:
   ▶ Indwelling urinary catheter;
   ▶ Urinary retention (at least 100 mL of residual urine after voiding);
   ▶ Neurogenic bladder;
   ▶ Obstructive uropathy (eg, nephrolithiasis, fibrosis);
   ▶ Renal impairment caused by intrinsic renal disease: estimated glomerular filtration rate <60 mL/min;
   ▶ Renal transplantation;
   ▶ Urinary tract modifications, such as an ileal loop or pouch;[15]
   ▶ Pyelonephritis and normal urinary tract anatomy.
2. And at least one of the following signs or symptoms:
   ▶ Chills or rigors associated with fever or hypothermia (temperature >38°C or below 36°C);
   ▶ Flank pain (pyelonephritis) or pelvic pain (cUTI);
   ▶ Dysuria, urinary frequency or urinary urgency;
   ▶ Costovertebral angle tenderness on physical examination;
   ▶ UTI-related altered mental state.
3. And urine culture with at least 10^5 colony-forming unit (CFU)/mL or greater of a uropathogen (no more than two species); or
4. At least one blood culture growing possible uropathogens (no more than two species) with no other evident site of infection.

If a patient has more than one episode of cUTI during the same hospitalisation, only the first episode will be included. Recurrence within 30 days will be considered as treatment failure.

Exclusion criteria

If any of the following exclusion criteria apply, the patient is not eligible for enrolment into this study:
1. Patients <18 years of age;
2. Prostatitis;
3. Polymicrobial infections that include *Candida* spp;
4. Polymicrobial infections that include more than two bacterial species;
5. cUTI with *Candida* spp. as sole uropathogen.

Definition of MDR bacteria

Bacterial multidrug resistance is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories according to the international expert proposal published by Magiorakos *et al*.[7]

Data collection

For patients recruited into the study, data will be collected retrospectively. These data items will be obtained from different sources, including the patient notes, electronic patient records, the hospital patient administration system and the hospital laboratory systems.

For all patients, a standardised set of information will be recorded. This will include demographics, comorbidities including those required to calculate a modified Charlson score,[23] functional capacity,[24] place of acquisition of infection, predisposing risk factors, clinical data, clinical pathology data, microbiological data, imaging test data, infection management, antibiotic therapy, outcomes, details of discharge and readmission.

Participant timeline

The follow-up period will be for up to 2 months after discharge from the admitting hospital.

OUTCOMES

Primary end point

The primary end point will be treatment failure, applying a slightly modified definition of FDA guidance on cUTIs: Developing Drugs for Treatment. Guidance for Industry.[20]

This definition includes any of the following conditions:
▶ Signs or symptoms of cUTI present at diagnosis that have not improved by days 5–7 with appropriate antibiotic therapy;
▶ New cUTI-related symptoms that have developed within 30 days of the original cUTI diagnosis;
▶ Urine culture taken within 30 days of the original cUTI diagnosis, either during or after completion of therapy, that grows $\geq 10^4$ CFU/mL of the original pathogen identified in the diagnostic sample;

▶ Death irrespective of cause within 30 days of the original cUTI diagnosis.

Secondary end points
The following secondary end points will be evaluated:
▶ Time to clinical response, in days;
▶ Time to urological intervention for source control, in days;
▶ Time to death, in days;
▶ Duration of antibiotic therapy, in days;
▶ Length of hospital stay, in days;
▶ In-hospital mortality;
▶ All-cause mortality within 30 days of the original cUTI diagnosis;
▶ All-cause mortality for 2 months after hospital discharge;
▶ Cost per case of cUTI;
▶ Readmissions to the hospital within 60 days of hospital discharge;
▶ Adverse events related to antibiotic treatment including moderate or severe allergic reactions, severe renal impairment, *Clostridium difficile* infection.

Health economic analysis
We will evaluate the cost of cUTI in participating countries, and the factors affecting these costs. The perspective will be the hospital provider, as this is where the majority of the cost burden of cUTI is expected to fall.[25 26] This will have three components:

1. We will estimate the cost per case of cUTI in participating countries. This will be based on collection of healthcare resource use data on length of hospital stay in different settings, medications and other treatment for infection, tests, and need of urological intervention and haemodialysis. Unit cost data for each cost component will be collected for each participating country from published and administrative sources, and multiplied by volume of resource used, and then summed across all components to calculate the costs per patient for cUTI caused by MDR GNB. Findings will be presented as means (with 95% CIs) and medians (with IQRs) of total costs, and also for each separate cost component.

2. Using data collected in this programme plus supplementary epidemiological data, the incidence of cUTI caused by MDR GNB in each country will be modelled and this will be multiplied by the mean incremental cost per patient to compute the total national cost of illness of cUTI caused by MDR GNB.

3. Multivariate regression analysis using patient-level cost data to investigate the factors associated with healthcare costs will be undertaken. The dependent variable will be mean costs per patient described under 1, given above. Independent variables will include age, gender, comorbidities, severity of infection, whether or not the patient died, signs and symptoms of UTI, and where the infection was acquired. To account for skewness of the cost data, a generalised linear model with γ family and log link[27] will be used. The impact of unobserved heterogeneity due to the hierarchical structure of the data (patients within hospitals within countries) will be explored and accounted for by considering the hospital and country fixed-effects and random-effects models.

Sample size
One thousand patients should afford a power of 0.83 (α=0.05) to detect an absolute difference of 10% in the treatment failure rate between MDR bacteria and other pathogens. This should allow for the introduction of about 20 independent risk factors (or their interaction) in a logistic regression model looking at risk factors for failure.

Statistical analysis
The χ^2 or Fisher's exact tests will be used to compare categorical data, and the Student's t-test or Mann-Whitney U test for continuous data, as appropriate (the Kolmogorov-Smirnoff test will be used to test whether the distribution of continuous variable is normal). Logistic regression analysis will be performed to identify independent variables associated with treatment failure. Variables with p<0.10 in univariate analysis (and variables that make clinical sense) will be included in the multivariate model to control for confounding. The adequacy of the final model will be tested using the Hosmer-Lemeshow goodness-of-fit test. All tests will be two-tailed, and a p<0.05 will be considered as statistically significant.

Time to appropriate therapy, clinical response, urological intervention for source control or death will be examined using competing risks.

Monitoring plans
At each site, a screening log will be kept of the patients who were detected according to the ICD codes, and detail the excluded patients and the reasons for exclusion.

For confirmation of the data quality and to avoid fraud, study sites will be monitored and/or audited. Monitoring and audit visits will be conducted by a designated third party. Spot check monitoring and source data verification will be conducted to confirm that the data entered in the database are retrieved from actual patients and their corresponding hospital files, and has been transferred correctly. All sites' study-related documents, including patient data source documents, will have to be made available for monitoring and audit.

ETHICAL ISSUES
The study will only use data routinely collected in the time frame January 2013 to December 2014. No extra tests or interventions will be undertaken on patients, and there will be no impact on patient care or outcome. Prior to initiation of a study site, approval will be sought

from all appropriate regulatory agencies and local Research Ethics Committees (REC) to conduct the study in accordance with local regulatory requirements at each site.

The processing of the patients' personal data collected in this study will comply with the European Directive on the Privacy of Data. All data to be collected, stored and processed will be anonymised (EU Directive 95/46/EC).[28]

All study-related documents will be retained on site in a secure location. No personal information will be stored on local computers during conduct of the study or after completion.

For data collection, an access controlled web-based electronic case report form (eCRF) will be used. Access to the eCRF, for data entry as well as change of any data fields, will be overviewed by an audit trail.

This study received first approval on 10 September 2015 by the REC of Bellvitge University Hospital. The informed consent form and information sheet were waived because of the retrospective nature of the study.

PUBLICATION PLANS

It is mandatory that the first publication is based on data from all sites, analysed as stipulated in the protocol by statisticians/epidemiologists, and in agreement with the COMBACTE-MAGNET publication policy. The investigator/research leads must agree not to present data gathered from one site or a small group of sites before the full initial publication and subsequently, only on agreement with the Scientific Committee Board and COMBACTE-MAGNET consortium. Any formal presentation or publication of data collected from this study will be considered as a joint publication by the participating investigator/research leads, and will follow the recommendations of the International Committee of Medical Journal Editors (ICMJE). Results will be reported in accordance with STROBE guidelines.

DISCUSSION

cUTIs are common and frequently caused by MDR GNB, which are increasingly difficult to treat. Moreover, patients with cUTI are changing over time; they are older, with a high prevalence of chronic renal failure and other chronic diseases, instrumentation of the urinary tract and polypharmacy. The study aims to improve knowledge regarding the management, response to treatment and outcome of patients with cUTI in European countries with high prevalence of MDR GNB. The main objective is to identify possible modifiable risk factors for treatment failure, especially those related to antibiotic therapy.

Expected impact: The study will increase knowledge of the epidemiology, clinical characteristics and outcomes of hospitalised patients with cUTI caused by MDR GNB, and will also assist in the selection of sites for future clinical trials with antimicrobial agents.

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