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Antimicrobial Stewardship Program Based on the Detection and Monitoring of Patients with *Clostridium difficile* infection.

NCT02951481 Protocol ID: JMA-MET-2016-01

Version 2.0
February 15, 2016

Infectious Diseases Unit.
Fundación de Investigación "i+12"
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Background and Rationale

Clostridium difficile is one of the most common causes of health care–associated infection. The incidence and severity of the CDI have increased alarmingly in many countries around the world since the outbreak of the hypervirulent strain NAP1 / BI / 027 at the beginning of the last decade. In Spain, it has also been a clear increase in incidence from 39 to 122 cases per 100,000 hospitalizations over 1999-2007 (1,2), despite the fact that the presence of the NAP1 / BI / 027 has been anecdotal until 2015. The higher incidence of CDI in Spain is related with the increment of antibiotic use, aging and more complex comorbidities of the hospitalized population (2). It is also likely that physicians' higher degree of suspicion and improved sensitivity of diagnostic tests had also contributed to magnify this rise.

In our country it has been shown that the use of antibiotics (in DDD) in the outpatient setting, especially fluoroquinolones and penicillin with beta-lactamase inhibitors (mainly amoxicillin-clavulanate) has increased significantly (3). Besides, the prevalence of fluoroquinolone use in hospital settings (patients receiving antibiotic per 100 hospitalized patients) has also risen significantly, going from 5.8 in 1999 to 10.2%in 2010 (4). In a recent study conducted in Canada, all antibiotics prescribed in hospital within 8 weeks of *C. difficile* infection (CDI) diagnosis were reviewed for appropriateness. More than 45% of antibiotic courses were deemed to be inappropriate because of incorrect diagnosis, inadequate or excessively broad spectrum of activity and prolonged duration of therapy (5). For this reason, programs of antibiotic stewardship have shown to

decrease the selective pressure that facilitates the emergence of multidrug resistant microorganisms and CDI. Development of hospital policies to limit the number and duration of antibiotic treatments has proved useful in reducing the incidence of CDI (6-9). In case of hospital outbreaks, programs improving antimicrobial use and strict cleaning measures and contact precautions are essential to control the spread of infection (10).

On the other hand, the risk of recurrence of CDI is high (between 20 and 30%). Patients with a first recurrence are at special risk of developing further episodes of recurrence, with the consequent inconveniences of that situation (repeated emergency department consults, numerous hospital admissions, negative effect on life quality, familiar disturbance…). Close monitoring of all patients with a CDI diagnosis may help to identify patients at particular risk of recurrence, in order to eliminate those potentially modifiable risk factors (11,12).

Early diagnosis and appropriate treatment of recurrent episodes, according to clinical practice guidelines (13), would improve patients' prognosis. Besides, monitoring by an infectious diseases physician who provided appropriate information to patients and families would ensure compliance with contact precautions and hygiene measures that would reduce the *C. difficile* dissemination. While prevention efforts have traditionally focused on the hospital setting, the recommendations should expand at community level (14). To sum up, CDI is a frequent nosocomial infection that often causes an increase in the average stay and medical expenses. Treatment, especially of successive recurrences, does not often conform to the guidelines for clinical practice. On the other hand, information that patients and families receive from physicians is usually poor. Specifically, it is unusual to provide information on measures to prevent the spread of infection once at home.

Evidence-based elements have been shown to reduce the incidence of multiple health-care associated and hospital acquired infections and, when bundled, led to even greater benefit than each of the strategies alone (15-19). Some studies have demonstrated a reduction in the incidence of CDI using a checklist of hospital interventions (20) or achieved the control of important outbreaks by means of a comprehensive "bundle" approach (21). A "bundle" for CDI should be based on interventions that have already shown to exert a high impact in reducing the risk of CDI (6, 22-25): prudent antibiotic prescribing, hand hygiene, environmental decontamination, isolation/cohort nursing and use of personal protective equipment. Apart from reducing the indiscriminate use of

antimicrobials, a stewardship program based on the detection and close monitoring of patients diagnosed with CDI, could offer personalized attention to this especially susceptible group of population, through systematic monographic medical visits and extended follow-up during the period of maximum risk of recurrence.

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Objectives

This study aims to evaluate the impact of an intervention, consisting on a bundle of measures.

Primary objective:

- To reduce the recurrence rate of patients with a first episode of CDI hospitalized during the period of intervention by increasing the compliance with clinical practice guidelines (appropriate length and choice of drug for CDI specific treatment according to the severity of the initial episode) and by a close follow-up during the period of higher risk, avoiding factors that are known to predispose to recurrence.

Secondary objectives:

- To reduce the rate of second and further recurrences by increasing the compliance with clinical practice guidelines (appropriate length and choice of drug for the treatment of first and further recurrences).
- To discontinue or to reduce the spectrum of unnecessary antibiotic treatments in this population ("antimicrobial stewardship"), especially during the episode of CDI and during the following 8 weeks.
- To discontinue inappropriate treatment of asymptomatic patients colonized by Clostridium difficile.
- To identify clinical and biological markers that could be used as predictors of recurrence.
- To identify patients with a high number of recurrences, that could benefit from novel or experimental treatments.

Hypothesis

1. A bundle of measures specifically designed for patients with ICD and applied by and Infectious Diseases expert would improve the prognosis and reduce the risk of recurrence.
2. Some measures have proved to be effective to improve the prognosis of patients with a first episode of CDI. Probably the most relevant action is to stop the antibiotic treatment as soon as possible (grade of recommendation AII according

to the IDSA guidelines), or at least to choose a low-risk antimicrobial treatment with minimum detrimental effect over the patient's microbiota. This measures cannot always be applied, but we hypothesize that an early assessment and monitoring by an Infectious Diseases expert would encourage attending physicians to evaluate the necessity of the inciting antimicrobial treatment and enable the decision of discontinue it, without substantial risk for the patient.

3. Although treatments shorter than 10 days of metronidazole have proved to increase the risk of recurrence and the recommendation is 10-14 days of metronidazole for a first mild or moderate episode of CDI (grade of recommendation AI), courses of 7 days are frequently prescribed. An initial assessment by an Infectious Diseases expert who makes a non-impositive recommendation would increase physicians' compliance with evidence-based recommendations.
4. Although oral vancomycin is the drug of choice for an initial episode of severe CDI (grade of recommendation BI) and vancomycin administered orally (and per rectum, if ileus is present) with or without intravenously administered metronidazole is the regimen of choice for the treatment of severe, complicated CDI, however, it is relatively frequent that the severity of the episode is not accurately assessed at diagnosis, which delays the start of appropriate therapy. An initial assessment by an Infectious Diseases expert who makes a non-impositive recommendation would increase physicians' compliance with evidence-based recommendations.
5. Although metronidazole should not be used beyond the first recurrence of CDI or for long-term chronic therapy because of potential for cumulative neurotoxicity, it is not uncommon that patients with multiple recurrences receive several courses of metronidazole. Patients with multiple recurrences would benefit from a close follow-up by an Infectious Diseases expert who appropriately diagnoses and treats every episode, following the evidence-based recommendations.

MATERIAL AND METHODS:

Study Design: Exploratory, interventional before-after prospective, quasi-experimental study comparing the baseline phase (2015) with the interventional phase (2017)

Study Subjects:

Inclusion criteria:

- Patients diagnosed with a first episode of CDI in the University Hospital "12 de Octubre", Madrid, Spain, requiring hospitalization or emergency room admission longer than 48 hours, from the beginning of the study on (1-February-2017).
- Patient or his/her representative sign the inform consent

Exclusion criteria:

- Patients younger than 18 years of age.
- Patients with the diagnosis of inflammatory bowel disease.

Patients selection and follow-up:

The first 100 patients fulfilling the inclusion criteria will be included in the prospective phase of the study. Patients will be identified by means of daily report of the positive results from the Microbiology lab. They will be prospectively followed 8 weeks after the end of treatment for the episode of CDI. If there are one or more recurrences, the follow-up will endure until 8 weeks after the end of the last CDI treatment.

They will be retrospectively compared with patients diagnosed with a first episode of CDI during the previous year (2015) in which there was not a systematical intervention by a member of the Infectious Diseases Unit.

To ensure comparability, patients from the retrospective period will be chosen and matched with patients included in the prospective period according to the severity of the initial episode of CDI and to the Charlson Age-Comorbidity Index (CACI).

If patients diagnosed during 2015 are not enough to fulfil those comparison criteria, we will search backwards through patients diagnosed with a first episode of CDI during 2014 to be matched.

The retrospective follow-up will also endure until 8 weeks after the end of the last CDI treatment.

Microbiological methods:

All unformed stools (taking the shape of the container) from patients with a clinical suspicion of CDI will be processed immediately or, when logistically unfeasible, kept at 4º C or frozen at −70º C until processing. Samples will be simultaneously tested for GDH

and toxin A/B with a single immunochromatographic assay, the TechLab® C. diff Quik Chek Complete™ (Inverness Medical Innovations, Princeton, NJ, USA). For samples with discordant results (GDH-positive, toxin A/B-negative), toxin production will be confirmed by the Xpert® C. difficile PCR assay (Cepheid, Sunnyvale, CA, USA).
The diagnostic algorithm used during the retrospective period was exactly the same, as it was implemented in our hospital in February 2011.

Specific "bundle" of measures for patients with ICD:

These measures are based in well-known and evidence-based elements that reduce the incidence and limit the spreading of Clostridium difficile (see references 6,13,22-25):

Systematic evaluation of all patients diagnosed with CDI by an Infectious Disease expert with the implementation of the following interventions:

- To ensure compliance with clinical practice guidelines about specific treatment for CDI, depending on the severity of the episode and the existence of previous episodes, thus improving the prognosis of these patients and avoiding side effects.
- To optimize concomitant antibiotic therapy ("antimicrobial stewardship") through the following interventions:
    - To remove unnecessary treatments.
    - To shorten antibiotic courses as far as possible.
    - To avoid, if possible, broad-spectrum or high risk for developing CDI antibiotics.
- To reduce indiscriminate use of proton-pump inhibitors (PPI) or H2 receptor antagonists (H2 blockers).
- To provide clear instructions to patients and their families about the measures that should be implemented at home after discharge. To answer their questions and calm their fears about the CDI and need for isolation.
- To ensure appropriate monitoring during the period of greatest risk of relapse (8 weeks after completion of antibiotic treatment for CDI) in order to reduce as far as possible, the number of relapses by the following interventions:
    - Personalized assistance by telephone or by email for early consultation in case of recurrence of symptoms, in order to make:
        - Early diagnostic of relapses.
        - Appropriate treatment of subsequent episodes.

    - Detection of patients who could benefit from fecal microbiota transplantation.
  - Personalized assistance by telephone or by email for consultation in case of necessity of a new antibiotic course in order to:
    - Avoid unnecessary antimicrobial treatments.
    - Choose the antibiotic class with less risk of selecting C. difficile.
    - Evaluate preventive measures in an attempt to prevent the development of CDI.

Definitions:

Diarrhoea: Loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7, plus a stool frequency of three stools in 24 or fewer consecutive hours or more frequently than is normal for the individual.

An **episode of CDI** is defined as: A clinical picture compatible with CDI and microbiological evidence of free toxins and the presence of C. difficile in stool without reasonable evidence of another cause of diarrhoea or Pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy.

Mild or moderate CDI/non-severe CDI: Diarrhoea without systemic symptoms, leukocytosis with a white blood cell count lower than 15,000 cells/mL and a serum creatinine level less than 1.5 times the premorbid level.

Severe CDI: systemic symptoms of infection and/or leukocytosis with a white blood cell count of 15,000 cells/mL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level.

Severe Complicated CDI/Fulminant CDI: was defined by the presence of severe disease accompanied by life-threatening conditions such as ileus, toxic megacolon, refractory hypotension and/or multi-organ failure attributable to CDI.

Ileus: Signs of severely disturbed bowel function such as vomiting and absence of stool with radiological signs of bowel distension.

Toxic megacolon: Radiological signs of distension of the colon (>6 cm in transverse width of colon) and signs of a severe systemic inflammatory response (nausea, vomiting, dehydration, lethargy or tachycardia addition to fever and abdominal pain).

Leukocyte count to consider severity of the CDI: Any white blood cell count (WBC) measured between two days before and two days following the date of the stool sample. If a patient had WBC measured on the date of the stool sample then this was selected. If they did not have WBC measured on the date of the stool sample but had WBC measured between one day before and one day following their stool sample, then this was selected. If they did not have WBC measured between one day before and one day following their stool sample but had WBC measured between two days before and two days following their stool sample, then this was selected. If they did not have WBC measured on the date of the stool sample but had WBC measured both one day before and one day following the date of stool sample, or had WBC measured both two days before and two days after the stool sample but not between these measurements, then the highest of the two measurements was selected.

Definition of treatment response: Treatment response is present when either stool frequency decreases or stool consistency improves and parameters of disease severity (clinical, laboratory, radiological) improve and no new signs of severe disease develop.

Definition of recurrent CDI: Recurrence is present when CDI re-occurs within 8 weeks of successfully completing treatment for CDI.

Duration of diarrhea: was the sum of days from day 1 to the last day with diarrhea, followed by 2 or more days without diarrhea.

Antibiotics of high, medium and low risk for CDI: according to the table proposed by Aldeyab et al (S3. J Antimicrob Chemother 2012; 67: 2988–2996).

Table S3. Risk classification of antibiotics

High risk	Medium risk	Low risk
Second-generation cephalosporins [J01DC; cefaclor, cefuroxime].	Combinations of penicillins including β-lactamase inhibitors [J01CR; amoxicillin/clavulanic acid]	Combinations of penicillins including β-lactamase inhibitors [J01CR; piperacillin/tazobactam]
		Penicillins with extended spectrum [J01CA; amoxicillin, ampicillin; pivmecillinam]
		β-Lactamase-sensitive penicillins [J01CE; phenoxymethylpenicillin, benzylpenicillin]
Third-generation cephalosporins [J01DD; cefotaxime, ceftazidime, ceftriaxone]	Macrolides [J01FA; azithromycin, clarithromycin, erythromycin]	β-Lactamase-resistant penicillins [J01CF; flucloxacillin]
		First-generation cephalosporins [J01DB; cefalexin, cefradine]
		Trimethoprim and derivatives [J01EA]
		Carbapenems [J01DH; ertapenem, meropenem]
Fluoroquinolones [J01MA; mainly profloxacin; others: norfloxacin; ofloxacin; levofloxacin]		Combination of sulphonamides and trimethoprim [J01EE]
		Aminoglycosides [J01GB; amikacin, gentamicin, neomycin]
		Glycopeptides [J01XA; teicoplanin, vancomycin]
Lincosamides [J01FF; clindamycin]		Steroid antibacterials [J01XC; sodium fusidate]
		Imidazole derivatives [J01XD; metronidazole]
		Nitrofuran derivatives [J01XE; nitrofurantoin]
		Other antibacterials [J01XX; linezolid]
		Tetracyclines [J01A; demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, lymecycline, tigecycline]

Charlson Age-Comorbidity Index (CACI): This index will be calculated by the electronic calculator www.pmidcalc.org/7722560 (Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245-51).

Based on previous authors (26-29) we proposed several terms to describe the appropriateness of prescription in each episode:

- **Right choice:** According to the current guidelines, the medication is effective for the condition an also used at optimal doses and duration, without duplication or association with unnecessary drugs.
- **Inapropriate/suboptimal prescription**:
    - **Overuse:** inclusion of unnecessary medication for the condition, which may result in an increased risk of adverse reactions, drug-drug interactions and increased costs.
    - **Underuse:** omission of a drug when there is a clear indication and no contraindications. The failure to prescribe essential medications may result in the worsening of the illness or therapeutic failure.

Our definition of right choice will be judged according to the latest European Society of Clinical Microbiology and Infectious Diseases guidelines (Debast SB, Bauer MP, Kuijper EJ; Committee. European Society of Clinical Microbiology and Infectious Diseases:

update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect. 2014 Mar;20 Suppl 2:1-26).

Data collection and analysis

Patients in the pre-intervention period will be retrospectively identified from microbiological data. All isolates of Clostridium difficile from 2015 (and 2014, if necessary) will be revised backwards to choose comparable patients with those included in the prospective period, according to the severity of the first episode.
Data will be collected from electronic medical records which include daily medical evaluations and daily treatments administered to the patient.
Patients in the intervention period will be identified by daily reporting of positive tests for CDI from the Microbiology laboratory and prospectively followed by a member of the research team.
The variables will be collected in a coded database for further analysis.

Statistical Plans

We present an exploratory study which aim is to evaluate the impact of an intervention, consisting on a bundle of measures for patients diagnosed with a first episode of CDI. The bundle includes antimicrobial stewardship, close follow-up, optimization of specific treatment for CDI and potential search for clinical and biological markers of recurrence.
The required sample size was estimated under the hypothesis that the application of a strategy based on a bundle to improve the management of CDI, would decrease the risk of recurrence as compared to the usual care performed in the retrospective period.
A recent review[1] that evaluated the frequency of treatment failure and recurrence of CDI showed a recurrence rate after metronidazole treatment of 27.6% in studies performed in Europe during the previous 10 years.
Based in the previous literature, we expected a cumulative incidence of recurrence in the control group of 27.6%. The study would require a sample size of 99 for each group (i.e. a total sample size of 198, assuming equal group sizes), to achieve a power of 80% for detecting a reduction in proportions of 0.15 between the two groups (reference group - intervention) at a two sided p-value of 0.05.

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The data of qualitative variables will be expressed as absolute values and relative frequencies. The data of quantitative variables will be shown as mean ± standard deviation should be demonstrated normal distribution or median with interquartile range otherwise. Categorical variables will be compared using X ^ 2 or Fisher's exact test for paired samples. Continuous variables will be compared using the Student's t-test or the Mann-Whitney U test for paired samples.

The impact of our intervention will be analyzed as a categorical variable and will be entered as a predictor variable into a conditional logistic regression model, adjusted by potential confounding factors. Associations will be given as relative risks.

A set of sensitivity analyses will be explored by restricting the overall cohort according to the type of episode (first episode versus recurrence) and by hospital ward (medical versus surgical).

Statistical analysis will be conducted using SPSS version 22.0 (SPSS Inc, Chicago, Illinois, USA).

MANAGEMENT AND REPORTING OF ADVERSE REACTIONS

Under current legislation, any adverse events appeared throughout the study should be notified by the standard notification procedure and clinical practice.

Definitions

According to the legislation regulating pharmacovigilance of medical products for human use ("Real Decreto" 1344/2007, 11 October), the following definitions shall apply:

Adverse reaction (AR):

Any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological function. This term also includes all adverse clinical consequences resulting from dependence, abuse and misuse of

drugs, including those caused by use outside of approved conditions or caused by medication errors.
The AR is characterized by the suspicion that there is a causal relationship between the drug and the episode.

Serious adverse reaction (SAR):
Any AR that results in death, are life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly or birth defect. For the purposes of notification, those suspected adverse reactions that are considered important from a medical point of view are also treated as serious, though not meet the above criteria, such that threatening to the patient or that require intervention to prevent any of previous outcomes. Likewise, for the purposes of notification, all suspected transmission of an infectious agent through a drug shall also be treated as serious.

Unexpected adverse reaction (UAR):
Any adverse reaction whose nature, severity or outcome is not consistent with the information described in the instructions linked with the product characteristics summary (for a product with marketing authorisation).

Management and communication of adverse reactions
According to paragraph 8.3 of the SAS / 3470/2009 Order, "Communication of suspected adverse reactions", and considering that the sponsor is formed by a group of professionals, suspicions of AR observed during this observational study will be reported sending yellow card to the corresponding regional pharmacovigilance center, indicating the name and code of the study from which it comes in the paragraph dedicated to “observations”.

PLANS TO DISEMINATE THE RESULTS OF THE STUDY

The data and / or results of this study will not be published or disseminated without the prior consent of the sponsor of the study. The results obtained in this study will be disseminated through international communications and posters at national and / or international conferences. The findings will be published in national and / or international scientific journals by the sponsor or by any person or entity that has been authorized by the sponsor.

RESOURCES FOR THE CONDUCT OF THE STUDY AND TASK ALLOCATION. FINANCING

The sponsor will finance the expenditure relating to the implementation and completion of the study, including materials and logistics necessary for recording, monitoring and statistical analysis of the data.
Partial funding will be requested of Astellas Pharma, SA to meet part of the budget costs associated with the study.
Since this is an observational study, there is no obligation to hire any insurance for patients.
The investigator is responsible for ensuring that the drugs given to patients have been prescribed in accordance with the approved indications in common medical practice, regardless of their participation in this study. Therefore, the corresponding insurance of the drug used will assume the potential costs of adverse reactions.

MONITORING AND FINAL REPORTS

Once the study is completed, the sponsor will send a final report to the responsible ethics committee and to relevant organizations, communicating with it CEIC study completion. Moreover, all relevant incidents occurring during the study must be reported immediately to the Ethics Committee of the University Hospital 12 de Octubre, and responsible health authorities.

ETHICAL ASPECTS:

Before the beginning of the study, this protocol will be submitted for consideration by the Spanish Agency for Medicines and Health Products ("AEMPS") for classification and by the Ethics Committee for Clinical Research (EC) of the University Hospital 12 de Octubre, to obtain the approval.

Since no active intervention on the pre-intervention group will be performed, the data will be collected in a database to which only research team have access and all information related to the study will be strictly confidential and treated according to the Organic Law

15/1999 on Protection of Personal Data, and Law 14/2007 of Biomedical Research, Ethics Committee will be asked to accept the study without the necessity of informed consent for this group.

Informed consent for the patients included in the study during the period of intervention will be requested.

The entire study will be conducted in accordance with the principles of the revision of Seoul, Korea (October 2008) of the Declaration of Helsinki for research in humans. Copies of the Declaration of Helsinki and its subsequent amendments will be provided upon specific request or can be downloaded from the website of the World Medical Association in http://www.wma.net/e/policy/b3 .htm.
The study will be conducted according to the protocol, which ensures compliance with the rules of Good Clinical Practice (GCP), as described in harmonised tripartite guidelines on Good Clinical Practice of 1996.

According to the guidelines of the SAS / 3470/2009 Order on post-authorization observational studies, such projects must be reviewed by an independent committee (except in certain specific cases). For these reasons, this study was sent to a clinical research ethics committee for evaluation and timely notification to the Spanish Agency for Medicines and Health Products (AEMPS) for classification will be sent.

Benefit-risk assessment for patients

This study does not involve additional risks for patients, as different tests from which are applied in routine clinical practice to patients who are in the same clinical situation won´t be made.

Interference with the doctor prescribing habits

Because the study was observational, at any time participation of patients may interfere with treatment decisions; the involvement of patients won't affect the treatment they need and which their doctor considers appropriate according to their clinical situation.
Furthermore, in accordance with the Order SAS / 3470/2009, the study investigators must ensure that the treatment given to patients included in the study met the conditions of clinical practice and current recommendations, always within the framework of the indication authorized in the product data sheet. The decision to administer a treatment will be taken previously, independently and dissociated from the patient's inclusion in the study.