

New research sheds light on treating bloodstream infections with fewer side effects

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Patients with bloodstream infections could avoid treatment with a combination of antimicrobial therapies if they are given the right drug as early as possible and if they are classified as at low risk of death. This would reduce the risk of adverse side effects, as well as the likelihood of drug resistance developing in the bacteria that cause the infection—carbapenemase-producing Enterobacteriaceae (CPE).

The results from the international INCREMENT study, presented at the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) today (Sunday) and published simultaneously in *The Lancet Infectious Diseases*, show for the first time that combination therapy is only better than treatment with a single antimicrobial in patients with bloodstream infections caused by CPE if they are at high risk of dying. In these patients combination therapy halved the risk of death, but it made no difference in patients at low risk.

A second presentation on the INCREMENT study showed that it was possible to avoid using carbapenems—the class of antimicrobial therapies considered as drugs of last resort—to treat bloodstream infections caused by another type of <u>bacteria</u> called extended-spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E), which are usually resistant to a range of antimicrobial drugs including cephalosporins. The research showed that if patients were treated with other drugs, thought to be active against the infection, and then switched



to a better-targeted drug once doctors had identified the bacteria, patients did as well as those who were treated immediately with carbapenems. This finding may help doctors to reduce the use of carbapenems so that they can be reserved for use only for infections that are definitely resistant to all other existing antimicrobial therapies.

When treating patients with potentially life-threatening bloodstream infections, doctors often use a combination of antimicrobial or broad spectrum antimicrobial drugs in order to try to start combating the infection as quickly as possible, but without knowing which treatments the bacteria are actually susceptible to. This means that the drugs may not be well targeted and it can lead to bacteria developing resistance to a range of antimicrobials, including the therapies of last resort.

In the first presentation, Professor Jesús Rodríguez-Baño, Head of the <u>infectious diseases</u> division at the University Hospital Virgen Macarena (Seville, Spain) and President-elect of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), reported results from 37 hospitals in 11 countries on 437 patients with bloodstream infections caused by CPE—a group of bacteria that are resistant to carbapenems. They can kill up to about half of patients who develop bloodstream infections.

Before starting antimicrobial treatment, patients were assessed for their risk of death; patients at low risk scored between 0-7 and those at high risk scored between 8-15 on the IMCREMENT-CPE score. Fifty-one percent of the patients were low risk.

At the start of treatment, 343 patients received antimicrobial therapy that was active against the bacteria causing the infection—either a single antimicrobial drug or a combination. This treatment more than halved the risk of death for the group as a whole. However, combination therapy was only associated with a reduced risk of death (a decrease of



44%) in the high-risk patients, and not in the low-risk patients.

Prof. Rodríguez-Baño said: "Contrary to present recommendations, combination therapy can be avoided in a substantial proportion of patients with bloodstream infections due to CPE. These patients can be identified using the INCREMENT-CPE score and if they are low risk they can be treated with a single active antimicrobial. This helps to avoid the problems that can be associated with combination therapy, such as a higher risk of adverse side effects, the development of resistance by the infection-causing bacteria to more antimicrobials, and the higher cost.

"We hope that, as a result of these findings, clinicians will be able to evaluate patients better so that only those at high risk will be given <u>combination therapy</u>."

In the second presentation, Dr Zaira Palacios Baena, an internal medicine resident at the Hospital Universitario Virgen Macarena (Seville, Spain), told the congress: "There is no consistent evidence about the use of different regimens of treatments for bloodstream infections due to extended-spectrum beta-lactamase producing Enterobacteriaceae. We wanted to assess the impact of starting treatment with drugs that were thought likely to be active against the infection, but before doctors had identified the precise microorganism causing the infection and which drugs it would be susceptible to.

"We found that even if we treated patients with antimicrobial drugs that proved to be inactive against the bug that was causing the infection, it did not increase death rates if we take into account their underlying risk of death and if we switch to a drug that is active against the infection as soon as we know which one will work. Nowadays, with the evolution of technology in the field of microbiology, we can know the susceptibility of a microorganism within 24 hours and then we can start using the right, targeted active treatment. This means that we do not have to start



treating patients immediately with carbapenems, but can try out other drugs first before switching to an active antimicrobial, that is not necessarily a carbapenem, if the first <u>drug</u> doesn't work."

Dr Palacios Baena and her colleagues included 855 patients with bloodstream infections caused by ESBL-E who were treated between 2004 and 2012 in the INCREMENT study and who received their first treatment within 24 hours. They assessed the patients' risk of dying within 30 days using the INCREMENT-ESBL score, which takes into account factors such as age, type and source of the infection (most were E.coli or Klebsiella bacteria), the severity of the infection and the presence of other diseases or conditions.

The patients who started antimicrobial therapies before the susceptibility of the infection was known were classified into three groups: 1) patients who were given carbapenems or another broad spectrum antimicrobial therapy called beta-lactamase/beta-lactamase inhibitors; this was called "choice therapy (CT)" and these patients were used as the reference group to compare the other two groups against; 2) patients who were given other <u>antimicrobial drugs</u>, either alone or in combination, that were known to work against ESBL-E in the laboratory, called "alternative therapy (AT)"; and 3) patients who were given <u>antimicrobial therapy</u> that proved to be inactive against the infection, called "inactive therapy (IT)".

The majority of patients (489, 57%) received choice therapy, 83 (10%) received alternative therapy, and 283 (33%) received inactive therapy. A total of 144 patients (17%) died. The death rates for CT patients was 17%, for AT patients it was 19%, and for IT patients, 15.5%. There was no statistically significant difference in death rates between patients who received CT and those who received either AT or IT.

The risk of death in high-risk patients increased by a third for each point



on the INCREMENT-ESBL score, and patients who were treated with a targeted therapy that had not been shown to work against the bacteria in laboratory tests (inactive targeted <u>therapy</u>) had a nearly three-fold increased risk of death. Dr Palacios Baena said these were the patients most likely to benefit from early treatment with broad-spectrum drugs known to be active against this type of bacteria.

She said that further research needed to be done to confirm their results before any changes were introduced in the way patients with these <u>bloodstream infections</u> are treated. "We hope these results might help other investigations, and maybe in the future we can stop the threatening development of carbapenem-resistant microorganisms by avoiding the use of carbapenems in selected patients.

"Many deaths can be prevented if we use the antimicrobials available to us appropriately and moderately. It's necessary to strengthen the research into new molecules and the development of old ones. Patients, politicians and the general population must be aware that the use of broad-spectrum antimicrobials needs to be reserved only for when they are really needed, as it is a disaster for patients who develop an <u>infection</u> due to a microorganism that is resistant to carbapenems."

More information: Abstract no: #OS0456, presented by Prof. Rodríguez-Baño in the "Treatment and mortality related with carbapenem-resistant Enterobacteriaceae" oral session, 14.30-15.30 hrs, Sunday 23 April, Hall F.

"Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study", by Belén Gutiérrez-Gutiérrez et al and the REIPI/ESGBIS/INCREMENT Investigators. *The Lancet Infectious Diseases*, dx.doi.org/10.1016/S1473-3099(17)30228-1



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