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Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients with E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial.

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IMPORTANCE: Extended-spectrum β-lactamases mediate resistance to third-generation cephalosporins (eg, ceftriaxone) in Escherichia coli and Klebsiella pneumoniae. Significant infections caused by these strains are usually treated with carbapenems, potentially selecting for carbapenem resistance. Piperacillin-tazobactam may be an effective "carbapenem-sparing" option to treat extended-spectrum β-lactamase producers.

OBJECTIVES: To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible E coli or K pneumoniae.

DESIGN, SETTING, AND PARTICIPANTS: Noninferiority, parallel group, randomized clinical trial included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017. Adult patients were eligible if they had at least 1 positive blood culture with E coli or Klebsiella spp testing nonsusceptible to ceftriaxone but susceptible to piperacillin-tazobactam. Of 1646 patients screened, 391 were included in the study.

INTERVENTIONS: Patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants) or meropenem, 1 g, every 8 hours (n = 191 participants) for a minimum of 4 days, up to a maximum of 14 days, with the total duration determined by the treating clinician.

MAIN OUTCOMES AND MEASURES: The primary outcome was all-cause mortality at 30 days after randomization. A noninferiority margin of 5% was used.

RESULTS: Among 379 patients (mean age, 66.5 years; 47.8% women) who were randomized appropriately, received at least 1 dose of study drug, and were included in the primary analysis population, 378 (99.7%) completed the trial and were assessed for the primary outcome. A total of 23 of 187 patients (12.3%) randomized to piperacillin-tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI, -∞ to 14.5%]; P = .90 for noninferiority). Effects were consistent in an analysis of the per-protocol population. Nonfatal serious adverse events occurred in 5 of 188 patients (2.7%) in the piperacillin-tazobactam group and 3 of 191 (1.6%) in the meropenem group.

CONCLUSIONS AND RELEVANCE: Among patients with E coli or K pneumoniae bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

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Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients: A Randomized Clinical Trial.

Wittekamp BH[1], Plantinga NL[2], Cooper BS[3], Lopez-Contreras J[4], Coll P[5], Mancebo J[6], Wise MP[7], Morgan MPG[7], Depuydt P[8], Boelens J[9], Dugernier T[10], Verbelen V[11], Jorens PG[12], Verbrugghe W[12], Malhotra-Kumar S[13], Damas P[14], Meex C[15], Leleu K[16], van den Abeele AM[17], Gomes Pimenta de Matos AF[18], Fernández Méndez S[19], Vergara Gomez A[20], Tomic V[21], Sifrer F[22], Villarreal Tello E[23], Ruiz Ramos J[23], Aragao I[24], Santos C[25], Sperning RHM[26], Coppadoro P[27], Nardi G[28], Brun-Buisson C[29], Bonten MJM[2].
Author information

IMPORTANCE: The effects of chlorhexidine (CHX) mouthwash, selective oropharyngeal decontamination (SOD), and selective digestive tract decontamination (SDD) on patient outcomes in ICUs with moderate to high levels of antibiotic resistance are unknown.

OBJECTIVE: To determine associations between CHX 2%, SOD, and SDD and the occurrence of ICU-acquired bloodstream infections with multidrug-resistant gram-negative bacteria (MDRGNB) and 28-day mortality in ICUs with moderate to high levels of antibiotic resistance.

DESIGN, SETTING, AND PARTICIPANTS: Randomized trial conducted from December 1, 2013, to May 31, 2017, in 13 European ICUs where at least 5% of bloodstream infections are caused by extended-spectrum β-lactamase-producing Enterobacteriaceae. Patients with anticipated mechanical ventilation of more than 24 hours were eligible. The final date of follow-up was September 20, 2017.

INTERVENTIONS: Standard care was daily CHX 2% body washings and a hand hygiene improvement program. Following a baseline period from 6 to 14 months, each ICU was assigned in random order to 3 separate 6-month intervention periods with either CHX 2% mouthwash, SOD (mouthpaste with colistin, tobramycin, and nystatin), or SDD (the same mouthpaste and gastrointestinal suspension with the same antibiotics), all applied 4 times daily.

MAIN OUTCOMES AND MEASURES: The occurrence of ICU-acquired bloodstream infection with MDRGNB (primary outcome) and 28-day mortality (secondary outcome) during each intervention period compared with the baseline period.

RESULTS: A total of 8665 patients (median age, 64.1 years; 5561 men [64.2%]) were included in the study (2251, 2108, 2224, and 2082 in the baseline, CHX, SOD, and SDD periods, respectively). ICU-acquired bloodstream infection with MDRGNB occurred among 144 patients (154 episodes) in 2.1%, 1.8%, 1.5%, and 1.2% of included patients during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were 0.3% (95% CI, -0.6% to 1.1%), 0.6% (95% CI, -0.2% to 1.4%), and 0.8% (95% CI, 0.1% to 1.6%) for CHX, SOD, and SDD, respectively, compared with baseline. Adjusted hazard ratios were 1.13 (95% CI, 0.68-1.88), 0.89 (95% CI, 0.55-1.45), and 0.70 (95% CI, 0.43-1.14) during the CHX, SOD, and SDD periods, respectively, vs baseline. Crude mortality risks on day 28 were 31.9%, 32.9%, 32.4%, and 34.1% during the baseline, CHX, SOD, and SDD periods, respectively. Adjusted odds ratios for 28-day mortality were 1.07 (95% CI, 0.86-1.32), 1.05 (95% CI, 0.85-1.29), and 1.03 (95% CI, 0.80-1.32) for CHX, SOD, and SDD, respectively, vs baseline.

CONCLUSIONS AND RELEVANCE: Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream infections caused by MDRGNB compared with standard care.

TRIAL REGISTRATION:
ClinicalTrials.gov Identifier: NCT02208154.

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Antibacterial Envelope to Prevent Cardiac Implantable Device Infection.

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BACKGROUND: Infections after placement of cardiac implantable electronic devices (CIEDs) are associated with substantial morbidity and mortality. There is limited evidence on prophylactic strategies, other than the use of preoperative antibiotics, to prevent such infections.

METHODS: We conducted a randomized, controlled clinical trial to assess the safety and efficacy of an absorbable, antibiotic-eluting envelope in reducing the incidence of infection associated with CIED implantations. Patients who were undergoing a CIED pocket revision, generator replacement, or system upgrade or an initial implantation of a cardiac resynchronization therapy defibrillator were randomly assigned, in a 1:1 ratio, to receive the envelope or not. Standard-of-care strategies to prevent infection were used in all patients. The primary end point was infection resulting in system extraction or revision, long-term antibiotic therapy with infection recurrence, or death, within 12 months after the CIED implantation procedure. The secondary end point for safety was procedure-related or system-related complications within 12 months.

RESULTS: A total of 6983 patients underwent randomization: 3495 to the envelope group and 3488 to the control group. The primary end point occurred in 25 patients in the envelope group and 42 patients in the control group (12-month Kaplan-Meier estimated event rate, 0.7% and 1.2%, respectively; hazard ratio, 0.60; 95% confidence interval [CI], 0.36 to 0.98; P = 0.04). The safety end point occurred in 201 patients in the envelope group and 236 patients in the control group (12-month Kaplan-Meier estimated event rate, 6.0% and 6.9%, respectively; hazard ratio, 0.87; 95% CI, 0.72 to 1.06; P<0.001 for noninferiority). The mean (±SD) duration of follow-up was 20.7±8.5 months. Major CIED-related infections through the entire follow-up period occurred in 32 patients in the envelope group and 51 patients in the control group (hazard ratio, 0.63; 95% CI, 0.40 to 0.98).

CONCLUSIONS: Adjunctive use of an antibacterial envelope resulted in a significantly lower incidence of major CIED infections than standard-of-care infection-prevention strategies alone, without a higher incidence of complications. (Funded by Medtronic; WRAP-IT ClinicalTrials.gov number, NCT02277990.).

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Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis.

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BACKGROUND: Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for up to 6 weeks. Whether a shift from intravenous to oral antibiotics once the patient is in stable condition would result in efficacy and safety similar to those with continued intravenous treatment is unknown.

METHODS: In a randomized, noninferiority, multicenter trial, we assigned 400 adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics to continue intravenous treatment (199 patients) or to switch to oral antibiotic treatment (201 patients). In all patients, antibiotic treatment was administered intravenously for at least 10 days. If feasible, patients in the orally treated group were discharged to outpatient treatment. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 months after antibiotic treatment was completed.

RESULTS: After randomization, antibiotic treatment was completed after a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group (P=0.48). The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, -3.4 to 9.6; P=0.40), which met noninferiority criteria.

CONCLUSIONS: In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POETClinicalTrials.gov number, NCT01375257 .).

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Oral versus Intravenous Antibiotics for Bone and Joint Infection.

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BACKGROUND: The management of complex orthopedic infections usually includes a prolonged course of intravenous antibiotic agents. We investigated whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for this indication.

METHODS: We enrolled adults who were being treated for bone or joint infection at 26 U.K. centers. Within 7 days after surgery (or, if the infection was being managed without surgery, within 7 days after the start of antibiotic treatment), participants were randomly assigned to receive either intravenous or oral antibiotics to complete the first 6 weeks of therapy. Follow-on oral antibiotics were permitted in both groups. The primary end point was definitive treatment failure within 1 year after randomization. In the analysis of the risk of the primary end point, the noninferiority margin was 7.5 percentage points.

RESULTS: Among the 1054 participants (527 in each group), end-point data were available for 1015 (96.3%). Treatment failure occurred in 74 of 506 participants (14.6%) in the intravenous group and 67 of 509 participants (13.2%) in the oral group. Missing end-point data (39 participants, 3.7%) were imputed. The intention-to-treat analysis showed a difference in the risk of definitive treatment failure (oral group vs. intravenous group) of -1.4 percentage points (90% confidence interval [CI], -4.9 to 2.2; 95% CI, -5.6 to 2.9), indicating noninferiority. Complete-case, per-protocol, and sensitivity analyses supported this result. The between-group difference in the incidence of serious adverse events was not significant (146 of 527 participants [27.7%] in the intravenous group and 138 of 527 [26.2%] in the oral group; P=0.58). Catheter complications, analyzed as a secondary end point, were more common in the intravenous group (9.4% vs. 1.0%).

CONCLUSIONS: Oral antibiotic therapy was noninferior to intravenous antibiotic therapy when used during the first 6 weeks for complex orthopedic infection, as assessed by treatment failure at 1 year. (Funded by the National Institute for Health Research; OVIVA Current Controlled Trials number, ISRCTN91566927 .).

N Engl J Med. 2018 Nov 8;379(19):1835-1845. doi: 10.1056/NEJMoa1706988.

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea.

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BACKGROUND: Antibiotic-resistant Neisseria gonorrhoeae has prompted the development of new therapies. Zoliflodacin is a new antibiotic that inhibits DNA biosynthesis. In this multicenter, phase 2 trial, zoliflodacin was evaluated for the treatment of uncomplicated gonorrhea.

METHODS: We randomly assigned eligible men and women who had signs or symptoms of uncomplicated urogenital gonorrhea or untreated urogenital gonorrhea or who had had sexual contact in the preceding 14 days with a person who had gonorrhea to receive a single oral dose of zoliflodacin (2 g or 3 g) or a single 500-mg intramuscular dose of ceftriaxone in a ratio of approximately 70:70:40. A test of cure occurred within 6±2 days after treatment, followed by a safety visit 31±2 days after treatment. The primary efficacy outcome measure was the proportion of urogenital microbiologic cure in the microbiologic intention-to-treat (micro-ITT) population.

RESULTS: From November 2014 through December 2015, a total of 179 participants (167 men and 12 women) were enrolled. Among the 141 participants in the micro-ITT population who could be evaluated, microbiologic cure at urogenital sites was documented in 55 of 57 (96%) who received 2 g of zoliflodacin, 54 of 56 (96%) who received 3 g of zoliflodacin, and 28 of 28 (100%) who received ceftriaxone. All rectal infections were cured in all 5 participants who received 2 g of zoliflodacin and all 7 who received 3 g, and in all 3 participants in the group that received ceftriaxone. Pharyngeal infections were cured in 4 of 8 participants (50%), 9 of 11 participants (82%), and 4 of 4 participants (100%) in the groups that received 2 g of zoliflodacin, 3 g of zoliflodacin, and ceftriaxone, respectively. A total of 84 adverse events were reported: 24 in the group that received 2 g of zoliflodacin, 37 in the group that received 3 g of zoliflodacin, and 23 in the group that received ceftriaxone. According to investigators, a total of 21 adverse events were thought to be related to zoliflodacin, and most such events were gastrointestinal.

CONCLUSIONS: The majority of uncomplicated urogenital and rectal gonococcal infections were successfully treated with oral zoliflodacin, but this agent was less efficacious in the treatment of pharyngeal infections. (Funded by the National Institutes of Health and Entasis Therapeutics; ClinicalTrials.gov number, NCT02257918 .).

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Once-Daily Plazomicin for Complicated Urinary Tract Infections.

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BACKGROUND: The increasing multidrug resistance among gram-negative uropathogens necessitates new treatments for serious infections. Plazomicin is an aminoglycoside with bactericidal activity against multidrug-resistant (including carbapenem-resistant) Enterobacteriaceae.

METHODS: We randomly assigned 609 patients with complicated urinary tract infections (UTIs), including acute pyelonephritis, in a 1:1 ratio to receive intravenous plazomicin (15 mg per kilogram of body weight once daily) or meropenem (1 g every 8 hours), with optional oral step-down therapy after at least 4 days of intravenous therapy, for a total of 7 to 10 days of therapy. The primary objective was to show the noninferiority of plazomicin to meropenem in the treatment of complicated UTIs, including acute pyelonephritis, with a noninferiority margin of 15 percentage points. The primary end points were composite cure (clinical cure and microbiologic eradication) at day 5 and at the test-of-cure visit (15 to 19 days after initiation of therapy) in the microbiologic modified intention-to-treat population.

RESULTS: Plazomicin was noninferior to meropenem with respect to the primary efficacy end points. At day 5, composite cure was observed in 88.0% of the patients (168 of 191 patients) in the plazomicin group and in 91.4% (180 of 197 patients) in the meropenem group (difference, -3.4 percentage points; 95% confidence interval [CI], -10.0 to 3.1). At the test-of-cure visit, composite cure was observed in 81.7% (156 of 191 patients) and 70.1% (138 of 197 patients), respectively (difference, 11.6 percentage points; 95% CI, 2.7 to 20.3). At the test-of-cure visit, a higher percentage of patients in the plazomicin group than in the meropenem group were found to have microbiologic eradication, including eradication of Enterobacteriaceae that were not susceptible to

aminoglycosides (78.8% vs. 68.6%) and Enterobacteriaceae that produce extended-spectrum β-lactamases (82.4% vs. 75.0%). At late follow-up (24 to 32 days after initiation of therapy), fewer patients in the plazomicin group than in the meropenem group had microbiologic recurrence (3.7% vs. 8.1%) or clinical relapse (1.6% vs. 7.1%). Increases in serum creatinine levels of 0.5 mg or more per deciliter (≥40 µmol per liter) above baseline occurred in 7.0% of patients in the plazomicin group and in 4.0% in the meropenem group.

CONCLUSIONS: Once-daily plazomicin was noninferior to meropenem for the treatment of complicated UTIs and acute pyelonephritis caused by Enterobacteriaceae, including multidrug-resistant strains. (Funded by Achaogen and the Biomedical Advanced Research and Development Authority; EPIC ClinicalTrials.gov number, NCT02486627.).

Lancet Infect Dis. 2018 Dec;18(12):1319-1328. doi: 10.1016/S1473-3099(18)30554-1. Epub 2018 Oct 25.

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial.

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BACKGROUND: Carbapenem-resistant Gram-negative bacteria represent the highest priority for addressing global antibiotic resistance. Cefiderocol (S-649266), a new siderophore cephalosporin, has broad activity against Enterobacteriaceae and non-fermenting bacteria, such as Pseudomonas aeruginosa and Acinetobacter baumannii, including carbapenem-resistant strains. We assessed the efficacy and safety of cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infection in patients at risk of multidrug-resistant Gram-negative infections.

METHODS: We did a phase 2, multicentre, double-blind, parallel-group non-inferiority trial at 67 hospitals in 15 countries. Adults (≥18 years) admitted to hospital with a clinical diagnosis of complicated urinary tract infection with or without pyelonephritis or those with acute uncomplicated pyelonephritis were randomly assigned (2:1) by an interactive web or voice response system to receive 1 h intravenous infusions of cefiderocol (2 g) or imipenem-cilastatin (1 g each) three times daily, every 8 h for 7-14 days. Patients were excluded if they had a baseline urine culture with more than two uropathogens, a fungal urinary tract infection, or pathogens known to be carbapenem resistant. The primary endpoint was the composite of clinical and microbiological outcomes at test of cure (ie, 7 days after treatment cessation), which was used to establish non-inferiority (15% and 20% margins) of cefiderocol versus imipenem-cilastatin. The primary efficacy analysis was done on a modified intention-to-treat population, which included all randomly assigned individuals who received at least one dose of study drug and had a qualifying Gram-negative uropathogen (≥1 × 10^5 colony-forming units [CFU]/mL). Safety was assessed in all randomly assigned individuals who received at least one dose of study drug, according to the treatment they received. This study is registered with ClinicalTrials.gov, number NCT02321800.

FINDINGS: Between Feb 5, 2015, and Aug 16, 2016, 452 patients were randomly assigned to cefiderocol (n=303) or imipenem-cilastatin (n=149), of whom 448 patients (n=300 in the cefiderocol group; n=148 in the imipenem-cilastatin group) received treatment. 371 patients (n=252 patients in the cefiderocol group; n=119 patients in the imipenem-cilastatin group) had qualifying Gram-negative uropathogen (≥1 × 10^5 CFU/mL) and were included in the primary efficacy analysis. At test of cure, the primary efficacy endpoint was achieved by 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem-cilastatin group, with an adjusted treatment difference of 18·58% (95% CI 8·23-28·92; p=0·0004), establishing the non-inferiority of cefiderocol. Cefiderocol was well tolerated. Adverse events occurred in 122 (41%) of 300 patients in the cefiderocol group and 76 (51%) of 148 patients in the imipenem-cilastatin group, with gastrointestinal disorders (ie, diarrhoea, constipation, nausea, vomiting, and abdominal pain) the most common adverse events for both treatment groups (35 [12%] patients in the cefiderocol group and 27 [18%] patients in the imipenem-cilastatin group).

INTERPRETATION: Intravenous infusion of cefiderocol (2 g) three times daily was non-inferior compared with imipenem-cilastatin (1 g each) for the treatment of complicated urinary tract infection in people with multidrug-resistant Gram-negative infections. The results of this study will provide the basis for submission of a New Drug Application to the US Food and Drug Administration. Clinical trials of hospital-acquired pneumonia and carbapenem-resistant infections are ongoing.

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Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection.

Huang DT1, Yealy DM1, Filbin MR1, Brown AM1, Chang CH1, Doi Y1, Donnino MW1, Fine J1, Fine MJ1, Fischer MA1, Holst JM1, Hou PC1, Kellum JA1, Khan F1, Kurz MC1, Lotfipour S1, LoVecchio F1, Peck-Palmer OM1, Pike F1, Prunty H1, Sherwin RL1, Southerland L1, Terndrup T1, Weissfeld LA1, Yabes J1, Angus DC1; ProACT Investigators.

BACKGROUND: The effect of procalcitonin-guided use of antibiotics on treatment for suspected lower respiratory tract infection is unclear.

METHODS: In 14 U.S. hospitals with high adherence to quality measures for the treatment of pneumonia, we provided guidance for clinicians about national clinical practice recommendations for the treatment of lower respiratory tract infections and the interpretation of procalcitonin assays. We then randomly assigned patients who presented to the emergency department with a suspected lower respiratory tract infection and for whom the treating physician was uncertain whether antibiotic therapy was indicated to one of two groups: the procalcitonin group, in which the treating clinicians were provided with real-time initial (and serial, if the patient was hospitalized) procalcitonin assay results and an antibiotic use guideline with graded recommendations based on four tiers of procalcitonin levels, or the usual-care group. We hypothesized that within 30 days after enrollment the total antibiotic-days would be lower - and the percentage of patients with adverse outcomes would not be more than 4.5 percentage points higher - in the procalcitonin group than in the usual-care group.

RESULTS: A total of 1656 patients were included in the final analysis cohort (826 randomly assigned to the procalcitonin group and 830 to the usual-care group), of whom 782 (47.2%) were hospitalized and 984 (59.4%) received antibiotics within 30 days. The treating clinician received procalcitonin assay results for 792 of 826 patients (95.9%) in the procalcitonin group (median time from sample collection to assay result, 77 minutes) and for 18 of 830 patients (2.2%) in the usual-care group. In both groups, the procalcitonin-level tier was associated with the decision to prescribe antibiotics in the emergency department. There was no significant difference between the procalcitonin group and the usual-care group in antibiotic-days (mean, 4.2 and 4.3 days, respectively; difference, -0.05 day; 95% confidence interval [CI], -0.6 to 0.5; P=0.87) or the proportion of patients with adverse outcomes (11.7% [96 patients] and 13.1% [109 patients]; difference, -1.5 percentage points; 95% CI, -4.6 to 1.7; P<0.001 for noninferiority) within 30 days.

CONCLUSIONS: The provision of procalcitonin assay results, along with instructions on their interpretation, to emergency department and hospital-based clinicians did not result in less use of antibiotics than did usual care among patients with suspected lower respiratory tract infection. (Funded by the National Institute of General Medical Sciences; ProACT ClinicalTrials.gov number, NCT02130986 .).

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Seven versus fourteen Days of Antibiotic Therapy for uncomplicated Gram-negative Bacteremia: a Non-inferiority Randomized Controlled Trial.

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BACKGROUND: Gram-negative bacteremia is a major cause of morbidity and mortality in hospitalized patients. Data to guide the duration of antibiotic therapy are limited.

METHODS: Randomized, multicenter, open-label, non-inferiority trial. Inpatients with Gram-negative bacteremia, afebrile and hemodynamically stable for at least 48 hours, were randomized to receive 7 (intervention) or 14 days (control) of covering antibiotic therapy. Patients with uncontrolled focus of infection were excluded. The primary outcome at 90 days was a composite of all-cause mortality; relapse, suppurative or distant complications; and re-admission or extended hospitalization (>14 days). The non-inferiority margin was set at 10%.

RESULTS: We included 604 patients (306 intervention, 298 control) between January 2013 and August 2017 in three centers in Israel and Italy. The source of the infection was urinary in 411/604 (68%); causative pathogens were mainly Enterobacteriaceae (543/604, 90%). A 7-day difference in the median duration of covering antibiotics was achieved. The primary outcome occurred in 140/306 (45.8%) patients in the 7 days group versus 144/298 (48.3%) in the 14 days group (risk difference [RD] -2.6%, 95% confidence interval [CI] -10.5% to 5.3%). No significant differences were observed in all other outcomes and adverse events, except for a shorter time to return to baseline functional status in the short therapy arm.

CONCLUSIONS: In patients hospitalized with Gram-negative bacteremia achieving clinical stability before day 7, an antibiotic course of 7 days was non-inferior to 14 days. Reducing antibiotic treatment for uncomplicated Gram-negative bacteremia to 7 days is an important antibiotic stewardship intervention. (ClinicalTrials.gov number, NCT01737320).