

LOS 10 HITOS EN ENFERMEDADES INFECCIOSAS

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Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial

Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, Lobo JL, Tomás L, Camino J, Nuñez J, Capelastegui A.

JAMA Intern Med 2016; 176: 1257-1265.

IMPORTANCE: The optimal duration of antibiotic treatment for community-acquired pneumonia (CAP) has not been well established.

OBJECTIVE: To validate Infectious Diseases Society of America/American Thoracic Society guidelines for duration of antibiotic treatment in hospitalized patients with CAP.

DESIGN, SETTING, AND PARTICIPANTS: This study was a multicenter, noninferiority randomized clinical trial performed at 4 teaching hospitals in Spain from January 1, 2012, through August 31, 2013. A total of 312 hospitalized patients diagnosed as having CAP were studied. Data analysis was performed from January 1, 2014, through February 28, 2015.

INTERVENTIONS: Patients were randomized at day 5 to an intervention or control group. Those in the intervention group were treated with antibiotics for a minimum of 5 days, and the antibiotic treatment was stopped at this point if their body temperature was 37.8°C or less for 48 hours and they had no more than 1 CAP-associated sign of clinical instability. Duration of antibiotic treatment in the control group was determined by physicians.

MAIN OUTCOMES AND MEASURES: Clinical success rate at days 10 and 30 since admission and CAP-related symptoms at days 5 and 10 measured with the 18-item CAP symptom questionnaire score range, 0-90; higher scores indicate more severe symptoms.

RESULTS: Of the 312 patients included, 150 and 162 were randomized to the control and intervention groups, respectively. The mean (SD) age of the patients was 66.2 (17.9) years and 64.7 (18.7) years in the control and intervention groups, respectively. There were 95 men (63.3%) and 55 women (36.7%) in the control group and 101 men (62.3%) and 61 women (37.7%) in the intervention group. In the intent-to-treat analysis, clinical success was 48.6% (71 of 150) in the

control group and 56.3% (90 of 162) in the intervention group at day 10 ($P = .18$) and 88.6% (132 of 150) in the control group and 91.9% (147 of 162) in the intervention group at day 30 ($P = .33$). The mean (SD) CAP symptom questionnaire scores were 24.7 (11.4) vs 27.2 (12.5) at day 5 ($P = .10$) and 18.6 (9.0) vs 17.9 (7.6) at day 10 ($P = .69$). In the per-protocol analysis, clinical success was 50.4% (67 of 137) in the control group and 59.7% (86 of 146) in the intervention group at day 10 ($P = .12$) and 92.7% (126 of 137) in the control group and 94.4% (136 of 146) in the intervention group at day 30 ($P = .54$). The mean (SD) CAP symptom questionnaire scores were 24.3 (11.4) vs 26.6 (12.1) at day 5 ($P = .16$) and 18.1 (8.5) vs 17.6 (7.4) at day 10 ($P = .81$).

CONCLUSIONS AND RELEVANCE: The Infectious Diseases Society of America/American Thoracic Society recommendations for duration of antibiotic treatment based on clinical stability criteria can be safely implemented in hospitalized patients with CAP.

TRIAL REGISTRATION: clinicaltrialsregister.eu Identifier: 2011-001067-51.

Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort

Charlier C, Perrodeau E, Leclercq A, Cazenave B, Pilmis B, Henry B, Lopes A, Maury MM, Moura A, Goffinet F, Dieye HB, Thouvenot P, Ungeheuer MN, Tourdjman M, Goulet V, de Valk H, Lortholary O, Ravaud P, Lecuit M, on behalf of the MONALISA study group.

Lancet Infect Dis 2017; 17: 510-519.

BACKGROUND: Listeriosis is a severe foodborne infection and a notifiable disease in France. We did a nationwide prospective study to characterise its clinical features and prognostic factors.

METHODS: MONALISA was a national prospective observational cohort study. We enrolled eligible cases declared to the National Reference Center for Listeria (all microbiologically proven) between Nov 3, 2009, and July 31, 2013, in the context of mandatory reporting. The outcomes were analysis of clinical features, characterisation of Listeria isolates, and determination of predictors of 3-month mortality or persisting impairment using logistic regression. A hierarchical clustering on principal components was also done for neurological and bacteraemic cases. The study is registered at ClinicalTrials.gov, number NCT01520597.

FINDINGS: We enrolled 818 cases from 372 centres, including 107 maternal-neonatal infections, 427 cases of bacteraemia, and 252 cases of neurolisteriosis. Only five (5%) of 107 pregnant women had an uneventful outcome. 26 (24%) of 107 mothers experienced fetal loss, but never after 29 weeks of gestation or beyond 2 days of admission to hospital. Neurolisteriosis presented as meningoencephalitis in 212 (84%) of 252 patients; brainstem involvement was only reported in

42 (17%) of 252 patients. 3-month mortality was higher for bacteraemia than neurolisteriosis (hazard ratio [HR] 0.54 [95% CI 0.41-0.69], $p < 0.0001$). For both bacteraemia and neurolisteriosis, the strongest mortality predictors were ongoing cancer (odds ratio [OR] 5.19 [95% CI 3.01-8.95], $p < 0.0001$), multi-organ failure (OR 7.98 [4.32-14.72], $p < 0.0001$), aggravation of any pre-existing organ dysfunction (OR 4.35 [2.79-6.81], $p < 0.0001$), and monocytopenia (OR 3.70 [1.82-7.49], $p = 0.0003$). Neurolisteriosis mortality was higher in blood-culture positive patients (OR 3.67 [1.60-8.40], $p = 0.002$) or those receiving adjunctive dexamethasone (OR 4.58 [1.50-13.98], $p = 0.008$).

INTERPRETATION: The severity of listeriosis is higher than reported elsewhere. We found evidence of a significantly reduced survival in patients with neurolisteriosis treated with adjunctive dexamethasone, and also determined the time window for fetal losses. MONALISA provides important new data to improve management and predict outcome in listeriosis.

Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis With Vasopressor-Dependent Shock: A Propensity Score-Matched Analysis From 130 US Hospitals

Kadri SS, Swihart BJ, Bonne SL, Hohmann SF, Hennessy LV, Louras P, Evans HL, Rhee C, Suffredini AF, Hooper DC, Follmann DA, Bulger EM, Danner RL.

Clin Infect Dis 2017; 64: 877-885.

BACKGROUND: Shock frequently complicates necrotizing fasciitis (NF) caused by group A Streptococcus (GAS) or Staphylococcus aureus. Intravenous immunoglobulin (IVIG) is sometimes administered for presumptive toxic shock syndrome (TSS), but its frequency of use and efficacy are unclear.

METHODS: Adult patients with NF and vasopressor-dependent shock undergoing surgical debridement from 2010 to 2014 were identified at 130 US hospitals. IVIG cases were propensity-matched and risk-adjusted. The primary outcome was in-hospital mortality and the secondary outcome was median length of stay (LOS).

RESULTS: Of 4127 cases of debrided NF with shock at 121 centers, only 164 patients (4%) at 61 centers received IVIG. IVIG subjects were younger with lower comorbidity indices, but higher illness severity. Clindamycin and vasopressor intensity were higher among IVIG cases, as was coding for TSS and GAS. In-hospital mortality did not differ between matched IVIG and non-IVIG groups (crude mortality, 27.3% vs 23.6%; adjusted odds ratio, 1.00 [95% confidence interval, .55-1.83]; $P = .99$). Early IVIG (≤ 2 days) did not alter this effect ($P = .99$). Among patients coded for TSS, GAS, and/or *S. aureus*, IVIG use was still unusual (59/868 [6.8%]) and lacked benefit ($P = .63$).

Median LOS was similar between IVIG and non-IVIG groups (26 [13-49] vs 26 [11-43]; $P = .84$). Positive predictive values for identifying true NF and debridement among IVIG cases using our algorithms were 97% and 89%, respectively, based on records review at 4 hospitals.

CONCLUSIONS: Adjunctive IVIG was administered infrequently in NF with shock and had no apparent impact on mortality or hospital LOS beyond that achieved with debridement and antibiotics.

Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial

Weber WP, Mujagic E, Zwahlen M, Bundi M, Hoffmann H, Soysal SD, Kraljević M, Delko T, von Strauss M, Iselin L, Da Silva RX, Zeindler J, Rosenthal R, Misteli H, Kindler C, Müller P, Saccilotto R, Lugli AK, Kaufmann M, Gürke L, Oertli D, Bucheli-Laffer E, Landin J, Widmer AF, Fux CA, Marti WR. *Lancet Infect Dis* 2017; April 3 (Online first)

BACKGROUND: Based on observational studies, administration of surgical antimicrobial prophylaxis (SAP) for the prevention of surgical site infection (SSI) is recommended within 60 min before incision. However, the precise optimum timing is unknown. This trial compared early versus late administration of SAP before surgery.

METHODS: In this phase 3 randomised controlled superiority trial, we included general surgery adult inpatients (age ≥ 18 years) at two Swiss hospitals in Basel and Aarau. Patients were randomised centrally and stratified by hospital according to a pre-existing computer-generated list in a 1:1 ratio to receive SAP early in the anaesthesia room or late in the operating room. Patients and the outcome assessment team were blinded to group assignment. SAP consisted of single-shot, intravenous infusion of 1.5 g of cefuroxime, a commonly used cephalosporin with a short half-life, over 2-5 min (combined with 500 mg metronidazole in colorectal surgery). The primary endpoint was the occurrence of SSI within 30 days of surgery. The main analyses were by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT01790529.

FINDINGS: Between Feb 21, 2013, and Aug 3, 2015, 5580 patients were randomly assigned to receive SAP early (2798 patients) or late (2782 patients). 5175 patients (2589 in the early group and 2586 in the late group) were analysed. Median administration time was 42 min before incision in the early group (IQR 30-55) and 16 min before incision in the late group (IQR 10-25). Inpatient follow-up rate was 100% (5175 of 5175 patients); outpatient 30-day follow-up rate was 88.8% (4596 of 5175), with an overall SSI rate of 5.1% (234 of 4596). Early administration of SAP

did not significantly reduce the risk of SSI compared with late administration (odds ratio 0.93, 95% CI 0.72-1.21, $p=0.601$).

INTERPRETATION: Our findings do not support any narrowing of the 60-min window for the administration of a cephalosporin with a short half-life, thereby obviating the need for increasingly challenging SAP timing recommendations.

FUNDING: Swiss National Science Foundation, Hospital of Aarau, University of Basel, Gottfried und Julia Bangerter-Rhyner Foundation, Hippocrate Foundation, and Nora van Meeuwen-Häfliger Foundation.

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Paño-Pardo JR, Venditti M, Tumbarello M, Daikos G, Cantón R, Doi Y, Tuon FF, Karaiskos I, Pérez-Nadales E, Schwaber MJ, Azap ÖK, Souli M, Roilides E, Pournaras S, Akova M, Pérez F, Bermejo J, Oliver A, Almela M, Lowman W, Almirante B, Bonomo RA, Carmeli Y, Paterson DL, Pascual A, Rodríguez-Baño J; REIPI/ESGBIS/INCREMENT Investigators.

Lancet Infect Dis 2017; April 22 (Online first)

BACKGROUND: The best available treatment against carbapenemase-producing Enterobacteriaceae (CPE) is unknown. The objective of this study was to investigate the effect of appropriate therapy and of appropriate combination therapy on mortality of patients with bloodstream infections (BSIs) due to CPE.

METHODS: In this retrospective cohort study, we included patients with clinically significant monomicrobial BSIs due to CPE from the INCREMENT cohort, recruited from 26 tertiary hospitals in ten countries. Exclusion criteria were missing key data, death sooner than 24 h after the index date, therapy with an active antibiotic for at least 2 days when blood cultures were taken, and subsequent episodes in the same patient. We compared 30 day all-cause mortality between patients receiving appropriate (including an active drug against the blood isolate and started in the first 5 days after infection) or inappropriate therapy, and for patients receiving appropriate therapy, between those receiving active monotherapy (only one active drug) or combination therapy (more than one). We used a propensity score for receiving combination therapy and a validated mortality score (INCREMENT-CPE mortality score) to control for confounders in Cox

regression analyses. We stratified analyses of combination therapy according to INCREMENT-CPE mortality score (0-7 [low mortality score] vs 8-15 [high mortality score]). INCREMENT is registered with ClinicalTrials.gov, number NCT01764490.

FINDINGS: Between Jan 1, 2004, and Dec 31, 2013, 480 patients with BSIs due to CPE were enrolled in the INCREMENT cohort, of whom we included 437 (91%) in this study. 343 (78%) patients received appropriate therapy compared with 94 (22%) who received inappropriate therapy. The most frequent organism was *Klebsiella pneumoniae* (375 [86%] of 437; 291 [85%] of 343 patients receiving appropriate therapy vs 84 [89%] of 94 receiving inappropriate therapy) and the most frequent carbapenemase was *K pneumoniae* carbapenemase (329 [75%]; 253 [74%] vs 76 [81%]). Appropriate therapy was associated with lower mortality than was inappropriate therapy (132 [38.5%] of 343 patients died vs 57 [60.6%] of 94; absolute difference 22.1% [95% CI 11.0-33.3]; adjusted hazard ratio [HR] 0.45 [95% CI 0.33-0.62]; $p < 0.0001$). Among those receiving appropriate therapy, 135 (39%) received combination therapy and 208 (61%) received monotherapy. Overall mortality was not different between those receiving combination therapy or monotherapy (47 [35%] of 135 vs 85 [41%] of 208; adjusted HR 1.63 [95% CI 0.67-3.91]; $p = 0.28$). However, combination therapy was associated with lower mortality than was monotherapy in the high-mortality-score stratum (30 [48%] of 63 vs 64 [62%] of 103; adjusted HR 0.56 [0.34-0.91]; $p = 0.02$), but not in the low-mortality-score stratum (17 [24%] of 72 vs 21 [20%] of 105; adjusted odds ratio 1.21 [0.56-2.56]; $p = 0.62$).

INTERPRETATION: Appropriate therapy was associated with a protective effect on mortality among patients with BSIs due to CPE. Combination therapy was associated with improved survival only in patients with a high mortality score. Patients with BSIs due to CPE should receive active therapy as soon as they are diagnosed, and monotherapy should be considered for those in the low-mortality-score stratum.

FUNDING: Spanish Network for Research in Infectious Diseases, European Development Regional Fund, Instituto de Salud Carlos III, and Innovative Medicines Initiative.

Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection

Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, Cornely OA, Rahav G, Bouza E, Lee C, Jenkin G, Jensen W, Kim YS, Yoshida J, Gabryelski L, Pedley A, Eves K, Tipping R, Guris D, Kartsonis N, Dorr MB, for the MODIFY I and MODIFY II Investigators.

N Engl J Med 2017; 376: 305-317.

BACKGROUND: *Clostridium difficile* is the most common cause of infectious diarrhea in hospitalized patients. Recurrences are common after antibiotic therapy. Actoxumab and bezlotoxumab are human monoclonal antibodies against *C. difficile* toxins A and B, respectively.

METHODS: We conducted two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection. Participants received an infusion of bezlotoxumab (10 mg per kilogram of body weight), actoxumab plus bezlotoxumab (10 mg per kilogram each), or placebo; actoxumab alone (10 mg per kilogram) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population.

RESULTS: In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, -10.1 percentage points; 95% confidence interval [CI], -15.9 to -4.3; $P < 0.001$; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -9.9 percentage points; 95% CI, -15.5 to -4.3; $P < 0.001$) and was significantly lower with actoxumab plus bezlotoxumab than with placebo (MODIFY I: 16% [61 of 383] vs. 28% [109 of 395]; adjusted difference, -11.6 percentage points; 95% CI, -17.4 to -5.9; $P < 0.001$; MODIFY II: 15% [58 of 390] vs. 26% [97 of 378]; adjusted difference, -10.7 percentage points; 95% CI, -16.4 to -5.1; $P < 0.001$). In prespecified subgroup analyses (combined data set), rates of recurrent infection were lower in both groups that received bezlotoxumab than in the placebo group in subpopulations at high risk for recurrent infection or for an adverse outcome. The rates of initial clinical cure were 80% with bezlotoxumab alone, 73% with actoxumab plus bezlotoxumab, and 80% with placebo; the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively. The rates of adverse events were similar among these groups; the most common events were diarrhea and nausea.

CONCLUSIONS: Among participants receiving antibiotic treatment for primary or recurrent *C. difficile* infection, bezlotoxumab was associated with a substantially lower rate of recurrent infection than placebo and had a safety profile similar to that of placebo. The addition of actoxumab did not improve efficacy. (Funded by Merck; MODIFY I and MODIFY II ClinicalTrials.gov numbers, NCT01241552 and NCT01513239).

Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and Clostridium difficile (the Benefits of Enhanced Terminal Room Disinfection study): a cluster-randomised, multicentre, crossover study

Anderson DJ, Chen LF, Weber DJ, Moehring RW, Lewis SS, Triplett PF, Blocker M, Becherer P, Schwab JC, Knelson LP, Lokhnygina Y, Rutala WA, Kanamori H, Gergen MF, Sexton DJ; CDC Prevention Epicenters Program.

Lancet 2017; 389: 805-814.

BACKGROUND: Patients admitted to hospital can acquire multidrug-resistant organisms and Clostridium difficile from inadequately disinfected environmental surfaces. We determined the effect of three enhanced strategies for terminal room disinfection (disinfection of a room between occupying patients) on acquisition and infection due to meticillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, C difficile, and multidrug-resistant Acinetobacter.

METHODS: We did a pragmatic, cluster-randomised, crossover trial at nine hospitals in the southeastern USA. Rooms from which a patient with infection or colonisation with a target organism was discharged were terminally disinfected with one of four strategies: reference (quaternary ammonium disinfectant except for C difficile, for which bleach was used); UV (quaternary ammonium disinfectant and disinfecting ultraviolet [UV-C] light except for C difficile, for which bleach and UV-C were used); bleach; and bleach and UV-C. The next patient admitted to the targeted room was considered exposed. Every strategy was used at each hospital in four consecutive 7-month periods. We randomly assigned the sequence of strategies for each hospital (1:1:1:1). The primary outcomes were the incidence of infection or colonisation with all target organisms among exposed patients and the incidence of C difficile infection among exposed patients in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01579370.

FINDINGS: 31 226 patients were exposed; 21 395 (69%) met all inclusion criteria, including 4916 in the reference group, 5178 in the UV group, 5438 in the bleach group, and 5863 in the bleach and UV group. 115 patients had the primary outcome during 22 426 exposure days in the reference group (51.3 per 10 000 exposure days). The incidence of target organisms among exposed patients was significantly lower after adding UV to standard cleaning strategies (n=76; 33.9 cases per 10 000 exposure days; relative risk [RR] 0.70, 95% CI 0.50-0.98; p=0.036). The primary outcome was not statistically lower with bleach (n=101; 41.6 cases per 10 000 exposure days; RR

0.85, 95% CI 0.69-1.04; $p=0.116$), or bleach and UV ($n=131$; 45.6 cases per 10 000 exposure days; RR 0.91, 95% CI 0.76-1.09; $p=0.303$) among exposed patients. Similarly, the incidence of *C difficile* infection among exposed patients was not changed after adding UV to cleaning with bleach ($n=38$ vs 36; 30.4 cases vs 31.6 cases per 10 000 exposure days; RR 1.0, 95% CI 0.57-1.75; $p=0.997$).

INTERPRETATION: A contaminated health-care environment is an important source for acquisition of pathogens; enhanced terminal room disinfection decreases this risk.

FUNDING: US Centers for Disease Control and Prevention.

Insidious risk of severe *Mycobacterium chimaera* infection in cardiac surgery patients

Chand M, Lamagni T, Kranzer K, Hedge J, Moore G, Parks S, Collins S, Del Ojo Elias C, Ahmed N, Brown T, Smith EG, Hoffman P, Kirwan P, Mason B, Smith-Palmer A, Veal P, Lalor MK, Bennett A, Walker J, Yeap A, Isidro Carrion Martin A, Dolan G, Bhatt S, Skingsley A, Charlett A, Pearce D, Russell K, Kendall S, Klein AA, Robins S, Schelenz S, Newsholme W, Thomas S, Collyns T, Davies E, McMenamin J, Doherty L, Peto TE, Crook D, Zambon M, Phin N.

Clin Infect Dis 2017; 64: 335-342.

BACKGROUND: An urgent UK investigation was launched to assess risk of invasive *Mycobacterium chimaera* infection in cardiothoracic surgery and a possible association with cardiopulmonary bypass heater-cooler units following alerts in Switzerland and The Netherlands.

METHODS: Parallel investigations were pursued: (1) identification of cardiopulmonary bypass-associated *M. chimaera* infection through national laboratory and hospital admissions data linkage; (2) cohort study to assess patient risk; (3) microbiological and aerobiological investigations of heater-coolers in situ and under controlled laboratory conditions; and (4) whole-genome sequencing of clinical and environmental isolates.

RESULTS: Eighteen probable cases of cardiopulmonary bypass-associated *M. chimaera* infection were identified; all except one occurred in adults. Patients had undergone valve replacement in 11 hospitals between 2007 and 2015, a median of 19 months prior to onset (range, 3 months to 5 years). Risk to patients increased after 2010 from <0.2 to 1.65 per 10000 person-years in 2013, a 9-fold rise for infections within 2 years of surgery (rate ratio, 9.08 [95% CI, 1.81-87.76]). Endocarditis was the most common presentation ($n = 11$). To date, 9 patients have died. Investigations identified aerosol release through breaches in heater-cooler tanks. *Mycobacterium chimaera* and other pathogens were recovered from water and air samples. Phylogenetic analysis found close clustering of strains from probable cases.

CONCLUSIONS: We identified low but escalating risk of severe *M. chimaera* infection associated with heater-coolers with cases in a quarter of cardiothoracic centers. Our investigations strengthen etiological evidence for the role of heater-coolers in transmission and raise the possibility of an ongoing, international point-source outbreak. Active management of heater-coolers and heightened clinical awareness are imperative given the consequences of infection.

Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses

Lockhart SR, Etienne KA, Vallabhanesi S, Farooqi J, Chowdhary A, Govender NP, Colombo AL, Calvo B, Cuomo CA, Desjardins CA, Berkow EL, Castanheira M, Magobo RE, Jabeen K, Asghar RJ, Meis JF, Jackson B, Chiller T, Litvintseva AP.

Clin Infect Dis 2017; 64: 134-140.

BACKGROUND: *Candida auris*, a multidrug-resistant yeast that causes invasive infections, was first described in 2009 in Japan and has since been reported from several countries.

METHODS: To understand the global emergence and epidemiology of *C. auris*, we obtained isolates from 54 patients with *C. auris* infection from Pakistan, India, South Africa, and Venezuela during 2012-2015 and the type specimen from Japan. Patient information was available for 41 of the isolates. We conducted antifungal susceptibility testing and whole-genome sequencing (WGS).

RESULTS: Available clinical information revealed that 41% of patients had diabetes mellitus, 51% had undergone recent surgery, 73% had a central venous catheter, and 41% were receiving systemic antifungal therapy when *C. auris* was isolated. The median time from admission to infection was 19 days (interquartile range, 9-36 days), 61% of patients had bloodstream infection, and 59% died. Using stringent break points, 93% of isolates were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% were resistant to 2 antifungal classes and 4% were resistant to 3 classes. WGS demonstrated that isolates were grouped into unique clades by geographic region. Clades were separated by thousands of single-nucleotide polymorphisms, but within each clade isolates were clonal. Different mutations in *ERG11* were associated with azole resistance in each geographic clade.

CONCLUSIONS: *C. auris* is an emerging healthcare-associated pathogen associated with high mortality. Treatment options are limited, due to antifungal resistance. WGS analysis suggests nearly simultaneous, and recent, independent emergence of different clonal populations on 3

continents. Risk factors and transmission mechanisms need to be elucidated to guide control measures.

Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure: The EMPIRICUS Randomized Clinical Trial

Timsit JF1, Azoulay E2, Schwebel C3, Charles PE4, Cornet M5, Souweine B6, Klouche K7, Jaber S8, Trouillet JL9, Bruneel F10, Argaud L11, Cousson J12, Meziani F13, Gruson D14, Paris A15, Darmon M16, Garrouste-Orgeas M17, Navellou JC18, Fouchier A19, Allaouchiche B20, Das V21, Gangneux JP22, Ruckly S23, Maubon D5, Jullien V24, Wolff M1; EMPIRICUS Trial Group.

JAMA 2016; 316: 1555-1564.

IMPORTANCE: Although frequently used in treating intensive care unit (ICU) patients with sepsis, empirical antifungal therapy, initiated for suspected fungal infection, has not been shown to improve outcome.

OBJECTIVE: To determine whether empirical micafungin reduces invasive fungal infection (IFI)-free survival at day 28.

DESIGN, SETTING, AND PARTICIPANTS: Multicenter double-blind placebo-controlled study of 260 nonneutropenic, nontransplanted, critically ill patients with ICU-acquired sepsis, multiple Candida colonization, multiple organ failure, exposed to broad-spectrum antibacterial agents, and enrolled between July 2012 and February 2015 in 19 French ICUs.

INTERVENTIONS: Empirical treatment with micafungin (100 mg, once daily, for 14 days) (n = 131) vs placebo (n = 129).

MAIN OUTCOMES AND MEASURES: The primary end point was survival without proven IFI 28 days after randomization. Key secondary end points included new proven fungal infections, survival at day 28 and day 90, organ failure, serum (1-3)- β -D-glucan level evolution, and incidence of ventilator-associated bacterial pneumonia.

RESULTS: Among 260 patients (mean age 63 years; 91 [35%] women), 251 (128, micafungin group; 123, placebo group) were included in the modified intent-to-treat analysis. Median values were 8 for Sequential Organ Failure Assessment (SOFA) score, 3 for number of Candida-colonized sites, and 99 pg/mL for level of (1-3)- β -D-glucan. On day 28, there were 82 (68%) patients in the micafungin group vs 79 (60.2%) in the placebo group who were alive and IFI free (hazard ratio [HR], 1.35 [95% CI, 0.87-2.08]). Results were similar among patients with a (1-3)- β -D-glucan level

of greater than 80 pg/mL (n = 175; HR, 1.41 [95% CI, 0.85-2.33]). Day-28 IFI-free survival in patients with a high SOFA score (>8) was not significantly different when compared between the micafungin vs placebo groups (HR, 1.69 [95% CI, 0.96-2.94]). Use of empirical micafungin decreased the rate of new invasive fungal infection in 4 of 128 patients (3%) in the micafungin group vs placebo (15/123 patients [12%]) (P = .008).

CONCLUSIONS AND RELEVANCE: Among nonneutropenic critically ill patients with ICU-acquired sepsis, *Candida* species colonization at multiple sites, and multiple organ failure, empirical treatment with micafungin, compared with placebo, did not increase fungal infection-free survival at day 28.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01773876.