Simplified control measures for ESBL-producing Enterobacteriacae?

Published Online
August 23, 2019
http://dx.doi.org/10.1016/
S1473-3099(19)30412-8
See Articles page 1069

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriacae have disseminated worldwide, with very high prevalence in countries of low and middle income[1] and a roughly 10% prevalence in the community and at hospital admission in high-income countries.[2,3] Infections caused by ESBL-producing Enterobacteriacae are associated with higher mortality and morbidity than are infections caused by β-lactamase-susceptible Enterobacteriacae. When compared with other multidrug-resistant organisms, ESBL-producing Enterobacteriacae have the highest prevalence and are an ever-increasing burden in European hospitals.[4]

How to control the spread of ESBL-producing Enterobacteriacae has been debated for years.[5] Schematically, several experts have argued for a horizontal approach, based on high compliance with hand hygiene and improving environmental cleaning. However, most current recommendations still push for a vertical approach, based on active surveillance culture and contact precautions for colonised patients.[6] Contact precautions include wearing gowns and gloves when in direct contact with the patient and are usually associated with placement in a single-bed room.

Placement of patients with ESBL-producing Enterobacteriaceae in single-bed rooms is also a matter of debate, considering the risk for transmission from a wardmate or directly from a contaminated environment. In *The Lancet Infectious Diseases*, Marjolein Kluytmans-van den Bergh and colleagues report findings of a cluster-randomised non-inferiority study at 16 hospitals in the Netherlands.[7] They showed that, for patients with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample, an isolation strategy of contact precautions in a multiple-bed room was non-inferior to a strategy of contact precautions in a single-bed room: of 275 index patients assigned to a single-bed room strategy, there were 11 (4%) cases of ESBL-producing Enterobacteriaceae transmitted to at least one wardmate, compared with 14 (7%) cases among 188 index patients assigned to a multiple-bed room strategy (crude risk difference 3·4%, 90% CI −0·3 to 7·1). The study had high enrolment of eligible patients and the authors did genomic analysis to assess transmission. The results were robust to sensitivity analyses, including duration of standard precautions before implementing contact precautions and type of ESBL-producing Enterobacteriacae. This study is the first randomised trial to answer the question about single-bed versus multiple-bed rooms, which previously has not been tackled adequately.[8]

Despite a pragmatic and well-designed study, several limitations should be noted. First, Kluytmans-van den Bergh and colleagues did not assess compliance with hand hygiene and contact precautions. Since compliance is an intermediate process stage between planned measures and their actual effect, we miss the effect of single-bed rooms on compliance with hand hygiene. Second, screening of wardmates occurred within 7 days after known exposure, which could miss positive yet still undetectable rectal colonisation because of low rectal concentration of ESBL-producing Enterobacteriacae. Third, 37 (12%) of 312 patients allocated to the single-bed room strategy and 116 (38%) of 304 patients assigned to the multiple-bed room strategy could not be adequately placed in the planned room, and this non-adherence could have affected the results. The non-inferiority margin was set at 10%, which is large with respect to the 5% observed frequency of transmission in the single-bed room. Non-inferiority would have held true with margins of at least 8% and 5% in per-protocol and intention-to-treat analyses, respectively, but these margins are still large.

These results might be generalisable to health-care facilities with high hand hygiene compliance, a high quality of environmental cleaning, and a low prevalence of ESBL-producers that are not *Escherichia coli*, such as facilities in the Netherlands. Similar to findings by others,[9] Kluytmans-van den Bergh and colleagues noted a higher risk of transmission from patients with ESBL-producing Enterobacteriaceae that were not *E coli*. Results could, therefore, be less pronounced in other species of ESBL-producing Enterobacteriacae, because environmental contamination is more frequently associated with non-*E coli* species and might have a role as a secondary reservoir for cross-transmission.[10]

The study findings accord with European guidelines,[11] with a balanced recommendation for putting patients with ESBL-producing non-*E coli* infections or patients from an epidemic outbreak in single-bed rooms while also enforcing contact precautions. On the other hand, in an endemic situation, with most cases being ESBL-producing *E coli* infections, standard precautions might be enough, with no need for a single-bed room.[11]

The study by Kluytmans-van den Bergh and colleagues did not address the question of the role of standard precautions compared with contact precautions for controlling the spread of ESBL-producing Enterobacteriacae and whether the combination of contact precautions and placement in a single-bed room could be synergistic. Findings of a cluster-randomised study[3] showed that contact precautions were not superior to standard precautions for control of the spread of ESBL-producing Enterobacteriacae, confirming results of several observational, cohort, and before-and-after studies.[12] The fact that only 5% of ESBL-colonised wardmates later had a positive clinical culture in the study by Kluytmans-van den Bergh and colleagues further supports a horizontal approach, with high adherence to hand hygiene required for all patients, irrespective of ESBL-producing Enterobacteriacae status.

Among multidrug-resistant organisms, including meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* spp, and emerging Gram-negative bacilli resistant to carbapenems, ESBL-producing Enterobacteriacae have not received enough attention. This study comes at the perfect time in view of the massive and widespread burden of these microorganisms.

*Jean-Christophe Lucet, Jean-Ralph Zahar
Université de Paris, Infection, Antimicrobiens, Modélisation, Évolution (IAME), Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France (J-CL, J-RZ); *Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Bichat, Infection Control Unit, F-75018 Paris, France (J-CL); and AP-HP, Hôpital Avicenne, Infection Control Unit, Bobigny, France (J-RZ)
jean-christophe.lucet@bch.aphp.fr

J-CL and J-RZ declare no competing interests.

1 Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin Microbiol Rev* 2013; **26:** 744–58.
2 Otter JA, Natale A, Batra R, et al. Individual- and community-level risk factors for ESBL Enterobacteriaceae colonization identified by universal admission screening in London. *Clin Microbiol Infect* 2019; published online March 6. DOI:10.1016/j.cmi.2019.02.026.
3 Maechler F, Schwab F, Hansen S, et al. Contact precautions versus standard precautions for carriers of ESBL-producing Enterobacteriaceae (ESBL-E) in non-ICUs with an active surveillance screening: a cluster-randomized cross-over trial. Presented at the 28th European Congress of Clinical Microbiology and Infectious Diseases; Madrid, Spain; April 21–24, 2018. Abstract O1130. https://www.escmid.org/escmid_publications/escmid_elibrary/material/?mid=64008 (accessed July 18, 2019).
4 Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; **19:** 56–66.
5 Tschudin-Sutter S, Lucet JC, Mutters NT, Tacconelli E, Zahar JR, Harbarth S. Contact precautions for preventing nosocomial transmission of extended-spectrum β lactamase-producing *Escherichia coli*: a point/counterpoint review. *Clin Infect Dis* 2017; **65:** 342–47.
6 Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control* 2007; **35:** S65–164.
7 Kluytmans-van den Bergh MFQ, Bruijning-Verhagen PCJ, Vandenbroucke-Grauls CMJE, et al. Contact precautions in single-bed or multiple-bed rooms for patients with extended-spectrum β-lactamase-producing Enterobacteriaceae in Dutch hospitals: a cluster-randomised, crossover, non-inferiority study. *Lancet Infect Dis* 2019; published online Aug 23. http://dx.doi.org/10.1016/S1473-3099(19)30262-2.
8 Stiller A, Salm F, Bischoff P, Gastmeier P. Relationship between hospital ward design and healthcare-associated infection rates: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 2016; **5:** 51.
9 Gurieva T, Dautzenberg MJD, Gniadkowski M, Derde LPG, Bonten MJM, Bootsma MCJ. The transmissibility of antibiotic-resistant Enterobacteriaceae in intensive care units. *Clin Infect Dis* 2018; **66:** 489–93.
10 Mitchell BG, Dancer SJ, Anderson M, Dehn E. Risk of organism acquisition from prior room occupants: a systematic review and meta-analysis. *J Hosp Infect* 2015; **91:** 211–17.
11 Tacconelli E, Cataldo MA, Dancer SJ, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. *Clin Microbiol Infect* 2014; **20:** 1–55.
12 Tschudin-Sutter S, Frei R, Schwahn F, et al. Prospective validation of cessation of contact precautions for extended-spectrum β-lactamase-producing *Escherichia coli*. *Emerg Infect Dis* 2016; **22:** 1094–97.

Enriching the antibiotic armamentarium for acute bacterial skin and skin structure infections

Omadacycline is a newly developed, once-daily, oral and intravenous aminomethylcycline with a broad spectrum of activity.[1] In 2018, the US Food & Drug Administration (FDA) approved omadacycline for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia on the basis of the results of two phase 3 randomised controlled trials (RCTs).[2,3]

To date, omadacycline has been shown to be non-inferior to linezolid in one RCT investigating an

Published **Online** August 29, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30404-9

See **Articles** page 1080