EClinicalMedicine 6 (2018) 3–4

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

EClinicalMedicine
Published by THE LANCET

Commentary

Control of Carbapenemase-producing Enterobacteriaceae: Beyond the Hospital

Vincent C.C. Cheng [a,b], Shuk-Ching Wong [b], Sally C.Y. Wong [a], Pak-Leung Ho [c], Kwok-Yung Yuen [c,*]

[a] Department of Microbiology, Queen Mary Hospital, Hong Kong Special Administrative Region, China
[b] Infection Control Team, Queen Mary Hospital, Hong Kong West Cluster, Hong Kong Special Administrative Region, China
[c] Department of Microbiology, The University of Hong Kong, Hong Kong Special Administrative Region, China

ARTICLE INFO

Article history:
Received 21 December 2018
Accepted 21 December 2018
Available online 7 January 2019

Carbapenem-resistant Enterobacteriaceae (CRE) are among the most worrying multidrug-resistant Gram-negative organisms that emerge as an increasingly serious public health threat. The presence of plasmid-mediated carbapenemase genes in the environment, companion and food animals enables them to act as potential reservoirs leading to community acquisition of carbapenemase-producing Enterobacteriaceae (CPE) [1]. A person may start as an asymptomatic CPE carrier with low bacterial load in the gastrointestinal tract, but the bacterial load increases with the use of broad-spectrum antimicrobial agents, especially during hospitalization [2]. Consequently, healthcare facilities are notorious epidemic centers for CPE transmissions, particularly in settings where hand hygiene and environmental hygiene are suboptimal due to low staff to patient ratio. Nosocomial outbreaks of CPE are frequently reported in clinical units and even at hospital level, posing a great challenge to infection control professionals [3].

Recognizing the need for controlling the spread of CPE in both community and healthcare settings, Shen Z et al. conducted a cross-sectional observational study to understand the prevalence of fecal carriage of CRE and CPE, with a particular focus on *E. coli*, among healthy volunteers in 19 provinces across China [4]. They found that the prevalence of CRE and CPE was 2.4% (92/non-duplicated 3859 stool specimens) and 1.1% (43/3859) respectively. The prevalence of CRE in the community was comparable to the corresponding figures in the hospitals, where the rate of CRE isolated in clinical specimens of *E. coli* was around 0.6–3.6%, as illustrated in the China Antimicrobial Resistance Surveillance Report, which is a nationwide survey with specimens collected from hospitals located in 25 provinces and municipalities in China [5]. In fact, the burden of asymptomatic gastrointestinal colonization of CRE and CPE might have been underestimated as the recruited subjects had not received antimicrobial agents 3 months prior to the collection of fecal specimens.

Rapid dissemination of plasmid IncX3 carrying the carbapenemase gene, bla_{NDM-5}, among *E. coli* isolates in healthy volunteers, along with the identification of bla_{NDM-5} in poultry opens a new horizon for the investigation of transmission dynamics of antimicrobial resistance. The extensive spread of bla_{NDM} in China is strongly linked to this epidemic plasmid which we first described in 2012 [6,7]. We believe that the global dissemination of CTX-M type extended-spectrum beta-lactamase (ESBL) foretells the future of bla_{NDM} in the next 5 to 10 years, which will most likely spread across the globe and render treatment by carbapenem futile.

In this study, co-existence of bla_{NDM-5} and *mcr-1* (plasmid-mediated colistin resistance) in 0.36% (14/3859) of healthy volunteers is a new but not unexpected finding. In fact, *mcr-1* carriage in *E. coli* isolates has been shown in 14.9% (78/523 samples) of raw meat and 21% (166/804) food animals, as well as 1% (16/1322 samples) from hospitalized patients with infection in China [8]. These carbapenem- and colistin-resistant *E. coli* will become nightmares for patients and doctors. Epidemiological analysis to understand risk factors for community acquisition of CPE and plasmid-mediated colistin-resistant Enterobacteriaceae is urgently warranted. Without the understanding of risk factors among silent CPE carriers in the community, universal admission screening or admission screening in high-risk clinical units such as transplant, oncology centers, or intensive care units, may be a potential option. These patients with newly diagnosed CPE upon admission should be placed in a single room with strict contact precautions, with particular emphasis on directly observed hand hygiene [9]. Otherwise, the risk of nosocomial transmission of CPE may not be minimized.

Dissemination of CPE as well as plasmid-mediated colistin-resistant Enterobacteriaceae has evidently spread beyond hospitals. An antimicrobial stewardship program in the healthcare setting alone is grossly insufficient in the grand scheme of things. Antimicrobial use must be tightly regulated to eliminate such selective pressure, including the illegalization of antimicrobials as growth promoters in animal feeds, and

DOI of original article: https://doi.org/10.1016/j.eclinm.2018.11.003.
* Corresponding author.
E-mail address: kyyuen@hku.hk (K.-Y. Yuen).

https://doi.org/10.1016/j.eclinm.2018.12.008

the regulation of antimicrobial use in veterinary practice in addition to human medicine [10].

Key factors that contribute to community transmission are inadequate hygiene (farms, food processing, kitchen, toilet, hand washing), waste disposal and antibiotic overuse. In terms of treatment, while New Delhi metallo-beta-lactamase (NDM) was first identified 10 years ago, little progress has been made in the antibiotic pipeline. All the new beta-lactamase inhibitors (relebactam, avibactam, vaborbactam) are ineffective against NDM leaving us few or no effective options to tackle infections caused by these organisms. This is why a worldwide orchestrated effort is desperately needed for the control of CPE, and understanding the prevalence of CPE in the community is definitely a start.

References

[1] Woodford N, Wareham DW, Guerra B, Teale C. Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making? J Antimicrob Chemother Feb 2014;69(2):287–91.
[2] Cheng VC, Chan JF, Wong SC, Chen JH, Tai JW, Yan MK, et al. Proactive infection control measures to prevent nosocomial transmission of carbapenem-resistant Enterobacteriaceae in a non-endemic area. Chin Med J (Engl) Dec 2013;126(23):4504–9.
[3] French CE, Coope C, Conway L, Higgins JP, McCulloch J, Okoli G, et al. Control of carbapenemase-producing Enterobacteriaceae outbreaks in acute settings: an evidence review. J Hosp Infect Jan 2017;95(1):3–45.
[4] Shen Z, Hu Y, Sun Q, Hu F, Zhou H, Shu L, et al. Emerging carriage of NDM-5 and MCR-1 in *Escherichia coli* from healthy people in multiple regions in China: a cross sectional observational study. EClinicalMedicine 2019. https://doi.org/10.1016/j.eclinm.2018.11.003.
[5] Zhang R, Liu L, Zhou H, Chan EW, Li J, Fang Y, et al. Nationwide surveillance of clinical carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EBioMedicine May 2017;19:98–106.
[6] Ho PL, Li Z, Lo WU, Cheung YY, Lin CH, Sham PC, et al. Identification and characterization of a novel incompatibility group X3 plasmid carrying bla NDM-1 in Enterobacteriaceae isolates with epidemiological links to multiple geographical areas in China. Emerg Microbes Infect Nov 2012;1(11):e39.
[7] Ho PL, Wang Y, Liu MC, Lai EL, Law PY, Cao H, et al. IncX3 epidemic plasmid carrying blaNDM-5 in *Escherichia coli* from swine in multiple geographic areas in China. Antimicrob Agents Chemother Feb 23 2018;62(3). https://doi.org/10.1128/AAC.02295-17 [pii: e02295-17].
[8] Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis Feb 2016;16(2):161–8.
[9] Cheng VCC, Wong SC, Wong SCY, Yuen KY. Directly observed hand hygiene - from healthcare workers to patients. J Hosp Infect Nov 26 2018. https://doi.org/10.1016/j.jhin.2018.11.016 [pii: S0195-6701(18)30671-6, Epub ahead of print].
[10] Cheng VC, Wong SC, Ho PL, Yuen KY. Strategic measures for the control of surging antimicrobial resistance in Hong Kong and mainland of China. Emerg Microbes Infect Feb 2015;4(2):e8.