

explain the low proportion of endocarditis cases compared with vascular infections in the Dutch series (15% vs. 36%, as reported by Kampschreur et al. (1)) compared with the series in our center (68% vs. 20%; unpub. data).

Endocarditis and vascular infections, whose first symptoms may be fatal decompensation or stroke, can be prevented in Q fever patients by implementing systematic screening echocardiography, phase I IgG monitoring, and PET scanning of patients with vascular disease (10). In our experience, only 1 patient with uncontrolled Q fever endocarditis has died since 2006, when we began following this protocol (3). The patient had a cardiac valve replacement 1 year before dying, but his phase I IgG titer was low (1:200), and *C. burnetii* PCR for his valve was negative, so no treatment was prescribed.

Reanalysis of the Q fever literature by different teams has brought challenging concepts to light (7). In a series from the Netherlands (1), 4 patients were shown to have died from endocarditis and 2 from vascular infections. These patients may have had better outcomes if the methods we propose here had been followed. Conversely, high serologic titers are not definite proof of persistent focalized infection, as illustrated in an outbreak in French Guiana, where exceptionally high serologic titers have been observed, but persistent focalized infections have rarely been diagnosed (10).

Accurate identification of persistent focalized *C. burnetii* infections will improve patient outcomes by preventing long-term, organ-specific, lethal complications (e.g., vascular infections are a risk for vascular rupture, lymphadenitis is a risk for lymphoma) and by avoiding drug side effects in patients with isolated elevated serologic test results. Clinicians should look beyond a diagnosis of chronic Q fever to determine whether a patient might have persistent focalized infection(s). The term fever in Q fever has evolved from a pathologic picture per se to a clinical epiphenomenon; it is now time to evolve from the concept of chronic Q fever to one of persistent focalized *C. burnetii* infection(s) (10).

Funding was provided by the French National Referral Center for Q Fever.

Dr. Million is a physician and PhD researcher. He is assistant to Professor Raoult at the French National Referral Center for Q Fever. Dr. Raoult is director of the French National Referral Center for Q Fever.

## References

- Kampschreur LM, Wegdam-Blans MC, Wever PC, Renders NH, Delsing CE, Sprong T, et al.; Dutch Q Fever Consensus Group. Chronic Q fever diagnosis—consensus guideline versus expert opinion. *Emerg Infect Dis*. 2015;21:1183–8. <http://dx.doi.org/10.3201/eid2107.130955>
- Limonard GJ, Nabuurs-Franssen MH, Weers-Pothoff G, Wijkman C, Besselink R, Horrevorts AM, et al. One-year follow-up of patients of the ongoing Dutch Q fever outbreak: clinical, serological and echocardiographic findings. *Infection*. 2010;38:471–7. <http://dx.doi.org/10.1007/s15010-010-0052-x>
- Fenollar F, Thuny F, Xeridat B, Lepidi H, Raoult D. Endocarditis after acute Q fever in patients with previously undiagnosed valvulopathies. *Clin Infect Dis*. 2006;42:818–21. <http://dx.doi.org/10.1086/500402>
- Million M, Walter G, Thuny F, Habib G, Raoult D. Evolution from acute Q fever to endocarditis is associated with underlying valvulopathy and age and can be prevented by prolonged antibiotic treatment. *Clin Infect Dis*. 2013;57:836–44. <http://dx.doi.org/10.1093/cid/cit419>
- Edouard S, Million M, Royer G, Giorgi R, Grisoli D, Raoult D. Reduction in incidence of Q fever endocarditis: 27 years of experience of a national reference center. *J Infect*. 2014;68:141–8. <http://dx.doi.org/10.1016/j.jinf.2013.10.010>
- Keijmel SP, Krijger E, Delsing CE, Sprong T, Nabuurs-Franssen MH, Bleeker-Rovers CP. Differentiation of acute Q fever from other infections in patients presenting to hospitals, the Netherlands. *Emerg Infect Dis*. 2015;21:1348–56. <http://dx.doi.org/10.3201/eid2108.140196>
- Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus. *J Infect*. 2012;65:102–8. <http://dx.doi.org/10.1016/j.jinf.2012.04.006>
- Million M, Thuny F, Bardin N, Angelakis E, Edouard S, Bessis S, et al. Antiphospholipid antibody syndrome with valvular vegetations in acute Q fever. *Clin Infect Dis*. 2016;62:537–44. <http://dx.doi.org/10.1093/cid/civ956>
- Barten DG, Delsing CE, Keijmel SP, Sprong T, Timmermans J, Oyen WJ, et al. Localizing chronic Q fever: a challenging query. *BMC Infect Dis*. 2013;13:413. <http://dx.doi.org/10.1186/1471-2334-13-413>
- Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q fever to *Coxiella burnetii* infection: a paradigm change. *Clin Microbiol Rev*. 2017;30:115–90. <http://dx.doi.org/10.1128/CMR.00045-16>

Address for correspondence: Didier Raoult, Institut Hospitalo-Universitaire Méditerranée Infection, 19-21 Blvd Jean Moulin, Marseille 13005, France; email: didier.raoult@gmail.com

## ESBL- and Carbapenemase-Producing *Enterobacteriaceae* in Patients with Bacteremia, Yangon, Myanmar, 2014

Tin O. Myat, Rachel F. Hannaway, Khwar N. Zin, Wah W. Htike, Kyu K. Win, John A. Crump, David R. Murdoch, James E. Ussher<sup>1</sup>

Author affiliations: University of Medicine 1, Yangon, Myanmar (T.O. Myat, W.W. Htike, K.K. Win); University of Otago, Dunedin, New Zealand (R.F. Hannaway, J.A. Crump, J.E. Ussher); Yangon General Hospital, Yangon (K.N. Zin); University of Otago, Christchurch, New Zealand (D.R. Murdoch); Southern Community Laboratories, Dunedin Hospital, Dunedin (J.E. Ussher)

DOI: <http://dx.doi.org/10.3201/eid2305.161100>

<sup>1</sup>All authors contributed equally to this article.

Among 42 gram-negative bloodstream isolates from inpatients in 3 hospitals in Yangon, Myanmar, admitted during July–December 2014, 16 (38%) were extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae* and 6 (14%) produced carbapenemase. The high prevalence of multi-drug-resistant gram-negative bacteria raises concerns about the empiric treatment of patients with sepsis in Yangon.

Infections with extended-spectrum  $\beta$ -lactamase (ESBL)-producing gram-negative bacteria and carbapenem-resistant *Enterobacteriaceae* (CRE) have been reported worldwide (1). Little is known about the occurrence of ESBL-producing and CRE bacteria in Yangon, Myanmar. Therefore, we characterized 42 gram-negative organisms isolated from routine blood cultures from adult inpatients in Yangon.

All bacteria had been isolated at the microbiology laboratories of 3 hospitals in Yangon during July–December 2014. During the study period, 592 blood cultures were processed, 536 from Yangon General Hospital (YGH) and 56 from 2 private hospitals. YGH is a 2,000-bed tertiary referral and teaching hospital in Yangon, providing free hospital care to civilians. The 2 private hospitals have 350 and 100 beds and provide secondary-level medical and surgical services to paying patients.

Of the 592 blood cultures, 42 (7.8%) yielded gram-negative bacteria, 28 (67%) from YGH and 14 (33%) from the 2 private hospitals. No clinical information was available about the patients from whom the cultures were taken. The identity and antimicrobial drug susceptibility

of isolates were confirmed at Southern Community Laboratories (Dunedin, New Zealand) by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Microflex LT; Bruker Daltonics, Billerica, MA, USA), disc diffusion testing using the Clinical and Laboratory Standards Institute method (2), and the Phoenix Automated Microbiology System (Bruker Daltonics) (panel NMIC/ID-95).

We conducted phenotypic confirmation of ESBL production on cefpodoxime-resistant isolates using cefotaxime and ceftazidime with and without clavulanic acid and that of carbapenemase production on meropenem-resistant isolates by modified Hodge test according to Clinical and Laboratory Standards Institute criteria (2). We performed PCR for  $\beta$ -lactamase genes on all ESBL- and potential carbapenemase-producing organisms (3,4). We conducted bidirectional Sanger sequencing of amplicons and identified DNA sequences by BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) and by comparison with known  $\beta$ -lactamase gene sequences.

Of the 42 isolates, 34 (81%) were *Enterobacteriaceae* (20 *Escherichia coli*, 7 *Klebsiella pneumoniae*, 6 *Salmonella enterica*, and 1 *Enterobacter cloacae*) and 8 (19.0%) were nonfermenting gram-negative bacilli. Of the *Enterobacteriaceae*, 20 (59%) were multidrug resistant (MDR), with resistance to  $\geq 3$  classes of antimicrobial drugs, and 7 (21%) were extensively drug resistant, with susceptibility to  $\leq 2$  classes of antimicrobial drugs (5). All MDR *Enterobacteriaceae* were susceptible to polymyxin (Table). Phenotypic testing

**Table.** Antimicrobial drug susceptibility of *Enterobacteriaceae* and *Acinetobacter* spp. isolated from blood cultures of inpatients from 3 hospitals in Yangon, Myanmar, 2014\*

Agent	Organism, no. (%) susceptible				
	<i>Escherichia coli</i> , n = 20	<i>Klebsiella pneumoniae</i> , n = 7	<i>Salmonella enterica</i> , n = 6	<i>Enterobacter cloacae</i> , n = 1	<i>Acinetobacter</i> spp., n = 3
Ampicillin	2 (10)	0	6 (100)	0	NT
Amoxicillin/clavulanic acid	5 (25)	1 (14)	6 (100)	0	NT
Piperacillin/tazobactam	13 (65)	2 (29)	6 (100)	0	2 (67)
Cefuroxime	5 (25)	1 (14)	NT	0	NT
Ceftriaxone	6 (30)	1 (14)	6 (100)	0	1 (33)
Ceftazidime	6 (30)	1 (14)	6 (100)	0	0
Cefipime	7 (35)	1 (14)	6 (100)	0	2 (67)
Cefoxitin	11 (55)	4 (57)	NT	0	NT
Aztreonam	6 (30)	1 (14)	6 (100)	0	NT
Ertapenem	17 (85)	4 (57)	6 (100)	1 (100)	NT
Imipenem	17 (85)	4 (57)	6 (100)	1 (100)	3 (100)
Meropenem	17 (85)	4 (57)	6 (100)	1 (100)	3 (100)
Gentamicin	14 (70)	2 (29)	NT	1 (100)	2 (67)
Tobramycin	9 (45)	1 (14)	NT	0	3 (100)
Ciprofloxacin	1 (5)	1 (14)	3 (43)	0	2 (67)
Chloramphenicol	11 (55)	2 (29)	6 (100)	0	NT
Colistin†	20 (100)	7 (100)	6 (100)	1 (100)	3 (100)
Nitrofurantoin	16 (80)	1 (14)	NT	0	NT
Trimethoprim/sulfamethoxazole	2 (10)	2 (29)	6 (100)	0	2 (67)

\*NT, not tested.

†Because there are no Clinical and Laboratory Standards Institute for susceptibility testing criteria for colistin for *Enterobacteriaceae*, European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria were used (susceptible if MIC  $< 2$  mg/L, per EUCAST criteria version 6.0, 2016; [http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/v\\_6.0\\_Breakpoint\\_table.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf)).

suggested the presence of an ESBL in 16 (38%) and a carbapenemase in 6 (14%) of all gram-negative isolates. Molecular analysis showed that 13 (81%) ESBL-producing isolates contained a group 1 CTX-M gene; all were confirmed as CTX-M-15 by sequencing. Carbapenemase-producing isolates, including 3 *E. coli* and 3 *K. pneumoniae*, contained the New Delhi metallo- $\beta$ -lactamase (NDM) gene, sequenced as NDM-4 in 5 (83%) and NDM-7 in 1 (17%).

Our study revealed a high proportion of ESBL- and carbapenemase-producing organisms among gram-negative bloodstream isolates during the study period from hospital inpatients in Yangon. Half of *E. coli* isolates and 43% of *K. pneumoniae* isolates produced ESBLs. This finding is consistent with the high proportion of ESBL production reported in isolates from India (>80%), China (>60%), and other Asia and Southeast Asia countries (>30%) (6). Carbapenemase production (15% in *E. coli* and 43% in *K. pneumoniae*) in this study was comparable to those previously reported from clinical isolates in India (7).

CTX-M-15 ESBL and NDM carbapenemase were the most prevalent mechanisms of resistance to  $\beta$ -lactams in our study. This finding is consistent with the current global dissemination of CTX-M-15 among *E. coli* isolates (8). All CRE isolates were NDM-4 or NDM-7. Two previous case reports have indicated the presence of NDM-producing *Enterobacteriaceae* from travelers to Myanmar: 1 NDM-7 (9) and 1 NDM-4 (10).

Two thirds of all isolates included in this study originated from YGH, the largest public hospital in Myanmar. All CRE isolates and 14 (88%) of 16 ESBL producers were isolated from YGH; this may reflect a higher prevalence of colonization with MDR organisms among patients in YGH or they may be healthcare-associated infections. Of concern, at YGH 11 (73%) of 15 *E. coli* and 6 (100%) of 6 *K. pneumoniae* isolates produced either an ESBL or carbapenemase; among these, 3 (20%) of 15 *E. coli* and 3 (50%) of 6 *K. pneumoniae* isolates were NDM producers.

Whereas all 23 (100%) of the *Enterobacteriaceae* at YGH were susceptible to treatment with colistin, an empiric treatment regimen of meropenem plus gentamicin would have covered only 18 (78%) isolates. This finding highlights the difficulties with designing an effective empiric antimicrobial regimen for patients with suspected gram-negative sepsis in a setting of a high prevalence of antimicrobial resistance, without providing further selective pressure for the spread of CRE and the emergence of colistin resistance.

Our study has limitations. First, clinical data were not prospectively collected, and it was not possible to obtain data retrospectively because of poor recording systems. Second, we cannot be certain that study isolates represent the population of organisms causing gram-negative sepsis in Yangon. However, the high proportion of ESBL- and carbapenemase-producing gram-negative bacteria among

bloodstream isolates from hospitalized patients in Yangon raises concern for the treatment of patients with gram-negative sepsis and suggests a need to reduce selective pressure and control the spread of resistant organisms.

This study was supported in part by a grant from the University of Otago Development Office, New Zealand.

Dr. Myat completed this work while she was working as a lecturer at the Department of Microbiology, University of Medicine 1 in Yangon, Myanmar. Currently, she is undertaking doctoral study from the University of Otago, New Zealand. Her research focuses on bacterial causes of febrile illness in Yangon.

## References

1. Vasoo S, Barreto JN, Tosh PK. Emerging issues in gram-negative bacterial resistance: an update for the practicing clinician. *Mayo Clin Proc.* 2015;90:395–403. <http://dx.doi.org/10.1016/j.mayocp.2014.12.002>
2. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement (M100–S24). Wayne (PA): The Institute; 2014.
3. Dalenne C, Da Costa A, Decré D, Favier C, Arlet G. Development of a set of multiplex PCR assays for the detection of genes encoding important  $\beta$ -lactamases in *Enterobacteriaceae*. *J Antimicrob Chemother.* 2010;65:490–5. <http://dx.doi.org/10.1093/jac/dkp498>
4. Poirrel L, Walsh TR, Cuvillier V, Nordmann P. Multiplex PCR for detection of acquired carbapenemase genes. *Diagn Microbiol Infect Dis.* 2011;70:119–23. <http://dx.doi.org/10.1016/j.diagmicrobio.2010.12.002>
5. Magiorakos APSA, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect.* 2012;18:268–81. <http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x>
6. Molton JS, Tambyah PA, Ang BS, Ling ML, Fisher DA. The global spread of healthcare-associated multidrug-resistant bacteria: a perspective from Asia. *Clin Infect Dis.* 2013;56:1310–8. <http://dx.doi.org/10.1093/cid/cit020>
7. Morey MK, Channe NM. Prevalence of carbapenem resistance and antibiotic resistance profiles of gram negative bacterial isolates from ICU in Ankola, India. *Int J Med Phar Sci.* 2015;5(12) [cited 2016 Jun 1]. <http://www.ejmanager.com/mnstemp/47/47-1441349259.pdf>
8. Cantón R, Coque TM. The CTX-M beta-lactamase pandemic. *Curr Opin Microbiol.* 2006;9 (5):466–75. <http://dx.doi.org/10.1016/j.mib.2006.08.011>
9. Cuzon G, Bonnin RA, Nordmann P. First identification of novel NDM carbapenemase, NDM-7, in *Escherichia coli* in France. *PLoS One.* 2013;8:e61322. <http://dx.doi.org/10.1371/journal.pone.0061322>
10. Espedido BA, Dimitrijovski B, van Hal SJ, Jensen SO. The use of whole-genome sequencing for molecular epidemiology and antimicrobial surveillance: identifying the role of IncX3 plasmids and the spread of blaNDM-4-like genes in the *Enterobacteriaceae*. *J Clin Pathol.* 2015;68:835–8. <http://dx.doi.org/10.1136/jclinpath-2015-203044>

Address for correspondence: Tin Ohn Myat, Centre for International Health, Dunedin School of Medicine, University of Otago, 55 Hanover St, PO Box 56, Dunedin 9054, New Zealand; email: tinohnmyat@gmail.com