mcr-1 Colistin Resistance in ESBL-Producing Klebsiella pneumoniae, France

Yvan Caspar, Mylène Maillet, Patricia Pavese, Gilles Francony, Jean-Paul Brion, Marie-Reine Mallaret, Richard Bonnet, Frédéric Robin, Racha Beyrouthy, Max Maurin

To cite this version:

Yvan Caspar, Mylène Maillet, Patricia Pavese, Gilles Francony, Jean-Paul Brion, et al.. mcr-1 Colistin Resistance in ESBL-Producing Klebsiella pneumoniae, France. Emerging Infectious Diseases, Centers for Disease Control and Prevention, 2017, 23 (5), pp.874 - 876. 10.3201/eid2305.161942. hal-01639760

HAL Id: hal-01639760
https://hal.uca.fr/hal-01639760
Submitted on 26 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
tests from Panama City versus other areas of Panama and might result in a sampling bias. Despite these limitations, the recent Zika outbreak has shown the speed at which vectorborne diseases can spread and highlights the importance of detecting emerging viruses like PTVs.

Acknowledgments
We thank staff in the Department of Research in Virology and Biotechnology at the Gorgas Memorial Institute for Health Studies in Panama and in the Ministry of Health National Epidemiology Department for the surveillance data and outbreak response during 2009. We also thank Meghan Tiptre for help creating the epidemiologic map.

This work was done in compliance with the Gorgas Bioethics Committee (1010/CBI/ICGES/15).

Funding was provided by the Panama Ministry of Economy and Finance (09.044.051 to S.L.-V. and 09.044.050 to J.M.P.); the Secretaría Nacional de Ciencia, Tecnología, e Innovación (SENACYT; FID-09-103 to J.-P.C); and Gorgas Memorial Institute, University of Alabama at Birmingham (to N.D.G.). J.M.P. and S.L.-V. are members of the Sistema Nacional de Investigación (SNI) of SENACYT in Panama.

Dr. Gundacker is an infectious disease fellow at the University of Alabama at Birmingham. His primary interest are the clinical description of febrile tropical infectious diseases, laboratory differential diagnosis of these diseases, and host–pathogen interactions. Mr. Carrera is an epidemiologist and virologist at Gorgas Memorial Institute. His primary research interests are ecology, evolution, and epidemiology of arthropodborne and zoonotic viruses.

References

Address for correspondence: Sandra López-Verges, Gorgas Memorial Institute for Health Studies, Department of Research in Virology and Biotechnology, Ave Justo Arosemena and St 35, No. 0816-02593, Panama City, Panama; email: slopez@gorgas.gob.pa

mcr-1 Colistin Resistance in ESBL-Producing Klebsiella pneumoniae, France

Yvan Caspar, Mylène Mailet, Patricia Pavese, Gilles Francony, Jean-Paul Brion, Marie-Reine Mallaret, Richard Bonnet, Frédéric Robin, Rachael Beyrouthy, Max Maurin

Author affiliations: Centre Hospitalier Universitaire Grenoble-Alpes, Grenoble, France (Y. Caspar, M. Mailet, P. Pavese, G. Francony, J.-P. Brion, M.-R. Mallaret, M. Maurin); University Grenoble Alpes, CNRS, Grenoble; Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France (R. Bonnet, F. Robin, R. Beyrouthy); Centre National de Référence de la Résistance Aux Antibiotiques, Clermont-Ferrand (R. Bonnet, F. Robin, R. Beyrouthy); Université Clermont Auvergne, Clermont-Ferrand (R. Bonnet, F. Robin, R. Beyrouthy); Institut National de la Santé et de la Recherche Médicale, Clermont-Ferrand (R. Bonnet, F. Robin, R. Beyrouthy); Institut National de la Recherche Agronomique, Clermont-Ferrand (R. Bonnet, F. Robin, R. Beyrouthy)

DOI: http://dx.doi.org/10.3201/eid2305.161942

We report intestinal carriage of an extended-spectrum β-lactamase–producing Klebsiella pneumoniae strain with high-level resistance to colistin (MIC 24 mg/L) in a patient in France who had been hospitalized for fungal meningitis. The strain had the mcr-1 plasmid gene and an inactivated mgrB gene, which are associated with colistin resistance.
Resistance to colistin in gram-negative bacteria stems mainly from structural modifications of bacterial lipopolysaccharide. These modifications include addition of 4-amino-4-deoxy-L-arabinose or phosphoethanolamine caused by chromosomal mutations in genes encoding the 2-component systems PhoPQ and PmrAB, or mutations in the mcr-1 gene, a negative regulator of PhoPQ (1).

The recent discovery of a horizontally transferable plasmid-mediated mcr-1 gene encoding a phosphoethanolamine transferase is a cause for concern, but few mcr-1–positive clinical strains of Klebsiella pneumoniae have been reported so far in Europe (2). Colocalization of carbapenemases or extended-spectrum β-lactamase (ESBL) genes and the mcr-1 gene on the same plasmids is of concern because it might lead to pandrug resistance (1,3). We report mcr-1 colistin resistance in ESBL-producing K. pneumoniae isolated from a patient in France.

The patient was a 38-year-old man who had chronic granulomatous disease that was diagnosed when he was 8 months old. Since then, he has had several minor and major diseases and conditions, including primitive femoral osteitis, hepatic abscesses, disseminated candidiasis, and bacteremia, which required several treatments with antimicrobial drugs. However, the patient was never given colistin.

In April 2016, he was hospitalized for surgical removal of a thyroid abscess. Fungal cultures of the abscess grew Aspergillus fumigatus. Despite antifungal treatment with fluconazole, clindamycin, meropenem, and vancomycin successively. However, arterial vasospasm at the Willis polygon, and hydrocephalus developed. The patient also received immunosuppressive therapy (methylprednisolone and anakinra) and emulsipotentiate colistin activity (Polymyxin B E-test strip; bioMérieux, Marcy L’Etoile, France).

The strain was sent to the French National Reference Center for Antibiotic Resistance in Enterobacteriaceae (Hôpital Gabriel Montpied, Clermont-Ferrand, France), which confirmed phenotypic resistance to colistin and identified the mcr-1 gene by using PCR and previously described primers (2). Whole-genome sequencing showed that the K. pneumoniae strain had genotype ST15 and confirmed the presence of the mcr-1 gene on a 33,303-kb transferable plasmid of incompatibility group IncX4 (online Technical Appendix). This plasmid differed by only 4 mutations from mcr-1.2–encoding plasmid pMCR-1.2.IT (GenBank accession no. KX236309) previously characterized in Italy (4). Conjugation of the plasmid into Escherichia coli K12 conferred colistin resistance (MIC increased from 0.25 mg/L to 4 mg/L) to the E. coli strain.

Other resistance genes were also identified (Table), including the ESBL-producing gene bla<sub>SHV</sub>-106 (online Technical Appendix). None of them were localized with the mcr-1 gene on the IncX4 plasmid. Moreover, insertion of mobile element IS5 in the mgrB gene was detected, which is also associated with colistin resistance (5). No mutations were found in the prmA, prnB, phoP, and phoQ genes.

There is currently no commercial medium to screen gram-negative bacteria harboring the mcr-1 gene. Nörmann et al. (6) described an in-house SuperPolymyxin medium composed of cefoxitin and cefoxitin, 3.5 mg/L of colistin sodium, 10 mg/L of daptomycin, and 5 mg/L of amphotericin B, which showed excellent sensitivity and specificity. Colistin resistance can be confirmed within 2 h by using an in-house rapid polymyxin Nordmann-Poirrel test (7). The mcr-1 gene can be rapidly detected by real-time PCR of DNA extracts obtained from bacterial strains or directly from stool samples (2,8,9).

We obtained subcultures of the strain from the patient on Columbia CNA agar containing 10 mg/L of colistin and 15 mg/L of nalidixic acid and 5% sheep blood (CNA*; bioMérieux) but not on Thayer-Martin agar medium containing unknown concentrations of vancomycin, colistin, amphotericin B, and trimethoprim (VCA3; bioMérieux). Lack of growth on this medium might be related to a high colistin concentration or the presence of vancomycin, which can potentiate colistin activity (6). Further investigations using the E-test method (Polymyxin B E-test strip; bioMérieux, Marcy L’Etoile, France).

Table. Resistance genes identified by whole-genome sequencing of an ESBL-producing mcr-1–positive Klebsiella pneumoniae strain isolated from a 38-year-old man, France

<table>
<thead>
<tr>
<th>Resistance gene</th>
<th>Target antimicrobial drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcr-1 and inactivation of mgrB by IS5 insertion</td>
<td>Colistin</td>
</tr>
<tr>
<td>bla&lt;sub&gt;SHV&lt;/sub&gt;-106</td>
<td>β-lactams</td>
</tr>
<tr>
<td>aac(3)-IId and aadA16-like</td>
<td>Aminoglycoside</td>
</tr>
<tr>
<td>aac(6’)-Ib-cr</td>
<td>Quinolone and aminoglycoside</td>
</tr>
<tr>
<td>fosA5</td>
<td>Fosfomycin</td>
</tr>
<tr>
<td>sulI and folP</td>
<td>Sulfonamide</td>
</tr>
<tr>
<td>dfrA27</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>tetD</td>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

*ESBL, extended-spectrum β-lactamase.
CNA+ medium did not identify intestinal carriage of ESBL-negative but mer-
1 l-positive enterobacteria in the index case-patient. On the basis of these resul-
ts, rectal screening of 39 contacts was performed by using an ESBL-screening
medium (BLSE agar [MacConkey agar and Drigalski agar]; bioMérieux). All of the tests showed negative results.

The origin of the mer-
l strain remains unknown. Nos-
{}nocomial acquisition cannot be ruled out because colistin-
{}resistant strains harboring the mer-
l gene might have been isolated in the hospital but not identified because this resistant-
{}ance mechanism was initially reported in February 2016. Food might also be incriminated (I); one study identified a 21% mer-
l prevalence among ESBL-producing E. coli in calves in France (10).

Multiple antimicrobial drug therapy for this patient might have selected for this multidrug-resistant bacte-
{}r. The presence of a plasmid containing the mer-
l and ESBL or other resistance genes in the same strain might be involved in selection of colistin-resistant strains during 
{}administration of any ineffective antimicrobial drug (3). Development of efficient tools for rapid detection of mer-
l–harboring strains should be a priority to prevent dis-
{}semination of these strains in hospital settings.

Dr. Caspar is a clinical microbiologist in the Bacteriology Laboratory, Grenoble-Alpes University Hospital, and a probationary lecturer in the Medicine Faculty, Grenoble-Alpes University, Grenoble, France. His primary research interests are bacterial resistance or treatment failures for tularemia and evaluation of novel antimicrobial compounds.

References


9. Bontron S, Poirel L, Nordmann P. Real-time PCR for detection of plasmid-mediated polymyxin resistance (mer-

10. Haenni M, Métayer V, Gay E, Madec J-Y. Increasing trends in mer-

Address for correspondence: Yvan Caspar, Laboratoire de Bactériologie, Institut de Biologie et Pathologie, Centre Hospitalier Universitaire Grenoble Alpes, CS10217, 38043 Grenoble CEDEX 9, France; email: ycaspar@chu-grenoble.fr

Chromosomal 16S Ribosomal RNA Methyltransferase RmtE1 in Escherichia coli Sequence Type 448

Bin Li, Marissa P. Pacey, Yohei Doi

Author affiliations: Fujian Medical University Union Hospital, Fuzhou, China (B. Li); University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA (B. Li, M.P. Pacey, Y. Doi)

DOI: http://dx.doi.org/10.3201/eid2305.162000

We identified rmtE1, an uncommon 16S ribosomal methyltransferase gene, in an aminoglycoside- and cephalosporin-resistant Escherichia coli sequence type 448 clinical strain co-harboring blaKPC2. Long-read sequencing revealed insertion of a 101,257-bp fragment carrying both resistance genes to the chromosome. Our findings underscore E. coli sequence type 448 as a potential high-risk multidrug-resistant clone.

RmtE (RmtE1 and its variant RmtE2) is an uncommon plasmid-mediated 16S rRNA methyltransferase (16S RMTase) found in gram-negative bacteria; only 4 strains have been reported to produce RmtE, all Escherichia coli, including 1 from the University of Pittsburgh Medical