Haut Conseil de la santé publique - French High Council for Public Health

OPINION

regarding measures to be taken with regard to the emergence of a plasmid-mediated resistance to (*mcr-1*) colistin in *Enterobacteriaceae*

27 September 2016

On 4 August 2016, the High Council for Public Health (HCPH) received a referral from the General Directorate of Health (GDH) regarding measures to be taken with regard to the emergence of a plasmid-mediated (*mcr-1*) colistin resistance in *Enterobacteriaceae*.

This referral to the HCPH arises following the recent notification in the United States of two cases of patients carrying strains of *Escherichia coli* with the *mcr-1* gene, likely to give rise to a colistin resistance and the reporting of 25 July 2016 by the Institut Pasteur in Noumea (New Caledonia) of the first detection in France of a strain of *Enterobacteriaceae* carrying the *mcr-1* plasmid-mediated colistin resistance gene, also producing an extended spectrum beta-lactamase.

So that the necessary measures can be set up as soon as possible within health establishments, the GDH has asked the HCPH to update the definition of emerging highly-resistant bacteria (eHRB) and the means of identification in order to take into account the development of the epidemiology of the resistance of these bacteria.

This referral to the HCPH from the GDH was followed by a Quick Health Alert Message (QHAM) sent to health establishments, dated 2 September 2016 [1].

The HCPH points out the following:

- Colistin is a polycationic antimicrobial peptide of the polymyxin family, which has long been ignored in human medical treatment protocols due to its undesirable effects. Nevertheless, given the increase in infections caused by multidrug resistant Gram-negative bacilli, particularly *Enterobacteriaceae* that are resistant to the latest generation of cephalosporin and to carbapenems (whether or not they produce carbapenemases), colistin is being prescribed as an antibiotic once again in the treatment of severe linked human infections for lack of therapeutic alternatives.
- *Enterobacteriaceae* have also developed resistance mechanisms to fluoroquinolones and to aminoglycosides, some of which are carried by plasmids [2,3].
- The increased use of colistin contributes to the emergence of resistant bacteria [4- 6] and to the frequency of infections caused by naturally resistant Enterobacteriaceae such as *Proteus*, *Providencia*, *Morganella* and *Serratia* [7-9].
- In certain geographical zones close to metropolitan France, colistin resistance is reaching worrying proportions: in *Klebsiella pneumoniae*, 18.6% of the KPC-type carbapenemase-producing strains in a hospital in Greece between 2007 and 2010, and 22.4% of the isolates in Italy during a national investigation carried out in 2011 [10,11].
- Until now, acquired colistin resistance has mainly been attributed to chromosomal mutations, little able to be transferred between bacteria. In 2015, the

first plasmid-mediated colistin resistance mechanism was described in China in animals, humans and in food [12]. The corresponding gene, *mcr-1*, codes for a plasmid phosphoethanolamine transferase, that confers a low level colistin resistance (modal minimum inhibitory concentration (MIC): 4 µg/mL). The gene's origin might be Paenibacillus spp., the bacterial species in which the first polymyxin was discovered. The mcr-1 gene was detected shortly afterwards in several countries in Europe, Asia, South-east Asia, South America, North America and in Africa. Retrospective investigations enabled the presence of the *mcr-1* gene to be established in China as soon as the 1980s and in Europe since at least 2005. The associated data, particularly in Europe, tends to show that the prevalence in humans is weak compared to animals. By way of example, a study carried out on 10,011 E. coli isolates between the years of 2012 and 2015 in a hospital in Barcelona [13], found 53 colistin-resistant isolates (0.5%). Of the 50 resistant isolates available, 15 carried the mcr-1 gene, in other words a prevalence of 0.15% in the E. coli species and 30% in colistin-resistant isolates. Seven isolates carrying mcr-1 were not multidrug resistant bacteria according to the international definition [14]. Two produced an ESBL and another overexpressed an AmpC. -type cephalosporinase. It should be noted that the study used a screening method based on the use of agar media, which are not recommended and might lead to an under-evaluation of the prevalence.

- Recommendations for the prevention of cross-transmission of "emerging Highly-Resistant Bacteria (eHRB)" issued by the HCPH in 2013 [15] define eHRB as gut commensal bacteria that can be spread by limited sporadic or epidemiological modes in France in hospital or communities, resistant to numerous antibiotics and presenting antibiotic resistance mechanisms that are transferable between bacteria. The list of eHRBs drawn up in 2013, taking into account the international and French epidemiology at the time, includes carbapenemase-producing Enterobacteriaceae (CPE) and enterococci (*E. faecium*) that are resistant to glycopeptides (GRE). Patients targeted for routine gut screening for carrying these two eHRBs are patients who have been hospitalised for more than 24 hours in a foreign health establishment over the past year, with or without direct repatriation. These recommendations indicate that the list can be revised in accordance with the international epidemiological context of the emergence of new antibiotic resistance
- The importance of keeping colistin as a backline antibiotic in the treatment of infections involving CPEs and the necessity of informing the clinician on the possibility of using it documenting the antibiotic-resistance profile of these CPEs;
- The importance of applying the HCPH's 2013 recommendations in controlling the spread of eHRBs [15] in the context of an emerging plasmid-mediated colistin resistance;

As current epidemiological knowledge stands, the HCPH recommends the following measures:

- Testing colistin resistance and screening for the presence of the mcr-1 gene in any isolated CPE strain:
    - either during routine screening when admitting a patient who has been hospitalised outside metropolitan France within the previous year, without or without direct repatriation,
    - either in a sample for diagnostic purposes during hospitalisation in a clinical and therapeutic context requiring use of colistin.

- Set up isolation precautions in addition to standard precautions for patient carrying mcr-1 gene positive *Enterobacteriaceae*, according to the French guidelines to control the spread of eHRBs [15].
- Report the case within the nosocomial infections framework and send the strain to the National Reference Centre for resistance to antibiotics.
- Set up national epidemiological prevalence studies of colistin resistance and the presence of the *mcr-1* resistance gene in *Enterobacteriaceae* (whatever their antibiotic sensitivity profile) based on data from community and hospital laboratories. These epidemiological studies could be coordinated by a national working group comprising, in particular, experts from the HCPH, the French National Observatory for Epidemiology of Bacterial Resistance to Antimicrobials (ONERBA), the National Reference Centre of resistance to antibiotics (CNR Clermont-Ferrand) and from the Public health system in France.

NB: A second opinion will be issued by the HCPH in the weeks ahead in order to indicate the means of detecting colistin resistance and the presence of the plasmid-mediated mcr-1 gene, based in particular on the expertise of the CNR of resistance to antibiotics. This opinion will include diagnostic developments of CPEs in the laboratory since the recommendations for the detection of CPEs in the HCPH's report in 2013 [15].

These recommendations have been drawn up on the basis of knowledge available at the date of publication and are subject to modification in the event of new data being available.

Opinion drawn up by a group of experts, members or non-members of the HCPH, around an Expert Committee on "Patient Safety: Nosocomial infections and other undesirable events linked to treatments and practices" and the Expert Committee on "Infectious Diseases". No conflict of interest has been identified.

The Expert Committee on "Patient safety: Nosocomial infections and other undesirable events linked to treatments and practices" met on 27 September 2016: 11 qualified members of 15 voting qualified members were present; the text was approved by 11 votes, 0 vote against, 0 abstention.

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