Colistin resistance: a major breach in our last line of defence

In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo-β-lactamase 1-producing organisms and many strains of carbapenem resistant Acinetobacter baumannii. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against many Gram-negative bacilli. Colistin-resistant and even pan-drug-resistant Gram-negative bacilli have already been reported.1,2 Typically, colistin resistance is due to chromosomally mediated modulation of two-component regulatory systems leading to modification of lipid A, resulting in reduced affinity for the polymyxins. Clones of colistin-resistant organisms have spread in some hospitals,3 but have not seriously affected the use of polymyxins. These resistance genes are generally not transmissible between bacteria and so have not disseminated widely.

In The Lancet Infectious Diseases, Yi-Yun Liu and colleagues4 describe plasmid-mediated colistin resistance for the first time. The implications of this finding are enormous. The investigators reported that the plasmid bearing the colistin resistance mechanism was readily passed between Escherichia coli strains, including strains with known epidemic potential, such as ST131. Furthermore, the plasmid could be passed to Klebsiella pneumoniae and Pseudomonas aeruginosa strains. The plasmids were quite stable, implying that even in the absence of selection pressure by colistin, the plasmids would be maintained. It therefore seems inevitable that plasmid-mediated transfer of colistin resistance will seriously limit the lifespan of the polymyxins as the backbone of regimens against multiply resistant Gram-negative bacilli.

How did this come about and is there anything we can do to limit the rate of spread of colistin resistance? Colistin has been used in agriculture since the 1950s.5 Indeed, in 2010 it was the fifth most sold group of antimicrobials used in agriculture in Europe.6 Historical data on its use in agriculture in Asia are limited. However, it is clear that its current use is substantial.

Liu and colleagues4 present data from China showing that E coli from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in E coli and K pneumoniae isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin use in agriculture. This will require substantial political will and we call upon Chinese leaders to act rapidly and decisively. Failure to do so will create a public health problem of major dimensions.

Is plasmid-mediated colistin resistance a purely Chinese phenomenon? A recent report has described colistin resistance in E coli from a pig and a person in Laos.6 The pig and human colistin-resistant E coli isolates were indistinguishable by pulsed field gel electrophoresis suggesting animal to human transmission. No known chromosomally encoded colistin resistance mechanisms were identified in these isolates, raising the question as to whether they could also have unrecognised plasmid-mediated colistin resistance mechanisms. As noted by Liu and colleagues, E coli bearing genes very similar to those that they describe causing plasmid-mediated colistin resistance have recently been detected in Malaysia.4 Given that substantial use of colistin in agriculture is highly likely throughout southeast Asia,7 it would hardly be surprising that plasmid-mediated colistin resistance will soon be detected in this region. At least one manufacturer of colistin for agriculture is based in India, raising the spectre of untreatable NDM-producing, colistin-resistant strains occurring in the Indian subcontinent.

In 2012, WHO reclassified colistin as critically important for human medicine.8 This classification remains true despite the ongoing development of new antibiotics against multiply resistant Gram-negative bacilli. There have been previous calls for curtailing the use of polymyxins in agriculture.9 We must all reiterate these appeals and take them to the highest levels of government or face increasing numbers of patients for whom we will need to say, “Sorry, there is nothing I can do to cure your infection”.

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CHAPAS-3 fills the gap

While the efficacy of protease inhibitors versus non-nucleoside reverse transcriptase inhibitors for first-line paediatric antiretroviral treatment (ART) has been carefully assessed in clinical trials, only one small trial (PENTA-5) has compared different nucleoside reverse transcriptase inhibitor (NRTIs) backbones in children. The PENTA-5 trial noted that abacavir-containing regimens were more effective than zidovudine plus lamivudine, but was done in resource-rich settings and the regimen included nevirapine in nearly half of participants, restricting its relevance to current treatment decision in Africa, where most paediatric HIV infections occur. Consequently, to inform its recommendations on the optimum dual NRTI backbone for paediatric ART, the WHO has relied on data from randomised trials without head-to-head comparisons of NRTIs, observational cohort data, and expert opinion. The near complete absence of trial data in children is unacceptable in the context of lifelong ART, which requires a good understanding of the effect of different NRTI backbones on toxicity, achievement and maintenance of viral suppression, and implications of mutations on future treatment options. The CHAPAS-3 trial now fills this gap by providing the first trial data comparing abacavir, stavudine, and zidovudine in combination with lamivudine and nevirapine or efavirenz for first-line treatment in HIV-positive children in Africa.

In 2013, the WHO recommended abacavir plus lamivudine as the preferred dual NRTI backbone in children because “abacavir can be used once daily, is available as a fixed-dose combination with 3TC [lamivudine], and harmonises with TDF [tenofovir] from a resistance perspective”. This change occurred despite the relatively high cost of abacavir and the association of abacavir with hypersensitivity reactions. Furthermore, observational data from two cohort studies indicated that abacavir might be less effective in achieving and maintaining viral suppression compared with similar regimens containing stavudine, raising concerns among clinicians and policy makers about the WHO recommendation.

In the multicentre CHAPAS-3 trial, 478 children age 1 month to 13 years were randomly assigned to receive fixed-dose combination tablets of one of three NRTIs (abacavir, stavudine, or zidovudine) plus lamivudine in combination with nevirapine or efavirenz, all dosed according to WHO weight bands. The trial included 365 ART-naive children and 113 virologically suppressed ART-experienced children on a stavudine-containing first-line regimen for 2 years or more. The study achieved superb completion rates with only 5% of children lost to follow-up and 98% of scheduled nurse visits completed. Clinical outcomes