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'MIC-Creep' in *Clostridium difficile*?

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Background: Antimicrobial resistance especially in nosocomial pathogens is of increasing concern. In *Clostridium (C.) difficile* reports on resistance against standard drugs (vancomycin and metronidazole) are still sparse. The increase of minimum inhibitory concentrations (MIC) within the range designated as sensitive, could precede future resistance ("MIC creep"). To look for such a MIC creep in *C. difficile* isolates from 1997-1999 were compared to those from the years 2007-2009 with regards to resistance to selected antimicrobials.

Methods: Antimicrobial resistance testing against vancomycin (VAN), metronidazole (MTZ), rifampin (RMP) and moxifloxacin (MXF) using E test method was performed in 103 clinical disease-associated strains collected from 1997-1999 (period 1) and 92 strains from 2007 to 2009 (period 2). Results between both groups were compared using standard statistical software.

Results: Mean MIC for both groups (period 1 vs. period 2) for VAN were 0.36 μg/ml vs. 0.70 μg/ml, for MTZ 0.046 μg/ml vs. 0.066 μg/ml, for RMP 3.65 μg/ml vs. 5.28 μg/ml and for MXF 7.45 μg/ml vs. 23.90 μg/ml, respectively. These results reached statistical significance (all $p < 0.05$) using T test and Mann-Whitney U test for VAN, MTZ und MXF. Only the median MIC increase in RMP was not significant (all $p > 0.2$). True resistance was detected in period 1 isolates only for RMP (10.7% of all strains) and MXF (21.4% of all strains), whereas 2.4% of strains from period 2 had VAN resistance, 16.5% had RMP resistance and 74.1% had MXF resistance.

Conclusion: Results presented demonstrate a possible MIC creep in *C. difficile*. To what extent this translates into clinical relevance remains to be clarified.

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Enteric fever in Cambodian children is dominated by multidrug resistant H58 *Salmonella enterica* serovar Typhi with decreased susceptibility to ciprofloxacin

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Background: Enteric fever (EF) infections with isolates of *Salmonella enterica* serovar Typhi and Paratyphi A that are multidrug resistant (MDR: resistant to chloramphenicol; ampicillin; trimethoprim-sulphamethoxazole) and have decreased ciprofloxacin susceptibility (DCS) are common in Asia. There is limited data about any EF from Cambodia.

Methods: We conducted a retrospective analysis of invasive salmonellosis in Cambodian children at Angkor Hospital for Children in Siem Reap, northwest Cambodia, between January 2007 and December 2011.

Results: *S.enterica* was isolated from blood in 161 children. There were 150 children with EF including 147 with serovar Typhi and 3 with serovar Paratyphi A. A further 11 children had bacteraemia with a non-typhoidal Salmonella (NTS) serovar. 125/147 (85%) of serovar Typhi isolates were MDR and 132/147 (90%) had DCS. None of the Paratyphi A isolates were MDR, all had DCS. Among the 127 children admitted to hospital with EF antimicrobial treatment was ceftriaxone alone in 58 (46%), ceftriaxone followed by oral ciprofloxacin in 25 (20%), by oral azithromycin in 41 (32%), by cefixime in 1 (0.8%) and azithromycin alone in 2 (1.6%). A complication developed in 36/127 (28%) children admitted with EF including gastrointestinal bleeding in 13, jaundice in 9, a lung infection in 9, cholecystitis in 6, haemodynamic shock in 3, encephalopathy in 2, one child required surgery and one child had a blood culture confirmed relapse. NTS blood stream infections were mostly a complication of severe diarrhoea in children <1 year old (5) or HIV infection (4). The case fatality rate among hospital admitted children was 2/10 (20.0%) of those with a NTS bloodstream infection compared with 2/127 (1.6%) of those with EF (OR 15.8; 95%CI 1.3-190; $p = 0.03$). In a subset of 102 serovar Typhi strains genotyped by investigation of a subset of single nucleotide polymorphism (SNPs), 94 (92%) belonged to the H58 haplotype and had the common serine to phenylalanine substitution at codon 83 in the DNA gyrase.

Conclusion: EF caused by the H58 haplotype of *S.enterica* Typhi that is MDR and has DCS is an important problem in Cambodian children. Strategies for its treatment and control are needed.

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