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Does frontline use of tigecycline versus meroepenem-based regimens for intra-abdominal infection reduce the risk for carbapenem-resistant-Klebsiella pneumoniae colonization or Clostridium difficile infection?

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Background: We hypothesized that the risk for colonization with carbapenem resistant-*Klebsiella pneumoniae* (CR-KP) or development of *Clostridium difficile* associated diarrhoea (CDAD) is reduced in patients who receive tigecycline (TIG) versus meropenem (MER)-based antimicrobial therapy for intrabdominal infections (IAI).

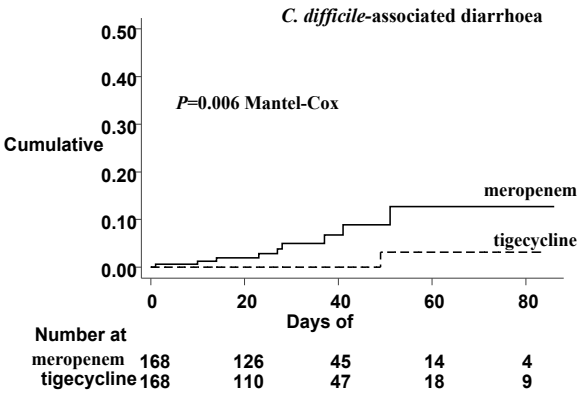
Material/methods: We performed a retrospective, single-center, matched (1:1) cohort analysis of patients who received either TIG-based (≥5 days) or MER-based (≥5 days) treatment for IAI from October 2011 to December 2015. Patients were matched based on: i) admission to the same hospital ward in the same month and year, ii) length of in-hospital stay, iii) duration of antibiotic administration, iv) APACHE II score at time of index infection and iv) immune status. Patients with previous CR-KP infection, CR-KP colonization and/or CDAD were excluded. Gathered data included demographics, comorbidities, concomitant medications, empirical and definitive antibiotic co-treatments and outcome. CDAD was diagnosed by positive *C. difficile* GHD antigen with ELISA enzyme immunoassay plus positive toxin A/B; CR-KP colonization was diagnosed by the rectal swab culture (carbapenemase production was confirmed by carbapenem hydrolysis test and/or disc-diffusion synergy test).

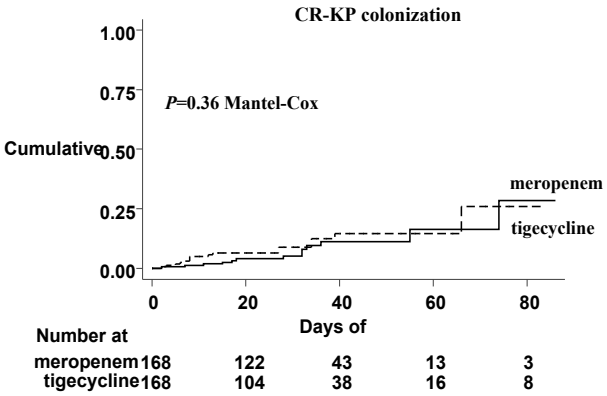
Results: We screened 2187 patient to identify 168 TIG-treated and 168 MER-treated eligible patients. Demographics, underlying diseases, immunosuppression and IAI severity were similar between the two groups. However, TIG-treated patients were less likely to have hospital-acquired IAI (61% vs 71% p=0.03), previous surgery (65% vs 51%, p=0.02) or require subsequent ICU admission (50% vs 40% p=0.06). TIG treated patients also had higher rates of co-treatment with piperacillin/tazobactam (80 vs. 23%, p <0.001), whereas patients in the MER group received more glycopeptides (48%vs. 14%, p<0.001). All-cause in-hospital mortality was similar among the two groups (9% vs 11%, p=0.59).

The cumulative incidence rate of CDAD was 10-fold lower in TIG-treated versus MER-treated patients (incidence rate ratio, IRR, 0.10 cases per 1000 patient hospital days, 95% CI 0.002-0.72, p=0.007) but was similar between TIG and MER-treated patients terms of CR-KP colonization (IRR 1.39 cases per 1000 patient days, 0.68-2.78, p=0.36). When analyzed by multivariate Cox-regression models that included treatment time period of diagnosis (to account for outbreaks) and antibiotic treatment duration as a time-dependent variable along with covariate risk factors for CDAD and CRE, receipt of TIG versus MER-based regimen was independently with significantly lower rates of CDAD (HR 0.094, 0.011-0.75, p=0.03) but not CRE colonization (HR 1.67, 0.79-3.51, P=0.182).

Conclusions: Compared to MER-containing treatment regimens, TIG-based antimicrobial treatment for IAI was associated with a 10-fold lower incidence of CDAD but had no apparent effect on the incidence of CRE colonisation. Further prospective studies are needed to confirm the potential benefits of carbapenem sparing strategies for reducing CDAD and CRE spread.

Figure. Incidence rate ratio of *C.difficile*-associated diarrhoea and carbapenem-resistant *Klebsiella pneumonia*e colonisation among patients receiving meropenem or tigecycline.


C. difficile-associated diarrhoea
0.50
0.40
0.30
0.20
0.10
0.00
Cumulative
P=0.006 Mantel-Cox
meropenem
tigecycline
0
20
40
60
80
Days of
Number at
meropenem 168 126 45 14 4
tigecycline 168 110 47 18 9


CR-KP colonization
1.00
0.75
0.50
0.25
0.00
Cumulative
P=0.36 Mantel-Cox
meropenem
tigecycline
0
20
40
60
80
Days of
Number at
meropenem 168 122 43 13 3
tigecycline 168 104 38 16 8