Superinfection: A forgotten quality measure of antimicrobial stewardship?

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Monitoring evidence of adverse events related to antibiotics was recommended by the 2016 Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines for implementing antibiotic stewardship programmes (ASP).[1] The guidelines however, have not addressed superinfections and which antibiotics are associated with higher risk of superinfections. This is likely due to limited data. Major concerns for the use of broad spectrum antibiotics include the emergence of superinfection during therapy.[2] Longer duration of antibiotics for ventilator-associated pneumonia (VAP) was associated with increased rates of susceptible and multidrug resistant superinfection.[3] The recommended antipseudomonal carbapenems for nosocomial pneumonia are imipenem and meropenem based on the current clinical practice guidelines but they should be reserved.[3] The authors hypothesised that these carbapenems might cause higher rates of superinfection attributed to their relatively broader spectrum of activity compared to other agents. Randomised controlled trials (RCTs) decrease the chance of selection bias but unfortunately do not consistently report superinfection rates and each is likely underpowered for detection of a statistically significant difference in occurrence of superinfections. Therefore, a meta-analysis was conducted with the aim of comparing the rate of superinfection between pneumonia patients who received imipenem or meropenem compared to non-carbapenem antibiotics.

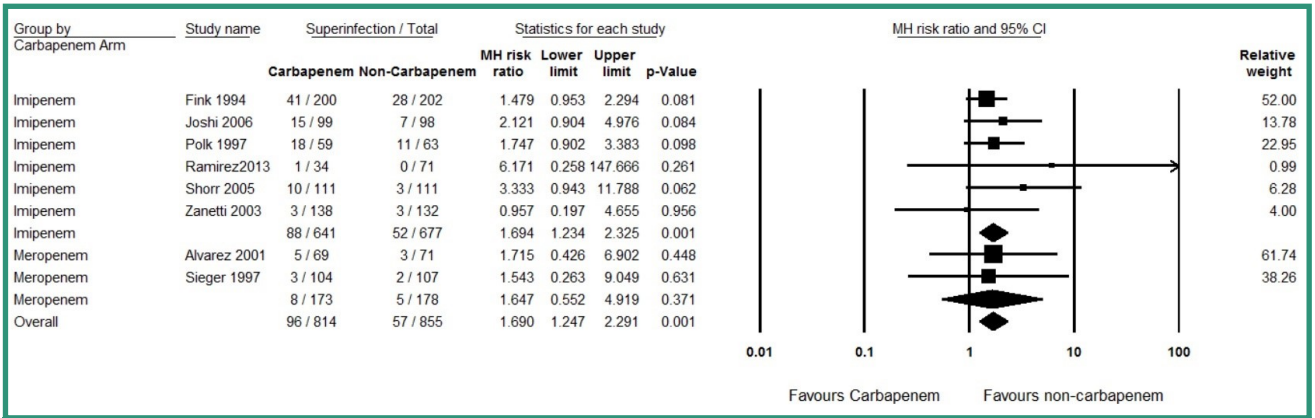
"Pneumonia treatment with imipenem associated with higher superinfection rates compared with non-carbapenem treatment."

Two researchers independently searched PubMed, Embase and Cochrane Library databases as well as the ClinicalTrials.gov and ClinicalTrialsRegister.eu websites without restriction of date or language until 25 February 2017 and performed the data extraction. The authors included RCTs of hospitalised adults with pneumonia that reported rates of superinfection and compared either imipenem or meropenem versus non-carbapenems. Superinfection was defined as isolation of a new pathogen after starting study antibiotic therapy and at least one of the following to reduce the likelihood of colonisation: symptoms and signs of infection and requiring treatment. The primary outcome was the superinfection rate based on the intention-to-treat (ITT) analysis. The secondary outcome was the superinfection rate among Clinically Evaluable (CE) patients. Subgroup analyses were done based on carbapenem type and pathogen according to the ITT principle and on presence of blinding. In addition, they analysed superinfection rates of carbapenems versus other antipseudomonal beta-lactams. Heterogeneity (I^2) was calculated using Cochrans's chi-squared test and risk ratios (RRs) with 95% confidence intervals (CIs) using random-effects models.

The search process identified 431 articles and eight RCTs (total of 1,874 patients) were included.[4-11] Based on ITT-analysis, the mean of superinfection was 11.79% (range, 2.88-30.51%) in the carbapenem group vs. 6.67% (range, 0-17.46%) in the non-carbapenem group. A statistically higher risk of superinfection (RR=1.69, 95% CI 1.25-2.29, p<0.001, I^2=0%) was associated with the two carbapenems compared to non-carbapenems **(Figure)**. In comparison with non-carbapenems, subgroup analysis showed that superinfection with imipenem was significantly higher (RR=1.69 [95% CI 1.23-2.33]; p<0.001; I^2=0%), while it was non-significant with meropenem (RR=1.65 [95% CI 0.55-4.92]; p=0.371; I^2=0%) (**Figure)**. The results did not change in subgroup analysis based on blinding and after restricting comparison group to anti-pseudomonal beta-lactams.

The difference was also statistically significant for CE-patients (RR=1.61 [95% CI 1.08-2.39]; p=0.018; I^2=0%). Only three studies reported the organisms causing superinfection[5,6,10]. *Pseudomonas aeruginosa* caused a statistically higher superinfection in the carbapenem group versus the fluoroquinolones group (RR=3.638 [95% CI 1.382-9.580]; p=0.047; I^2=0%; Q=0.009). There was no significant difference with other pathogens. However, it was not reported in any of the studies included if the bacteria causing superinfection were susceptible or resistant to the study antibiotic.

This is the first meta-analysis of RCTs showing higher risk of superinfection with carbapenems, especially imipenem, compared to other antibiotics including anti-



Forest plot showing the risk ratios of superinfection based on intent to treat analysis for patients receiving carbapenem versus non-carbapenem. Vertical line, "no difference" point between the 2 groups; horizontal line, 95% confidence interval; squares, risk ratios; diamonds, pooled risk ratios.

pseudomonal agents. Antibiotics change the normal protective microflora and its ecological balance in the body, leading to opportunistic pathogens overgrowth and superinfections.[12] It is a common clinical question to ask if carbapenem use causes more superinfections than other beta-lactam alternatives. The results provide support for using other antipseudomonal beta-lactams and reserving carbapenems for scenarios when they are really needed. A limitation of this meta-analysis is that superinfection was not characterised in all the studies included and thus superinfection may refer to fungal infection or the development of drug-resistant bacteria. Only three studies reported the organisms causing superinfection.[4,5,9] In this meta-analysis, the definition of superinfection was a clinical definition that took into account the development of symptoms and/or signs of infection and the need for treatment. This was done to reduce the possibility of colonisation, which is another dimension of antibiotic use. However, not all studies defined superinfection uniformly. For meropenem, only a few studies were included (post-hoc power calculation: 14.5%) and the pooled superinfection rate was not precise because the CI was wide. Another drawback is the fact that the imipenem studies were funded by the comparative drug manufacturers[5-9,11] and the two meropenem studies[4,10] were funded by the meropenem manufacturer. Thus, the presence of bias in reporting could not be entirely excluded.

In conclusion, a meta-analysis of pneumonia data of RCTs showed significantly higher superinfection with imipenem compared to non-carbapenems. Larger sample size is likely needed to determine if the same results apply to meropenem. This additional adverse outcome of carbapenem use provides added evidence to support reserving these valuable agents for the treatment of pneumonia caused by multidrug resistant organisms. Antibiotic stewardship programmes should seek to reduce unnecessary use of carbapenems.

References

1. Barlam TF *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016
2. Bliziotis IA *et al*. Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2005
3. Kalil AC *et al*. Executive Summary: Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016
4. Lerma FA *et al*. Efficacy of Meropenem as Monotherapy in the Treatment of Ventilator-Associated Pneumonia. *J Chemother* 2001
5. Fink MP *et al*. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group. *Antimicrob Agents Chemother* 1994
6. Joshi M *et al*. Comparison of piperacillin/tazobactam and imipenem/cilastatin, both in combination with tobramycin, administered every 6 h for treatment of nosocomial pneumonia. *Respir Med* 2006
7. Polk HC *et al.* Treatment of pneumonia in mechanically ventilated trauma patients. Results of a prospective trial. *Arch Surg* 1997
8. Ramirez J *et al.* Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 2013
9. Shorr AF *et al*. Levofloxacin for treatment of ventilator-associated pneumonia: a subgroup analysis from a randomized trial. *Clin Infect Dis* 2005
10. Sieger B *et al*. Empiric treatment of hospital-acquired lower respiratory tract infections with meropenem or ceftazidime with tobramycin: a randomized study. Meropenem Lower Respiratory Infection Group. *Crit Care Med* 1997
11. Zanetti G *et al*. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother* 2003
12. Sullivan A Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis* 2001
13. Masterton RG. Carbapenems in serious infections: maximizing the power, minimizing resistance. *Clin Microbiol Infect* 1999
14. Paul M *et al*. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. *BMJ* 2004