

**Diagram D2:****Meta-analysis of randomized trials using piperacillin-containing regimens exploring renal failure**

Identification	Potentially relevant Randomized trials investigating piperacillin regimens: PubMed search term [piperacillin]. Limits: “Randomized controlled trial”, “English” and “All adult: 19+ years” (N=212)	
Screening	Screened (N=212)	Excluded (N=78) Not RCT (unsystematic review, letter, comment): 9 Economic study: 3 Laboratory or other non-clinical study: 30 Prophylaxis study (1-3 administrations): 33 Not access to article (journal no longer exists or other reason): 3
Eligibility	Assessed for eligibility (N=134)	Excluded (N=127) Not investigating a piperacillin regimen: 31 Piperacillin administered in both arms: 20 All patients had end stage renal failure at baseline: 2 N<50: 10 Aminoglycoside in one or both arms: 39 Did not report renal failure*: 25
Included	Included (N=7)	Renal failure defined biochemically or referred to any adopted standard: 2 (1, 2)  Renal failure not defined biochemically or referred to any adopted standard: 5 (3-7)

**Results:**

- In the initial identification phase, four ICU studies were found: They were excluded, since A) only a (non-defined) part of the patients received piperacillin(8), B) Both groups received piperacillin(9), C) one or both groups received aminoglycosides concomitantly(10, 11) .
- In the 7 (non-ICU) trials eventually included, 1592 episodes of therapy were observed.
- 21 cases of renal failure (not defined) occurred, corresponding to 1.3%.
- Hypothesizing, that the incidence of renal failure is 0.5% in non-piperacillin containing beta-lactam therapies, and aiming to find a risk increase to totally 1.5% (relative risk of 3.0), using conventional type I risk limit of 5% and a power of 80%, the sample size for such a trial investigating this should be approx. 3300 patients (non-ICU setting).
- In an ICU setting, the incidence of renal failure is often >20%. A trial of 1000 patients would be able to detect a risk increase to 28% (Relative risk:1.4) from e.g. piperacillin

\*All articles were reviewed for this. Additionally, in adobe documents with the search option (those not scanned), a search was made in each pdf document with search terms: “renal”, “kidney”, “nephro”, “creatinine” and “gfr”. More than the noted 25 of the articles did not report renal failure, however, if they fulfilled one or more of the other exclusion criteria, they were excluded because of this.

## References (for meta-analysis)

1. Anaissie EJ, Fainstein V, Bodey GP, et al. Randomized trial of beta-lactam regimens in febrile neutropenic cancer patients. *Am J Med.* 1988; 84: 581-9.
2. Winston DJ, Ho WG, Bruckner DA, et al. Beta-lactam antibiotic therapy in febrile granulocytopenic patients. A randomized trial comparing cefoperazone plus piperacillin, ceftazidime plus piperacillin, and imipenem alone. *Ann Intern Med.* 1991; 115: 849-59.
3. Schmitt DV, Leitner E, Welte T, et al. Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study. *Infection.* 2006; 34: 127-34.
4. Dela Pena AS, Asperger W, Kockerling F, et al. Efficacy and safety of ertapenem versus piperacillin-tazobactam for the treatment of intra-abdominal infections requiring surgical intervention. *J Gastrointest Surg.* 2006; 10: 567-74.
5. Philpott-Howard J, Burroughs A, Fisher N, et al. Piperacillin-tazobactam versus ciprofloxacin plus amoxicillin in the treatment of infective episodes after liver transplantation. *J Antimicrob Chemother.* 2003; 52: 993-1000.
6. Marra F, Reynolds R, Stiver G, et al. Piperacillin/tazobactam versus imipenem: a double-blind, randomized formulary feasibility study at a major teaching hospital. *Diagn Microbiol Infect Dis.* 1998; 31: 355-68.
7. Bohme A, Just-Nubling G, Bergmann L, et al. A randomized study of imipenem compared to cefotaxime plus piperacillin as initial therapy of infections in granulocytopenic patients. *Infection.* 1995; 23: 349-55.
8. Combes A, Luyt CE, Fagon JY, et al. Impact of piperacillin resistance on the outcome of *Pseudomonas* ventilator-associated pneumonia. *Intensive Care Med.* 2006; 32: 1970-8.
9. Rafati MR, Rouini MR, Mojtahedzadeh M, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. *Int J Antimicrob Agents.* 2006; 28: 122-7.
10. Alvarez-Lerma F, Insausti-Ordenana J, Jorda-Marcos R, et al. Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial. *Intensive Care Med.* 2001; 27: 493-502.
11. Brun-Buisson C, Sollet JP, Schweich H, et al. Treatment of ventilator-associated pneumonia with piperacillin-tazobactam/amikacin versus ceftazidime/amikacin: a multicenter, randomized controlled trial. VAP Study Group. *Clin Infect Dis.* 1998; 26: 346-54.