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## Vancomycin plus piperacillin/tazobactam and acute kidney injury in adults: a systematic review and meta-analysis

Megan Luther

Tristan Timbrook

Aisling R. Caffrey

*University of Rhode Island, aisling\_caffrey@uri.edu*

David Dosa

Thomas Lodise

See next page for additional authors  
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**Authors**

Megan Luther, Tristan Timbrook, Aisling R. Caffrey, David Dosa, Thomas Lodise, and Kerry L. LaPlante

1 Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: A systematic review  
2 and meta-analysis

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6 Megan K. Luther, Pharm.D.<sup>1-3\*</sup>, Tristan T. Timbrook, Pharm.D., MBA, BPCS<sup>1,2</sup>, Aisling R.  
7 Caffrey, Ph.D., MS<sup>1-4</sup>, David Dosa, MD, MPH<sup>3,4</sup>, Thomas P. Lodise, Pharm.D., Ph.D.<sup>5</sup>, Kerry L.  
8 LaPlante, Pharm.D., FCCP<sup>1-4</sup>

9 1. Rhode Island Infectious Diseases (RIID) Research Program, Veterans Affairs Medical Center,  
10 Providence, RI

11 2. University of Rhode Island, College of Pharmacy, Kingston, RI

12 3. Center of Innovation in Long-Term Services and Supports, Veterans Affairs Medical Center,  
13 Providence, RI

14 4. Brown University, Providence, RI

15 5. Albany College of Pharmacy and Health Sciences, Albany, NY

16 \*Corresponding author: Megan K. Luther, PharmD, Research Fellow, Rhode Island Infectious  
17 Diseases Research Program, Providence VA Medical Center Building 7, 830 Chalkstone Ave,  
18 Providence, RI 02908. Office: 401-273-7100 x6425; email: megankluther@gmail.com

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33 Abstract:

34 Objective: The objective of this systematic review and meta-analysis was to assess acute  
35 kidney injury (AKI) with combination therapy of vancomycin plus piperacillin-tazobactam  
36 (VAN+PT) in general adult patients and in critically ill adults. Rates of AKI, time to AKI, and odds  
37 of AKI were compared to vancomycin monotherapy (VAN), vancomycin plus cefepime or  
38 carbapenem (VAN+FEP/CAR), or piperacillin-tazobactam monotherapy (PT).

39 Data Sources: Studies were identified by searching Pubmed, Embase, Web of Science, and  
40 Cochrane from inception to April 2017. Abstracts from selected conference proceedings were  
41 manually searched.

42 Study selection: Articles not in English, pediatric studies, and case reports were excluded.

43 Data Extraction: Two authors independently extracted data on study methods, rates of AKI, and  
44 time to AKI. Effect estimates and 95% confidence intervals (CI) were calculated using the  
45 random effects model in RevMan 5.3.

46 Data synthesis: Literature search identified 15 published studies and 17 conference abstracts  
47 with at least 24,799 patients. The overall incidence of AKI was 16.7%, with 22.2% for VAN+PT  
48 and 12.9% for comparators. This yielded an overall number needed to harm of 11. Time to AKI  
49 was faster for VAN+PT than VAN+FEP/CAR, but not significantly (mean difference -1.30,  
50 95%CI -3.00-0.41 days). The odds of AKI with VAN+PT were increased versus VAN (OR 3.40;  
51 95%CI 2.57-4.50), versus VAN+FEP/CAR (OR 2.68; 95%CI 1.83-3.91) and versus PT (OR  
52 2.70; 95% CI 1.97-3.69). In a small sub-analysis of 968 critically ill patients, the odds of AKI  
53 were increased versus VAN (OR 9.62, 95%CI 4.48-20.68), but not significantly different for  
54 VAN+FEP/CAR (OR 1.43, 95%CI 0.83-2.47) or PT (OR 1.35, 95%CI 0.86-2.11).

55 Conclusion: The combination of VAN+PT increased the odds of acute kidney injury over VAN,  
56 VAN+FEP/CAR, and PT. Limited data in critically ill patients suggest the odds of AKI are  
57 increased versus VAN, and mitigated versus the other comparators. Further research in the  
58 critically ill population is needed.

59 Introduction

60 Acute kidney injury (AKI) is associated with increased morbidity and mortality (1-4).  
61 There are several definitions, but recent consensus documents focus on three: 1) Risk, Injury,  
62 Failure, Loss, End-stage (RIFLE) (5), 2) Acute Kidney Injury Network (AKIN) (6), and 3) Kidney  
63 Disease: Improving Global Outcomes (KDIGO) (7), which is a combination of the other two  
64 definitions. When defined as an increase in serum creatinine of 0.5mg/dL or greater, one  
65 component of the RIFLE definition, AKI increases length of hospital stay by approximately 3.5  
66 days and costs by ~\$7500 (1). Mortality is also increased approximately 6.5-fold, and increases  
67 even more with larger increases in serum creatinine (1). The poor outcomes associated with  
68 AKI have also been demonstrated in several studies of critically ill patients (2, 4, 8, 9), with rates  
69 of AKI in intensive care unit (ICU) populations ranging from 28-67% (8, 10-12).

70 Historically, risk of AKI during vancomycin treatment has been widely known, and  
71 ranged from 5 to 7% (13, 14). Increases in doses and target trough concentrations may be  
72 responsible for the recent observed increases in rates of vancomycin-associated AKI, up to  
73 43%.(15-19) Although there is some controversy over whether vancomycin monotherapy can  
74 cause nephrotoxicity or AKI in an otherwise healthy person, it is generally agreed that  
75 concomitant nephrotoxic agents, as well as many comorbid conditions and drug exposure  
76 factors, such as dosing, trough concentrations, and duration of therapy, increase this risk (15,  
77 20-22). Risk factors, including vasoactive medications, hypotension, and increased disease  
78 severity, are often associated with the critically ill population, where vancomycin is prevalent  
79 (23, 24).

80 Since 2011, there have been multiple studies demonstrating an increase in AKI with  
81 combination therapy of vancomycin plus piperacillin-tazobactam (25-56). Vancomycin plus  
82 piperacillin-tazobactam is one of the most commonly used combinations of antimicrobials with

83 widespread use in hospitals (57). Rates of AKI in these initial studies ranged from 18 to 49%  
84 with the combination (32, 33, 49, 52). Initial reports were small observational studies, often in  
85 very specific patient populations, such as diabetic patients with osteomyelitis or patients in the  
86 surgical ICU.(33, 41, 52) Given increases in mortality and length of stay associated with AKI  
87 and the widespread use of vancomycin plus piperacillin-tazobactam, this combination could  
88 have a substantial effect on patient outcomes

89           This systematic review and meta-analysis was performed to determine the association  
90 between vancomycin plus piperacillin-tazobactam and acute kidney injury in adults. . AKI rates  
91 and odds ratios were calculated for each comparator: vancomycin alone, vancomycin plus other  
92 beta-lactams (cefepime or carbapenem), and piperacillin-tazobactam alone. Time to AKI was  
93 evaluated to determine whether onset occurred faster with the combination of vancomycin plus  
94 piperacillin-tazobactam. Additionally, a sub-analysis in critically ill patients was performed for  
95 each comparator group to determine if the effects were enhanced or mitigated.

96

97 Methods

98 Literature Search

99 Two authors (MKL and TTT) independently performed a systematic literature review.  
100 Pubmed, Embase, Web of Science, and Cochrane were systematically searched from inception  
101 to April 15, 2017. Keywords of vancomycin, piperacillin, and kidney, renal, nephrotoxicity,  
102 nephropathy, nephritis, safety or adverse were used. Reference lists of included studies were  
103 manually searched for relevant studies.

104 Study Selection

105 Titles and abstracts of potentially relevant studies were reviewed. Randomized or  
106 observational reports were eligible to be included in the meta-analysis if they: 1) enrolled adult  
107 patients ( $\geq 18$  years old), 2) included patients on concomitant vancomycin and piperacillin-  
108 tazobactam and either vancomycin alone, vancomycin plus another beta-lactam, or piperacillin-  
109 tazobactam alone, and 3) nephrotoxicity/ acute kidney injury rates or odds ratios could be  
110 extracted for each group. All definitions of AKI that referenced specific changes in serum  
111 creatinine (e.g. 1.5-fold or 0.5mg/dL increase), urine output, or need for dialysis/ renal  
112 replacement therapy were included. Studies that used a definition referring to an upper limit of  
113 normal serum creatinine were excluded. Pediatric studies, case reports/ series, and articles not  
114 in English were excluded. Abstracts from conference proceedings were included. In addition to  
115 conference abstracts included in the database search, we manually searched abstract  
116 collections from IDweek, Interscience Conference on Antimicrobial Agents and Chemotherapy  
117 (ICAAC), Kidney Week, American College of Clinical Pharmacy (ACCP), Society of Critical Care  
118 Medicine (SCCM), and American Society of Health-System Pharmacists (ASHP) midyear  
119 meeting for full text abstracts using the keywords vancomycin, piperacillin, or zosyn. Data from  
120 final posters were used when available online. Authors were not contacted for missing data.

121 Study Quality

122 The quality of included studies was assessed using the Newcastle-Ottawa quality  
123 assessment score (58). Each study was scored from 0 to 9, based on eight criteria covering  
124 selection of cohort, comparability of groups, and outcome. Discrepancies between the two  
125 authors were resolved by consensus.

126 Data extraction

127 Data collected from each study included author, publication year, study design, location  
128 and dates of enrollment, inclusion and exclusion criteria, definition of acute kidney injury used,  
129 medications included, and measures of outcomes (e.g. acute kidney injury rates).

130 Outcomes

131 The primary outcome for the meta-analysis was acute kidney injury, as defined by the  
132 individual study. Most studies used AKIN, RIFLE, KDIGO, or vancomycin consensus guidelines  
133 to define acute kidney injury or nephrotoxicity (5-7, 20). The percentage of patients developing  
134 AKI with each drug regimen were calculated, and used to calculate an overall number needed to  
135 harm. Time to AKI was extracted from studies when provided for groups of interest. Median and  
136 interquartile range were converted to mean and standard deviation using methods from Wan et  
137 al.(59) A secondary analysis was performed for critically ill patients, defined as being in an  
138 intensive care unit, to determine whether the impact of these medications on AKI was mitigated  
139 or enhanced in ICUs.

140 Statistical Analysis

141 AKI rate differences, and corresponding p-values, as well as the number needed to harm  
142 were calculated from OpenEpi.(60) Meta-analysis was performed in Review Manager 5.3  
143 (RevMan; Cochrane Library, UK) (61). Pooled odds ratios (OR) and 95% confidence intervals



144 (CI) were calculated using the generic inverse variance random effects model for each  
145 comparator (vancomycin monotherapy, piperacillin-tazobactam monotherapy, or vancomycin  
146 plus cefepime or a carbapenem). Crude odds ratios were calculated from the raw AKI rates in  
147 each study. Adjusted odds ratios were used over the crude odds ratio when provided for the  
148 groups of interest. Mean difference in time to AKI was calculated using a random effects model.  
149 Publication bias was assessed using funnel plots. Heterogeneity was assessed by  $I^2$  statistic  
150 and Cochran's  $Q$ . A p-value <0.10 was considered statistically significant since Cochran's  $Q$  has  
151 low power. Sensitivity analyses were performed (1) by removing each study individually in order  
152 to determine whether an individual report has higher contribution to the heterogeneity or overall  
153 effect estimate, (2) analyzing published studies separately from abstracts, (3) including only  
154 high quality reports (Newcastle Ottawa score  $\geq 7$ ), and (4) including only reports that used  
155 methods to control for confounding. Reporting for this meta-analysis is in accordance with the  
156 Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidance (62).

157

158 Results

159 A flow diagram of the literature search is shown in Figure 1. The search identified 15  
160 published studies meeting inclusion and exclusion criteria for the meta-analysis (Supplemental  
161 Table 1). Six studies compared vancomycin plus piperacillin-tazobactam to vancomycin  
162 monotherapy (26, 27, 30, 32, 37, 39), while eight studies compared to vancomycin plus  
163 cefepime or carbapenem (25, 28, 29, 33, 34, 36, 38, 39) and four compared to piperacillin-  
164 tazobactam monotherapy (30, 31, 35, 37). Three studies had multiple comparisons (30, 37, 39).  
165 One study was excluded from the vancomycin plus cefepime analysis because the data  
166 overlapped another study (34, 39). We also identified 17 abstracts from conference proceedings  
167 (Supplemental Table 2) (40-56), with a total number of patients from published studies and  
168 conference abstracts of at least 24,799. There is overlap between separate studies from the  
169 same research groups against different comparator antibiotics.(34, 37-39) However, patients in  
170 overlapping groups were not double-counted, so the total number of patients in Supplemental  
171 Tables 1 and 2 is greater than this number.

172 There were significant differences in study populations evaluated. Mean age ranged  
173 from 48 to 74, and severity of illness differed between studies (29, 30, 36, 52). There were also  
174 differences among the exclusion criteria for studies which included varying serum creatinine  
175 values of >1.2mg/dL(34), >1.5mg/dL(26, 40), >2mg/dL(27), and >2.5mg/dL (36), or creatinine  
176 clearance values of <30(26), <40(33), and <60mL/min(28, 63) (See Supplemental Tables 1 and  
177 2) . Administration of antibiotics was continuous or extended in some patients, but not  
178 others.(41) Comorbidities, such as diabetes, infection type, and other concomitant medications  
179 frequently play a role in AKI, but were not uniform across studies (27, 33). Some studies  
180 controlled for confounding factors in their analyses, by matching patients on other risk factors for  
181 AKI or using logistic regression (27, 32, 34, 44, 53). Not all studies, however, adjusted for the  
182 same variables.

183 In all reports evaluated, the rate of acute kidney injury ranged from 5 to 65% for  
184 vancomycin plus piperacillin-tazobactam (Figure 2) (27, 29, 33, 46, 51). Overall, 16.7%  
185 developed (4133/24799) acute kidney injury. AKI developed with vancomycin plus piperacillin-  
186 tazobactam for 22.2% (2212/9945) of patients, while AKI was reported in 12.9% (1921/14854)  
187 of patients exposed to vancomycin monotherapy, vancomycin plus cefepime or carbapenem, or  
188 piperacillin-tazobactam monotherapy. Using these overall rates of acute kidney injury with  
189 vancomycin plus piperacillin-tazobactam versus comparator antibiotics led to a number needed  
190 to harm of 11. Compared with vancomycin plus piperacillin-tazobactam, AKI rates were  
191 significantly lower in the comparison groups ( $p < 0.00001$ ): 8.1% for vancomycin alone (risk  
192 difference 13.4%, 95% CI 12.2-14.6%), 20.0% for vancomycin plus cefepime or carbapenem  
193 (risk difference 3.8%, 95% CI 2.1-5.5%), and 10.5% for piperacillin-tazobactam alone (risk  
194 difference 10.7%, 95% CI 9.5-11.9%).

195 Time to AKI, in days, was analyzed (Figure 3). Only studies comparing vancomycin plus  
196 piperacillin-tazobactam to vancomycin plus cefepime reported time to AKI separately for each  
197 group. Among five studies reporting this outcome, time to AKI was shorter with vancomycin plus  
198 piperacillin-tazobactam, but not significantly (mean difference -1.30, 95% CI -3.00-0.41,  $p = 0.14$ ).  
199 Among other studies reporting an average time to AKI for all patients, average AKI onset  
200 occurred by 8 days (27, 28, 32-34, 37, 38, 45, 47, 50). Unfortunately, some studies only  
201 identified AKI within the first 7 days of therapy, or excluded patients with AKI within 48-72h  
202 depending on the study's inclusion criteria for minimum antibiotic duration (26, 50, 51).

203 Vancomycin plus piperacillin-tazobactam increased the odds of AKI versus each  
204 comparator. The odds of AKI increased with vancomycin plus piperacillin-tazobactam versus  
205 vancomycin monotherapy (OR 3.40, 95% CI 2.57-4.50; Figure 4A). Compared to vancomycin  
206 plus cefepime or carbapenem, the OR for AKI with vancomycin plus piperacillin-tazobactam was  
207 2.68 (95% CI 1.83-3.91; Figure 4B), and compared to piperacillin-tazobactam monotherapy, the  
208 OR was 2.70 (95% CI 1.97-3.69; Figure 4C). Heterogeneity was significant for each of these

209 analyses ( $I^2 \geq 53\%$ ,  $p \leq 0.01$ ). In an analysis separating studies with vancomycin plus cefepime  
210 and vancomycin plus carbapenem, no significant differences in the OR for AKI were found (2.39  
211 vs 3.46, respectively,  $p=0.33$ , see Supplemental material).

212         Among critically ill populations, the odds of AKI vary depending on the comparator  
213 antibiotic. One recent study of the critically ill found no significant increase in AKI with the  
214 combination of vancomycin and piperacillin-tazobactam compared to vancomycin plus cefepime  
215 (29). Another study found an almost 10-fold increase compared to vancomycin monotherapy in  
216 patients from a surgical ICU (52). Two studies in patients in burn units also found 7 to 10-fold  
217 increases in AKI over vancomycin monotherapy (46, 54). The meta-analysis of critically ill  
218 patients included three studies comparing to vancomycin alone, three studies comparing to  
219 vancomycin plus cefepime or carbapenem, and one study comparing to piperacillin-tazobactam  
220 alone, for a total of 968 patients. In the subset of critically ill patients, the odds of AKI compared  
221 to vancomycin were increased (OR 9.62; 95%CI 4.48-20.68; Figure 5). The odds of AKI  
222 compared to vancomycin plus cefepime or carbapenem, or piperacillin-tazobactam alone were  
223 decreased and no longer significantly different.

224         Multiple sensitivity analyses were conducted, which resulted in overall similar odds  
225 ratios. In a sensitivity analysis evaluating the removal of individual studies, only Rutter et al.  
226 comparing vancomycin plus piperacillin-tazobactam to vancomycin alone resulted in significant  
227 changes in the heterogeneity, which accounted for over 2/3rds of patients in this analysis, with a  
228 relatively small confidence interval.(37) In a sensitivity analyses looking at published studies  
229 versus abstracts, the ORs for published manuscripts were similar to the overall analysis  
230 (published and abstracts) for vancomycin monotherapy and vancomycin plus cefepime or  
231 carbapenem, but the heterogeneity was lower for published studies ( $p > 0.10$ ; see Supplemental  
232 material). The point estimate for published manuscripts was slightly lower for piperacillin-  
233 tazobactam (1.89 vs 2.70), but heterogeneity was still significant ( $I^2=59\%$ ,  $p=0.06$ ). In the quality  
234 assessment, the range of NOS scores was between 3 and 9 (maximum of 9; see supplemental

235 Table 3). Sensitivity analyses using only high quality reports with a NOS $\geq$ 7 and one with reports  
236 that utilized methods to control for confounding, demonstrated similar odds ratios to the primary  
237 analysis which included all reports (see supplemental material). Of note, all high quality reports  
238 used methods to control confounding. In these analyses, only two studies compared  
239 vancomycin plus piperacillin-tazobactam to piperacillin-tazobactam monotherapy. Between-  
240 study heterogeneity remained significant.

241 Discussion

242 This systematic review and meta-analysis demonstrated increased odds of acute kidney  
243 injury with concomitant vancomycin and piperacillin-tazobactam use. This increase was  
244 observed with multiple comparison groups, including vancomycin monotherapy, vancomycin  
245 plus cefepime or a carbapenem, and piperacillin-tazobactam monotherapy.

246 The results of this meta-analysis are overall similar to another meta-analysis published  
247 on vancomycin and piperacillin-tazobactam, which demonstrated aORs of 2.50 (95%CI 0.41-  
248 15.44) for vancomycin alone, 3.78 (95%CI 2.48-5.78) for vancomycin plus cefepime, and 3.15  
249 (95%CI 1.72-5.76) for adults (63). A second, recent meta-analysis also demonstrated OR of  
250 3.65 (95%CI 2.16-6.17) for vancomycin plus beta-lactam and 3.98 (95%CI 2.75-5.76) for  
251 vancomycin alone (64). Of note, the other meta-analyses on this topic have included pediatric  
252 studies. This is the first meta-analysis, to our knowledge, to calculate a number needed to harm  
253 for AKI with vancomycin plus piperacillin-tazobactam therapy. It also includes a sub-analysis of  
254 only critically ill patients, which have not been documented in previous meta-analyses.  
255 Hammond et al. included an analysis by percentage of patients in ICUs (63). This analysis  
256 demonstrated non-significant results for studies with more than 50% ICU patients with an aOR  
257 of 2.83 (95%CI 0.74-10.85) using four studies, mostly in children.

258 Among the critically ill adult population, there was wide variability in the odds of AKI,  
259 depending on the comparator medication (Figure 5). Within each comparator group, however,  
260 there was no heterogeneity observed. The meta-analysis subgroup of critically ill patients is  
261 relatively small, since not all studies included data specifically on ICU patients, but was able to  
262 demonstrate statistically significant results for vancomycin plus piperacillin-tazobactam versus  
263 vancomycin monotherapy (OR 9.62; 95% CI 4.48-20.68). Only seven studies included critically  
264 ill data, with a total of 968 patients. None of these studies included adjusted odds ratios for  
265 these patients, so it is possible that risk factors for kidney injury, such as severity or type of

266 illness, contrast media, hypotension, or other factors are responsible or playing a role in these  
267 cases of AKI. Randomized controlled trials comparing monotherapy and combination therapy  
268 are unlikely, but by comparing vancomycin plus piperacillin-tazobactam to vancomycin plus  
269 cefepime or carbapenem, some of the concerns about confounding can be limited. These  
270 patients would theoretically have similar risks of sepsis or ICU admission, however this may not  
271 eliminate potential confounding entirely. The critically ill subset of this meta-analysis with  
272 vancomycin plus cefepime or carbapenem did not demonstrate significant differences in AKI  
273 from vancomycin plus piperacillin-tazobactam (OR 1.43; 95% CI 0.83-2.47) which may indicate  
274 that these patients are similar, or have more similar risks for AKI. Only one study in the literature  
275 search included data on AKI in critically ill patients on piperacillin-tazobactam monotherapy, in  
276 patients with intraabdominal infections (35). This study was included as a comparator in the  
277 critically ill sub-analysis, but should be considered carefully due to the limited size and lack of  
278 similar studies in the meta-analysis. The analysis demonstrates possible differential effects in  
279 ICU patients, which should be investigated in future studies. In addition, prospective randomized  
280 controlled trials investigating vancomycin plus piperacillin-tazobactam versus vancomycin plus  
281 cefepime would be helpful in determining the true effect size.

282         It may be of clinical interest to compare the vancomycin plus cefepime and vancomycin  
283 plus carbapenem subgroups. In these analyses, there was no significant difference in the odds  
284 of AKI versus vancomycin plus piperacillin-tazobactam. One study included both cefepime and  
285 carbapenem, with a wide confidence interval (1.54-33.15) (36), but the chi-square test remained  
286 non-significant when removed, indicating no difference between the cefepime and carbapenem  
287 subgroups. There were, however, only three studies, and a limited number of patients, that used  
288 vancomycin plus carbapenem (see Supplemental material). Consideration may be given to  
289 clinical scenarios or select patients in which vancomycin plus cefepime or a carbapenem may  
290 be preferable for antibiotic coverage to limit the risk of AKI.

291           Given the number needed to harm of 11, along with the widespread use of this  
292 combination therapy, AKI with vancomycin plus piperacillin-tazobactam likely has a large impact  
293 on patient outcomes with the increased length of stay, costs, and mortality associated with AKI  
294 (1). Although AKI with vancomycin is typically reversible, even transient AKI in critically ill  
295 patients has been associated with increased mortality (8). Daily ICU costs can also be much  
296 higher, which would increase the costs above the \$7500 previously quoted for hospital-wide  
297 patients (1). Reducing the use and duration of vancomycin and piperacillin-tazobactam could  
298 reduce AKI incidence (31, 34). Strategies to aid in this aim include utilizing antimicrobial  
299 stewardship policies; such as protocols for using alternative antibiotics when appropriate,  
300 institution-specific guidance on when combination therapy is necessary, and institutional  
301 antibiograms for susceptibility. Other stewardship programs have utilized antibiotic restriction  
302 and time-outs to decrease use of vancomycin and/or piperacillin-tazobactam (31, 65).  
303 Stewardship programs have thus demonstrated reduced rates of AKI (27). Most studies in the  
304 meta-analysis required at least 48-72h of antibiotic therapy to be included, and the analysis of  
305 time to AKI noted an onset within 8 days. Rapid diagnostic test implementation in hospital  
306 settings may help to de-escalate from vancomycin plus piperacillin-tazobactam therapy sooner,  
307 potentially avoiding AKI.(66) Unfortunately, time to AKI was not available for studies in ICU  
308 populations, so further research is needed.

309           The mechanism of increased AKI with vancomycin and piperacillin-tazobactam is not  
310 known. Though there are reports of acute kidney injury or acute interstitial nephritis with  
311 cefepime, carbapenems, and other non-piperacillin-tazobactam beta-lactams, these reports are  
312 rare compared to the studies of piperacillin-tazobactam (67-69). One study also noted that  
313 piperacillin-tazobactam had the lowest renal recovery rate (measured by change in creatinine  
314 clearance) among beta-lactams tested, indicating possible kidney hazard with piperacillin-  
315 tazobactam (70). Piperacillin-tazobactam has not traditionally been considered a nephrotoxic



316 medication, however several studies, and the pooled percentages of AKI we calculated,  
317 demonstrated increased odds of AKI with piperacillin-tazobactam monotherapy over  
318 vancomycin monotherapy (30, 41, 42, 44, 49, 55). Since both vancomycin and piperacillin-  
319 tazobactam have been associated with interstitial nephritis, and vancomycin has also been  
320 associated with acute tubular necrosis, it is possible that this combination has augmented  
321 effects on nephrotoxicity rates (71-73). Recent studies have also identified compatibility issues  
322 with different concentrations of vancomycin and piperacillin-tazobactam (74-78). Although it is  
323 not clear from these studies what happens in the bloodstream, precipitation of these  
324 medications could lead to kidney damage.

325         There are other limitations to this analysis. These observational studies are subject to  
326 possible bias such as confounding by indication, since patients receiving different therapies are  
327 likely different in other ways. There is also the possibility of misclassification bias; it is not clear  
328 in all the studies whether the vancomycin alone group received other antibiotics (ie, not  
329 piperacillin-tazobactam) that may include cefepime or carbapenems. The results, however, of  
330 the meta-analyses for vancomycin alone and vancomycin plus cefepime or carbapenem were  
331 similar, and any changes from misclassification would likely be small. We cannot rule out  
332 publication bias among the included reports (supplemental material). Larger studies and studies  
333 indicating a higher risk of AKI with combinations of vancomycin and piperacillin-tazobactam may  
334 be more likely to be published than those not demonstrating a significant difference. In the  
335 funnel plots in supplemental material, this is indicated by the lack of studies with low ORs and  
336 higher standard errors. We chose to present the results of conference abstracts, to see the  
337 impact on the overall odds ratio and compare the results. Of course, conference abstracts have  
338 limitations, including that they may have been edited before final presentation, they are not  
339 always peer-reviewed, and some information may be missing. Additionally, not all abstracts  
340 from the included conferences could be accessed in the collections searched. Our results,

341 including abstracts from well-known infectious diseases, critical care, and pharmacy  
342 conferences, however, indicated similar odds of AKI as published studies.

343 Conclusion

344 Available literature suggests that the combination of vancomycin plus piperacillin-  
345 tazobactam increases the odds of acute kidney injury approximately 3-fold. This increased risk  
346 was present versus vancomycin monotherapy, piperacillin-tazobactam monotherapy, and  
347 vancomycin plus cefepime or carbapenem combination therapy. Although small, the analysis of  
348 critically ill patients suggests the odds of AKI with vancomycin plus piperacillin-tazobactam are  
349 increased over vancomycin monotherapy, but mitigated versus vancomycin plus cefepime or  
350 carbapenem. Further research in critically ill patients is needed.

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353 Acknowledgements

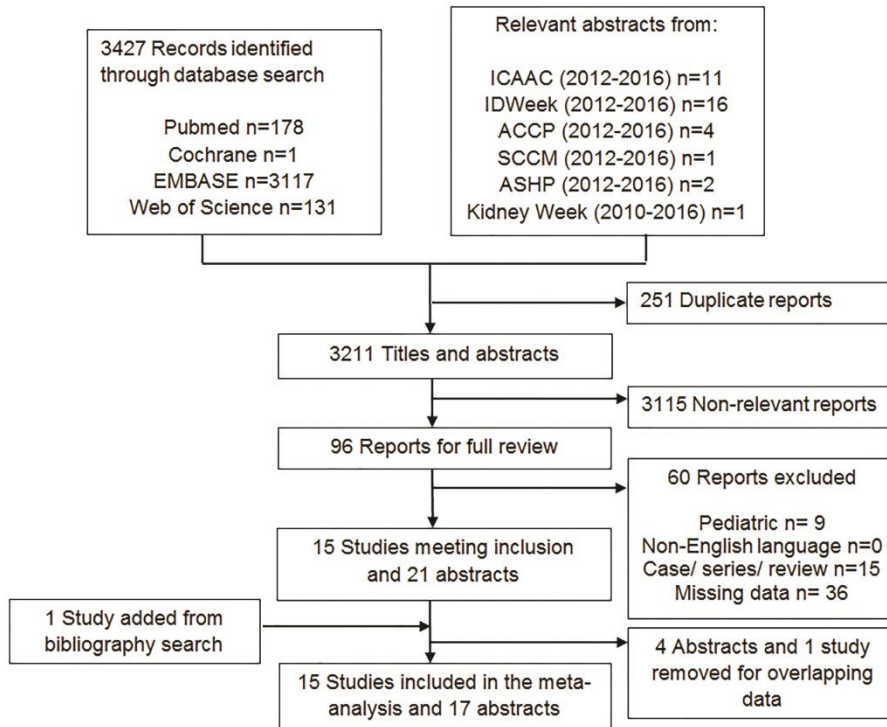
354           This material is the result of work supported in part by resources and use of facilities at  
355 the Providence Veterans Affairs Medical Center. The contents do not represent the views of the  
356 U.S. Department of Veterans Affairs or the United States government. An earlier version of this  
357 meta-analysis was presented as a poster (#1805) at IDweek 2016, October 29, 2016, New  
358 Orleans, LA.

359

360 Figure 1. Literature search flow diagram.

361 Abbreviations: ICAAC, Interscience Conference on Antimicrobial Agents and Chemotherapy;  
362 ACCP, American College of Clinical Pharmacy; SCCM, Society of Critical Care Medicine;  
363 ASHP, American Society of Health-System Pharmacists

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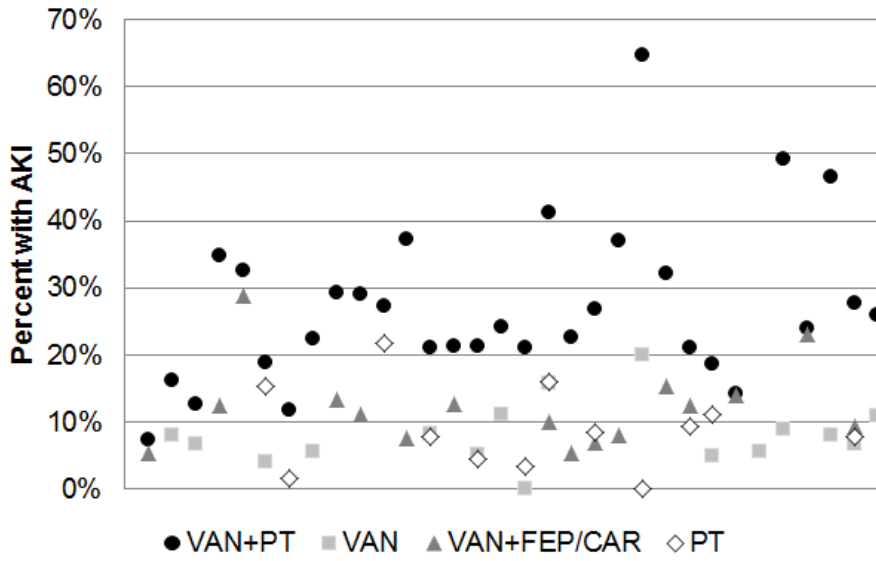
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368 Figure 2. Scatterplot of percentage of patients with acute kidney injury in included studies.

369

370 Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; VAN, vancomycin;

371 FEP/CAR, cefepime or carbapenem; PT, piperacillin-tazobactam; AKI, acute kidney injury.



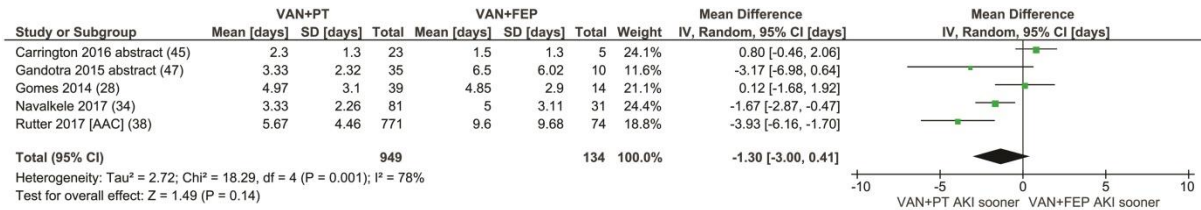
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374 Figure 3. Mean difference in time (days) to acute kidney injury for vancomycin plus piperacillin-  
 375 tazobactam versus vancomycin plus cefepime.

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377 Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; FEP, cefepime; IV, inverse  
 378 variance; SD, standard deviation; CI, confidence interval.



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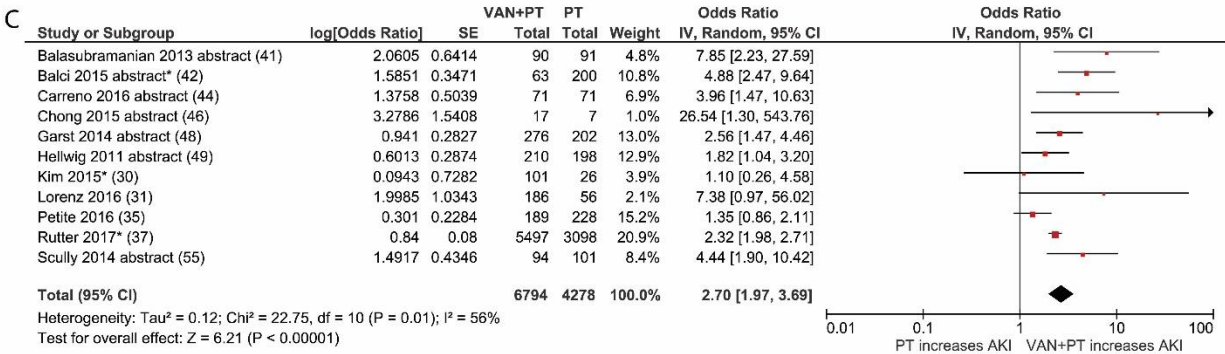
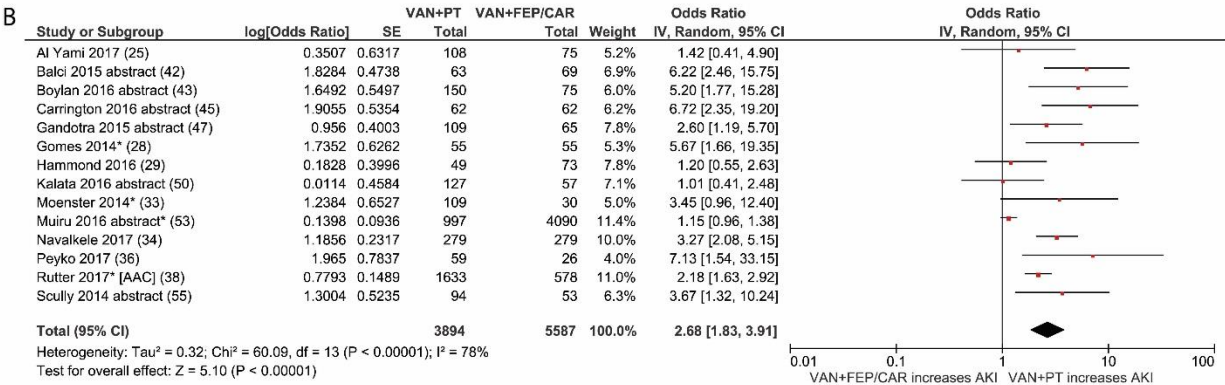
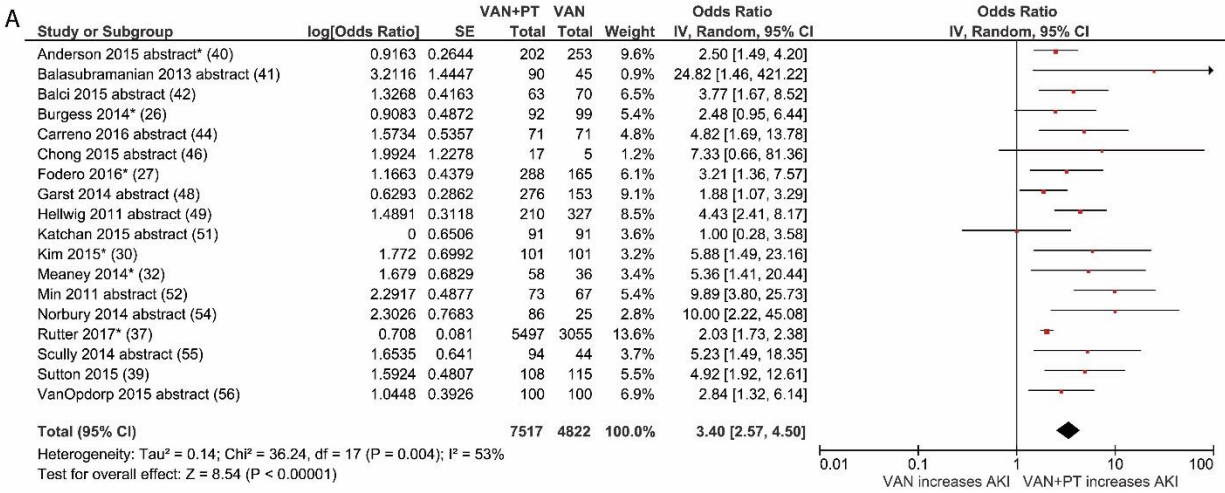
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381 Figure 4. Forest Plot demonstrating the odds of acute kidney injury with vancomycin plus  
382 piperacillin-tazobactam versus A) vancomycin monotherapy B) vancomycin plus cefepime or a  
383 carbapenem C) piperacillin-tazobactam monotherapy.

384 \*Indicates adjusted odds ratio.

385 Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; VAN, vancomycin  
386 monotherapy; FEP/CAR, cefepime or a carbapenem; PT, piperacillin-tazobactam monotherapy;  
387 SE, standard error; IV, inverse variance; CI, confidence interval; AKI, acute kidney injury

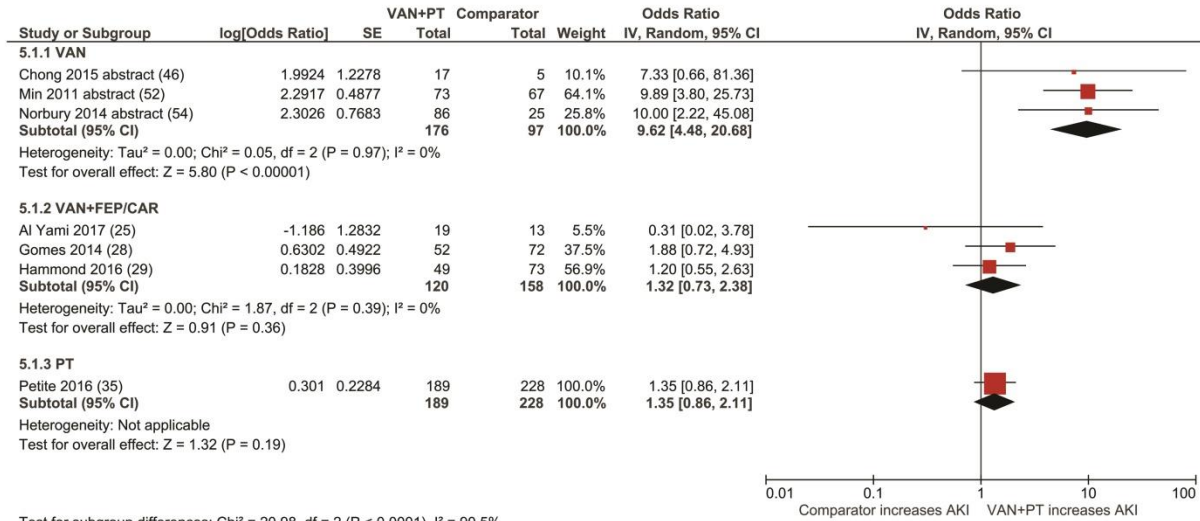




389 Figure 5. Forest Plot demonstrating the odds of acute kidney injury in critically ill patients.

390 Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; VAN, vancomycin  
 391 monotherapy; FEP/CAR, cefepime or a carbapenem; PT, piperacillin-tazobactam monotherapy;  
 392 SE, standard error; IV, inverse variance; CI, confidence interval; AKI, acute kidney injury

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