

2017

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

Megan Luther

Tristan Timbrook

See next page for additional authors

Follow this and additional works at: https://digitalcommons.uri.edu/php_facpubs

**The University of Rhode Island Faculty have made this article openly available.
Please let us know how Open Access to this research benefits you.**

This is a pre-publication author manuscript of the final, published article.

Terms of Use

This article is made available under the terms and conditions applicable towards Open Access Policy Articles, as set forth in our [Terms of Use](#).

Citation/Publisher Attribution

Luther MK, Timbrook TT, Caffrey AR, Dosa D, Lodise TP, LaPlante KL. Vancomycin plus piperacillin/tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. *Critical Care Medicine* 2018; 46(1):12-20. doi: 10.1097/CCM.0000000000002769

Available at: <http://dx.doi.org/10.1097/CCM.0000000000002769>

This Article is brought to you for free and open access by the Pharmacy Practice at DigitalCommons@URI. It has been accepted for inclusion in Pharmacy Practice Faculty Publications by an authorized administrator of DigitalCommons@URI. For more information, please contact digitalcommons@etal.uri.edu.

Authors

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

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

3

4 Date: August 19, 2017

5

6 Megan K. Luther, Pharm.D.^{1-3*}, Tristan T. Timbrook, Pharm.D., MBA, BPCS^{1,2}, Aisling R.
7 Caffrey, Ph.D., MS¹⁻⁴, David Dosa, MD, MPH^{3,4}, Thomas P. Lodise, Pharm.D., Ph.D.⁵, Kerry L.
8 LaPlante, Pharm.D., FCCP¹⁻⁴

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

19

20 Abstract: 295

21 Word Count: 3507

22

23 Keywords: acute kidney injury, nephrotoxicity, renal failure, glycopeptide, beta-lactam, antibiotic,
24 vancomycin, piperacillin-tazobactam, cefepime, carbapenem, critically ill

25

26 Conflicts of Interest and Source of Funding

27 MKL: Pfizer, Cubist (Merck) research funding, VA OAA fellowship. TTT: VA OAA fellowship,
28 Biofire Diagnostics, GenMark Diagnostics, speaker and/or consultancy. ARC: Cubist (Merck),
29 Pfizer, and The Medicines Company research funding. DD: none declared. TPL: Cubist (Merck),
30 the Medicines Company, research funding, speaker, and/or consultancy. KLL: Pfizer, Cubist
31 (Merck), Forest (Allergan), The Medicines Company, and Melinta research funding, speaker,
32 and/or consultancy.

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 (≥ 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 ≥ 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.

351

352

353 Acknowledgements

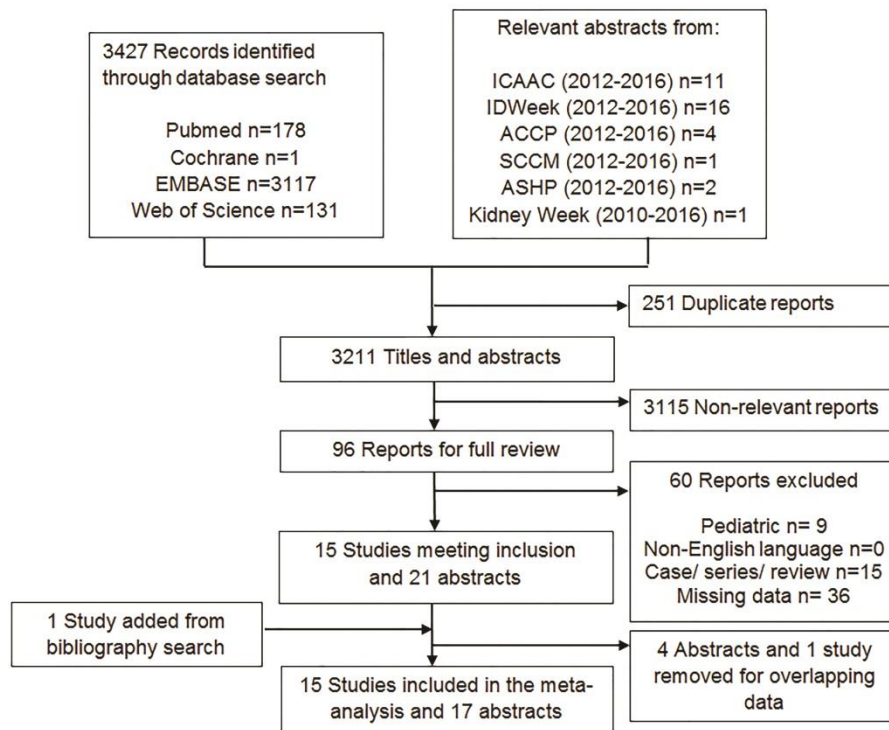
354 This material is the result of work supported in part by resources and use of facilities at
355 the Providence Veterans Affairs Medical Center. The contents do not represent the views of the
356 U.S. Department of Veterans Affairs or the United States government. An earlier version of this
357 meta-analysis 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

364



365

366

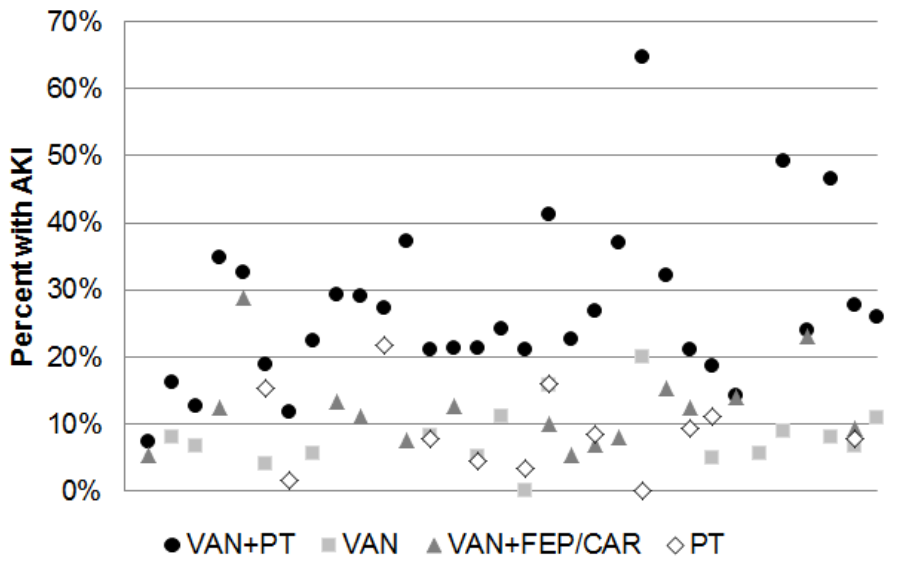
367

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.



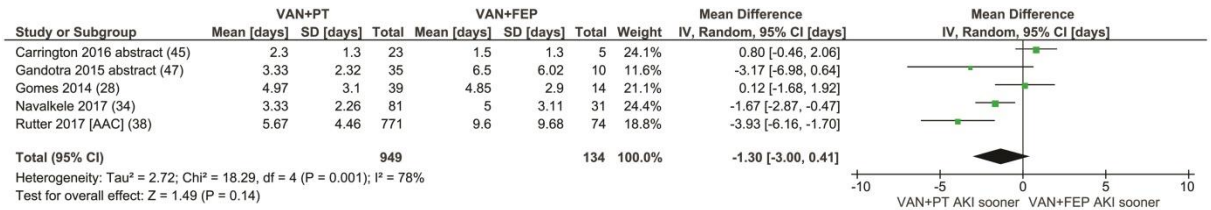
372

373

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

376

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



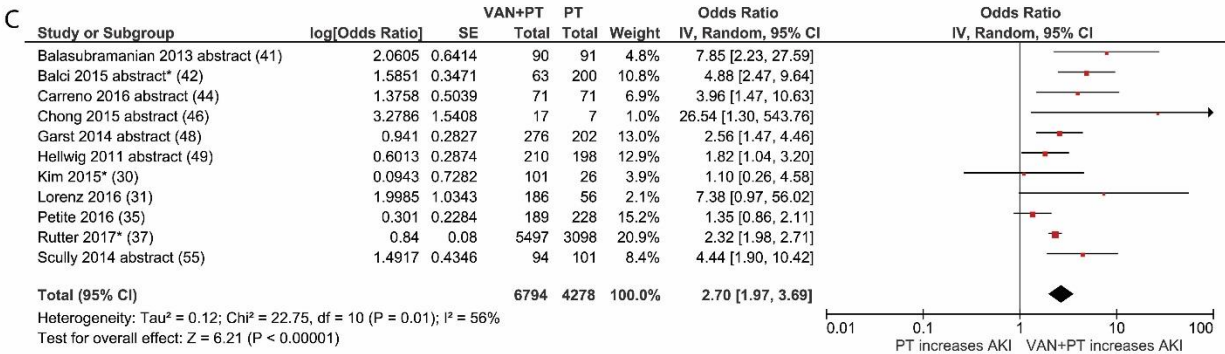
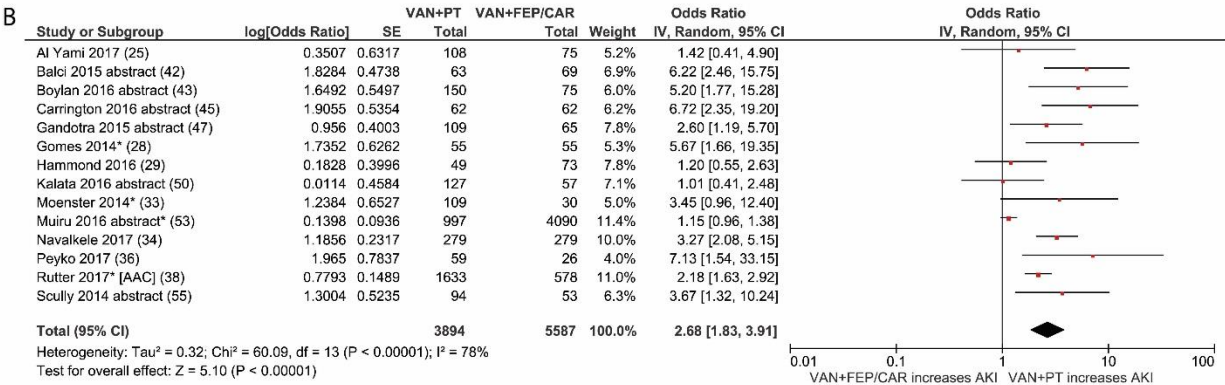
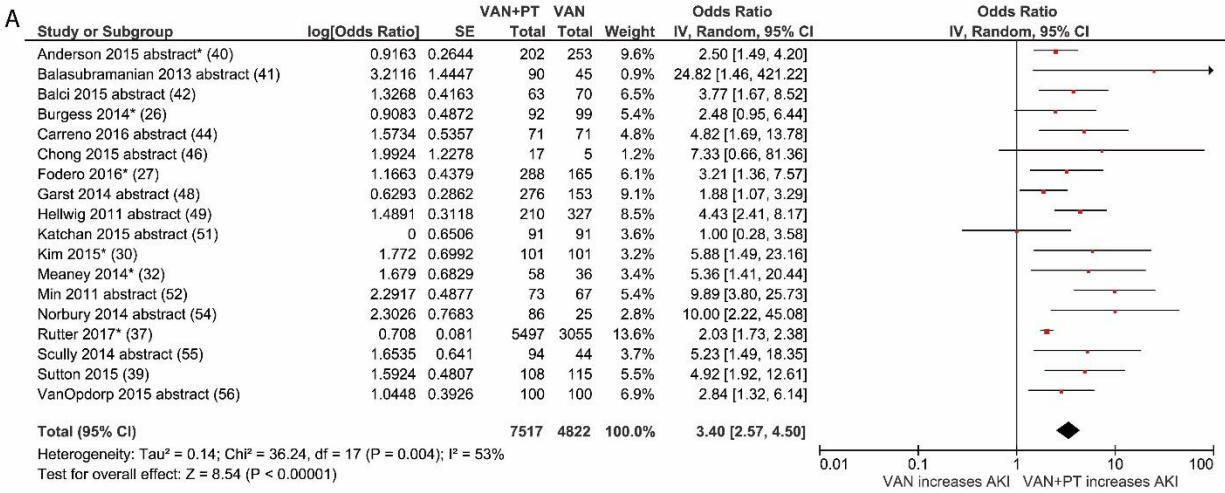
379

380

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.

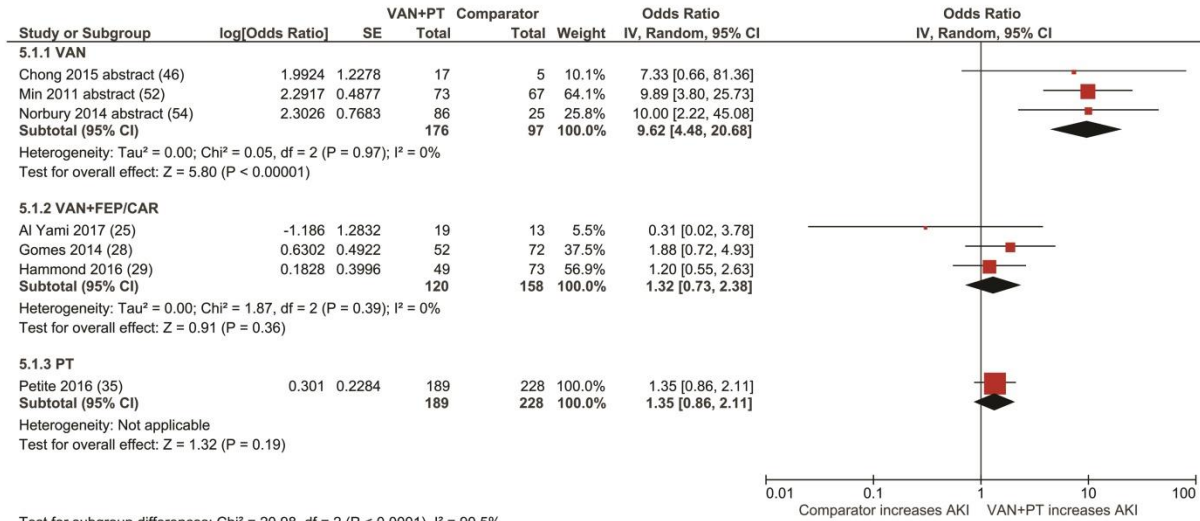
385 Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; VAN, vancomycin
386 monotherapy; FEP/CAR, cefepime or a carbapenem; PT, piperacillin-tazobactam monotherapy;
387 SE, standard error; IV, inverse variance; CI, confidence interval; AKI, acute kidney injury



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

393



394

395

396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444

REFERENCES

1. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;16(11):3365-3370.
2. Sileanu FE, Murugan R, Lucko N, et al. AKI in low-risk versus high-risk patients in intensive care. *Clin J Am Soc Nephrol* 2015;10(2):187-196.
3. Kellum JA, Murugan R. Effects of non-severe acute kidney injury on clinical outcomes in critically ill patients. *Crit Care* 2016;20(1):159.
4. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;41(8):1411-1423.
5. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8(4):R204-212.
6. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11(2):R31.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012;2:1-138.
8. Perinel S, Vincent F, Lautrette A, et al. Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients: Results of a Multicenter Cohort Study. *Crit Care Med* 2015;43(8):e269-275.
9. Sanchez-Pinto LN, Goldstein SL, Schneider JB, et al. Association Between Progression and Improvement of Acute Kidney Injury and Mortality in Critically Ill Children. *Pediatr Crit Care Med* 2015;16(8):703-710.
10. Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009;35(10):1692-1702.
11. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? *Kidney Int* 2015;87(1):46-61.
12. Hoste EA, Clermont G, Kersten A, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006;10(3):R73.
13. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. *Therapeutic Advances in Endocrinology and Metabolism* 2016;7(3):136-147.
14. Farber BF, Moellering RC, Jr. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother* 1983;23(1):138-141.
15. Dong MH, Wang JW, Wu Y, et al. Evaluation of body weight-based vancomycin therapy and the incidence of nephrotoxicity: a retrospective study in the northwest of China. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2015;37:125-128.
16. Alvarez CA, Giuliano CA, Haase KK, et al. Empiric weight-based vancomycin in intensive care unit patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Am J Med Sci* 2014;348(5):371-376.
17. Hall RG, 2nd, Hazlewood KA, Brouse SD, et al. Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study. *BMC Pharmacol Toxicol* 2013;14:12.
18. Ley EJ, Liou DZ, Singer MB, et al. Supratherapeutic vancomycin levels after trauma predict acute kidney injury and mortality. *J Surg Res* 2013;184(1):501-506.

- 445 19. Jeffres MN, Isakow W, Doherty JA, et al. A retrospective analysis of possible renal
446 toxicity associated with vancomycin in patients with health care-associated methicillin-resistant
447 *Staphylococcus aureus* pneumonia. *Clin Ther* 2007;29(6):1107-1115.
- 448 20. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in
449 adult patients: a consensus review of the American Society of Health-System Pharmacists, the
450 Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.
451 *American journal of health-system pharmacy : AJHP : official journal of the American Society of*
452 *Health-System Pharmacists* 2009;66(1):82-98.
- 453 21. Lodise TP, Patel N, Lomaestro BM, et al. Relationship between initial vancomycin
454 concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis*
455 2009;49(4):507-514.
- 456 22. Rostas SE, Kubiak DW, Calderwood MS. High-dose intravenous vancomycin therapy
457 and the risk of nephrotoxicity. *Clin Ther* 2014;36(7):1098-1101.
- 458 23. Spapen HD, Janssen van Doorn K, Diltoer M, et al. Retrospective evaluation of possible
459 renal toxicity associated with continuous infusion of vancomycin in critically ill patients. *Ann*
460 *Intensive Care* 2011;1(1):26.
- 461 24. Hanrahan TP, Harlow G, Hutchinson J, et al. Vancomycin-associated nephrotoxicity in
462 the critically ill: a retrospective multivariate regression analysis*. *Crit Care Med*
463 2014;42(12):2527-2536.
- 464 25. Al Yami MS. Comparison of the incidence of acute kidney injury during treatment with
465 vancomycin in combination with piperacillin-tazobactam or with meropenem. *J Infect Public*
466 *Health* 2017.
- 467 26. Burgess LD, Drew RH. Comparison of the Incidence of Vancomycin-Induced
468 Nephrotoxicity in Hospitalized Patients with and without Concomitant Piperacillin-Tazobactam.
469 *Pharmacotherapy* 2014;34(7):670-676.
- 470 27. Fodero KE, Horey AL, Krajewski MP, et al. Impact of an Antimicrobial Stewardship
471 Program on Patient Safety in Veterans Prescribed Vancomycin. *Clin Ther* 2016;38(3):494-502.
- 472 28. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during
473 treatment with vancomycin in combination with piperacillin-tazobactam or cefepime.
474 *Pharmacotherapy* 2014;34(7):662-669.
- 475 29. Hammond DA, Smith MN, Painter JT, et al. Comparative Incidence of Acute Kidney
476 Injury in Critically Ill Patients Receiving Vancomycin with Concomitant Piperacillin-Tazobactam
477 or Cefepime: A Retrospective Cohort Study. *Pharmacotherapy* 2016;36(5):463-471.
- 478 30. Kim T, Kandiah S, Patel M, et al. Risk factors for kidney injury during vancomycin and
479 piperacillin/tazobactam administration, including increased odds of injury with combination
480 therapy. *BMC research notes* 2015;8:579.
- 481 31. Lorenz MA, Moenster RP, Linneman TW. Effect of piperacillin/tazobactam restriction on
482 usage and rates of acute renal failure. *J Med Microbiol* 2016;65(2):195-199.
- 483 32. Meaney CJ, Hynicka LM, Tsoukleris MG. Vancomycin-associated nephrotoxicity in adult
484 medicine patients: incidence, outcomes, and risk factors. *Pharmacotherapy* 2014;34(7):653-
485 661.
- 486 33. Moenster RP, Linneman TW, Finnegan PM, et al. Acute renal failure associated with
487 vancomycin and beta-lactams for the treatment of osteomyelitis in diabetics: piperacillin-
488 tazobactam as compared with cefepime. *Clinical Microbiology and Infection* 2014;20(6):O384-
489 O389.
- 490 34. Navalkele B, Pogue JM, Karino S, et al. Risk of Acute Kidney Injury in Patients on
491 Concomitant Vancomycin and Piperacillin-Tazobactam Compared to Those on Vancomycin and
492 Cefepime. *Clin Infect Dis* 2017;64(2):116-123.
- 493 35. Petite SE, Bauer SR, Bollinger JE, et al. Antimicrobial Monotherapy versus Combination
494 Therapy for the Treatment of Complicated Intra-Abdominal Infections. *Pharmacotherapy*
495 2016;36(11):1138-1144.

- 496 36. Peyko V, Smalley S, Cohen H. Prospective Comparison of Acute Kidney Injury During
497 Treatment With the Combination of Piperacillin-Tazobactam and Vancomycin Versus the
498 Combination of Cefepime or Meropenem and Vancomycin. *J Pharm Pract* 2017;30(2):209-213.
- 499 37. Rutter WC, Burgess DR, Talbert JC, et al. Acute kidney injury in patients treated with
500 vancomycin and piperacillin-tazobactam: A retrospective cohort analysis. *J Hosp Med*
501 2017;12(2):77-82.
- 502 38. Rutter WC, Cox JN, Martin CA, et al. Nephrotoxicity during Vancomycin Therapy in
503 Combination with Piperacillin-Tazobactam or Cefepime. *Antimicrob Agents Chemother*
504 2017;61(2).
- 505 39. Sutton JD, Mynatt RP, Kaye KS, et al. Nephrotoxicity comparison of two commercially
506 available generic vancomycin products. *Antimicrob Agents Chemother* 2015;59(9):5470-5474.
- 507 40. Anderson C, Cazares K, Denunzio T. Vancomycin versus vancomycin/
508 piperacillin/tazobactam associated acute kidney injury in non-critically ill patients. e427. *Journal*
509 *of the American Pharmacists Association* 2015;55(5):e427.
- 510 41. Balasubramanian R, Bero J, Golfus G, et al. Impact of concomitant use of vancomycin
511 and piperacillin-tazobactam on nephrotoxicity in adult inpatients in a community hospital. 5-043.
512 In: ASHP Midyear Clinical Meeting; 2013; Orlando, FL; 2013.
- 513 42. Balci C, Ozun O, Arici M, et al. Nephrotoxicity of Piperacillin-Tazobactam Combined with
514 Vancomycin: Should it be a Concern? K-328 In: Interscience Conference on Antimicrobial
515 Agents and Chemotherapy (ICAAC) San Diego, CA. 18 Sept 2015.
- 516 43. Boylan P, Cofsky R. Incidence of acute kidney injury in patients receiving intravenous
517 vancomycin in combination with piperacillin-tazobactam or cefepime #376. In: American College
518 of Clinical Pharmacy (ACCP) annual meeting; Hollywood, FL. 23-26 Oct 2016.
- 519 44. Carreno JJ, Smiraglia T, Hunter C, et al. A Matched Cohort Study Evaluating the
520 Comparative Incidence of Adverse Renal Outcomes in Patients Receiving Vancomycin and
521 Piperacillin-tazobactam in Combination or as Monotherapy#1011 In: IDweek; New Orleans, LA.
522 28 Oct 2016.
- 523 45. Carrington J, Beardsley J, Williamson J, et al. Incidence of acute kidney injury during
524 treatment with vancomycin in combination with piperacillin-tazobactam or cefepime #155 In:
525 American College of Clinical Pharmacy (ACCP) annual meeting; Hollywood, FL. 23-26 Oct
526 2016.
- 527 46. Chong S, Fan C, Tan B. A preliminary report of potential increased risk of acute kidney
528 injury in severe burn patients by concomitant use of vancomycin and piperacillin-tazobactam
529 #292. *Journal of Burn Care and Research* 2015;36:S211.
- 530 47. Gandotra S, Hite M, Hix JK, et al. Save the Beans! Acute Kidney Injury During
531 Vancomycin and Piperacillin-Tazobactam (VP) Compared With Vancomycin and Cefepime (VC)
532 Therapy #127. *Open Forum Infectious Diseases* 2015;2(suppl 1).
- 533 48. Garst MJ. et al. Does vancomycin or piperacillin/tazobactam have the greater potential
534 for acute kidney injury? 4-176. In: ASHP Midyear clinical meeting; 2014; Anaheim, CA; 2014.
- 535 49. Hellwig T, Hammerquist R, Loecker B, et al. Retrospective evaluation of the incidence of
536 vancomycin and/or piperacillin-tazobactam induced acute renal failure #301. *Critical Care*
537 *Medicine* 2011;39:79.
- 538 50. Kalata KB, Kim S, Patel UC, et al. Efficacy, nephrotoxicity, and incidence of *Clostridium*
539 *difficile* infection with broad-spectrum antibiotic regimens in patients with noscomial pneumonia
540 #1266. In: IDweek; 2016; New Orleans, LA; 2016.
- 541 51. Katchan L, Seidel T, Bui J, et al. Does concomitant administration of Piperacillin-
542 Tazobactam with Vancomycin really increase the incidence of acute kidney injury? #1.
543 *Pharmacotherapy* 2015;35(11):E175.
- 544 52. Min E, Box K, Lane J, et al. Acute kidney injury in patients receiving concomitant
545 vancomycin and piperacillin/tazobactam #714. *Critical Care Medicine* 2011;39:200.

- 546 53. Muiru A, Lundquist A, Allegretti A. Comparative Incidence of Acute Kidney Injury
547 between Vancomycin/Cefepime and Vancomycin/Piperacillin-tazobactam Combination Therapy
548 SA-PO558. In: Kidney Week; Chicago, IL; 19 Nov 2016.
- 549 54. Norbury WB, Killion EA, Song C, et al. An increased incidence of acute kidney injury in
550 severely injured burns patients is associated with administration of vancomycin with piperacillin-
551 tazobactam. *Journal of Burn Care and Research* 2014;35:S84.
- 552 55. Scully M, Hassoun A, Ibrahim F, et al. Incidence of acute kidney injury in patients
553 receiving vancomycin and piperacillin-tazobactam compared to other antibiotic combinations.
554 #186. *Open Forum Infectious Diseases* 2014;1(suppl 1):S85.
- 555 56. VanOpdorp J, Kim A, Cox M, et al. Dose-Stratified Incidence of Vancomycin-induced
556 Nephrotoxicity with and without Concomitant Piperacillin-Tazobactam A-979 In: Interscience
557 Conference on Antimicrobial Agents and Chemotherapy (ICAAC); San Diego, CA. 20 Sept
558 2015.
- 559 57. Davies SW, Efird JT, Guidry CA, et al. Top Guns: The "Maverick" and "Goose" of
560 Empiric Therapy. *Surg Infect (Larchmt)* 2016;17(1):38-47.
- 561 58. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing
562 the quality of nonrandomized studies in meta-analyses. . 2013 [cited 20 August 2016]Available
563 from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
- 564 59. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from
565 the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*
566 2014;14:135.
- 567 60. Dean AG SK, Soe MM. . OpenEpi: Open Source Epidemiologic Statistics for Public
568 Health, Version. www.OpenEpi.com, updated 2013/04/06, accessed 2017/08/15. [cited
569 Available from:
- 570 61. Review Manager (RevMan) [Computer Program]. Version 5.3. In. Copenhagen: The
571 Nordic Cochrane Center, The Cochrane Collaboration; 2014.
- 572 62. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in
573 epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology
574 (MOOSE) group. *Jama* 2000;283(15):2008-2012.
- 575 63. Hammond DA, Smith MN, Li CH, et al. Systematic Review and Metaanalysis of Acute
576 Kidney Injury Associated With Concomitant Vancomycin and Piperacillin/Tazobactam. *Clinical*
577 *Infectious Diseases* 2017;64(5):666-674.
- 578 64. Giuliano CA, Patel CR, Kale-Pradhan PB. Is the Combination of Piperacillin-Tazobactam
579 and Vancomycin Associated with Development of Acute Kidney Injury? A Meta-analysis.
580 *Pharmacotherapy* 2016;36(12):1217-1228.
- 581 65. Graber CJ, Jones MM, Glassman PA, et al. Taking an antibiotic time-out: Utilization and
582 usability of a self-stewardship time-out program for renewal of vancomycin and piperacillin-
583 tazobactam. *Hospital Pharmacy* 2015;50(11):1011-1024.
- 584 66. Fan SL, Miller NS, Lee J, et al. Diagnosing sepsis - The role of laboratory medicine. *Clin*
585 *Chim Acta* 2016;460:203-210.
- 586 67. Baldwin DS, Levine BB, McCluskey RT, et al. Renal failure and interstitial nephritis due
587 to penicillin and methicillin. *N Engl J Med* 1968;279(23):1245-1252.
- 588 68. Liu P, Tepperman BS, Logan AG. Acute renal failure induced by semi-synthetic
589 penicillins. *Can Fam Physician* 1981;27:507-512.
- 590 69. Mac K, Chavada R, Paull S, et al. Cefepime induced acute interstitial nephritis--a case
591 report. *BMC Nephrol* 2015;16:15.
- 592 70. Jensen JUS, Hein L, Lundgren B, et al. Kidney failure related to broad-spectrum
593 antibiotics in critically ill patients: Secondary end point results from a 1200 patient randomised
594 trial. *BMJ Open* 2012;2(2).
- 595 71. Wai AO, Lo AM, Abdo A, et al. Vancomycin-induced acute interstitial nephritis. *The*
596 *Annals of pharmacotherapy* 1998;32(11):1160-1164.

- 597 72. Kraleti S, Khatri N, Jarrett D. Piperacillin-Tazobactam Induced Interstitial Nephritis,
598 Hepatitis and Serum Sickness-Like Illness. *J Ark Med Soc* 2016;112(14):278-280.
- 599 73. Elyasi S, Khalili H, Dashti-Khavidaki S, et al. Vancomycin-induced nephrotoxicity:
600 mechanism, incidence, risk factors and special populations. A literature review. *Eur J Clin*
601 *Pharmacol* 2012;68(9):1243-1255.
- 602 74. Kufel WD, Miller CD, Johnson PR, et al. Y-site Incompatibility Between Premix
603 Concentrations of Vancomycin and Piperacillin-Tazobactam: Do Current Compatibility Testing
604 Methodologies Tell the Whole Story? *Hosp Pharm* 2017;52(2):132-137.
- 605 75. Leung E, Venkatesan N, Ly SC, et al. Physical compatibility of vancomycin and
606 piperacillin sodium-tazobactam at concentrations typically used during prolonged infusions.
607 *American journal of health-system pharmacy : AJHP : official journal of the American Society of*
608 *Health-System Pharmacists* 2013;70(13):1163-1166.
- 609 76. Meyer K, Santarossa M, Danziger LH, et al. Compatibility of Ceftazidime-Avibactam,
610 Ceftolozane-Tazobactam, and Piperacillin-Tazobactam with Vancomycin in Dextrose 5% in
611 Water. *Hosp Pharm* 2017;52(3):221-228.
- 612 77. O'Donnell JN, Venkatesan N, Manek M, et al. Visual and absorbance analyses of
613 admixtures containing vancomycin and piperacillin-tazobactam at commonly used
614 concentrations. *American journal of health-system pharmacy : AJHP : official journal of the*
615 *American Society of Health-System Pharmacists* 2016;73(4):241-246.
- 616 78. Wade J, Cooper M, Ragan R. Simulated Y-Site Compatibility of Vancomycin and
617 Piperacillin-Tazobactam. *Hosp Pharm* 2015;50(5):376-379.

618

619

