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Megan Luther

Tristan Timbrook

See next page for additional authors

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

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Megan K. Luther, Pharm.D.[1-3]*, Tristan T. Timbrook, Pharm.D., MBA, BPCS[1,2], Aisling R. Caffrey, Ph.D., MS[1-4], David Dosa, MD, MPH[3,4],Thomas P. Lodise, Pharm.D., Ph.D.[5], Kerry L. LaPlante, Pharm.D., FCCP[1-4]

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

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

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

4. Brown University, Providence, RI

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

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

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Abstract:

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

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

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

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

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

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

Introduction

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

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

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

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

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

Methods

Literature Search

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

Study Selection

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

Study Quality

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

Data extraction

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

Outcomes

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

Statistical Analysis

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

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

Results

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

Conclusion

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

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358 Orleans, LA.

359

Figure 1. Literature search flow diagram.

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

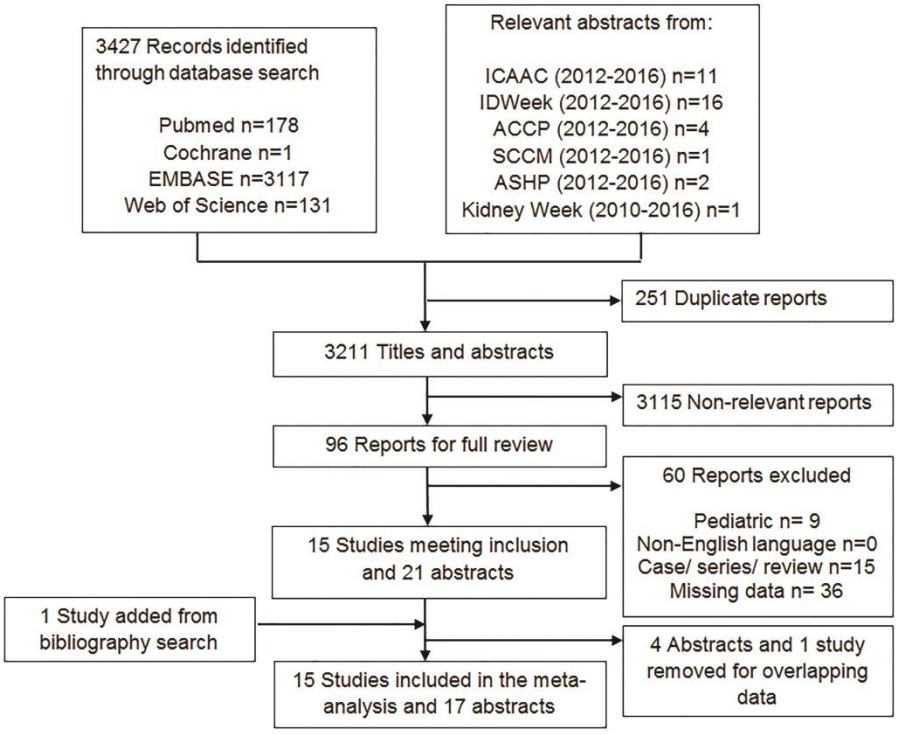


Figure 2. Scatterplot of percentage of patients with acute kidney injury in included studies.

Abbreviations: VAN+PT, vancomycin plus piperacillin-tazobactam; VAN, vancomycin; FEP/CAR, cefepime or carbapenem; PT, piperacillin-tazobactam; AKI, acute kidney injury.

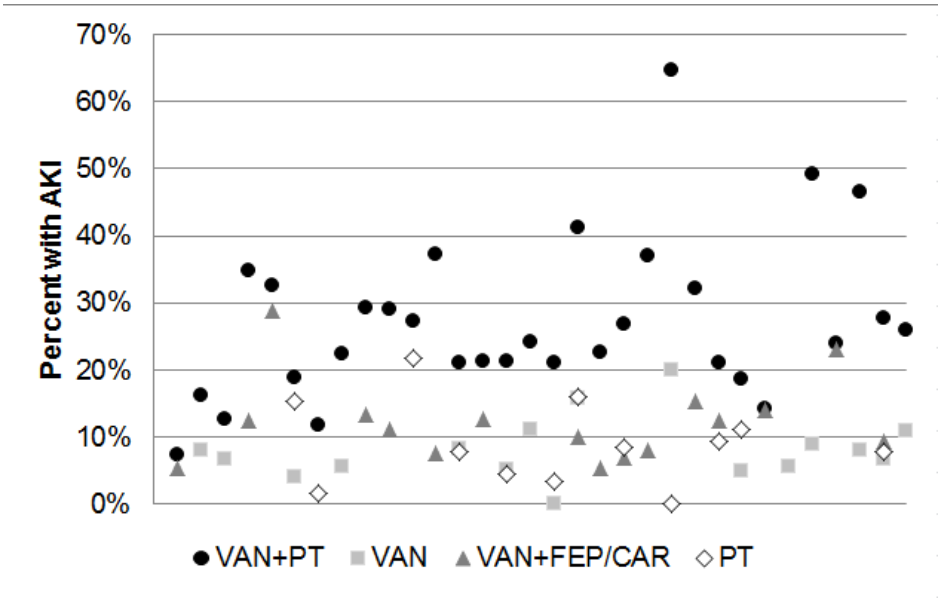


Figure 3. Mean difference in time (days) to acute kidney injury for vancomycin plus piperacillin-tazobactam versus vancomycin plus cefepime.

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

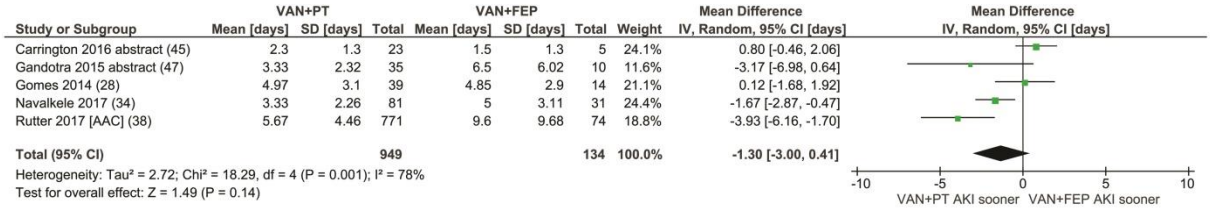


Figure 4. Forest Plot demonstrating the odds of acute kidney injury with vancomycin plus piperacillin-tazobactam versus A) vancomycin monotherapy B) vancomycin plus cefepime or a carbapenem C) piperacillin-tazobactam monotherapy.

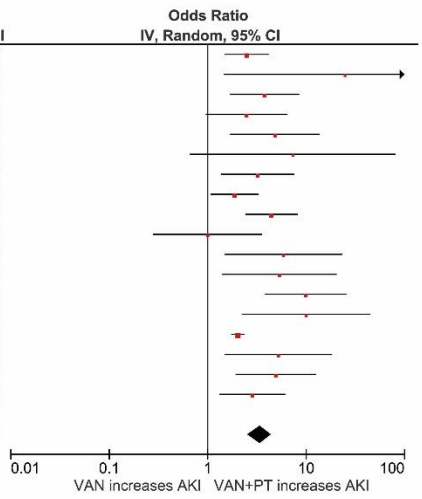
*Indicates adjusted odds ratio.

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

A

Study or Subgroup	log[Odds Ratio]	SE	VAN+PT Total	VAN Total	Weight	Odds Ratio IV, Random, 95% CI
Anderson 2015 abstract* (40)	0.9163	0.2644	202	253	9.6%	2.50 [1.49, 4.20]
Balasubramanian 2013 abstract (41)	3.2116	1.4447	90	45	0.9%	24.82 [1.46, 421.22]
Balci 2015 abstract (42)	1.3268	0.4163	63	70	6.5%	3.77 [1.67, 8.52]
Burgess 2014* (26)	0.9083	0.4872	92	99	5.4%	2.48 [0.95, 6.44]
Carreno 2016 abstract (44)	1.5734	0.5357	71	71	4.8%	4.82 [1.69, 13.78]
Chong 2015 abstract (46)	1.9924	1.2278	17	5	1.2%	7.33 [0.66, 81.36]
Fodero 2016* (27)	1.1663	0.4379	288	165	6.1%	3.21 [1.36, 7.57]
Garst 2014 abstract (48)	0.6293	0.2862	276	153	9.1%	1.88 [1.07, 3.29]
Hellwig 2011 abstract (49)	1.4891	0.3118	210	327	8.5%	4.43 [2.41, 8.17]
Katchan 2015 abstract (51)	0	0.6506	91	91	3.6%	1.00 [0.28, 3.58]
Kim 2015* (30)	1.772	0.6992	101	101	3.2%	5.88 [1.49, 23.16]
Meaney 2014* (32)	1.679	0.6829	58	36	3.4%	5.36 [1.41, 20.44]
Min 2011 abstract (52)	2.2917	0.4877	73	67	5.4%	9.89 [3.80, 25.73]
Norbury 2014 abstract (54)	2.3026	0.7683	86	25	2.8%	10.00 [2.22, 45.08]
Rutter 2017* (37)	0.708	0.081	5497	3055	13.6%	2.03 [1.73, 2.38]
Scully 2014 abstract (55)	1.6535	0.641	94	44	3.7%	5.23 [1.49, 18.35]
Sutton 2015 (39)	1.5924	0.4807	108	115	5.5%	4.92 [1.92, 12.61]
VanOpdorp 2015 abstract (56)	1.0448	0.3926	100	100	6.9%	2.84 [1.32, 6.14]
Total (95% CI)			**7517**	**4822**	**100.0%**	**3.40 [2.57, 4.50]**

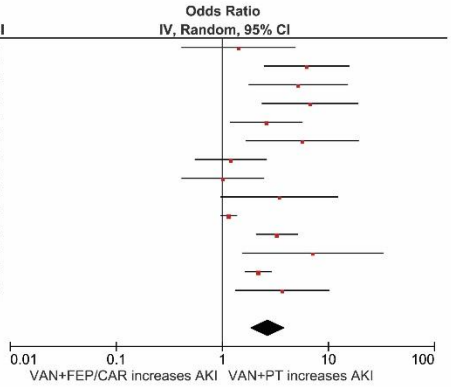
Heterogeneity: Tau² = 0.14; Chi² = 36.24, df = 17 (P = 0.004); I² = 53%
Test for overall effect: Z = 8.54 (P < 0.00001)



B

Study or Subgroup	log[Odds Ratio]	SE	VAN+PT Total	VAN+FEP/CAR Total	Weight	Odds Ratio IV, Random, 95% CI
Al Yami 2017 (25)	0.3507	0.6317	108	75	5.2%	1.42 [0.41, 4.90]
Balci 2015 abstract (42)	1.8284	0.4738	63	69	6.9%	6.22 [2.46, 15.75]
Boylan 2016 abstract (43)	1.6492	0.5497	150	75	6.0%	5.20 [1.77, 15.28]
Carrington 2016 abstract (45)	1.9055	0.5354	62	62	6.2%	6.72 [2.35, 19.20]
Gandotra 2015 abstract (47)	0.956	0.4003	109	65	7.8%	2.60 [1.19, 5.70]
Gomes 2014* (28)	1.7352	0.6262	55	55	5.3%	5.67 [1.66, 19.35]
Hammond 2016 (29)	0.1828	0.3996	49	73	7.8%	1.20 [0.55, 2.63]
Kalata 2016 abstract (50)	0.0114	0.4584	127	57	7.1%	1.01 [0.41, 2.48]
Moenster 2014* (33)	1.2384	0.6527	109	30	5.0%	3.45 [0.96, 12.40]
Muiru 2016 abstract* (53)	0.1398	0.0936	997	4090	11.4%	1.15 [0.96, 1.38]
Navalkele 2017 (34)	1.1856	0.2317	279	279	10.0%	3.27 [2.08, 5.15]
Peyko 2017 (36)	1.965	0.7837	59	26	4.0%	7.13 [1.54, 33.15]
Rutter 2017* [AAC] (38)	0.7793	0.1489	1633	578	11.0%	2.18 [1.63, 2.92]
Scully 2014 abstract (55)	1.3004	0.5235	94	53	6.3%	3.67 [1.32, 10.24]
Total (95% CI)			**3894**	**5587**	**100.0%**	**2.68 [1.83, 3.91]**

Heterogeneity: Tau² = 0.32; Chi² = 60.09, df = 13 (P < 0.00001); I² = 78%
Test for overall effect: Z = 5.10 (P < 0.00001)



C

Study or Subgroup	log[Odds Ratio]	SE	VAN+PT Total	PT Total	Weight	Odds Ratio IV, Random, 95% CI
Balasubramanian 2013 abstract (41)	2.0605	0.6414	90	91	4.8%	7.85 [2.23, 27.59]
Balci 2015 abstract* (42)	1.5851	0.3471	63	200	10.8%	4.88 [2.47, 9.64]
Carreno 2016 abstract (44)	1.3758	0.5039	71	71	6.9%	3.96 [1.47, 10.63]
Chong 2015 abstract (46)	3.2786	1.5408	17	7	1.0%	26.54 [1.30, 543.76]
Garst 2014 abstract (48)	0.941	0.2827	276	202	13.0%	2.56 [1.47, 4.46]
Hellwig 2011 abstract (49)	0.6013	0.2874	210	198	12.9%	1.82 [1.04, 3.20]
Kim 2015* (30)	0.0943	0.7282	101	26	3.9%	1.10 [0.26, 4.58]
Lorenz 2016 (31)	1.9985	1.0343	186	56	2.1%	7.38 [0.97, 56.02]
Petite 2016 (35)	0.301	0.2284	189	228	15.2%	1.35 [0.86, 2.11]
Rutter 2017* (37)	0.84	0.08	5497	3098	20.9%	2.32 [1.98, 2.71]
Scully 2014 abstract (55)	1.4917	0.4346	94	101	8.4%	4.44 [1.90, 10.42]
Total (95% CI)			**6794**	**4278**	**100.0%**	**2.70 [1.97, 3.69]**

Heterogeneity: Tau² = 0.12; Chi² = 22.75, df = 10 (P = 0.01); I² = 56%
Test for overall effect: Z = 6.21 (P < 0.00001)

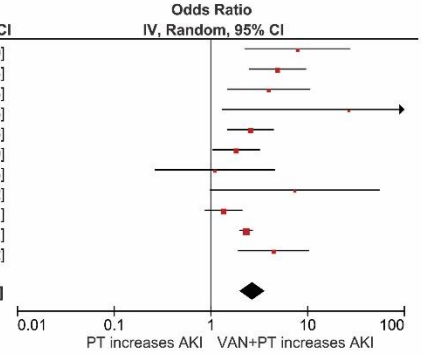


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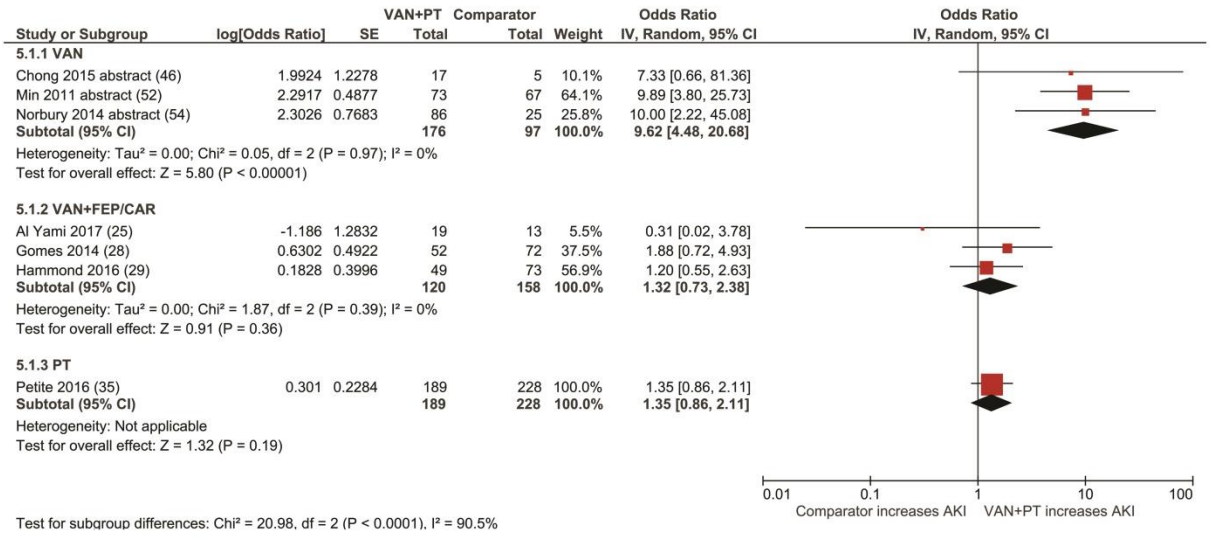
Figure 5. Forest Plot demonstrating the odds of acute kidney injury in critically ill patients.

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



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