COMMENTARY

Clinical Outcomes of Patient Subgroups in the TANGO II Study

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ABSTRACT

Introduction: Meropenem–vaborbactam (M-V), a new approved antimicrobial, was developed specifically to be effective treatment for the increasingly prevalent and difficult to treat carbapenem-resistant Enterobacterales (CRE) infections. However, registration phase 3 clinical studies offer limited applicability to daily medical practice as they often focus on indications such as urinary tract infections or skin and soft tissue infections, which generally have patients with fewer comorbid conditions that the typical patients who develops infection with CRE. The more useful studies are pathogen-focused trials which do not exclude the more complicated subjects with conditions such as renal failure, immunocompromised status, or exposure to prior antibiotic therapy.
Methods: The TANGO II study was an open-label investigation of M-V compared with the best available treatment (BAT) in hospitalized adults with a confirmed infection that was known or suspected to be a CRE infection. TANGO II specifically included patients with comorbidities, prior antibiotic therapy, renal failure, and immunocompromised status that are typical in patients with a CRE infection. Interim data analysis indicated that a significant benefit was seen for those patients receiving M-V over BAT. This analysis reports on subsets of TANGO II study patients with multiple comorbidities and high severity of illness, specifically those with prior antibiotic therapy, renal failure, and immunocompromised status. A patient case that highlights particular complexities and challenges of treating patients with CRE infections in the real world is also presented.
Results: Subjects with comorbid conditions had better outcomes when given M-V rather than BAT.
Conclusion: M-V is a welcome addition to the antibiotic armamentarium for the treatment of severe CRE infections in complicated patients.
Trial Registration: ClinicalTrials.gov identifier NCT02168946.

Keywords: Carbapenem-resistant organisms; Meropenem–vaborbactam; Multidrug-resistant organisms; Vabomere

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Key Summary Points

Meropenem–vaborbactam (M-V) was developed for and is an effective treatment for serious infections caused by carbapenem-resistant Enterobacterales (CRE).

Patients with multiple comorbidities are not included in clinical trials, but in real-world settings patients with infections caused by CRE are often complex cases with multiple comorbidities.

The TANGO II study compared M-V with the best available treatment for patients with CRE infections, and enrolled patients with multiple comorbidities and high severity of illness, specifically those with prior antibiotic therapy, renal failure, and immunocompromised status.

This subgroup analysis reports on the outcomes of M-V treatment in TANGO II patients with prior antibiotic therapy, renal failure, and immunocompromised status. Also, a real-world patient case is presented which highlights the particular complexities and challenges of treating patients with CRE infections.

Subjects with comorbidities, immunocompromised status, and those with impaired renal function who were treated with M-V demonstrated better outcomes compared to best available treatment.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13615253.

INTRODUCTION

Antibiotic resistance is a worldwide epidemic. As a result, the World Health Organization (WHO) created a list of the priority pathogens that pharmaceutical research and development should target when developing new antimicrobial agents. Carbapenem-resistant, extended-spectrum beta-lactamase-producing Enterobacterales (CR ESBL) are one of the top three organisms listed in the priority 1 category designated as "critical". The name of "Enterobacteriaceae" pathogens has been updated and are now referred to as Enterobacterales. Moreover, the emergence of *Klebsiella pneumoniae* carbapenemase (KPC)-2 phenotype across the USA may make many frontline agents inappropriate [1].

Antibiotic-resistant bacteria, in particular carbapenem-resistant Enterobacterales (CRE), are a worldwide public health threat. Various methods have been employed in an effort to combat this issue from mandating antimicrobial stewardship in the USA [2] to providing incentives from the government to develop new antimicrobials and diagnostic testing strategies [3].

Infections with drug-resistant pathogens have high morbidity and mortality [4, 5]. Initial clinical trials focus on common indications such as skin and soft tissue infection (SSTI) or urinary tract infection (UTI), and include healthier patients with fewer comorbidities. Moreover, most trials focus on disease state rather than pathogen resistance patterns. Once approved, these antibiotics are often used off-label for more serious infections [6–8].

Unfortunately, patients with CRE infection often have multiple comorbidities and have a higher severity of illness compared to their antibiotic-susceptible counterparts [9–11]. Recruitment for clinical trials evaluating antibiotic efficacy against patients with resistant organisms is difficult, particularly because these patients are severely ill making the consent process more sensitive. Additionally, targeting of specific drug resistance limits the number of qualifying subjects, thereby

requiring many more patients to be screened to be able to enroll an adequate sample size [12].

These factors make it difficult to study the newly developed drugs in the real-world setting for which they were created. The comorbidities and disease severity of patients contribute complicating factors to treatment approach, influencing pharmacokinetic/pharmacodynamic elements. Patients with renal failure often require antibiotic dose adjustments, immunocompromised patients can be impacted by drug interactions or are at higher risk for adverse events, and prior antibiotic therapy increases the risk for treatment failure [13]. Given these limitations of enrollment into clinical trials, real-world efficacy of medications is often demonstrated by case reports, case series, and registry trials well after the medication comes to market.

METHODS

TANGO II was a multicenter, randomized, open-label study of meropenem–vaborbactam (2 g/2 g q8h) (M-V) versus best available therapy (BAT) in hospitalized adults with a confirmed range of diagnosed infections requiring administration of intravenous (IV) antibacterial therapy, due to a known or suspected CRE infection [14]. It was a trial conducted in which a new antimicrobial agent was used against infections due to drug-resistant pathogens rather a trial enrolling patients with a specific disease state with infections due to mostly antibiotic-sensitive bacteria [15]. This trial simulated real-world use of the drug in a group of patients who were severely ill. In the comparator group, 64% received combination therapy—which is often the method of last resort for treating severely ill patients. It took 31 months to enroll and randomize 77 patients for the TANGO II trial. The study was stopped prematurely when interim data analysis indicated that a significant benefit was seen for those patients receiving M-V over BAT and it was concluded that randomization was not justified. The details for the clinical trial are described elsewhere [14].

This analysis reports on subsets of TANGO II study patients with multiple comorbidities and high severity of illness, specifically those with prior antibiotic therapy, renal failure, and immunocompromised status. Each comorbid condition was individually assessed with descriptive statistics for this paper. Table 1 describes the baseline demographic and clinical characteristics of TANGO II (mCRE-MITT) patient population [14].

The patient vignette that follows demonstrates the multiple comorbidities and high severity of illness that often accompany the diagnosis of infection with a CRE organism. The patient provided written informed consent to the use of their patient information in the case study.

RESULTS

Case Example

A 45-year-old man with childhood agammaglobulinemia was admitted with fevers, fatigue, and transient rash. Laboratory data on admission revealed leukopenia, normal renal function, and an elevated lactate dehydrogenase (LDH) and he was diagnosed with hemophagocytic lymphohistiocytosis (HLH) early in his hospital course. HLH is a disease of excess immune activation which can lead to severe inflammation resulting in multiorgan failure and be life-threatening [16]. He clinically decompensated and was admitted to the intensive care unit with respiratory failure requiring intubation, septic shock requiring vasopressors, and acute renal failure requiring hemodialysis. During his hospital course, he initially received piperacillin–tazobactam from hospital days 1 to 9 which was then changed to meropenem from hospital days 10 to 18. Cultures performed on tracheal secretions on hospital days 5 and 10 grew a carbapenem-resistant *K. pneumoniae* (piperacillin–tazobactam minimum inhibitory concentration [MIC] $> 64/4\,\mu g/ml$, meropenem MIC $4\,\mu g/ml$, ceftazidime–avibactam MIC $0.75\,\mu g/ml$ by E-test, M-V disc diffusion zone diameter of 22 mm) which was believed to be a colonizer. He subsequently developed bacteremia with positive blood cultures on hospital day 17 with this

Table 1 Baseline demographic and clinical characteristics of TANGO II (mCRE-MITT) [14]

Characteristic	M-V (*n* = 32)	BAT (*n* = 15)	Total (*n* = 47)
Age, mean (SD), years	63.5 (14.1)	60.2 (13.0)	62.5 (13.7)
Age cohort, *n* (%)			
< 65 years	17 (53.1)	9 (60.0)	26 (55.3)
≥ 65 years	8 (25.0)	3 (20.0)	11 (23.4)
≥ 75 years	7 (21.9)	3 (20.0)	10 (21.3)
Female gender, *n* (%)	18 (56.3)	5 (33.3)	23 (48.9)
White race, *n* (%)	28 (87.5)	12 (80.0)	40 (85.1)
BMI, mean (SD)	27.9 (9.0)	25.8 (7.6)	27.2 (8.5)
Infection type, *n* (%)			
Bacteremia	14 (43.8)	8 (53.3)	22 (46.8)
cUTI/AP	12 (37.5)	4 (26.7)	16 (34.0)
HABP/VABP	4 (12.5)	1 (6.7)	5 (10.6)
cIAI	2 (6.3)	2 (13.3)	4 (8.5)
Baseline pathogen, *n* (%)[a]			
Klebsiella pneumoniae	29 (90.6)	12 (80.0)	41 (87.2)
Escherichia coli	3 (9.4)	1 (6.7)	4 (8.5)
Enterobacter cloacae sp.	1 (3.1)	2 (13.3)	3 (6.4)
Proteus mirabilis	0 (0)	2 (13.3)	2 (4.3)
Serratia marcescens	1 (3.1)	1 (6.7)	2 (4.3)
Enrolled as confirmed CRE, *n* (%)	23 (71.9)	14 (93.3)	37 (78.7)
Enrolled as suspected CRE, *n* (%)	9 (28.1)	1 (6.7)	10 (21.3)
Creatinine clearance, ml/min, *n* (%)			
≥ 50	24 (75.0)	9 (60.0)	33 (70.2)
30–49	4 (12.5)	2 (13.3)	6 (12.8)
20–29	1 (3.1)	2 (13.3)	3 (6.4)
< 20	2 (6.3)	0 (0)	2 (4.3)
Missing	1 (3.1)	2 (13.3)	3 (6.4)
Charlson comorbidity index, *n* (%)			
≤ 2	4 (12.5)	1 (6.7)	5 (10.6)
3–4	3 (9.4)	2 (13.4)	5 (10.6)
5	11 (34.4)	1 (6.7)	12 (25.5)
≥ 6	14 (43.8)	11 (73.3)	25 (53.2)
Diabetes mellitus, *n* (%)	12 (37.5)	7 (46.7)	19 (40.4)

Table 1 continued

Characteristic	M-V (*n* = 32)	BAT (*n* = 15)	Total (*n* = 47)
SIRS, *n* (%)	15 (46.9)	6 (40.0)	21 (44.7)
ICU admission, *n* (%)	5 (15.6)	3 (20.0)	8 (17.0)
Immunocompromised[b], *n* (%)	11 (34.4)	8 (53.3)	19 (40.4)
Prior antibiotic failure[c], *n* (%)	9 (28.1)	0 (0)	9 (19.1)

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BAT best available therapy, *BMI* body mass index, *cIAI* complicated intra-abdominal infection, *CRE* carbapenem-resistant Enterobacteriaceae, *cUTI/AP* complicated urinary tract infection/acute pyelonephritis, *HABP/VABP* hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, *ICU* intensive care unit, *mCRE-MITT* microbiologic carbapenem-resistant Enterobacteriaceae modified intent-to-treat, *M-V* meropenem–vaborbactam, *SD* standard deviation, *SIRS* systemic inflammatory response syndrome

[a] Baseline pathogens listed occurred in 2 or more patients

[b] Receipt of immunosuppressive medications or bone marrow ablative chemotherapy, underlying lymphoma or leukemia (not in remission), previous transplantation, splenectomy, or presence of neutropenia

[c] Clinical evidence of prior antimicrobial failure as ascertained by the study investigator at screening and randomization

same organism. His hospital course was complicated by disseminated intravascular coagulation, severe hepatitis, encephalopathy, acute punctate infarct in the left cerebellum, aspergillosis of the scrotum, and necrotizing pancreatitis associated with fluid collections of which cultures also grew the same carbapenem-resistant *K. pneumoniae*, now resistant to M-V. He was treated with multiple antibiotics and eventually changed to ceftazidime–avibactam for completion of therapy. He received dexamethasone, etoposide, and intrathecally administered methotrexate for HLH with repeat BM biopsy showing no disease. He was discharged after a 5-month hospital stay to a rehabilitation center.

This case demonstrates the complexity of patients who develop CRE infections. Some have an underlying immunocompromising condition such as cancer, organ transplant, or receipt of immunosuppressants and then clinically deteriorate with sepsis due to an infection by a CRE resulting in organ dysfunction or organ failure.

Subgroup analyses of patients without prior antibiotic therapy, immunocompromised state, and renal insufficiency in the TANGO II study suggest that at both the end of therapy (EOT) and test of cure (TOC = EOT + 7 days) time points, M-V had higher clinical cure rates in addition to decreased 28-day all-cause mortality when compared to BAT.

This is the only report to our knowledge to evaluate subgroups of patients with carbapenem-resistant organisms.

Prior Antibiotic Therapy

Most patients who develop infections with CRE have been exposed to multiple previous antibiotics as in the previously described case. Some have failed therapy, by either developing resistance to the treatment administered or lack of clinical response despite antibiotic administration, may have an empiric change of antibiotic agents. The patient case described earlier had improved with empiric treatment with a less broad-spectrum antibiotic agent; however, he subsequently developed septic shock for which a change in antibiotics was warranted.

BAT was chosen at the discretion of the study investigator and consisted of antibiotic therapy either alone or in combination of carbapenems, aminoglycosides, colistin, polymixin B, tigecycline or monotherapy with ceftazidime–avibactam (C-A). Prior antibiotic failure was determined by the study investigator at the time of enrollment. Of the 38 patients who were analyzed, 23 received M-V and 15 received BAT.

Of the patients who were not categorized as prior antibiotic failure in the TANGO II trial, those who received primary therapy with M-V had better outcomes compared with those who received BAT within the microbiologic-CRE modified intent-to-treat (mCRE-MITT) group [17]. The mCRE-MITT was defined as patients who received at least one dose of study drug and had culture confirmation of a baseline isolate that was CRE (Table 2) [17].

The baseline pathogen was *K. pneumoniae* in approximately 90% of these patients, the same pathogen isolated in our patient case. Clinical cure at TOC was higher (69.6% vs. 26.7%, absolute difference + 42.9) in the M-V group compared to BAT. This difference continued through the evaluation of clinical cure at EOT (82.6% vs. 33.3%). Similarly, M-V showed better efficacy than BAT when evaluated for microbiologic cure at EOT (82.6% vs. 40%), microbiologic cure at TOC (69.9% vs. 33.3%), and 28-day mortality (4.3% vs. 33.3%). This analysis supports the clinical application of M-V over BAT in patients who have not failed prior antibiotic therapy.

Immunocompromised

Among patients with solid tumors or hematologic malignancy and CRE infections, mortality rates are extremely high—up to 60% [18, 19]. The patient described in our case did not have a malignancy; however, it is evident that his immune system was compromised as demonstrated by the development of disseminated aspergillus infection, which is rarely seen in the immunocompetent host [20]. Unlike most phase 3 studies of new antimicrobials, TANGO II included immunocompromised patients.

Immunocompromised status was defined as underlying active leukemia, lymphoma, prior

Table 2 Efficacy results in patients without prior antimicrobial failure in the mCRE-MITT population [17]

Efficacy endpoints (mCRE-MITT)	Meropenem–vaborbactam (*n* = 23)	Best available therapy (*n* = 15)	Absolute difference (95% CI)
Clinical cure at TOC	16 (69.6)	4 (26.7)	+ 42.9 (+ 13.7 to + 72.1)
Clinical cure at EOT	19 (82.6)	5 (33.3)	+ 49.3 (+ 20.8 to + 77.7)
Microbiologic cure[a] at EOT	19 (82.6)	6 (40.0)	+ 42.6 (+ 13.4 to + 71.8)
Microbiologic cure[a] at TOC	16 (69.6)	5 (33.3)	+ 36.2 (+ 5.9 to + 66.6)
Day-28 mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to − 3.7)

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CI confidence intervals, *EOT* end of therapy, *mCRE-MITT* microbiologic carbapenem-resistant Enterobacteriaceae modified intent-to-treat, *TOC* test of cure

[a] Microbiologic cure was defined as microbial eradication or presumed eradication

transplant or splenectomy on medical history, any active receipt of immunosuppressive drugs including selective immunosuppressants, calcineurin inhibitors, or high-dose systemic steroids (equivalent to more than 20 mg/day of prednisone for more than 2 weeks) or neutropenia (absolute neutrophil count [ANC] less than 1000 cells/mm^3) at any point during the study period.

Of the 50 subjects who had a baseline pathogen (m-MITT population), 19 (38.0%) were immunocompromised: four leukemia/lymphoma, five medication, and 10 transplant cases. Forty-three of these 50 patients had an identified baseline pathogen which was CRE (mCRE-MITT); 18 (41.9%) were categorized as immunocompromised. The most common infection types among immunocompromised subjects (mCRE-MITT) were bacteremia (11/18, 61.1%), cUTI/AP (3/18, 16.7%), HABP/VABP (2/18, 11.1%), and cIAI (2/18, 11.1%).

Clinical cure rates for mCRE-MITT immunocompromised subjects were higher for those in the M-V arm compared to the BAT arm with an absolute increase of 47.5% at EOT and 70% at TOC. On ad hoc analysis, the increase in cure rate at TOC achieved statistical significance (95% CI 41.6–98.4, $p < 0.0001$). Rates of microbial cure (defined as either microbial eradication or presumed eradication) for the 18 immunocompromised subjects were higher for those in the M-V arm vs. BAT arm (absolute increase of 47.5% at EOT and 70% at TOC). The all-cause mortality at day 28 was lower for those patients who received M-V compared to those who received BAT (20% vs. 37.5%). This was associated with an absolute risk reduction (mortality) of 17.5% and relative risk reduction of 46.7%. Table 3 shows the efficacy endpoints of the mCRE-MITT patient population, including those with immunocompromised and renal insufficiency [14].

In addition, there were no marked treatment adverse events (AE) noted. Among immunocompromised subjects, M-V was associated with fewer adverse events compared to BAT (84.6% vs. 100%), drug-related AEs (30.8% vs. 40.0%), serious AEs (38.5% vs. 50.0%), discontinuations of study drug or study due to AEs (15.4% vs. 30.0%), and renal-related AEs (7.7% vs. 40.0%).

Renal Insufficiency

Most patients with sepsis have some degree of acute kidney injury sometimes requiring hemodialysis as exemplified in the case previously described. Patients with decreased kidney function have an increased risk for hospital-related infection in a linear distribution [21]. In addition, renal insufficiency impacts accurate dosing of medications and limits use of agents such as colistimethate and polymixin B which have adverse side effects of renal failure [22, 23]. Among the 43 subjects who had a baseline CRE organism and were included in the mCRE-MITT population, nine (20.9%) subjects had a baseline creatinine clearance (CrCl) less than 50 ml/min. Dose reduction of M-V was given on the basis of CrCl. If the CrCl was less than 50 ml/min, a standard dose of 2 g–2 g was administered every 8 h. If the CrCl was between 30 and 49 ml/min, the dose was reduced by half to 1 g–1 g every 8 h. The dose was reduced to one-third of the standard dose with CrCl between 20 and 29 ml/min, to one-sixth of the dose for CrCL between 10 and 19, and finally to one-twelfth of the dose to 500 mg–500 mg every 24 h. Although hemodialysis patients could be enrolled in the study, those patients who required continuous renal replacement therapy (CRRT) were not eligible for study participation. Since CRRT is more physiologic compared to hemodialysis, we do not see this as a negative to the study exclusion.

Subjects with renal impairment with a CrCl less than 50 ml/min had lower clinical cure rates across all infection types at EOT compared with subjects with normal renal function, though there were only nine patients with impaired renal function in the mCRE-MITT cohort. Two of the five patients in the M-V group and one of the four in the BAT group achieved both clinical cure at the end of therapy and microbiologic eradication.

Patients with renal insufficiency had lower clinical cure rates across all infection times at the end of IV therapy compared to those with normal renal function regardless of treatment type (M-V 40% vs. 68.2%; BAT 25% vs. 44.4%). In terms of AEs, M-V had similar rates of treatment emergent adverse events (TEAE) compared

Table 3 Efficacy endpoints among all patients with confirmed CRE infections (mCRE-MITT) in TANGO II study [14]

	M-V (n = 32) n (%)	BAT (n = 15) n (%)	Difference[a] (95% CI)	p value	Relative difference[b]
Efficacy endpoints					
Clinical cure at EOT	21 (65.6)	5 (33.3)	32.3 (3.3 to 61.3)	0.03	97.0
Clinical cure at TOC	19 (59.4)	4 (26.7)	32.7 (4.6 to 60.8)	0.02	122.5
Microbiologic cure[c] at EOT	21 (65.6)	6 (40.0)	25.6 (− 4.1 to 55.4)	0.09	64.0
Microbiologic cure[c] at TOC	17 (53.1)	5 (33.3)	19.8 (− 9.7 to 49.3)	0.19	59.5
Day-28 mortality	5 (15.6)	5 (33.3)	− 17.7 (− 44.7 to 9.3)	0.20	− 53.2
Exploratory analysis of risk–benefit profile of M-V compared to BAT					
Day-28 all-cause mortality or nephrotoxicity[e]	8 (25.0)	6 (40.0)	− 15.0 (− 44.0 to 14.0)	0.31	− 37.5
Clinical failure or nephrotoxicity[f]	10 (31.3)	12 (80.0)	− 48.7 (− 74.6 to − 22.9)	< 0.001	− 60.9
Day-28 all-cause mortality or renal AEs[g]	6 (18.8)	9 (60.0)	− 41.2 (− 69.5 to − 13.0)	0.004	− 68.7
Clinical failure or renal AEs[h]	9 (28.1)	12 (80.0)	− 51.9 (− 77.4 to − 26.3)	< 0.001	− 64.9

Sensitivity analysis of clinical cure at TOC and all-cause mortality at day 28 across all infection types (mCRE-MITT) excluding prior antibiotic failure[d]

	M-V (n = 23) n (%)	BAT (n = 15) n (%)	Difference[a] (95% CI)	p value	Relative difference[b]
Clinical cure at TOC	16 (69.6)	4 (26.7)	42.9 (13.7 to 72.1)	0.004	160.7
Day-28 all-cause mortality	1 (4.3)	5 (33.3)	− 29.0 (− 54.3 to − 3.7)	0.02	− 87.1

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AE adverse event, *BAT* best available therapy, *CI* confidence interval, *cUTI/AP* complicated urinary tract infection/acute pyelonephritis, *EOT* end of treatment, *mCRE-MITT* microbiologic carbapenem-resistant Enterobacteriaceae modified intent-to-treat, *M-V* meropenem–vaborbactam, *TOC* test of cure

[a] Data represent the difference in percentages for meropenem–vaborbactam and BAT (95% CI for that difference)

[b] Data represent (difference in percentage for meropenem–vaborbactam and BAT)/BAT

[c] Composite of either microbiologic eradication or presumed eradication at respective visit

[d] Patients assessed as having prior antibiotic failure at randomization (meropenem–vaborbactam, 9; BAT, 0) were excluded from this analysis

[e] Composite outcome of either day-28 all-cause mortality or a post-baseline increase in serum creatinine ≥ 1.0 mg/dL

[f] Composite outcome of either clinical failure at test of cure or a post-baseline increase in serum creatinine ≥ 1.0 mg/dL

[g] Composite outcome of either day-28 all-cause mortality or adverse event of renal failure, renal failure acute, or renal impairment

[h] Composite outcome of either clinical failure at test of cure or adverse event of renal failure, renal failure acute, or renal impairment

to BAT in the 19 patients who had renal insufficiency (8/10 vs. 8/9).

There is no increased safety signal associated with M-V in patients with renal impairment.

M-V is a safe and effective treatment for serious gram-negative infections in renally impaired patients when the dose is adjusted on the basis of creatinine clearance.

DISCUSSION

The newer β-lactam/β-lactamase agents (M-V, C-A) have been much needed additions to the antibiotic armamentarium for the treatment of carbapenem-resistant infections. Physicians can more readily avoid use of colistin which has inherent difficulties for appropriate dosing, adverse effects most concerning of which is acute kidney injury [24]. At the Clinical Laboratory Standards Institute (CLSI) meeting in June 2019, the colistin breakpoints were tentatively revised such that no MIC was considered susceptible [25]. In addition, the newer agents have potentially fewer toxicities than other classes of drugs used to treat multidrug-resistant organisms.

Indications for UTIs and SSTIs have been most commonly used in clinical trials evaluating newer antimicrobials, and owing to the higher prevalence of these types of infections, recruiting sufficient number of patients is easier. Additionally, strict exclusion criteria result in enrolled patients with minimal or no comorbidities, less severe infections, or other serious health conditions. Therefore, the true niche for these broad-spectrum agents is not represented, including those with acute renal failure, prior antibiotic therapy without failure, immunocompromised status, or patients with malignancies. In contrast, the TANGO II trial was different, and investigators enrolled patients with renal insufficiency and on hemodialysis and accepted patients with malignancies, organ and stem cell transplantation, and receipt of immunosuppressive medications.

There are not many pathogen-directed clinical trials [26–29]. Most have small sample sizes and study drug is compared to BAT similar to the TANGO II trial. Despite the less stringent

exclusion criteria in terms of comorbid conditions, the enrollment of patients with suspected or proven CRE infections remained slow. Despite almost 3 years of recruitment for the clinical trial, only 77 patients were enrolled—a testament to the difficulty of recruitment in pathogen specific trials. TANGO II was stopped early because the data safety monitoring board felt the superior efficacy of M-V vs. BAT on interim analysis meant it was inappropriate to continue with the study.

This analysis has some limitations. It is a post hoc evaluation of 77 patients into specific subgroups resulting in even smaller numbers of patients to examine. With fewer subjects, matched controls and regression analysis are not possible. Therefore, the conclusions that are drawn are more observational in nature. Future prospective studies are needed to better evaluate each subgroup; however, this will be a challenging endeavor as demonstrated by the mere difficulty with recruitment for TANGO II which, although strict in terms of recruitment criteria based on pathogen, encompassed all the subgroups.

With newer agents, we still need to be vigilant and cognitive of their limitations. Already there have been reports of the development of treatment-emergent resistance to ceftazidime–avibactam [7, 30–34]. Athans et al. [35] described a liver transplant recipient who developed an infection with a CRE *K. pneumoniae* which was initially susceptible to C-A, subsequently developed resistance to C-A while on therapy, and eventually received M-V which allowed a second liver transplant [18].

CONCLUSION

M-V, which was frequently used as monotherapy in the TANGO II trial, has been shown to be effective for the treatment of serious infections caused by carbapenem-resistant Enterobacterales—the purpose for which M-V was developed. It has been shown to have better outcomes when compared to receipt of BAT, with an even lower incidence of adverse events. Moreover, this subgroup analysis demonstrates effectiveness in patients who have do not have

previous antibiotic failure, are immunocompromised, and those with impaired renal function.

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