MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2020-0074
Protocol Title	An Investigator Initiated, Phase II Single-Center, Randomized, Open-Label, Prospective, Study To Determine The Impact Of Serial Procalcitonin On Improving Antimicrobial Stewardship And On The Efficacy, Safety, And Tolerability Of Imipenem-Cilastatin-Relebactam Plus/Minus Vancomycin Or Linezolid Versus Standard Of Care Antipseudomonal Beta-Lactams Plus/Minus Vancomycin Or Linezolid As Empiric Therapy In Febrile Neutropenic Adults With Cancer
Protocol Phase	II
Protocol Version	8
Version Date	06/20/2022
Protocol PI	Issam Raad, M.D.
Department	Infectious Diseases
IND Sponsor	MD Anderson Cancer Center
IND #	155191

AN INVESTIGATOR INITIATED, PHASE II SINGLE-CENTER,

RANDOMIZED, OPEN-LABEL, PROSPECTIVE, STUDY TO DETERMINE THE IMPACT OF SERIAL PROCALCITONIN ON IMPROVING ANTIMICROBIAL STEWARDSHIP AND ON THE EFFICACY, SAFETY, AND TOLERABILITY OF IMIPENEM-CILASTATIN-RELEBACTAM PLUS/MINUS VANCOMYCIN OR LINEZOLID VERSUS STANDARD OF CARE ANTIPSEUDOMONAL BETA-LACTAMS PLUS/MINUS VANCOMYCIN OR LINEZOLID AS EMPIRIC THERAPY IN FEBRILE NEUTROPENIC ADULTS WITH CANCER

TABLE OF CONTENTS

1.0 TABLE 2–1. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment or Procedure	*Baseline*[a]	*Treatment*		*Follow-up*	
		Study Days 1 to ≤ 14[b]	*EOIV*[c]	*TOC*[d]	*LFU*[e]
Informed consent[f]	X				
Inclusion/exclusion criteria	X				
Medical and surgical history[g]	X				
Height and weight[h]	X				
Chest radiography[i]	X		If clinically indicated		
Physical examination	X	X[j]	X	X	X[k]
Vital signs[l]	X	X	X	X	X[k]
Prior/concomitant medications[m]	X	X	X	X	X
AEs and SAEs	X	X	X	X	X
Clinical outcome			X	X	***X***
Laboratory tests[n]	X	If clinically indicated[o]	X[p]		
Absolute neutrophil count	X	X[q]	X		
Urine or Serum pregnancy test[r]	X				
CrCl calculation[s]	X	X[j]	if clinically indicated		
Blood culture	X	X[T]	X[u]	as clinically indicated	
Urine culture/urine analysis (when clinically needed)	X	as clinically indicated		as clinically indicated	
Other samples for culture from possible suspected infected site if clinically indicated[t]	if clinically indicated				
Randomization	X				
Study drug administration		X[v]	X		

a Perform baseline assessments within 36 hours of enrollment.

b Study Day 1 is the first day of inpatient IV study drug administration; subsequent study days are consecutive calendar days. Baseline and Study day 1 assessment could be combined if they occur on the same calendar day.. On
Study Days 1 to ≤ 14, study drug administration applies to all patients, and assessments are to be performed for patients on inpatient IV study drug only. Treatment duration is 2 to 14 days with a minimum of 2 days (ie, 48 hours and a minimum of 8 doses for *Imipenem-Cilastatin-Relebactam* and SOC therapies, except piperacillin/tazobactam, which is a minimum of 8 doses) of inpatient IV study drug.

c Perform EOIV assessments in person within 72 hours after administration of the last dose of inpatient IV study drug. A patient may be eligible to switch to oral or other simplified IV therapy after at least 48 hours of IV gram negative antimicrobial coverage and procalcitonin () downward drops by 30% from baseline or is below than 0.25 (Section 9.4.1.4).

d Perform TOC assessments in person between Study Days 21 and 28.

e Perform LFU assessments between Study Days 35 and 42. LFU assessments may be conducted via telephone for any patient who has not experienced clinical failure since TOC, did not have ongoing study drug related AEs or SAEs at TOC, or did not develop any study drug related AEs or SAEs since TOC. If symptoms consistent with clinical failure or new study drug related AEs or SAEs are noted, or at the

discretion of the Investigator, the patient should be immediately scheduled for an in-person visit. Also, telephone visit is acceptable for patients who cannot present for a clinic visit.

f Obtain written informed consent before initiating any study assessment or procedure.

g Obtain a complete medical and surgical history, including all active conditions and all conditions diagnosed within the previous 3 months.

h If height or weight is not obtained , use the last known or stated height and weight.

i CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms.

j Every 3 days after first dose, while the patient is hospitalized and receiving inpatient IV study drug, whereby the week begins on the day of enrollment. The patient could receive unscheduled assessment, if deemed necessary at the discretion of the investigator. The investigator can rely on the physical exam performed by a professionally trained physician or health professional licensed to perform physical examinations.

k Do not perform if LFU is conducted via telephone.

l Blood pressure (systolic and diastolic) and pulse rate, respiratory rate, oxygen saturation (if applicable), and highest daily temperature.

m Record medications, including antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the- counter medications (eg, vitamins, herbal medications), and parenteral nutrition taken or received within 30 days of first dose of ***inpatient*** IV study drug through LFU.

n Refer to Section 9.5.2.5 for a detailed list of laboratory tests. Results from unscheduled laboratory tests will not be collected, unless associated with an SAE or AE leading to discontinuation of IV study drug. Any abnormal laboratory test possibly attributable to IV study drugs will be repeated at appropriate intervals until it returns to normal.

o Perform on Study Day 7 if still on IV study drug.

p At EOIV, perform laboratory tests if laboratory tests for EOIV is obtained ≥ 24 hours prior to the last dose (if applicable).

q Record absolute neutrophil count a minimum of 3 times per week while on study therapy (IV or oral). For patients who switch to oral ***or IV*** therapy, at the discretion of the Investigator, record absolute neutrophil count as clinically indicated between EOIV and TOC.

r Women of childbearing potential only (including those who are fewer than 2 years postmenopausal); ensure test is negative before randomization within 5 days.

s The estimated CrCl should be calculated with the Cockcroft-Gault formula using the actual weight. If weight is not obtained, use the last known or stated weight.

t Obtain 1-2 sets of blood samples from an existing CVC, if present, and from a peripheral vein site if possible, preferably before antibiotics are administered. If no CVC is present, collect 1-2 blood cultures from separate venipuncture sites, preferably. Obtain blood samples for culture every other day until temperature is ≤ 100.4°F (38.0°C) and cultures are negative.

u If baseline cultures were positive, repeat blood cultures at EOIV if clinically indicated to determine microbiological response.

v Administer study drug per Section 9.4.1.

AE = adverse event; CrCl = creatinine clearance; CT = computed tomography; CVC = central venous catheter; CXR = chest radiography; EOIV = End of ***Inpatient*** Intravenous Therapy; IV = intravenous; LFU = Late Follow-up; SAE = serious adverse event; TOC = Test-of-Cure.

2.0 LIST OF IN-TEXT TABLES

3.0 LIST OF IN-TEXT FIGURES

4.0 LIST OF ABBREVIATIONS

%*f*T > CT	percent of time that free drug concentrations are above a threshold concentration over a dose interval
%*f*T > MIC	percent of time that free drug concentrations are above the minimum inhibitory concentration over a dose interval
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AmpC	Ambler Class C
AST	aspartate aminotransferase
CE	clinically evaluable
CFR	Code of Federal Regulations
cIAI	complicated intra-abdominal infection
CrCl	creatinine clearance
CT	computed tomography
cUTI	complicated urinary tract infection
CXR	chest x-ray
eCRF	electronic case report form
EDC	electronic data capture
EOIV	End of ***Inpatient*** Intravenous Therapy
ESBL	extended-spectrum β-lactamase

FDA	US Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IMI	Imipenem/cilastatin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous, intravenously
LAR	legally authorized representative
LFU	Late Follow-up
MDR	multidrug resistant
ME	microbiologically evaluable
MedDRA	*Medical Dictionary for Regulatory Activities*
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
MTZ	metronidazole
PCS	potentially clinically significant
PHL	potential Hy's Law
PID	patient identification
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
q8h	every 8 hours

q6h	every 6 hours
REL	Relebactam
RSM	Regional Site Manager
SAE	serious adverse event
SOC	standard of care
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 Institutional Review Board

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Merck, Inc. along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRB in conformance with the CFR, Title 21, Part 56.

5.2 Ethical Conduct of the Study

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and Good Clinical Practice (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

5.3 Patient Information and Informed Consent

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) before participating in any study-related procedures.

Each patient (or his or her legally authorized representative) will read, assent to an understanding of, and sign an instrument of ICF after having had an opportunity to discuss it with the study staff before signing; each patient will be made aware that he or she may withdraw from the study at any time.

The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF will be given to the patient, and both documents will be placed in the Investigator's study files.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at 1 study center in the United States (MD Anderson Cancer Center, Houston, Texas).

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator must meet his or her obligations to the patients, ethics committee, Funder, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance consistent with the study investigational plan. The Investigator will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

7.1 Background and Study Rationale

Infections caused by multidrug-resistant Gram-negative pathogens, ESBL-producing Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp., are difficult to treat and associated with high mortality (1-5). Carbapenems fulfil a critical role in the treatment of serious bacterial infections due to these pathogens, both as empirical therapy in settings with high background levels of antibiotic resistance and as definitive therapy for confirmed MDR strains (6-10). The increasing prevalence of carbapenem-resistant bacterial pathogens is therefore a major global health threat, with the US CDC considering carbapenemresistant Enterobacteriaceae, one of only three bacterial threats at the highest hazard level (11-13). The most common carbapenem resistance mechanism is the production of carbapenemases, which are b-lactamase enzymes able to hydrolyse carbapenem-class antibacterials (14).
Resistance can also be mediated by other b-lactamases combined with additional mechanisms, such as porin loss and/or efflux pump expression (7, 15-18).

Among various strategies, the most successful in increasing the life span of -lactam antibiotics has been their combination with new agents capable of inhibiting a broad spectrum of –lactamases (10). Relebactam is a -lactamase inhibitor that inhibits two different classes of -lactamases: class A -lactamases (serine-containing -lactamases, such as the Klebsiella pneumoniae carbapenemase) and class C -lactamases (such as AmpC cephalosporinases) (7) Relebactam is suitable for combination with the well-established carbapenem imipenem/cilastatin (IMI): inhibiting AmpC frequently restores Pseudomonas aeruginosa susceptibility to imipenem but not other carbapenems, neither agent is subject to efflux in P. aeruginosa, and their pharmacokinetic/pharmacodynamic profiles complement each other (9, 10). Combining relebactam with IMI (IMI/REL) can restore IMI activity against many imipenem-nonsusceptible gram-negative pathogens, including extended-spectrum β-lactamase (ESBL)-, AmpC-, and KPC-producing Enterobacteriaceae (19, 20). Two phase 2 trials found IMI/REL safe and no less effective than IMI for complicated intraabdominal and urinary tract infections (14, 21-23). In addition the Pivotal RESTORE-IMI 2 Phase 3 Study of Merck's RECARBRIO™ (imipenem, cilastatin, and relebactam) in Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP). This trial met Primary Endpoint. For both the primary and secondary efficacy end points, IMI/REL was non-inferior ($p < 0.001$) to PIP/TAZ. The rates of adverse events (AEs) in the safety population (IMI/REL 226/266 [85.0%] vs PIP/TAZ 233/269 [86.6%]), as well as therapy discontinuations due to both overall AEs and specifically due to drug-related AEs, were similar across both treatment arms. Diarrhea, increase alanine aminotransferase, and increased aspartate aminotransferase were the most common AEs (6/266 [2.3%] each). Therefore IMI/REL is an efficacious and well-tolerated treatment option for HABP/VABP. Pharmacokinetic/pharmacodynamic analyses (21, 24) confirmed 500 mg IMI plus 250 mg REL as the optimum IMI/ REL dose for further clinical evaluation.

Therefore, the novel β-lactamase inhibitors relebactam are being developed to address the need for agents with activity against carbapenem-resistant Gram-negative, such as Imipenem–Relebactam. This antibiotic (Imipenem-Cilastatin-Relebactam) will be compared to standard of

care other anti-pseudomonal beta-lactams (e.g.Cefepime, Meropenem or Piperacillin/Tazobactam) in patients with neutropenia and fever. This study uses Procalcitonin (PCT) as a theragnostic biomarker that promotes antimicrobial stewardship and the need to switch and streamline these broad spectrum IV antibiotics by 48-72 hours in most of the cases. PCT has been studied by our group in cancer patients in the setting of neutropenic fever and has been shown to be a useful tool for assessing the response to antimicrobial therapy particularly between 48 and 72 hours (25-31). Furthermore, it has been highly studied in high risk patients such as critically ill patients and patients with lower respiratory tract infections and was found to be a useful tool for antimicrobial stewardship and for streamlining antimicrobial therapy (to either oral regimen or simplified IV regimen) or discontinuing antimicrobial therapy (32-35). Hence, it is being used in this current study for antimicrobial stewardship to prevent unnecessary prolonged use of broad spectrum antimicrobial therapy.

7.2 Clinical Overview

The activity of imipenem against Gram-negative bacteria is either retained or enhanced with the addition of relebactam. Significant increases in activity of imipenem with the addition of relebactam are observed against imipenem non-susceptible and b-lactamase (ESBL, KPC, and serine carbapenemase) producing Enterobacteriaceae (2- to 128-fold MIC reductions) and against P. aeruginosa (eightfold MIC reduction). Clinical trials completed to date are summarized in Table (12), including two imipenem–relebactam phase II clinical trials for the treatment of cIAI and cUTI/AP (NCT01506271 and NCT01505634).

7.2.1 Summary of Efficacy In Completed Clinical Studies

The efficacy, tolerability, and safety of imipenem–relebactam has been studied for the treatment of cIAI in a global, double-blind, randomized, phase II, non-inferiority trial (NCT01506271) (Table II) (21). Imipenem/cilastatinrelebactam (500/500/250 mg and 500/500/125 mg) were compared to imipenem/cilastatin alone (500/500 mg), administered IV (t’ 30 min) q6 h for 4–14 days. The dose of imipenem was adjusted for renal insufficiency and/or low body weight according to the approved label at the time of the trial, and the dose of relebactam was adjusted proportionally. In this study, 351 patients were BLOCK randomized (1:1:1) . Clinical response in the ME population at EFU and LFU was similar to the response seen at DCIV, and was similar across all three treatment groups (Table II).

The efficacy, tolerability, and safety of imipenem–relebactam has been studied for the treatment of cUTI and AP in a global, double-blind, randomized, phase II, non-inferiority trial) (14). Imipenem/cilastatin-relebactam (500/500/250 mg and 500/500/125 mg) was compared to imipenem/cilastatin alone (500/500 mg), administered IV (*t*’ 30 min) q6 h with optional oral step-down to ciprofloxacin after at least 4 days of IV therapy. The total treatment duration was a maximum of 14 days. The dose of imipenem was adjusted for renal insufficiency and/or low body weight according to the approved label at the time of the trial, and the dose of relebactam was adjusted proportionally. In this study, 302 patients were block randomized 1:1:1.

The primary outcome was a favorable microbiological response in the ME population at DCIV. Microbiological response was determined based on urine culture results on follow-up relative to the pathogen(s) isolated at baseline. The ME population was defined as subjects with an

eligible diagnosis of cUTI or AP, a prestudy culture growing at least one Gram-negative enteric and/or anaerobic pathogen at a sufficient quantity, and no significant protocol deviations, who received at least 4 days of IV study therapy.

The ME population at DCIV included 77.2% of randomized patients. A non-inferiority margin was set at ≥ 15% for the lower bound of the 95% CI, with 87% power to determine non-inferiority of imipenem–relebactam compared to imipenem alone. Microbiological response in the ME population at DCIV (primary outcome) for the relebactam arm 250 mg was 95.5 versus 98.7% for imipenem alone, a difference of − 3.1% (95% CI − 11.3 to 3.2), while response for the relebactam 125 mg arm was 98.6 versus 98.7% for imipenem alone (95% CI − 6.4 to 5.9). Therefore, both regimens were non-inferior to imipenem alone for the primary outcome.

7.3 Summary of Safety

In a Phase II study comparing the treatment of cUTI and AP, drug-related adverse events occurred in 10.1, 9.1, and 9% of patients for treatment with imipenem/cilastatin-relebactam 500/500/250 mg, imipenem/cilastatin-relebactam 500/500/125 mg, and imipenem/cilastatin 500/500 mg, respectively (14). No deaths occurred; however, serious treatment-emergent adverse events were reported in 3.0, 1.0, and 3.0%, respectively. The most common treatment-emergent adverse events included nausea, headache and diarrhea, which were relatively similar in all three treatment groups (range of 2.0–7.1%). Treatment-related adverse events leading to discontinuation occurred in four patients, 2 (2%), 1 (1%), and 1 (1%) in the three treatment groups, respectively, due to diarrhea, rash, nausea, and diarrhea. One patient in the relebactam 250 mg group experienced AST elevations ≥ 5× ULN, determined to be drug related.

7.4 In vitro Activity of Imipenem/relebactam and Comparator Agents

Organism	(No. Tested)	Agent	MIC (in µg/ml)[a]		
			50%	90%	Range
Escherichia coli (ESBL negative)	(50)	IPM/REL	0.06	0.125	≤0.03-0.5
		FEP	0.06	2.0	<0.03->64.0
		MEM	≤0.03	0.125	≤0.03-0.5
		IPM	0.06	0.5	≤0.03-0.5
		TZP	4.0	8.0	0.5-16.0
		TGC	0.125	0.5	≤0.03-0.5
		AMK	2.0	4.0	1.0-8.0
Escherichia coli (ESBL positive)	(50)	IPM/REL	0.06	0.25	<0.03-1.0
		FEP	8.0	64.0	≤0.03->64.0
		MEM	0.06	0.125	≤0.03-0.5
		IPM	0.125	1.0	0.06-8.0
		TZP	16.0	>256.0	1.0->256.0
		TGC	0.25	0.5	<0.03-2.0
		AMK	2.0	16.0	0.25-64.0
Klebsiella pneumoniae (ESBL negative)	(63)	IPM/REL	0.06	0.125	<0.03-0.5
		FEP	0.25	16.0	<0.03->64.0
		MEM	<0.03	0.125	<0.03-8.0
		IMP	0.125	0.5	<0.03-16.0
		TZP	8.0	64.0	0.5->256.0
		TGC	0.25	2.0	<0.03-4.0
		AMK	1.0	2.0	0.5->64.0
Klebsiella pneumoniae (ESBL positive)	(37)	IPM/REL	0.06	0.25	<0.03-4.0
		FEP	16.0	>64.0	0.5->64.0
		MEM	0.06	0.125	<0.03-32.0
		IPM	0.215	0.5	0.06-4.0
		TZP	16.0	64.0	2.0->256.0
		TGC	1.0	4.0	0.125-4.0
		AMK	<4.0	16.0	<4.0->64.0
Carbapenem-resistant *Enterobacteriaceae*	(30)	IPM/REL	0.125	8.0	<0.03-64.0
		FEP	>64.0	>64.0	2.0->64.0
		MEM	8.0	>64.0	<0.03-64.0
		IPM	4.0	32.0	0.06-64.0
		TZP	>256.0	>256.0	1.0->256.0
		TGC	1.0	2.0	<0.03-8.0
		AMK	4.0	64.0	0.5->64.0
Acinetobacter spp.	(20)	IPM/REL	0.125	64.0	<0.03-64.0
		FEP	2.0	64.0	0.06->64.0
		MEM	0.25	64.0	<0.03-64.0
		IPM	0.125	64.0	<0.03->64.0
		TZP	1.0	64.0	<0.125->256.0
		TGC	0.25	1.0	<0.03-4.0
		AMK	4.0	8.0	0.125->64.0
Pseudomonas aeruginosa (non-MDR)	(65)	IPM/REL	0.125	0.5	
		FEP	1.0	8.0	
		MEM	0.25	4.0	
		IPM	1.0	8.0	
		TZP	8.0	>256.0	
		TGC	8.0	8.0	
		AMK	1.0	2.0	
Pseudomonas aeruginosa (MDR)	(35)	IPM/REL	0.5	64.0	
		FEP	16.0	32.0	
		MEM	8.0	>64.0	
		IPM	8.0	>64.0	
		TZP	128.0	>256.0	
		TGC	8.0	16.0	
		AMK	2.0	64.0	
Enterobacter cloacae	(50)	IPM/REL	0.125	0.125	
		FEP	0.06	8.0	
		MEM	0.06	0.25	
		IPM	0.5	>64.0	
		TZP	4.0	128.0	
		TGC	0.25	2.0	
		AMK	1.0	8.0	
Citrobacter spp.	(10)	IPM/REL	<0.06	0.125	
		FEP	<0.03	8.0	
		MEM	0.06	1.0	
		IPM	0.5	1.0	
		TZP	64.0	>256.0	
		TGC	0.125	2.0	
		AMK	1.0	2.0	
Serratia spp.	(10)	IPM/REL	0.125	0.125	
		FEP	<0.03	<0.03	
		MEM	0.06	0.06	
		IPM	0.25	0.25	
		TZP	4.0	4.0	
		TGC	0.125	2.0	
		AMK	2.0	4.0	
Achromobacter spp	(10)	IPM/REL	0.25	2.0	
		FEP	16.0	>64.0	
		MEM	1.0	16.0	
		IPM	0.5	2.0	
		TZP	2.0	>256.0	
		TGC	2.0	2.0	
		AMK	16.0	>64.0	
Stenotrophomonas maltophilia	(50)	IPM/REL	>64.0	>64.0	
		FEP	64.0	>64.0	
		MEM	64.0	>64.0	
		TZP	128.0	>256.0	
		IPM	>64.0	>64.0	
		TGC	1.0	4.0	
		AMK	64.0	>64.0	
Sphingomonas paucimobilis	(10)	IPM/REL	<0.03	0.125	
		FEP	0.25	4.0	
		MEM	<0.03	4.0	
		IPM	0.25	0.5	
		TZP	8.0	>256.0	
		TGC	0.125	0.5	
		AMK	0.5	2.0	

8.0 STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of imipenem–cilastatin-relebactam plus/minus vancomycin, daptomycin or linezolid vs standard of care (SOC) plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response at ***End of Inpatient Intravenous Therapy (***EOIV***)*** in the Modified Intent-to-Treat (MITT) Analysis Set.

- To evaluate the safety and tolerability of imipenem-cilastatin–relebactam plus/minus vancomycin, daptomycin, or linezolid compared with SOC plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer.

Secondary:

- To evaluate the efficacy of imipenem-cilastatin–relebactam plus/minus vancomycin, daptomycin or linezolid compared with SOC plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to the following:

  - Favorable clinical response at EOIV in the mMITT and Clinically Evaluable (CE) analysis sets.

  - Favorable clinical response at TOC (ie, 21 to 28 days after start of IV therapy) ***and LFU (ie, 35 to 42 days after start of IV therapy)*** in the MITT Analysis Set.

  - Favorable clinical response by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU*** in the mMITT and CE analysis sets.

  - Favorable microbiological response by patient and by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU*** in the mMITT and ME analysis sets.

  - Infection-related mortality rate at TOC ***and LFU*** in the MITT and mMITT analysis sets.

  - 30-day all-cause mortality rate in the MITT and mMITT analysis sets.

- To evaluate the role of PCT in promoting antimicrobial stewardship resulting in the switch of most patients from the broad spectrum agents (Imipenem/Cilastatin/Relebactam & SOC) to a more simplified IV or oral antibiotic therapy within 48-72 hours.

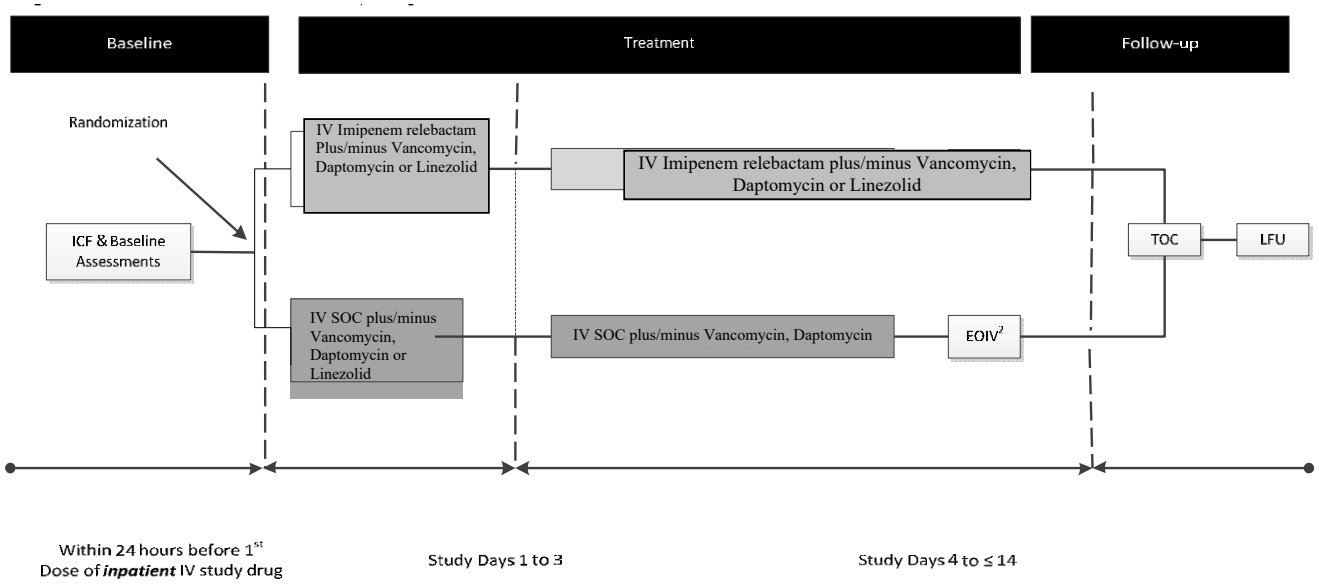
9.0 Investigational Plan:

9.1 Overall Study Design and Plan: Description

This clinical study will be a single-center, randomized, open-label, parallel-group study comparing imipenem-cilastatin–relebactam plus/minus vancomycin, daptomycin or linezolid with SOC plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer. The total duration of study therapy will be 2 to 14 days; a minimum of 2 days (ie, 48 hours of IV antimicrobial gram negative coverage is required;

duration of treatment is discussed in Section 9.4.1.5. ***IV study drug is defined as the IV treatment for Gram-negative coverage (or SOC) that the patient is receiving for the neutropenic febrile episode*****).** A switch to open-label oral ***or IV*** therapy may be allowed after at least 48 hours IV gram negative antimicrobial coverage per Section 9.4.1. Doses of SOC antibiotics given before signing informed consent will be counted.
Gram positive antimicrobial coverage (ie vancomycin, linezolid or daptomycin) is optional and can be given if clinically indicated at the discretion of the primary team or emergency center physician. Gram positive antimicrobial coverage can also be switched at any time during the study.

Figure 9.1–1. Study Design



9.2 This Section Intentionally Omitted

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

To be eligible to participate in the study, a patient must meet the following criteria:

1. Has provided written informed consent, and has the willingness and ability to comply with all study procedures
2. Male or female, ≥ 18 years old
3. Patients with neutropenic fever who have existing malignancy or have undergone hematopoietic stem cell transplantation. Neutropenic fever is defined as the presence of neutropenia defined by: 1) Absolute neutrophil count (ANC) < 500 cells/mm^3 or has an ANC that is expected to decrease to < 500 cells/mm^3 within 48 hours of trial entry and fever defined as: 2) Single oral temperature measurement of > 100.4°F (38.0°C)
4. Requires hospitalization for IV empiric antibiotic therapy
5. If female:

- Not breastfeeding
- Agrees to not attempt to become pregnant during the study

- Is surgically sterile or at least 2-years postmenopausal, or if of childbearing potential, has negative screening serum or urine pregnancy test within 5 days

- If of childbearing potential (including being < 2 years postmenopausal), is willing to practice sexual abstinence or use an effective dual form of contraception with her partner (eg, 2 barrier methods, barrier method plus hormonal method) during treatment and up 28 days post treatment.

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study**:**

1. History of any hypersensitivity or allergic reaction to any carbapenem
2. Fever suspected to be caused by a noninfectious cause (eg, fever related to drug or blood product administration)
3. Confirmed fungal infection (eg, *Pneumocystis jirovecii* etiology in patients with pneumonia) that justifies adding additional empiric antimicrobial therapy (eg, antifungals)
4. Confirmed viral infection that justifies adding additional empiric antiviral therapy (eg, ganciclovir, foscarnet)
5. Evidence of significant hepatic impairment (any of the following):

- Known acute viral hepatitis

  Alanine aminotransferase (ALT) level > 5 times the upper limit of normal (× ULN).
  Total bilirubin > 3 × ULN unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert disease
- Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy

6. Known to be human immunodeficiency virus positive
7. Severely impaired renal function, defined as creatinine clearance (CrCl) ≤ 30 mL/min estimated by the Cockcroft-Gault formula (Section 9.5.3.1)
8. Expected requirement for hemodialysis while on study therapy
9. Received > 36 hours of IV antibacterial therapy (with study drugs) within 72 hours of the initiation of ***inpatient*** IV study drug for treatment of suspected infection. Antibiotic prophylaxis and oral antibiotics is allowed. Prophylactic use of antiviral or antifungal medication is permitted.
10. Past or current history of epilepsy or seizure disorder; **exception:** well-documented febrile seizure of childhood
11. Evidence of immediately life-threatening disease, progressively fatal disease, or life expectancy of 3 months or less (eg, moribund or with shock unresponsive to fluid replacement)

12. Unable or unwilling to adhere to the study-specified procedures and restrictions

13. Any condition that would make the patient, in the opinion of the Investigator, unsuitable for the study (eg, would place a patient at risk or compromise the quality of the data

14. Participation in any other ongoing imipenem-cilastatin–relebactam trial.

15. Prior participation on this trial

9.3.3 Removal of Patients from Therapy or Study Assessment

Patients should be encouraged to complete all study assessments. However, a patient may be discontinued from ***inpatient*** IV study drug ***or*** oral ***or IV*** therapy or may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled.

A premature discontinuation from the study will occur when a patient who signed the ICF, regardless of circumstances, ceases participation in the study, before the completion of all study assessments (ie, before completing all protocol-stipulated activities). In addition, patients can be prematurely discontinued from the study after careful consideration for one of the reasons listed in Section 9.3.3.4.

Follow-up of patients prematurely discontinued from *inpatient* IV study drug or oral or IV therapy or withdrawn from the study will be conducted as described below.

9.3.3.1 Premature Discontinuation from Inpatient IV Study Drug Due To Safety

Reasons: Possible reasons for premature discontinuation from study drug administration *due to safety* include, but are not limited to:

Occurrence of a related, possibly or probably related AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from IV study drug

Known pregnancy or breastfeeding during the study therapy administration period.

The patient meets criteria for drug-induced liver injury per Appendix V, at the discretion of the Investigator

Investigator determines that it is in the best interest of the patient to discontinue study drug, due to reasons other than an adverse event (AE)

Assessments and Procedures: A patient who is prematurely discontinued from ***inpatient*** IV study drug (ie, before the anticipated full course of study therapy required for effective treatment of febrile neutropenia) *for safety reasons* should have EOIV assessments conducted

and undergo safety assessments at TOC and LFU.

Clinical Outcome Assessment: See Table 9.7.5.3–1

9.3.3.2 Premature Discontinuation from Inpatient IV Study Drug Due To Insufficient Therapeutic Effect

Reasons: Possible reasons for discontinuation from study drug *due to insufficient therapeutic effect* include, but are not limited to:

Clinical worsening: A patient who shows signs of clinical worsening may be prematurely discontinued from ***inpatient*** IV study drug at any time. If the Investigator deems the benefit-to-risk ratio of ***inpatient*** IV study drug continuance acceptable, administration of at least 48 hours is encouraged before discontinuation.

Lack of clinical progress: For a patient who is stable, yet does not show signs of improvement, the Investigator is encouraged to continue ***inpatient*** IV study drug for at least 48 hours before such a patient is considered a clinical failure and is prematurely discontinued from IV study drug

Assessments and Procedures: A patient who is prematurely discontinued from ***inpatient*** IV study drug *due to insufficient therapeutic effect* should have EOIV assessments conducted and undergo safety assessments at TOC and LFU. If a patient is discontinued from ***inpatient*** IV study drug *due to insufficient therapeutic effect* and is switched to an alternative IV antibiotic, that therapy should be recorded.

Clinical Outcome Assessment: See Table 9.7.5.3–1.

9.3.3.3 Premature Discontinuation from Oral or IV Therapy

A patient who is prematurely discontinued from oral ***or IV*** therapy for any reason will not have protocol assessments conducted until TOC (ie, there is no scheduled visit between EOIV and TOC). At an unscheduled visit or at TOC, whichever occurs first, record the date of and reason for discontinuation. See Table 9.7.5.3–1 for clinical outcome definitions at TOC.

9.3.3.4 Withdrawal from Study

Reasons: Possible reasons for withdrawal from study depend on the timing of the withdrawal, and include, but are not limited to:

Before administration of first dose of study therapy:

Screen failure (failure to meet inclusion/exclusion criteria)

Withdrawal of consent at any time during the study period.

AE

Protocol violation

Lost to follow-up

Study terminated by Funder

Site terminated by Funder

Investigator determines that it is in the best interest of the patient to withdraw from the study protocol, due to reasons other than an AE

An AE should not be a reason for withdrawal from study after study drug has been administered. The patient may be discontinued from study drug due to an AE, in which case they should be encouraged to stay in the study for follow-up safety assessments.

Note: If death was due to an AE, then the AE is the reason for discontinuing study drug and death is the reason for withdrawal from study. If the death is due to lack of efficacy, then lack of efficacy is the reason for discontinuing study drug, and death is the reason for withdrawal from study.

Assessments and Procedures: Patients may withdraw from the study, or be withdrawn at the request of the Investigator or Funder. A patient who is withdrawn completely from the study during ***inpatient*** IV study drug ***or*** oral ***or I***V therapy should be encouraged to undergo, if possible, EOIV (if on ***inpatient*** IV study drug) or TOC (if on oral ***or IV*** therapy) assessments on the day of withdrawal. Patients withdrawn from the study need not undergo subsequent TOC efficacy assessments (if on ***inpatient*** IV study drug) or LFU (if on oral ***or IV*** therapy) assessments.

Clinical Outcome Assessment: A patient withdrawn from the study who is not assessed as a clinical failure should be assessed as indeterminate at all subsequent outcome evaluation time points (Table 9.7.5.3–1).

9.3.4 Patient Replacement Procedures

Randomized patients who are withdrawn and have received at least one dose of study drug will not be replaced. Patients who withdraw consent prior to receiving any dose of study drug will be replaced by an evaluable patient.

9.4.1 TREATMENTS

Treatments Administered

9.4.1 Treatment Group

As shown in Table 9.4.1.3-1, patients randomized to the Imipenem-Cilastatin-Relebactam

treatment group will receive:

Imipenem-Relebatam: 500 mg Imipenem, 500 mg cilastatin and 250 mg of Relebactam IV over 30 min Q6 hours

IV Imipenem/Cilastatin/Relebactam ***(minimum of 8 doses)***

Gram positive antimicrobial coverage (ie vancomycin, linezolid or daptomycin) is optional and can be given if clinically indicated at the discretion of the primary team or emergency center physician. Gram positive antimicrobial coverage can also be switched at any time during the study.
Daptomycin could be given if there is no evidence of pneumonia.

Patient may continue on the study drug up to 14 days if clinically indicated by the assessment of the treating physician

Patients may receive other additional therapy as discussed in Section 9.4.1.3. Patients may be eligible to switch to ***outpatient IV or*** oral therapy, as discussed in
Section 9.4.1.4.

9.4.1.3 Standard of Care Treatment Group

As shown Table 9.4.1.3–1, patients randomized to the SOC treatment group will receive:

One of the following IV therapies:

Cefepime (minimum of 6 doses)

Meropenem (minimum of 6 doses)

Piperacillin/tazobactam (minimum of 8 doses)

Doses given before signing informed consent will be counted if antibiotics remain the same (dose and frequency) after signing informed consent.

Gram positive coverage is optional as clinically indicated with IV vancomycin, daptomycin or linezolid (oral linezolid is allowed)**.** Daptomycin could be given if there is no evidence of pneumonia.

Patients may receive other additional therapy as discussed in Section 9.4.1.3. Patients may be eligible to switch to ***outpatient IV or*** oral therapy, as discussed in
Section 9.4.1.4.

9.4.1.3 Other Additional Antibacterial Therapy

Patients in either treatment group may receive other additional therapy as needed (Table 9.4.1.3–1) at the discretion of the primary physician or Investigator, per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II; or Appendix III for patients with documented or suspected pneumonia), as follows:

Double Gram-negative coverage should be considered with complicated tissue-based infections, neutropenic enterocolitis, pneumonia, and perirectal infections; if indicated, add Tobramycin, Amikacin Ciprofloxacin, Minocycline, Tigecycline, Doxycycline, or Bactrim.
Table 9.4.1.3–1

Additional antibacterial therapy may be added at any time during the study for management of complications or if antibacterial resistance is suspected or proven

A Switch to a Once-Daily Gram- Negative IV Agent for the Purposes of Outpatient Or Home IV Treatment Is Allowed After 48 Hours As Described In Table 9.4.1.3–1

Empirical Treatment of patients with colitis, abdominal symptoms or C. Difficile with Oral Vancomycin or Metronidazole (IV or oral) May Be Added at any time during the study.

Table 9.4.1.3–1. Investigational Products

Investigational Product	***Dosage[a] and Route***	***Form and Strength***	***Supplier***
Treatment Group:			
Imipenem-Cilastatin-Relebactam	500 mg Imipenem, 500 mg Cilastatin and 250 mg of Relebactam IV over 30 min Q6h	***Investigational***	FRI
PLUS/MINUS one of the following adjunctive Gram-positive therapies (optional):			
Vancomycin[b]	15 mg/kg (rounded to nearest 250-mg dose) IV q12h (+/– 30 min)	***Commercial Supply as per FDA approved package insert***	MDA
Linezolid[b]	600 mg IV (or oral) q12h	***Commercial Supply as per FDA approved package insert***	MDA
Optional for Either Treatment Group (IV Gram-Positive Adjunctive Therapy Switch at any time for Patients With Suspected Line Infections and/or Bacteremia)			
Daptomycin[b]	***6-8 mg/kg IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Standard of Care (Comparator) Treatment Group:			

ONE of the following:			
Cefepime	2 g IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Meropenem	1 g IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Piperacillin/tazobactam	4.5 g IV q6h	***Commercial Supply as per FDA approved package insert***	MDA
PLUS/MINUS one of the following adjunctive Gram-positive therapies (optional):			
Vancomycin[b]	15 mg/kg (rounded to nearest 250-mg dose) IV q12h	***Commercial Supply as per FDA approved package insert***	MDA
Linezolid[b]	600 mg IV (or oral) q12h	***Commercial Supply as per FDA approved package insert***	MDA
Optional for Either Treatment Group (IV Gram-Negative Therapy Switch After at Least 48 Hours of IV Gram-Negative antimicrobial coverage)			
Ceftriaxone	***2 g IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Ertapenem	***1 g IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Optional for Either Treatment Group (IV Gram-Positive Adjunctive Therapy Switch at any time for Patients With Suspected Line Infections and/or Bacteremia)			
Daptomycin[b]	***6-8 mg/kg IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***

Table 9.4.1.3–1. Investigational Products

Investigational Product	*Dosage[a] and Route*	*Form and Strength*	*Supplier*
Optional for Either Treatment Group (Adjunctive Double Gram-Negative Therapy):			
Tobramycin[c]	7 mg/kg IV q24h	***Commercial Supply as per FDA approved package insert***	MDA
Optional for Either Treatment Group (Adjunctive Double Gram-Negative Therapy):			
Amikacin[c]	***15 - 20 mg/kg IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Ciprofloxacin[c]	400 mg IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Minocyclin	100mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Tigecycline	100 mg/day (day 1- day 2 on) 50 mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Doxycycline	100 mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Bactrim	5-20mg/kg/day	***Commercial Supply as per FDA approved package insert***	MDA

a Dosages shown for patients with normal renal/hepatic function. Appropriate dosage modifications for renal function will be made per Section 9.4.5.1-1

b Per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

c As needed for double Gram-negative coverage per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II).

Imipenem Cilastatin Relebactam; IV = intravenous; MDA = MD Anderson; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.

All antibiotic doses and infusion time will be administered according to standard doses and time of administration defaulted in EPIC system.

Subsequent antibiotic doses may be administered according to MDACC policy (Standard 28Medication Administration Time Policy (UTMDACC Institutional Policy # CLN1091) timed on the next whole hour. If unable to administer a dose at scheduled time, give the next dose ASAP (according to MDACC institutional policy # 1091, Standard medication administration Exception list attachment). Once the delay has been resolved, re-time future doses to coincide with the most recent administration time.

9.4.1.4 Optional Oral or IV Therapy Switch

9.4.1.4.1 Criteria for Switching to Oral or IV Therapy

A switch to oral *or IV* therapy may be allowed after at least 48 hours of IV gram negative antimicrobial coverage if all of the following criteria are met:

Oral therapy or IV therapy (for outpatient or home administration) is clinically indicated

Patient received at least 48 hours of IV gram negative antimicrobial coverage.

EOIV clinical signs and symptoms have been assessed

Patient has the ability to maintain oral intake

Patient is clinically stable

Patient is afebrile

Improvement in clinical signs and symptoms of infection from baseline

Patient has negative blood culture (taken within past 24 hours) (for patients with positive blood cultures at baseline with a gram negative organism)

.

For Patients Who Are Randomized To SOC, Doses Given Before Signing The Informed Consent Will Be Counted If Antibiotics Remain The Same (Dose and Frequency) After Signing The Informed Consent.

Exploratory: We will evaluate how often repeat PCT at 48-72 hours after study drug initiation has dropped by ≥ 30 % from baseline (day 0= start of therapy) or PCT level within 48-72 hours is below 0.25. This will not be considered a switching criterion and if not met will not constitute a protocol deviation. This is an exploratory criterion that will be evaluated to explore the role of PCT used as a biomarker in adjunct to the clinical judgement to guide antibiotic therapy.

9.4.4.4.2 Oral and IV Switch Therapy Options

After completion of at least 48 hours of IV gram negative antimicrobial coverage, the patient may be switched to an appropriate combination of oral and/or IV therapy such as:

Linezolid (oral)

Ampicillin

Amoxicillin

Amoxicillin/clavulanate (oral)

Minocycline (oral)

Ciprofloxacin (oral)

Levofloxacin (oral)

Cefpodoxime (Oral)

Trimethoprim/sulfamethoxazole (oral)

Ceftriaxone (IV)

Ertapenem (IV)

Daptomycin (IV)

Vancomycin (IV)

The specific combination chosen is at the discretion of the Investigator *in accordance with local SOC* and should provide coverage for isolated pathogens and appropriate empirical therapy in the absence of microbiological data.

Consult the package inserts, labels, and local dosing guidelines regarding storage, administration, maximum doses, contraindications (eg, drug-drug interactions), warnings, precautions, and adverse drug reactions reported with the use of oral *or IV* therapies.

9.4.1.5 Duration of Treatment

The total duration of study therapy will be 2 to 14 days; a minimum of 2 days (ie, 48 hours) of IV gram negative antimicrobial coverage is required. After at least 2 days (ie, 48 hours [of IV gram negative antimicrobial coverage, the Investigator will assess if inpatient IV study drug should be continued or a switch to oral or IV therapy is warranted (Section 9.4.1.4). After at least 48 hours (ie, 2 days, typically on or after Study Day 2) of antibiotic therapy (IV plus oral), the Investigator will assess if inpatient IV study drug or oral or IV switch therapy should be continued or if all therapy should be discontinued.

Duration of therapy is at the discretion of the Investigator, considering clinical response, presence of clinically and /or microbiologically documented infections, and signs of bone marrow recovery.

An assessment of clinical outcome will be made at the end of all study therapy as defined in **Section 9.7.5.3.**

9.4.2 Identity of Investigational Products

Investigational product Imipenem-Cilastatin-Relebactam contains Imipenem, Cilastatin and Relebactam, which will be administered together in a single infusion bag. A single vial filled with the sterile crystalline form of Imipenem (500 mg), cilastatin 500mg, and the sterile crystalline form of Relebactam (250mg) for IV administration. The crystalline powders are reconstituted using saline or various dextrose solution for Injection, resulting in a concentrate solution. An amount of this solution, corresponding to the dose to be administered, is withdrawn from the vial and transferred into an infusion bag containing 100 mL saline.

Preparation of RECARBRIO Solution for Intravenous Administration
RECARBRIO is supplied as a dry powder in a single-dose vial that must be constituted and further diluted using aseptic technique prior to intravenous infusion. To prepare the infusion solution, contents of the vial must be constituted with the appropriate diluent as instructed below. A list of appropriate diluents is as follows:

- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP
- 5% Dextrose Injection, USP + 0.9% Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP + 0.45% Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP + 0.225% Sodium Chloride Injection, USP

RECARBRIO has low aqueous solubility. To ensure complete dissolution of RECARBRIO it is important to adhere to the following instructions:
Step 1) For diluents available in 100 mL prefilled infusion bags, proceed to step 2. For diluents not available in 100 mL prefilled infusion bags, aseptically withdraw 100 mL of the desired diluent and transfer it to an empty infusion bag, then proceed to step 2.

Step 2) Withdraw 20 mL (as two 10 mL aliquots) of diluent from the appropriate infusion bag and constitute the vial with one 10 mL aliquot of the diluent. The constituted suspension is for intravenous infusion only after dilution in an appropriate infusion solution.
Step 3) After constitution, shake vial well and transfer resulting suspension into the remaining 80 mL of the infusion bag.
Step 4) Add the second 10 mL aliquot of infusion diluent to the vial and shake well to ensure complete transfer of vial contents; repeat transfer of the resulting suspension to the infusion solution before administering. Agitate the resulting mixture until clear.
Constituted solutions of RECARBRIO range from colorless to yellow. Variations of color within this range do not affect the potency of the product.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.

The above instructions for preparation of RECARBRIO solution for intravenous administration must be followed for all patients, irrespective of the intended patient's renal function. The volume of this prepared RECARBRIO solution to be administered to patients is determined based on renal function [see Dosage and Administration].

Preparation of RECARBRIO Solution for Intravenous Administration in Patients with Renal Impairment
For patients with renal impairment, prepare a reduced dose of RECARBRIO (1 gram, 0.75 grams, or 0.5 grams) by preparing a 100 mL solution containing 1.25 grams (as described above) then withdrawing and discarding the excess according to Table 2.
Table 2: Preparation of Reduced RECARBRIO Doses for Intravenous Administration in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Dosage of RECARBRIO (imipenem/cilastatin/relebactam)	After preparation as instructed above, remove from the 100 mL prepared bag the volume indicated below and discard	Resulting volume that provides the indicated reduced dose
60 to 89	1 gram (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	20 mL	80 mL
30 to 59	0.75 grams (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	40 mL	60 mL
15 to 29 or ESRD on hemodialysis	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	60 mL	40 mL

With the exception of Imipenem-Cilastatin-Relebactam all other study drugs (IV or oral) will be commercially labeled. All inpatient IV study drug and oral and IV therapies should be kept in a secure place under appropriate storage conditions, as specified on the drug labeling and package insert.

Upon completion of the study or termination of the site, all used and unused study drugs that were supplied by the funder will be destroyed according to the standard operating procedures of MD Anderson.

9.4.3 Method of Assigning Patients to Treatment Groups

After patient enrollment, randomization will be conducted by the clinical coordinator on an institutional Clinical Trial Conduct (CTC) website, developed by the Department of Biostatistics. At the end of the study, 50% patients will be divided equally at the end of the study between both arms. If the patient is started on one of the three agents, we will continue the same agent if he is assigned to SOC arm. The choice of the antibiotic will be kept at the discretion of the primary team.

Patients in SOC arm will be analyzed as one treatment group in the intent to treat analysis and other analysis.

At the time of signing the ICF and consenting to participate in this study. The first patient to sign the ICF at the study center will be assigned the first accession number, and each subsequent patient will be assigned the next sequential number. This patient identification number will be used to identify the patient at all phases of the study.

9.4.4 Selection of Dosages in the Study

The dosages of each investigational product are shown in Table 9.4.1.3–1 and, if applicable, in the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines
(Appendix III).

The dose of Imipenem-Cilastatin-Relebactam that was selected for this study was based on clinical trial for the treatment of cIAI and cUTI table II

The dosages of the other investigational products are considered SOC and are used in current treatment of febrile neutropenic patients at MD Anderson, as shown in the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

9.4.5 Selection and Timing of Dose for Each Patient

Investigational products will be administered per Table 9.4.1.3–1 and, if applicable, per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients

with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

9.4.5.1 Dose Adjustments for Imipenem-Cilastatin-Relebactam

In the case of renal impairment, at any time, the dose of Imipenem-Cilastatin-Relebactam (including the initial dose) may be adjusted by the pharmacist or designee per the dosage regimen in Table 9.4.5.1–1. At any time, the dose of Imipenem-Cilastatin-Relebactam may be readjusted to the appropriate dosage when renal function improves. If a patient's estimated CrCl (as calculated using the Cockcroft-Gault formula [Section 9.5.3.1]) decreases to ≤ 30 mL/min during the treatment period, the Study Physician should be contacted immediately to discuss if continuation of study drug therapy is appropriate and to discuss additional dose adjustments for CrCl ≤ 30 mL/min.

Table 9.4.5.1–1. Dosage Adjustments for Renal Impairment

Dosage Adjustments In Patients With Renal Impairment
Dosage adjustment is recommended in patients with renal impairment. Patients who have a CLcr less than 90 mL/min require dosage reduction of RECARBRIO (Table I). For patients with fluctuating renal function, CLcr should be monitored.

Table I: Dosage of RECARBRIO for Adult Patients with Renal Impairment

Estimated CLcr (mL/min)[a]	Recommended Dosage of RECARBRIO (imipenem/cilastatin and relebactam) (mg)[b]	Dosing Interval
60 to 89	1 gram (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg)	Every 6 hours
30 to 59	0.75 grams (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg)	Every 6 hours
15 to 29	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours
End Stage Renal Disease (ESRD) on Hemodialysis[c]	0.5 grams (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg)	Every 6 hours

[a]CLcr calculated using the Cockroft-Gault formula
[b]Administer by IV over 30 minutes.
[c]Administration should be timed to follow hemodialysis.
RECARBRIO is provided as a single vial in a fixed-dose combination; the dose for each component will be adjusted equally during preparation [see Preparation of RECARBRIO

Solution for Intravenous Administration in Patients with Renal Impairment].

Patients with CLcr less than 15 mL/min should not receive RECARBRIO unless hemodialysis is instituted within 48 hours. There is inadequate information to recommend usage of RECARBRIO for patients undergoing peritoneal dialysis. Imipenem, cilastatin, and relebactam are cleared from the circulation during hemodialysis. For patients maintained on hemodialysis, administer RECARBRIO after hemodialysis and at intervals timed from the end of that hemodialysis session.

9.4.5.2 Dose Adjustments - Other Investigational Products

For all other investigational products, appropriate dosage modifications for renal function will be made per the respective package insert or institutional guidelines.

9.4.6 Blinding

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

9.4.7 Unblinding

Not applicable.

9.4.8 Prior and Concomitant Therapy

All prior (taken or received within 30 days before the first dose of IV study drug) and concomitant (taken during the study) medications, including but not limited to, antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition, will be documented on the appropriate screens of the eCRF (concomitant meds will be captured in subjects medical record in Epic).

Concomitant use of the following is not permitted: 1) potentially effective systemic antibacterial therapy; 2) any drug known to exhibit a contraindicated drug-drug interaction with any of the study therapies or a labeled contraindication to use of any study therapies.

All other concomitant medications and nutrients necessary for the health and well-being of the patient are permitted.

9.4.9 Monitoring Treatment Compliance

Treatment compliance will be closely monitored by recording the date, time, and whether or not each dose of ***inpatient*** IV study drug ***or IV switch therapy*** was infused and, if applicable, whether or not each intended dose of oral ***switch*** therapy was taken.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Primary and Secondary Efficacy Assessments

Primary Efficacy Assessment

The ***Investigator's*** assessment of clinical response will be used to determine the primary efficacy assessment. The Investigator should consider the entirety of the patient's clinical course and current status, including an evaluation of infection signs and symptoms (eg, fever, neutropenia), radiological findings (if applicable), and physical examination in order to classify the patient's clinical response at EOIV according to the definitions listed in Table 9.7.5.3–1. The investigator could rely on physical exam performed by a professionally trained physician or health professional licensed to perform physical examinations.
The investigator will use the serial PCT levels drawn at baseline and at 48-72 hours as an adjunct to the clinical judgement to guide antibiotic therapy and prevent unnecessary prolonged therapy with broad spectrum agents (Imipenem/Cilastatin/Relebactam & SOC).

Secondary Efficacy Assessments

Clinical Assessments
The ***Investigator's*** assessment of clinical response at EOIV***,*** TOC***, and LFU*** will be used to determine the secondary clinical efficacy endpoints according to the definitions listed in Table 9.7.5.3–1.

Microbiological and Molecular Assessments
A patient's microbiological response at EOIV***,*** TOC***, and LFU*** will be determined programmatically based on individual outcomes for each baseline pathogen according to the definitions listed in Table 9.7.5.4–1.

9.5.1.2 Microbiological Assessments

Blood Samples for Culture

Blood samples for culture will be obtained at the following time points, preferably before the next scheduled dose of study antibiotics is administered:

Baseline

Study Days 1 to ≤ 14: every other day until temperature is ≤ 100.4°F (38.0°C) and blood cultures are negative and PCT is < 0.25 or dropped by 30% or more within 48 -72 hours compared to baseline on Day 0 (start of therapy). PCT will be collected at baseline and at 48-72 hours after study drug initiation.

EOIV: if baseline cultures were positive (to determine microbiological response)

TOC and LFU: as clinically indicated per the discretion of the Investigator (eg, if clinical

worsening and/or persistence of fever ***or other signs or symptoms consistent with clinical failure***)

Blood cultures should be repeated upon knowledge of a positive result from any visit until sterilization is confirmed.

When blood cultures are required, 1-2 sets of blood samples should be obtained from an existing central venous catheter, if present, and from a peripheral vein site if patient agrees. If no central venous catheter is present, collect 1-2 blood cultures from separate venipuncture sites.

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility to all drugs used.

Microbiological samples for blood cultures will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

Other Samples for Culture

Culture specimens from other sites of suspected infection should be obtained as clinically indicated.

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility to all drugs used.

Microbiological samples will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

9.5.1.3 Clinical Outcome of the Infection

Per the Schedule of Assessments and Procedures (Table 2–1), the Investigator or sub-investigator is to assess the Clinical Outcome at EOIV, TOC and LFU.

9.5.2 Safety Assessments

Throughout the clinical trial, each patient will be observed for adverse reactions. All patients will be monitored for the development of study-related adverse events through the entire study period including the thirty (30) days following the last dose of study drug. Any serious, unexpected adverse event(s) will be reported to the funder and IRB per policy, and reported to the FDA accordingly. Patients who have received at least one dose of the study drug will be included in the safety analysis. Patients who withdraw consent prior to receiving any dose of study drug, will not be included in the analysis and will be replaced by an evaluable patient. Evaluation done by the primary team and the attending physician following the patient are

acceptable.

9.5.2.1 Adverse Events

Recording of Adverse Events.
An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Reportable adverse events for this protocol will be documented into the Adverse Events log (source document) and entered into the case report form in RedCap according to the Recommended Adverse Event Guidelines for Phase II Protocols (please refer to chart on page 46). The patients' records will be reviewed and only reportable AEs (AEs of any grade that are possibly, probably and definitely related to the study drug, and any AE grade 3 or above regardless of their attribution to study drug) will be documented in the AE log and case report form". The Investigator or physician designee is responsible for verifying and providing source documentation for all reportable adverse events and assigning the attribution for each event for all subjects enrolled on the trial. AEs not recorded on the AE log and case report form are considered grade 1 or 2 and unrelated or unlikely related to the study drug. This recording will apply to all patients enrolled on the protocol including future, current and previously enrolled patients. Labs that are not deemed clinically significant by the investigator will not be reported as AEs. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution for all adverse events for subjects enrolled.

Version 5.0 of the Common Toxicity Criteria for adverse events will be used to assess AEs and SAE (please refer to **Section 9.5.2.1**)

- **Attribution** - the determination of whether an adverse event is related to a medical treatment or procedure.
- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

Study subjects should be instructed to report all adverse events to the Investigator. In addition, the Investigator should seek to elicit any clinical or objective reactions by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded on the case report form. All clearly related signs, symptoms and abnormal diagnostic procedures should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. For each adverse, the Investigator is to assess the severity of the reaction, and to determine the relationship to study drug. In addition, the duration

will be noted, and whether intermittent or continuous **also** documentation of the outcomes and what was done with study drug is needed.
Events not included in the NCI CTCAE will be scored as follows:

- Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
- Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- Grade 4: Life Threatening: discomfort that represents immediate risk of death

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

Any worsening of the infection under study because of lack of therapeutic effect of any study drug is captured as an efficacy analysis variable and is not to be considered an AE, unless the event is an SAE resulting in death (Section 9.5.2.3).

Pregnancies should not be automatically assessed as AEs.

9.5.2.2 Causality Assessment

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Assessments done by the primary team following the patient are acceptable.

Is there a reasonable possibility the investigational product caused the event?

Yes: There Is Evidence To Suggest A Causal Relationship Between The Investigational Product and The Ae; Ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There Is No Evidence To Suggest A Causal Relationship Between The Investigational Product and The Ae, Ie:

- There is no reasonable temporal relationship between the investigational product and the event,

or

- The patient did not take the investigational product, or
- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsored Single Site IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there

has been acceptable resolution of the event.

- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

Any worsening of the infection under study because of lack of therapeutic effect of any study drug is captured as an efficacy analysis variable and is not to be considered an SAE, unless the event results in death.
Pregnancy will be reported to the IND Office via eSAE application as "Other Important Medical Event

This study will collect adverse events according to phase II guidelines on the table below:

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Reporting to the sponsor:
Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Potential Incident Reporting: Principal Investigator shall forward to Merck's Global "Merck GPV") group, any SAE or SUSAR, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format such as eSAE) within two (2) business days of but not longer than three (3) calendar days of receipt of the information. The phrase "business days" means a day in which Institution has regular business operations and would exclude weekends and holidays observed by Institution's administrative staff. This information shall be transmitted to Merck. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code.

The below terms shall be defined as follows:

"**Adverse Event**" or "**AE**" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

"**Serious Adverse Event**" or "**SAE**" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life- threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

"**Suspected Unexpected Serious Adverse Reaction**" or "**SUSAR**" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

9.5.2.5 Clinical Laboratory Determinations

Blood sample and urine culture/urine analysis (when clinically needed) will be collected according to the Schedule of Assessments and Procedures (Table 2-1). Specific labs important to the analysis will only be entered in REDCap and include procalcitonin, white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin, platelet count, alanine aminotransferase (ALT), albumin, alkaline phosphatase, creatinine, and total bilirubin.

Women of childbearing potential (including those who are fewer than 2 years postmenopausal) will be required to have a serum or urine pregnancy test at baseline (within 5 days). The test must be negative before randomization. If the serum test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

The following clinical laboratory levels will be measured (those marked with an asterisk [*] are required for eligibility):

Hematology: Basophils (absolute count and %), eosinophils (absolute count and %), erythrocyte count, hematocrit, hemoglobin, leukocytes (absolute count and differential), lymphocytes (absolute count and %), monocytes (absolute count and %), neutrophils (absolute count* and %), immature neutrophils (bands; %), platelet count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Albumin, ALT*, bilirubin* (total), blood urea nitrogen, calcium, creatinine*, electrolytes (ie, bicarbonate, chloride, potassium, sodium), glucose, Procalcitonin (which will be repeated between 48-72 hours after initiation of therapy).

Urinalysis if clinically indicated: Appearance (color, clarity), bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, and urine microscopy (ie, red blood cells, white blood cells, casts, crystals, bacteria, yeast cells, parasites)

Other: pregnancy test*
The MD Anderson local laboratory will be used to evaluate all urine and blood samples. Results from unscheduled laboratory tests will not be collected, unless associated with an SAE or AE leading to discontinuation of IV study drug. EXCEPTION: At the discretion of the Investigator, unscheduled ANC values will be recorded as clinically indicated while on oral ***or IV Switch therapy*** (ie, between EOIV and TOC).

Any abnormal laboratory test possibly attributable to ***inpatient*** IV study ***drug*** will be repeated at appropriate intervals until stabilization.

9.5.2.6 Vital Signs, Body Weight, and Height

Vital signs will be recorded at every visit; the parameters are:

Blood pressure: systolic and diastolic

Pulse rate

Respiratory rate

Oxygen saturation: patients with respiratory signs or symptoms

Temperature: record highest daily temperature

Body weight and height will be measured at baseline. If height or weight is not obtained, the last known or stated height and weight may be used.

9.5.2.7 Chest Radiography

A chest x-ray (CXR) (posteroanterior and lateral) or chest computed tomography (CT) scan will be obtained at baseline for patients with respiratory signs or symptoms. If the patient's condition does not allow for a standard posteroanterior and lateral examination, a portable anteroposterior CXR is acceptable. Chest radiography will be obtained postbaseline, ie, at EOIV, TOC, or LFU if clinically indicated.

9.5.2.8 Physical Examination

A complete physical examination will be conducted by a professionally trained physician or health professional licensed to perform physical examinations.

9.5.3 Schedule of Assessments

The schedule of study assessments and procedures is tabulated by visit in Table 2–1. The descriptions of the procedures to be performed at each visit are provided below.

9.5.3.1 Baseline

Baseline procedures must be completed within 24 hours before the start of the first dose of ***inpatient*** IV study drug. Any protocol-required eligibility laboratory evaluations already done as part of the patient's regular medical care within 24 hours before the start of the ***inpatient*** IV study drug infusion on Study Day 1 do not have to be repeated to determine patient eligibility.

At baseline, informed consent will be obtained, a review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment, and study procedures will be reviewed with the patient and/or caregiver, and the legally authorized representative (if different from the caregiver). After signing the ICF, the patient will be assigned a unique PID number (or accession number) (see Section 9.4.3). If, after review of the inclusion/exclusion criteria, it is determined that the patient is eligible to enter the study, the patient will be randomized according to the randomization procedures in Section 9.4.3.

At baseline, the following procedures will be performed:

Obtain written informed consent per Section 5.3

Verify that inclusion criteria are met and none of the exclusion criterion apply

Obtain medical and surgical history including all active conditions and all conditions diagnosed within the previous 3 months

Abnormal baseline labs will not be captured as baseline AEs or medical history as deemed not clinically significant pertaining to our protocol. A changing in the grade of the abnormal labs during study treatment will be captured as AEs if clinically significant.

Obtain height and weight (if height or weight is not obtained, use the last known or stated height and weight)

Perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms (per Section 9.5.2.11)

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record prior medications, including antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition taken or received within 30 days of first dose of ***inpatient*** IV study drug.

Evaluate and record infection signs and symptoms

Laboratory assessments:
Collect blood and urine samples for clinical laboratory determinations per Section 9.5.2.5.

Record ANC

Collect blood sample for pregnancy test (females of childbearing potential only, including those who are fewer than 2 years postmenopausal); ensure test is negative before randomization. If the serum test results cannot be obtained before randomization within 5 days, a urine pregnancy test may be used for enrollment

Estimate CrCl using the following Cockcroft-Gault formula (use actual body weight and conventional units; if weight is not obtained, use the last known or stated weight):

Males: CrCl= (140 – age in years) X weight in kg / 72 X serum creatinine (mg/dL)

Female: CrCl= 0.85 X (140-age in years) X weight in kg / 72 X serum creatinine (mg/dL)
Microbiological assessments:

Collect blood sample for culture and PCT per Section 9.5.1.2 (See pages 33-34).

If clinically indicated, collect other samples for culture per Section 9.5.1.2

Randomize patient after verifying that the patient meets all study inclusion criteria and no exclusion criteria

9.5.3.2 Study Days 1 To ≤ 14

Study Day 1 is the calendar day that ***inpatient*** IV study drug is first administered. Baseline and Study day 1 assessment could be combined if they occur on the same calendar day.

On Study Days 1 to ≤ 14, administer study therapy to all patients and conduct the following assessments and procedures daily *while the patient is hospitalized and receiving IV study drug*, unless otherwise specified:

Perform complete physical examination twice a week after first dose of inpatient IV study drug, at least every 3 days, ***whereby the week begins on the day of enrollment. The physical examination will be conducted by a professionally trained physician or health professional licensed to perform physical examinations. Patients may have unscheduled visit sooner than the scheduled date if deemed necessary by the investigator.***

Record vital signs (blood pressure and pulse rate a, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms

Laboratory assessments:

Collect blood and urine samples for clinical laboratory determinations (Section 9.5.2.5) if clinically indicated

On Study Day 7 +/- 24 hours, if still on IV study drug, collect blood and urine samples for clinical laboratory determinations (Section 9.5.2.5).

Record ANC a minimum of 3 times per week while on study therapy (IV or oral)

> Record estimated CrCl ***every 3 days after first dose of inpatient IV study drug beginning on Study Day 1***

Microbiological assessments:

Obtain blood samples (per Section 9.5.1.2) for culture every other day until temperature is ≤ 100.4°F (38.0°C) and cultures are negative

If clinically indicated, collect other samples for culture per Section 9.5.1.2.

Administer study therapies per Section 9.4.1 and Table 9.4.1.3–1

9.5.3.3 End of Inpatient Intravenous Therapy

Conduct EOIV assessments within 72 hours after administration of the last dose of ***inpatient*** IV study drug.

Administer the last dose of ***inpatient*** IV study drug, and conduct the following assessments and procedures in all patients, unless otherwise specified:

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Laboratory assessments:

Collect blood and urine samples for clinical laboratory determinations (Section 9.5.2.5) if laboratory tests for EOIV is performed ≥ 24 hours prior to EOIV (if applicable)

Record ANC

If clinically indicated, record estimated CrCl

For patients on oral ***or IV*** therapy: At the discretion of the Investigator, record ANC as clinically indicated (ie, during an unscheduled visit between EOIV and TOC)

Microbiological and molecular (PCT) assessments:

If baseline blood cultures were positive, repeat blood cultures (per Section 9.5.1.2)

If clinically indicated, collect other samples for culture (per Section 9.5.1.2)

9.5.3.4 Test-of-Cure (Toc)

Conduct TOC assessments in person at any time between Study Days 21 and 28 (ie, 21 to 28 days after the start of ***inpatient*** IV study drug).

For patients who were switched to oral ***or IV*** therapy: Assess if oral ***or IV*** therapy was completed and if not, record date of and reason for discontinuation

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Laboratory assessments:

Record ANC

Microbiological assessments:

If clinically indicated, collect blood sample for culture (per Section 9.5.1.2)

If clinically indicated, collect other samples for culture (per Section 9.5.1.2)

9.5.3.5 Late Follow-Up

Conduct LFU assessments any time between Study Days 35 and 42 (ie, 35 to 42 days after the start of ***inpatient*** IV study drug). The LFU may be conducted by telephone for any patient who has not experienced clinical ***failure since TOC***, did not have ongoing study drug related AEs or SAEs at TOC, or did not develop study drug related AEs or SAEs since TOC. If symptoms ***consistent with clinical failure*** or new study drug related AEs or SAEs are noted, or at the discretion of the Investigator, the patient should be immediately scheduled for an in-person visit. Also, telephone visit is acceptable for patients who cannot present for a clinic visit.

If LFU is conducted by telephone:

Record new concomitant medications

Review and record AEs and SAEs

Record Infection Symptoms, Including Recurring or Worsening Symptoms

Indicative of Clinical Failure

Note: If symptoms consistent with clinical failure or new AEs or SAEs are noted during the telephone interview, or at the discretion of the investigator, the subject should be immediately scheduled for an in-person visit

Assess clinical outcome per Section 9.7.5.3

If LFU is conducted in person:

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and Record Infection Signs and Symptoms Per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Microbiological assessment: ***In patients experiencing clinical failure after TOC or if*** clinically indicated, collect samples for culture per Section 9.5.1.2.2

Any clinical findings obtained during the final examination or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. A follow-up visit, if one should be necessary, will take place within 30 days of investigational product termination.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Recording, Documentation and Monitoring

The Investigator and the study site staff will be responsible for data entry of patient data into REDCap. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording and Documentation

Data collection will involve the use of REDCap to which only authorized personnel will have access. Patient's data are to be entered into the system by the Investigator or designee using their assigned user account. After data entry into the system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents, etc) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for., its authorized representatives, and the FDA or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

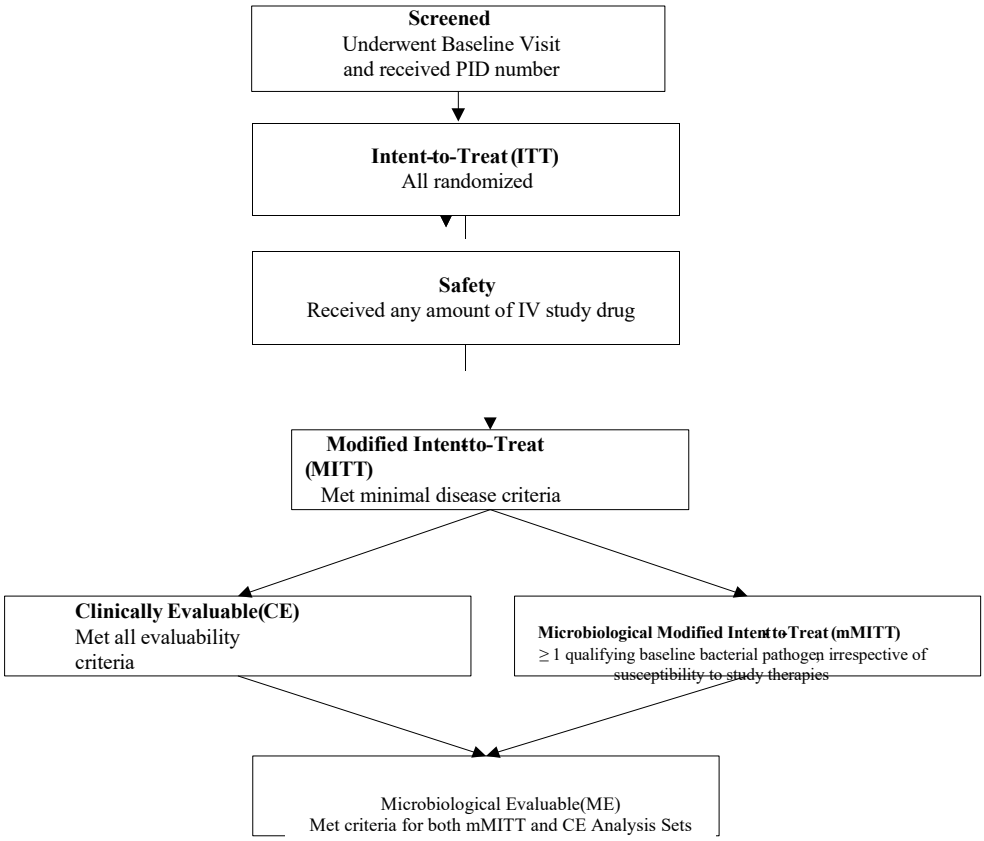
Descriptive statistics (number, mean, SD, median, minimum, and maximum) will be provided for continuous variables, and frequency distributions (counts and percentages) will be shown for categorical variables. All summary statistics will be presented by treatment group. In addition, the the summary statistics will be provided for all randomized patients that received any amount of ***inpatient*** IV study drug (MITT Analysis Set) and for the subgroup of patients with a pathogen identified (mMITT Analysis Set). Listings of individual patients' data will also be produced.

A comprehensive statistical analysis plan will be prepared and finalized before database lock and analysis of the data.

9.7.1 Analysis Sets

Analysis sets are described below and displayed in Figure 9.7.1–1.

Figure 9.7.1–1. Analysis Sets for Study



9.7.1.1 Screened Analysis Set

The Screened Analysis Set will consist of all patients who undergo the Baseline Visit and receive a PID number.

9.7.1.2 Intent-To-Treat Analysis Set

The Intent-to-Treat Analysis Set will consist of all patients in the Screened Analysis Set who are randomized to a treatment group in the study.

9.7.1.3 Safety Analysis Set

The Safety Analysis Set will be a subset of the ITT Analysis Set and will include all randomized patients who receive any amount of ***inpatient*** IV study drug. Patients will be analyzed according to the treatment actually received.

9.7.1.4 Modified Intent-To-Treat Analysis Set

The MITT Analysis Set will be a subset of the ITT Analysis Set and will include all randomized patients who received any amount of ***inpatient*** IV study drug and meet minimal disease criteria (Inclusion Criterion 3). Patients will be analyzed according to randomized treatment group, regardless of treatment received.

9.7.1.5 Microbiological Modified Intent-To-Treat Analysis Set

The mMITT Analysis Set will be a subset of the MITT Analysis Set and will include those patients for whom at least 1 qualifying bacterial pathogen was isolated from an appropriate microbiological specimen at baseline, irrespective of susceptibility to study therapies.

9.7.1.6 Clinically Evaluable Analysis Set

The CE Analysis Set will be a subset of the ***MITT*** Analysis Set and will include patients who meet the following specific conditions for evaluability:

Received at least 80% of the intended doses of ***inpatient*** IV study drug

Received at least 48 hours of ***inpatient*** IV study drug to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE

> Received at least 48 hours *of IV* gram negative antimicrobial coverage to be considered an evaluable clinical cure

Did not receive any amount of ***inpatient*** IV study drug from the treatment arm to which the patient was not randomly assigned

Had clinical outcome assessment at TOC (other than indeterminate) or was assessed as a clinical failure at EOIV (or at any time up to TOC)

Did not receive > 36 hours of any potentially effective, systemic antibacterial therapy within 72 hours before randomization for treatment of suspected infection. Any amount of prophylactic (in

the absence of an infection) antimicrobial (eg, antibacterial, antifungal, antiviral) therapy administered prior to starting study therapy is allowed.

9.7.1.7 Microbiologically Evaluable Analysis Set

The ME Analysis Set will include patients who meet the criteria for both the CE and mMITT analysis sets.

9.7.2 Patient Disposition

Patient disposition (enrollment, discontinuations from ***inpatient*** IV study drug, oral ***or IV*** therapy, and the study) by treatment group will be provided based on the ITT Analysis Set. The number of patients with a TOC and/or LFU visit will be summarized. Reasons for exclusion from study analysis sets will be summarized for the ITT Analysis Set.

The number of patients in the Safety and ITT analysis sets will be summarized by treatment group.

Screen failures (ie, patients screened but not randomized) and the associated reasons for failure will be tabulated overall.

The number and percentage of patients who complete the treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Analysis Set. The reasons for premature discontinuation from the treatment period as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for all randomized patients.

9.7.3 Demographics and Other Baseline Characteristics

Demographics (eg, age, race, gender, body mass index), medical and surgical history, description of the infection, markers of disease severity and co-morbidities (eg, presence of bacteremia, renal impairment), type of malignancy, baseline assessment of the clinical signs and symptoms, and microbiological assessment of the primary infection site will be summarized by treatment group in the MITT Analysis Set.

Prior medication is defined as any medication taken before the date of the first dose of investigational product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product. Any prior medications stopped more than 3 days before the date of the first dose of investigational product and any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables, but will be included in the patient data listings. Medications that are ongoing at the time of first dose of ***inpatient*** IV study drug will be counted both as prior and concomitant.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Analysis Set. Multiple administrations of the same medication to a patient will be counted only once for the given patient. Medication-related summaries will be presented separately by “systemic antimicrobial medications” and “other medications not in this class” subgroups.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to ***inpatient*** IV study drug***,*** oral ***and IV switch*** therapy will be summarized by treatment group for the Safety Analysis Set. Calendar days of exposure of ***inpatient*** IV only, oral ***or IV switch*** only, and overall (***inpatient*** IV plus oral ***or IV switch***) will be calculated as the number of calendar days on ***inpatient*** IV study drug/oral ***or IV switch*** therapy (***ie the difference between*** the last dose of specified ***inpatient*** IV study drug/oral ***or IV switch*** therapy ***and*** the first dose of specified ***inpatient*** IV study drug/oral ***or IV switch*** therapy ***date and time converted to days*** + 1 day). For each type of exposure both descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) and a frequency tabulation of days of specified study drug treatment by classes < 3 days, 3-5 days, 6-8 days, 9-***14*** days, and > ***14*** days and oral therapy by classes < 3, 3, 4, 5 and > 5 days will be presented.

The number and percentage of patients who switch to oral ***or IV*** therapy will be presented. Among this subset of patients, the number and percentage of patients receiving each specific protocol-approved oral ***or IV*** therapy will be summarized. Descriptive statistics will be provided for either the study day of switch to oral or ***IV*** therapy, as well as calendar days of oral ***or IV*** therapy (calculated as the date of last dose of the oral ***or IV*** therapy – date of the first dose of the oral ***or IV*** therapy + 1 day).

Measurement of Treatment Compliance

Each patient's compliance with study therapy (***inpatient*** IV or oral ***or IV switch***) will be calculated based on the number of doses of study drug the patient would have been expected to receive based on the number of treatment days, the specific dosing regimen indicated for the given treatment, and the start and stop date and times of the first and last dose of each specific study therapy. Treatment compliance is defined as the number of doses actually received divided by the number of doses expected (× 100) over the time period of first dosing date and time to last dosing date and time.

Three types of study therapy compliance will be calculated: IV study therapy compliance, all study therapies (both IV and oral) compliance, and, in the subgroup of patients who switch to oral ***or IV*** therapy, oral ***or IV*** therapy compliance. For each compliance measure, descriptive statistics (number of patients, mean, SD, minimum, median, and maximum value) and the number and percentage of patients whose compliance is < 80% versus ≥ 80% will be presented by treatment group for the Safety and MITT analysis sets.

9.7.5 Efficacy Analyses

The primary efficacy analysis will be based on the MITT analysis set at EOIV. The secondary efficacy analyses will be based on MITT, mMITT CE, and ME analysis sets at different time points (EOIV, TOC, and LFU). The clinical outcomes definitions with their time points are described on section 9.7.5.3. The baseline time point for the efficacy analyses is defined as the last measurement collected just before the first dose of inpatient IV study drug.
The goal of the primary objective of the study is to show that the efficacy of Imipenem-Cilastatin-Relebactam plus/minus vancomycin, daptomycin or linezolid is non-inferior to the standard of care (SOC) plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response.

The non-inferiority margin of efficacy is 10%. The rate of favorable clinical response will be estimated for each arm and the rate difference (treatment arm – control arm) and its two-sided 95% confidence interval will be calculated. Non-inferiority of Imipenem-Cilastatin-Relebactam to the SOC will be declared if the lower confidence interval limit is greater than -10%.

For each secondary efficacy parameter listed below (Sections: 9.7.5.1 and 9.7.5.2), a 2-sided chi square tests or Fisher's exact tests will be used to compare the two treatments. When appropriate, logistic model will be used to assess the relationship between the efficacy parameter and treatment, while adjusting for other factors.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the proportion of patients in the MITT Analysis Set with favorable clinical response at EOIV ***in accordance with Section 9.7.5.3***

9.7.5.2 Secondary Efficacy Parameters

- The proportion of patients in the mMITT and CE analysis sets with favorable clinical response at EOIV
- The proportion of patients in the MITT Analysis Set with favorable clinical response at TOC ***and LFU***
- The proportion of patients in the mMITT and CE analysis sets with favorable clinical response by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU***
- The proportion of patients in the mMITT and ME analysis sets with a favorable microbiological response by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU***. A favorable microbiological response is defined as eradication or presumed eradication of the infecting pathogen among patients with microbiologically document infections
- The proportion of patients in the MITT and mMITT analysis sets with infection-related mortality at TOC ***and LFU***
- The proportion of patients in the MITT and mMITT analysis sets with 30-day all-cause mortality

9.7.5.3 Clinical Outcome Definitions

The definitions of Investigator-determined clinical outcome, by time point, are shown in Table 9.7.5.3–1.

Successful antimicrobial stewardship (AS) outcome is considered to occur if ≥ 50% of the patients enrolled achieve clinical cure at TOC (as per table 9.7.5.3-1) with switch of the study drug or SOC to oral or simplified streamline IV therapy by 72 hours.

Table 9.7.5.3–1. Clinical Outcome Definitions

Applicable Time Point	***Outcome***	***Definition***
EOIV	Favorable clinical response	Resolution of all acute signs and symptoms of the primary infection (primarily fever) or improvement to such an extent that no additional antibacterial therapy is required (ie, except for protocol-allowed adjunctive therapies and/or oral or IV switch) ***and such that no more than 14 days of total IV antibacterial therapy is required unless indicated for a complicated infection.***
TOC[a]	Clinical cure[b]	***Sustained resolution*** of all acute signs and symptoms of the primary infection or ***continued*** improvement to such an extent that no further IV antibacterial therapy is required for the original episode. ***Another episode of neutropenic fever during the follow-up period will not be considered to be a failure unless the patient present for a relapse of the same documented infection that was present at baseline.***
LFU[a]	***Clinical cure[b]***	***Sustained resolution of all acute signs and symptoms (or of symptoms only if LFU visit is conducted by telephone) of the primary infection or continued improvement to such an extent that no further IV antibacterial therapy is required for the original episode. Another episode of neutropenic fever during the follow-up period will not be considered to be a failure unless the patient present for a relapse of the same documented infection that was present at baseline.***

EOIV[a] TOC[a] ***LFU[a]***	Clinical failure	Patients who meet **any** of the following: • Has persistent fever (ie, a single oral temperature measurement of > 38.0°C [100.4°F]) 96 hours after the initiation of study drug. (NOTE: if the febrile neutropenia is documented to be caused by an invasive fungal or viral infection at any time during the study, the patient should be considered to have an indeterminate outcome for all clinical outcome assessments) • Has documented breakthrough gram negative bacteremia (ie, recurrence of bacteremia that resolved or occurrence of new bacteremia with gram negative organisms not present at baseline while the patient is receiving IV study drug) • Has a documented pathogen that is resistant to any study therapy received and requires alternative nonstudy antimicrobial therapy • Discontinuation of study therapy(ies) due to insufficient therapeutic effect including persistence, incomplete clinical resolution, or worsening in signs and symptoms of primary documented infection that requires alternative nonstudy antimicrobial therapy (Investigator is encouraged to continue study therapy[ies] for at least 48 hours before such a patient is considered a clinical failure and is prematurely discontinued from study therapy[ies].) • Developed shock, acute respiratory distress syndrome, disseminated intravascular coagulation, or multiorgan failure related to the primary infection • Discontinuation of study drug therapy(ies) due to an AE and requirement for alternative nonstudy antimicrobial therapy for the primary infection

Table 9.7.5.3–1. Clinical Outcome Definitions

Applicable Time Point	*Outcome*	*Definition*
		• Died as a result of the primary infection
EOIV[a] TOC[a] ***LFU[a]***	Indeterminate	• Patients who developed a documented invasive fungal infection or a documented viral infection at any time during the study (Note: the documented fungal or viral infection must be the cause of the study qualifying episode of febrile neutropenia) • Study data are not available for evaluation of efficacy for **any** reason, including: o Death in which febrile neutropenia is clearly noncontributory o Lost to follow-up o Extenuating circumstances precluding classification as a clinical cure or clinical failure • Subjects withdrawn from the study not assessed as a clinical failure should be assessed as indeterminate at all subsequent outcome evaluation time points as noted in Section 9.3.3.3

a A clinical failure at EOIV will be carried forward to TOC. ***A clinical failure at TOC will be carried forward to LFU.*** TOC evaluations include events between EOIV and TOC ***(including events through the end of oral or IV switch therapy, if applicable). LFU evaluations include events between TOC and LFU.*** No scheduled assessment is performed at end of oral ***or IV switch*** therapy***.***

b Favorable outcome at TOC ***or LFU***.

AE = adverse event; EOIV = End of ***Inpatient*** Intravenous Therapy; ***LFU = Late Follow-up;*** TOC = Test-of-Cure.

Perform EOIV assessments within 72 hours after administration of the last dose of inpatient IV study drug (Day 1-14).
Perform TOC assessments between Study Days 21 and 28.
Perform LFU assessments between Study Days 35 and 42.

9.7.5.4 Microbiological Response Definitions

The timing and definitions of per-pathogen microbiological response are shown in Table 9.7.5.4–1. Per-patient microbiological response will be determined programmatically based on individual outcomes for each baseline pathogen. For a patient to have a favorable microbiological response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence or presumed persistence), the patient will be considered to have an unfavorable microbiological response.

Table 9.7.5.4–1. Microbiological Response Definitions

Applicable Time Point	***Microbiological Response***	***Definition***
EOIV TOC ***LFU***	Eradication[a]	Source specimen demonstrates absence of the original baseline pathogen
EOIV TOC ***LFU***	Presumed eradication[a]	Source specimen was not available to culture and the patient was assessed as a clinical cure
EOIV TOC ***LFU***	Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
EOIV TOC ***LFU***	Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure
EOIV TOC ***LFU***	Indeterminate	Source specimen was not available to culture and the patient's clinical response was assessed as indeterminate

a Favorable outcome.

EOIV = End of ***Inpatient*** Intravenous Therapy; ***LFU = Late Follow-up;*** TOC = Test-of-Cure.

9.7.5.5 Emergent Infections

Organisms or pathogens first appearing after baseline (emergent infections) are defined in

Table 9.7.5.5–1 ***and will be summarized separately***.

Table 9.7.5.5–1. Emergent Infections

Infection Category	***Definition***
Colonization	Isolation of a new organism(s) different than any isolated at baseline from the site of infection in a patient who is assessed as a clinical cure
Superinfection	Isolation of a new pathogen(s) different than any isolated at baseline from the site of infection during treatment with study drug therapy, which is associated with emergence or worsening of signs and symptoms of infection
New infection	Isolation of a new pathogen(s) different than any isolated at baseline from the site of infection after completion of all study drug therapy, which is associated with emergence or worsening of signs and symptoms of infection

Safety Analyses

For the primary safety and tolerability objective, the incidence of TEAEs, SAEs, deaths, and discontinuations due to AEs will be summarized by treatment group, system organ class and preferred term according to the *Medical Dictionary for Regulatory Activities*, type, frequency, relationship to study therapy, and severity. Safety summaries will be presented using the Safety

Analysis Set, according to the treatment actually received. For each safety parameter, the last assessment made before the first dose of ***inpatient*** IV study drug will be used as the baseline for all analyses. Descriptive statistics of observed results and the change from baseline will be presented for clinical laboratory results and vital signs. The incidence of potentially clinically significant (PCS) laboratory results will be summarized. A list of all TEAEs/SAEs that resulted in deaths will also be generated. The changes in clinical laboratory parameters and vital sign parameters in the Safety Analysis Set at each study visit that assessments will be performed.

.

9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it was not present before the date of the first dose of investigational product or was present before the date of the first dose of investigational product and increased in severity during the treatment period. If more than 1 AE is reported before the date of the first dose of investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the treatment period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group.

The incidence of common (eg, ≥ 2% of patients in any treatment group) TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind investigational product and within 30 days of the date of the last dose of investigational product.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline

values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of patients with PCS post baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 post baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post baseline value. A supportive listing of patients with PCS post baseline values will be provided, including the PID number, and baseline and post baseline values. A listing of all AEs that occur in patients who have PCS laboratory values will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (ie, systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation [if applicable], temperature) and changes from baseline values at each visit and at end of study will be presented by treatment group.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with baseline values and at least one postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS vital sign values will also be provided.

9.7.6.4 Chest Radiography

Readings of the baseline chest radiographs including the presence of pleural effusion, whether the pleural effusion was unilateral or bilateral, and whether the pulmonary infiltrate was uni- or multi-lobar and/or cavitated will be summarized by treatment group for the MITT Analysis Set.

9.7.6.5 Toxicity Stopping Monitoring Rule

We monitor toxicity using the Bayesian optimal phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017)[34]. Toxicities used for this monitoring rule consist of severe (Grade ≥3) drug related adverse events leading to the discontinuation of the study drug. Toxicity monitoring will be carried out independently for the two arms, in cohort size of 10. Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{tox} denote the probability of toxicity and define the null hypothesis $H_0: p_{tox} > 0.35$, under which the treatment is deemed as unacceptable. Thus, we will stop enrolling patients and inspect the safety data for possible trial termination if

$$Pr(p_{tox} \leq 0.35|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

where λ=0.86 and α=0.62 are design parameters optimized to maximize the probability of correctly concluding that a safe treatment is acceptable under the alternative hypothesis $H_1: p_{tox} = 0.2$, while controlling the type I error rate (i.e., the probability of incorrectly concluding that an overly toxic treatment is acceptable) at 0.1. This optimization is performed assuming a vague prior Beta(0.35,0.65) for p_{tox}. The above decision rule leads to the following optimal stopping boundaries:

Table 9.7.6.5–1. Optimized stopping boundaries

# patients treated	Stop if # toxicity >=
10	5
20	8
30	10
40	13
50	14

Based on **Table 9.7.6.5–1,** we perform the interim analysis when the number of enrolled patients reaches 10, 20, 30, 40. When the total number of patients reaches the maximum sample size of 50, we reject the null hypothesis and conclude that the treatment is acceptable if the number of toxicities are less than 14; otherwise we conclude that the treatment is unacceptable.

Below are the operating characteristics of the design using the BOP2 web application, which is available at http://www.trialdesign.org.

Table 9.7.6.5–2. Operating characteristics

Toxicity rate	Early stopping (%)	Claim acceptable (%)	Sample size
0.1	0.22	99.76	49.9
0.2	9.75	85.12	47.3
0.3	52.57	29.36	36.0
0.4	90.64	2.40	22.6
0.5	99.44	0.04	15.2

The Investigator is responsible for completing an efficacy/safety summary report and submitting it to the IND office Medical Affairs and Safety Group, for review and approval.

This should be submitted after the first 10 evaluable patients per arm, complete in-patient intravenous therapy, and every 10 evaluable patients per arm, thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "funder correspondence".

9.7.6.6 Pregnancy Related Risk

Birth Control Specifications: If you can become pregnant or father a child, you must use 2 forms of birth control. Acceptable forms of birth control include either 2 barrier methods (like a condom or diaphragm with spermicide) or 1 barrier method plus a hormonal method (such as birth control pills/injections/patches).

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy while on study or within 28 days after your last dose of study drugs. If your partner/spouse becomes pregnant while you are on this study, the sponsor would like to collect information about the pregnancy. The study sponsor's contact information will be made available so that, if you and your partner wish to, you can share information about the outcome of the pregnancy with the sponsor. If you and/or your partner choose not to share this information, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

9.7.7 Antimicrobial Stewardship and Outcomes Research Analyses

Successful antimicrobial stewardship (AS) outcome is considered to occur if ≥ 50% of the patients enrolled achieve clinical cure at TOC (as per table 9.7.5.3-1) with switch of the study drug or SOC to oral or simplified streamline IV therapy by 72 hours.

9.7.8 Interim Analysis

No futility interim analysis is planned for this study as Imipenem-Cilastatin-Relebactam has FDA approval for the treatment of HABP/VABP, and also approved for cUTI and cIAI, and Imipenem has over 35 years of clinical use and proven efficacy. Safety interim analysis is provided in Section 9.7.6.5.

9.7.9 Determination of Sample Size

The primary objective of the study is determine the efficacy of Imipenem-Cilastatin-Relebactam plus/minus vancomycin, daptomycin or linezolid is non-inferior to the standard of care (SOC) plus/minus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response. The historical favorable clinical response for the SOC is approximately 65%. We expect that the favorable clinical response of Imipenem-Cilastatin-Relebactam plus/minus vancomycin, daptomycin or linezolid is 80%. Given the non-inferiority margin of 10% (i.e., if the favorable clinical response of Imipenem-Cilastatin-Relebactam is >55%, it is deemed non-inferior to the SOC), the sample size of 50 patients per arm will have 80% power to establish the non-inferiority. This power calculation was performed using East with null response rate of 0.55, alternative response rate of 0.8, one-sided chi-squared test at significance level of 0.05.

9.7.10 Computer Methods

Statistical analyses will be performed using SAS version 9.3.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, and scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients.

The IRB must be notified according to the criteria and time period dictated by the IRB associated with this study.

10.0 STUDY FUNDERSHIP

MD Anderson Cancer Center IND office (Study Funder); Merck, Inc. (Supporting Company)

10.1 STUDY TERMINATION

Merck, Inc. reserves the right to terminate the study in its entirety before study completion.

10.2 REPORTING AND PUBLICATION

An integrated clinical and statistical report will be prepared at the completion of the study. Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Merck Institute, Inc., and will follow ***the current Applicable*** SOP on publications

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must maintain the following during the study:

A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1

A copy of the IRB-approved ICF

11.2 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigators listed on Form FDA 1572. The investigational products must be stored in a secured place and must be locked. The MDA standard operating procedures for drug accountability will be followed. All unused investigational products will be destroyed according to the standard operating procedures at MD Anderson. It is the Investigator's responsibility to ensure that patients return their investigational product.

11.3 CASE REPORT FORMS

All patient data relating to the study will be recorded on REDCap. The Investigator is responsible for verifying that all data entries in the REDCap are accurate and correct. The Investigator must maintain and retain accurate documentation that supports the information entered for source document verification and possible regulatory inspection.

11.4 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and electrocardiogram reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) must be retained by the Investigator according to institutional policies.

The Investigator must permit access to any documentation relating to the study upon request of the Funder or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party.

11.5 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and accession number.

12.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; Merck, Inc.; the IRB; or an authorized contract research organization may inspect the records

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate . . .")

- A place for the patient's signature and date of signing

- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

- A copy of the signed consent form must be given to the patient. All participants will be registered in the Clinical Oncology Research System (CORe).

APPENDIX II. MD ANDERSON NEUTROPENIC FEVER INPATIENT ADULT TREATMENT GUIDELINES

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Neutropenic Fever Inpatient Adult Treatment

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

Patient presents with fever or develops fever at MDACC -Consider Sepsis[1]

- Complete Physical Exam
- Start IV fluids
- Heme Survey with ANC, BUN, creatinine, Sodium, Potassium, Chloride, CO2
- Urinalysis
- Lactic Acid
- Urine culture and sensitivity, Blood Cultures (with a set collected from each lumen simultaneously if CVC present, and 1 peripheral. If no CVC present, 2 blood cultures from peripheral site) and other cultures as clinically indicated.
- Chest x-ray if clinically indicated (signs/symptoms of respiratory involvement) or other tests as clinically indicated.

Hemodynamically stable? **(Does patient meet SIRS criteria[1])** See Appendix A for signs of organ dysfunction

Yes

- See Adult Sepsis Management Algorithm and use Sepsis Order Set
- If pneumonia is suspected, see algorithm for Pneumonia in Adult Patients (18 years and older) with Cancer
- See Early Intervention for Suspected Adult Sepsis Algorithm and Early Intervention Sepsis Order Set.
- See Pages 2 - 4 to determine appropriate antibiotic regimen and use Inpatient Neutropenic Fever Order Set.

No

- Please call MERIT (Medical Emergency Rapid Intervention Team)
- See Adult Sepsis Management Algorithm and use Sepsis Order Set.
- Consider adding ICU Addendum Severe Sepsis or Septic Shock Order Set.

[1] **SIRS Criteria (Systemic Inflammatory Response Syndrome)**
Patient exhibits two or more of the following :

- Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart Rate greater than 90 beats/minute
- Respiratory rate greater than or equal to 20 breaths/minute or $PaCO_2$ less than or equal to 32 mmHg
- WBC greater than or equal to 12,000/mm^3 or less than or equal to 4,000/mm^3
- Suspected or proven infection

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature greater than or equal to 38.3°C or equal to 38°C for 1 hour or longer.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

Criteria for Selecting Antibiotics
(antibiotics should be given within 2 hrs)
SIRS patients refer to sepsis treatment algorithm.
When selecting antibiotic regimen, take into account the following:
-Recent culture and sensitivity results
-History of positive VRE, MRSA, Multi-Drug Resistant organisms (i.e. Pseudomonas aeruginosa and Stenotrophomonas maltophilia)
-CVC in place
-Antibiotic history and prophylaxis
-Source of infection if identified
-Antibiotic allergies (see page 4 for beta lactam allergy)
-Organ dysfunction

[1] Consider Meropenem if patient has:
- allergy to alternative agents or
- failed treatment with cefepime or piperacillin/tazobactam or
- infection with ESBL (extended spectrum beta-lactamase) organism
- infection with organism only susceptible to carbapenem

[2] Double gram negative coverage should be considered with complicated tissue based infections, neutropenic enterocolitis, pneumonia and perirectal infections. If quinolone prophylaxis, add vancomycin to the regimen.

FINDINGS | **ANTIMICROBIAL THERAPY RECOMMENDATIONS**

A — Neutropenic Fever

Choose one:
- Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or**
- Cefepime 2 grams IVPB every 8 hours **or**
- Meropenem[1] 1 grams IVPB every 8 hours

If indicated, for double gram negative coverage[2], add one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Beta-lactam allergy: see Page 4 for antibiotic options

B — Suspected Line Infection and/or Bacteremia

Choose one:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

Plus one of the following:
- Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or**
- Cefepime 2 grams IVPB every 8 hours **or**
- Meropenem[1] 1 gram IVPB every 8 hours

If indicated, for double gram negative coverage[2], add one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Beta-lactam allergy: see Page 4 for antibiotic options

C — MRSA Colonization/ Skin and Soft Tissue Infection/ Mucositis greater than or equal to Grade 2

Choose one:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia) **or**
- Linezolid 600 mg IVPB every 12 hours

Plus one of the following:
- Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or**
- Cefepime 2 grams IVPB every 8 hours **or**
- Meropenem[1] 1 gram IVPB every 8 hours

If indicated, for double gram negative coverage[2], add one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Beta-lactam allergy: see Page 4 for antibiotic options

See Page 5 for Day 5 Re-assessment

NOTES:
- Doses indicated are for patients with normal renal/hepatic function.
- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

See Pages 3 and 4 for additional findings and antibiotic options

Department of Clinical Effectiveness V5
Approved by the Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature greater than or equal to 38.3°C or equal to 38°C for 1 hour or longer.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

Continued from previous page – see Page 2 for "Antibiotic Selection Criteria"

ANTIMICROBIAL THERAPY RECOMMENDATIONS

FINDINGS

Stenotrophomonas maltophilia →
Consider adding one of the following antibiotics to one of the regimens from Box A, B, or C on Page 2 or 3 of this algorithm:
- Sulfamethoxazole and Trimethoprim (TMP) 3.75 mg TMP/kg IVPB or oral every 6 hours **or**
- If sulfa allergy, Tigecycline 100 mg IVPB times 1 dose then 50 mg IVPB every 12 hours

Multi-Drug Resistant Organisms →
- Consider Infectious Disease Consult
- Consider adding the following antibiotic to one of the regimens from Box A, B, or C on Page 2 or 3 of this algorithm:
  Colistin 2.5 mg/kg every 12 hours

VRE Colonization or Infected Patients →
Consider using one of the following antibiotics, in place of vancomycin, with one of the regimens from Box A, B, or C on Page 2 of this algorithm:
- Linezolid 600 mg IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

See Page 5 for Day 5 Re-assessment

NOTES:
- Doses indicated are for patients with normal renal/hepatic function.
- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

Department of Clinical Effectiveness V5
Approved by the Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature greater than or equal to 38.3°C or equal to 38°C for 1 hour or longer.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

FINDINGS

ANTIMICROBIAL THERAPY RECOMMENDATIONS

Serious beta-lactam allergy

Neutropenic Fever[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours

Suspected Line Infection and/or Bacteremia[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

MRSA Colonization/ Skin and Soft Tissue Infection[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

Mucositis[1] greater than or equal to Grade 2

Choose:
- Aztreonam 2 grams IVPB every 8 hours **and** Clindamycin 900 mg IVPB every 8 hours **and** Tobramycin 7 mg/kg IVPB daily

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours

See Page 4 for Day 5 Re-assessment

[1]NOTES:
- Doses indicated are for patients with normal renal/hepatic function.
- Double gram negative coverage recommended due to reduced aztreonam susceptibility to gram negative pathogens according to local antibiograms
- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

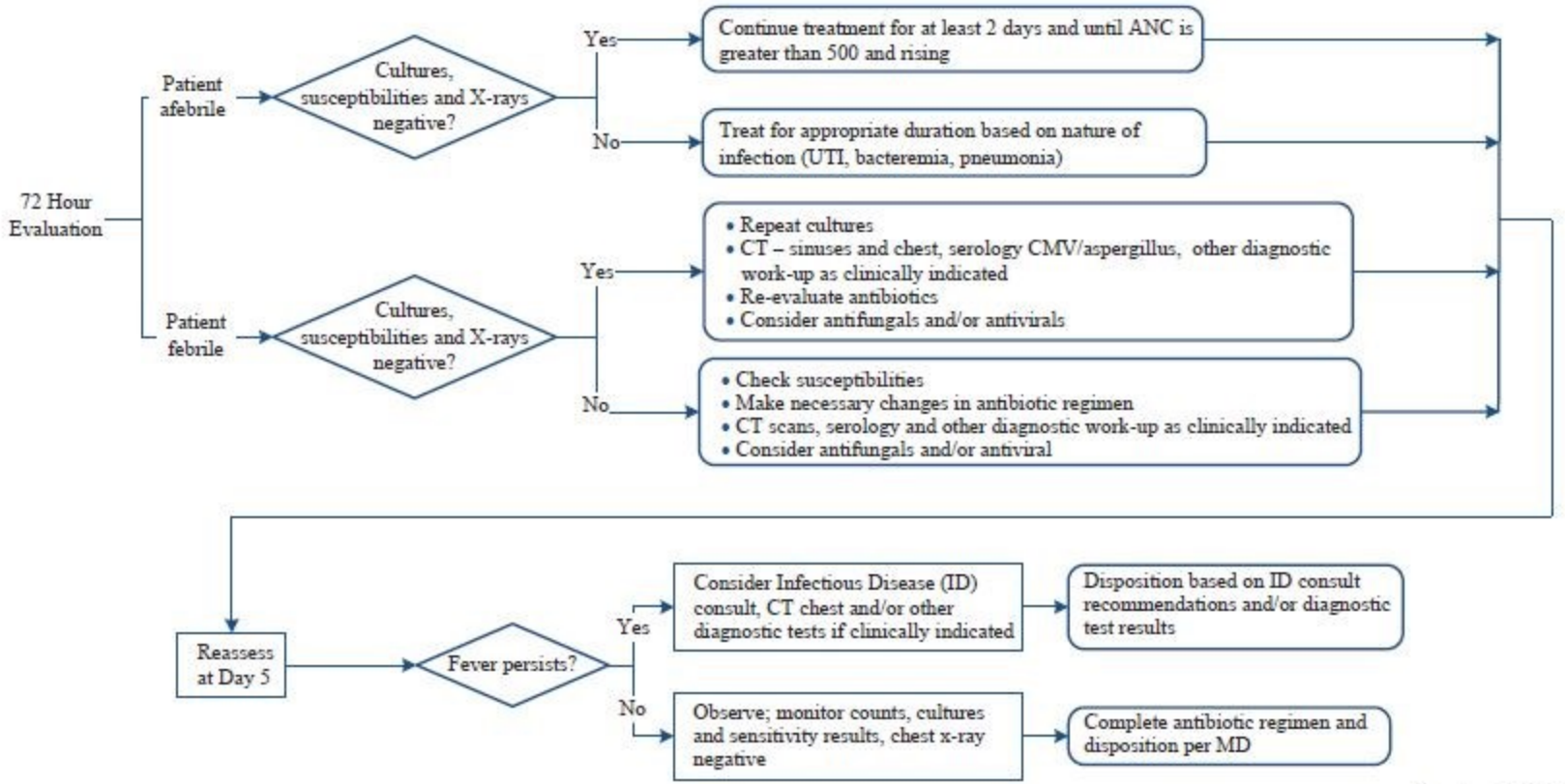
Department of Clinical Effectiveness V5
Approved by the Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature greater than or equal to 38.3°C or equal to 38°C for 1 hour or longer.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.



Department of Clinical Effectiveness V5
Approved by the Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature greater than or equal to 38.3°C or equal to 38°C for 1 hour or longer.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

APPENDIX A: Suspicion of Organ Dysfunction

- Decreased perfusion (capillary refill greater than 3 seconds, skin mottling, cold extremities, lactate greater than 2 mmol/L)
- Circulatory (SBP less than 90 mmHg, MAP less than 65 mmHg, decrease in SBP greater than 40 mmHg)
- Respiratory (PaO_2/FiO_2 less than 300; PaO_2 less than 70 mmHg; SaO_2 less than 90%)
- Hepatic (jaundice; total bilirubin greater than 4 mg/dL; increased LFT's; increased PT)
- Renal (creatinine greater than 0.3 mg/dL; urine output less than 0.5 mL/kg/hour for at least 2 hours)
- Central nervous system (altered consciousness, confusion, psychosis)
- Coagulopathy (INR greater than 1.5 or aPTT greater than 60 seconds); thrombocytopenia (platelets less than 100,000/mm^3)
- Splanchnic circulation (absent bowel sounds)

MAP = Mean Arterial Pressure
LFT = Liver Function Test

APPENDIX B: Criteria for ICU Admission

Major Criteria - one required for admission to ICU:

- Need for mechanical ventilation
- Septic shock with the need of vasopressor(s) (See Institutional Sepsis Algorithm)

Minor Criteria - at least 3 required for admission to ICU:

- Noninvasive ventilation
- PaO_2/FiO_2 ratio less than 250
- Respiratory rate greater than 30 breaths per minute
- SBP less than 90 mmHg
- Oxygen supplementation greater than 50%
- Hypotension requring aggressive fluid resuscitation
- Acute renal failure
- Multilobar pulmonary infiltrates
- Confusion
- BUN greater than 20 mg/dL
- WBC less than 4,000/mm^3
- Thrombocytopenia less than 100,000/mm^3
- Hypothermia (less than 36°C)

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

SUGGESTED READINGS

Baden LR, Bensinger W, Angarone M, et al. (2012). Prevention and treatment of cancer – related infections. *J Natl Compr Canc Netw*; 10:1412-1445.

Bow EJ, Rotstein C, Noskin GA, et al. (2006). A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. *Clin Infect Dis;* 43(4):447-59.

Caillot D, Casasnovas O, Bernard A, et al. (1997). Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*; 15(1):139-47.

Corapcioglu F, Sarper N, Zengin E. (2006). Monotherapy with piperacillin/tazobactam versus cefepime as empirical therapy for febrile neutropenia in pediatric cancer patients: a randomized comparison. *Pediatr Hematol Oncol*. 23(3):177-86.

Cornely OA, Maertens J, Winston DJ, et al. (2007). Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. see comment. *N Engl J Med*. 356(4):348-59.

Cruciani M, Rampazzo R, Malena M, et al. (1996). Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. see comment. *Clin Infect Dis;* 23(4):795-805.

Dellinger RP, Levy MM, Rhodes A, et al. (2013). Surviving sepsis campaign: international guidelines for management of sever sepsis and septic shock: 2012. *Crit Care Med*; 41(2):580-637. doi:10.1097/CCM.0b013e31827e83af.

Dykewicz CA, Centers for Disease C, Prevention, et al. (2001). Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*; 33(2):139-44.

Freifeld A, Bow E, Sepkowitz K, et al. (2010). Executive summary clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Disease Society of America. *Clin Infect Dis*; 52(4) : 427-431.

Hachem R, Hanna H, Kontoyiannis D, et al. (2008). The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. see comment. *Cancer*. 112(11):2493-9.

Hughes WT, Armstrong D, Bodey GP, et al. (2002). 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. see comment. *Clin Infect Dis*; 34(6):730.

Jaksic B, Martinelli G, Perez-Oteyza J, et al. (2006). Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clin Infect Dis*; (5):597-607.

Kim SH, Kwon JC, Choi SM, et al. (2013). Escherichia coli and klebsiella pneumoniae bacteremia in patients with neutropenic fever: factors associated with extended-spectrum b-lactamase production and its impact on outcome. *Ann Hematol*; 95:533-541. doi:10.1007/s00277-012-1631-y

Klastersky J, Paesmans M, Rubenstein EB, et al. (2000). The multinational associated for supportive care in cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol*; 15:3008-3051.

Kuhlman JE, Fishman EK, Siegelman SS. (1985). Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. *Radiology*. 157(3):611-4.

Lee A, Mirrett S, Reller LB, Weinstein MP. (2007). Detection of bloodstream infections in adults: how many blood cultures are needed? see comment. *J Clin Microbiol*; 45(11):3546-8.

Leibovici L, Paul M, Cullen M, et al. (2006).Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Review 46 refs. *Cancer*. 107(8):1743-51.

Continued on Next Page

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

SUGGESTED READINGS - continued

Limaye AP, Huang ML, Leisenring W, et al. (2001). Cytomegalovirus (CMV) DNA load in plasma for the diagnosis of CMV disease before engraftment in hematopoietic stem-cell transplant recipients. *J Infect Dis*; 183(3):377-82.

Lodise TP Jr., Patel N, Kwa A, et al. (2007). Predictors of 30-day mortality among patients with Pseudomonas aeruginosa bloodstream infections: impact of delayed appropriate antibiotic selection. *Antimicrob Agents Chemother*; 51(10):3510-5.

Maertens J, Theunissen K, Verhoef G, et al. (2005). Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. see comment. *Clin Infect Dis*. 41(9):1242-50.

Marti F, Cullen M, Roila F, et al. (2009). Management of febrile neutropenia: ESMO clinical recommendations. *Annals of Oncology*; 20(4):166-69. doi:10.1093/annonc/mdp163

Martino R, Ramila E, Rabella N, et al. (2003). Respiratory virus infections in adults with hematologic malignancies: a prospective study. *Clin Infect Dis*; 36(1):1-8.

Morris PG, Hassan T, McNamara M, et al. (2008). Emergence of MRSA in positive blood cultures from patients with febrile neutropenia--a cause for concern. *Support Care Cancer*; 16(9):1085-8.

Nichols WG, Guthrie KA, Corey L, et al. (2004). Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. see comment. *Clin Infect Dis*; 39(9):1300-6.

Nucci M, Landau M, Silveira F, et al. (2001). Application of the IDSA guidelines for the use of antimicrobial agents in neutropenic patients: impact on reducing the use of glycopeptides. *Infect Control Hosp Epidemiol*; 22(10):651-3.

Owens RC, Owens CA, Holloway WJ. (2000). Reduction in vancomycin consumption in patients with fever and neutropenia [abst 458]. *Clin Infect Dis*. 31:291.

Pacheco-Rosas DO, Huelgas-Plaza AC, Miranda-Novales MG, et al. (2014). Serum lactate as a biomarker of sever sepsis in children with cancer, neutropenia and fever. *Rev Med Inst Mex Seguro Soc*; 52(2):S24-9. PMID:24983551

Paul M, Schlesinger A, Grozinsky-Glasberg S, et al. (2003). Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database of Sys Rev*; (3)2003, Art. No.: CD003038. DOI: 10.1002/14651858.CD003038.

Raad, II, Escalante C, Hachem RY, et al. (2003). Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. Cancer. 98(5):1039-47.

Segal BH, Almyroudis NG, Battiwalla M, et al. (2007). Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis*. 44(3):402-9.

Walsh TJ, Pappas P, Winston DJ, et al. (2002). Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*; 346(4):225-34.

Wisplinghoff H, Seifert H, Wenzel RP, et al. (2003). Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. see comment. *Clin Infect Dis*; 36(9):1103.

Zuckermann J, Moreira LB, Stoll P, et al. (2008) Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. *Ann Hematol*; 87(2):139-45.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Neutropenic Fever Inpatient Adult Treatment

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

DEVELOPMENT CREDITS

This practice consensus algorithm is based on majority expert opinion of the Neutropenic Fever Work Group at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following core group members:

Roy F. Chemaly, MD[T]
Tami N. Johnson, PharmD, BCPS, FCCM
Joseph L. Nates, MD
Terry W. Rice, MD[T]
Kenneth V. Rolston, MD
Frank P. Tverdek, PharmD, BCPS

[T] Core Development Team Lead

APPENDIX III. MD ANDERSON PNEUMONIA IN ADULT PATIENTS WITH CANCER TREATMENT GUIDELINES

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

PATIENT PRESENTATION

Patient presents with:
- Cough, with or without sputum production
- Temperature greater than 38°C
- Dyspnea
- Pulmonary infiltrates
- Unexplained crackles, dullness or egophony on physical examination
- Hypoxemia

- Focused History and Exam (include vaccination and smoking history[1])
- Vital signs
- Oxygen Saturation
- CBC
- Sputum Culture
- Nasal wash (if indicated during high risk season)
- Chest x-ray (PA and Lateral)
- Isolation precautions as indicated
- Blood Cultures[2]: at least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing CVC, if present, and from a peripheral vein site. Two blood culture sets from separate venipunctures should be sent if no central catheter present.

History, exam or chest x-ray compatible with pneumonia?

Yes
- Verify blood and sputum cultures obtained
- Complete history with information on vaccinations and smoking history[1]

No
- Work up for other diagnosis and disposition as clinically indicated

Is patient high risk* requiring hospitalization?

Yes → Is patient hemodynamically unstable[3] and/or with signs and symptoms of respiratory distress?

Yes
- If in clinic, call Emergency Center (EC) and send patient to EC

No
- Initiate Adult Pneumonia Admission Orders and admit to hospital

See Page 2

No
- Low risk community acquired pneumonia, treat as outpatient
- Give first dose of antibiotic as soon as possible [4]
- If in Emergency Center, give first dose(s) of each indicated antibiotic while in EC [5]
- Discharge patient if discharge criteria met (see Appendix C) and if able to take oral medications/fluids and patient able to take care of self
- Refer to General Internal Medicine or Primary Care Physician to be seen in 3 working days to receive vaccines
- Refer to Tobacco Treatment Program, if indicated

RECOMMENDED

*High risk patient:
- Health Care Associated Pneumonia (HCAP), Hospital Acquired Pneumonia (HAP) or Multidrug-Resistant Pathogen (MDRP) suspected (Appendix A) and/or
- Neutropenic (ANC less than 1 K/microliter) or
- Stem cell transplant or
- Radiation therapy to chest within 4 weeks of pneumonia or
- Community Acquired Pneumonia (Appendix A) with PSI higher than 2 (Appendix B)

[1] Information to request from all patients:
- Has the patient received Pneumococcal vaccine in the last 5 years? (If Stem Cell Transplantation and Cellular Therapy, per physician recommendation.)
- Has the patient received Influenza Virus vaccine during season (October – March)?
- Is the patient a smoker?

[2] Collect blood cultures prior to antibiotic administration.

[3] Hemodynamically unstable is defined as new onset of hypoxemia, oxygen saturation less than 90 % or hypotension (blood pressure less than 90 mmHg); patient in respiratory distress. Respiratory Distress may include the following: acute onset of dyspnea, tachypnea, hypoxemia, increased accessory muscle use with breathing, and/or intercoastal and sternal retractions.

[4] The goal is to give the antibiotics as soon as possible, preferably within 2 hours of evaluation and diagnosis.

[5] Antibiotics with gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

Department of Clinical Effectiveness V3
Approved by Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

Patient Admission to Hospital

Patient hemodynamically unstable[1] and/or in respiratory distress[1] and sent to EC for further evaluation and admission to hospital

→ Patient meets one or more of the criteria for ICU admission*?

Yes →
- Blood cultures, if not previously obtained
- Lactic Acid
- Give first dose of antibiotic[2] in EC (See Pages 3 - 5 for medications)
- Admit to ICU
- Activate ICU orders
- Consider consults with Pulmonology and Infectious Diseases (ID) Specialists[3]

No →

Patient hemodynamically stable and not in respiratory distress[1] and admission to hospital initiated →
- Blood cultures, if not previously obtained
- Give first dose of antibiotic[2] in Clinic (See Pages 3 - 5 for medications)
- Activate Pneumonia Admission Orders
- Admit to regular floor
- Activate appropriate vaccination orders, if indicated
- Early consult with Pulmonology and/or ID Specialists[3], if indicated
- Tobacco Treatment Program Consult, if indicated

→
- Once patient is stable and ready to be discharged from hospital: see Appendix C for discharge criteria
- Once discharge criteria met, administer vaccines as clinically indicated
- Refer to Tobacco Treatment Program if indicated
- Reconcile vaccinations in patient's medical records

***ICU Admission Criteria**

Major Criteria - one required for admission to ICU:
- Need for mechanical ventilation
- Septic shock with the need of vasopressor(s) (See Institutional Sepsis Algorithm)

Minor Criteria - at least 3 required for admission to ICU:
- Noninvasive ventilation
- PaO_2/FiO_2 ratio less than 250
- Respiratory rate greater than 30 breaths per minute
- Systolic blood pressure less than 90 mmHg
- Oxygen supplementation greater than 50%
- Hypotension requiring aggressive fluid resuscitation
- Acute renal failure
- Multilobar pulmonary infiltrates
- Confusion
- BUN greater than 20 mg/dL
- WBC less than 4 K/microliter
- Platelets less than 100 K/microliter
- Hypothermia (less than 36°C)

[1] Hemodynamically unstable: new onset of hypoxemia, oxygen saturation less than 90% or hypotension (blood pressure less than 90 mmHg); patient in respiratory distress. Respiratory Distress may include the following: Acute onset of dyspnea, tachypnea, hypoxemia, increased accessory muscle use with breathing, and/or intercoastal and sternal retractions.

[2] The goal is to give the antibiotics as soon as possible, preferably within 2 hours of arrival to the EC or admission to inpatient unit. If septic or admitted to ICU, the goal is to give the antibiotic within one hour of arrival.

[3] ID Specialist consultation should be considered but not limited in the following clinical scenarios:
- Suspicion for viral pneumonia (interstitial pneumonia in the setting of seasonal activity of community respiratory viruses)
- Pneumocystis (carinii) jiroveci (interstitial pneumonia in the setting of steroid tapering)
- Early re-admission or recent bacteremia
- Multiple antibiotic allergies
- Known colonization by multi-drug resistant pathogen

Department of Clinical Effectiveness V3
Approved by Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

SUSPECTED PNEUMONIA

Initiate institutional pneumonia order and give first dose of the 3 antibiotic regimen (dosing is based on normal renal function):

One of the following:

- Cefepime 2 grams IV every 8 hours or
- Piperacillin/tazobactam 4.5 grams IV every 6 hours or
- Meropenem[2] 1 gram IV every 8 hours or
- If PCN allergic, aztreonam 2 grams IV every 8 hours

Plus one of the following:

- If no quinolone prophylaxis:
  - --Ciprofloxacin 400 mg IV every 8 hours or
  - --Levofloxacin 750 mg IV every 24 hours or
- Amikacin 20 mg/kg or tobramycin 7-10 mg/kg IV every 24 hours
  - --For patients receiving amikacin or tobramycin, obtain drug levels 4 and 10 hours after start of dose for individualized pharmacokinetics

Plus one of the following:

- Linezolid 600 mg IV every 12 hours or
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IV every 12 hours

HAP, HCAP[1] or MDRP[1] →

CAP[1] →

If planned admission to general floor, one of the following options:

- Ceftriaxone 2 grams IV every 24 hours AND azithromycin 500 mg IV every 24 hours or
- Ceftriaxone 2 grams IV every 24 hours AND doxycycline 100 mg IV every 12 hours (if intolerant of macrolides) or
- Ampicillin/sulbactam 3 grams IV every 8 hours AND azithromycin 500 mg IV every 24 hours or
- Ampicillin/sulbactam 3 grams IV every 8 hours AND doxycycline 100 mg IV every 12 hours (if intolerant of macrolides) or
- Levofloxacin 750 mg IV every 24 hours or
- Moxifloxacin 400 mg IV every 24 hours

If planned admission to the ICU or stepdown, one of the following options:

- Ceftriaxone 2 grams IV every 24 hours AND azithromycin 500 mg IV every 24 hours or
- Ceftriaxone 2 grams IV every 24 hours AND levofloxacin 750 mg IV every 24 hours or
- Ceftriaxone 2 grams IV every 24 hours AND moxifloxacin 400 mg IV every 24 hours or

AND

- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IV every 12 hours or
- Linezolid 600 mg IV every 12 hours

→ Once patient is stable and discharge criteria met (see Appendix C), disposition as clinically indicated

[1] See Appendix A for description of each pneumonia
CAP – Community Acquired Pneumonia
HAP – Hospital Acquired Pneumonia
HCAP – Healthcare Associated Pneumonia
MDRP – Multidrug Resistant Pathogens

[2] Consider Meropenem if patient has: allergy to alternative agents; failed treatment with cefepime or piperacillin/tazobactam; infection with extended spectrum beta-lactamase (ESBL) organism; infection with organism only susceptible to carbapenem

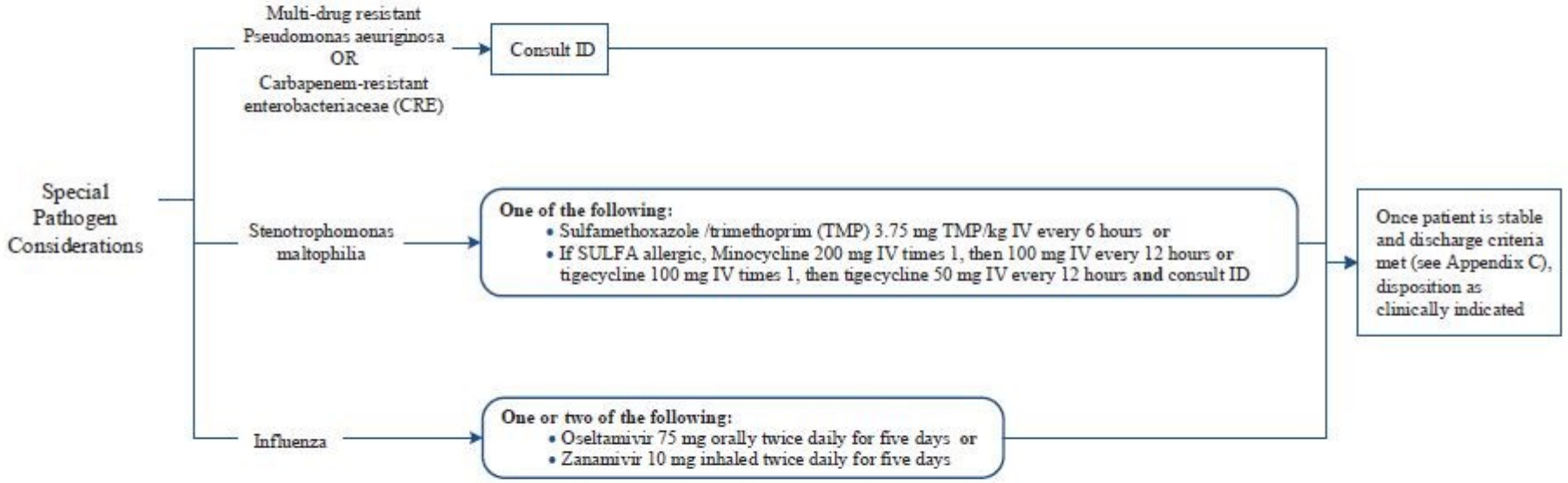
Department of Clinical Effectiveness V3
Approved by Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

NOTE: antibiotic dosing based on normal renal function



Special Pathogen Considerations continued on next page

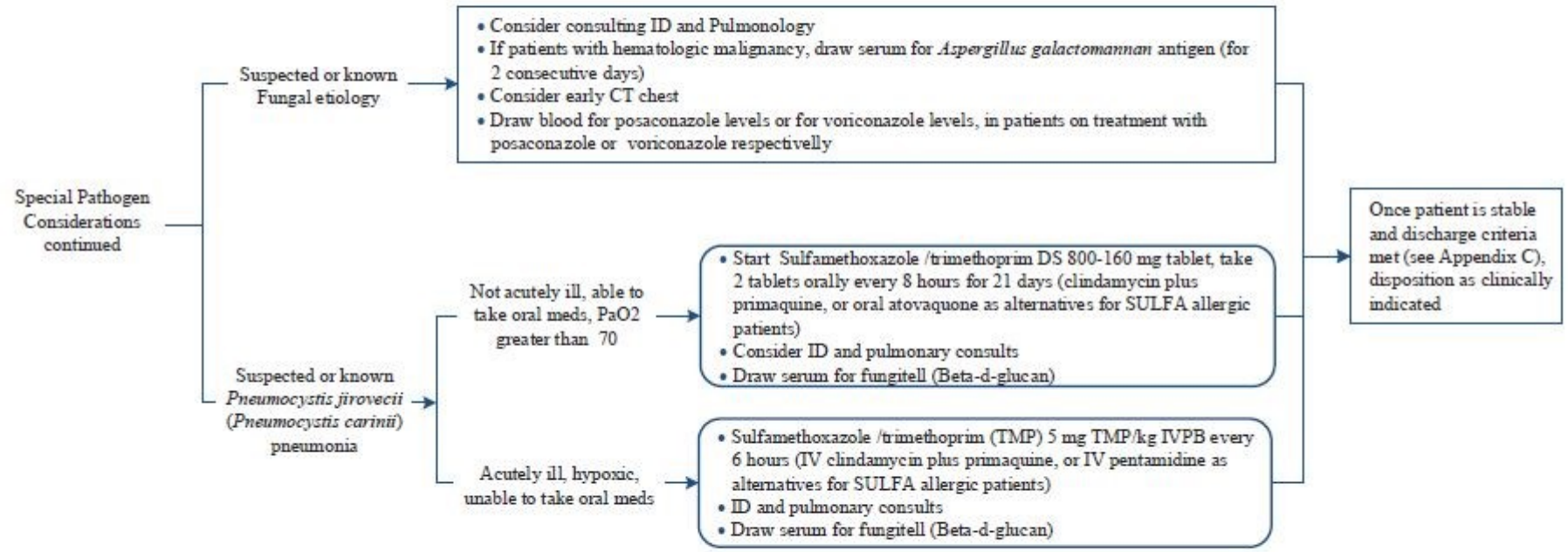
Department of Clinical Effectiveness V3
Approved by Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

NOTE: Antibiotic dosing based on normal renal function



THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

APPENDIX A: Suspicion of Health Care-Associated Pneumonia (HCAP), Hospital-Acquired Pneumonia (HAP), Community Acquired Pneumonia (CAP), and Multi-Drug-Resistant Pathogen (MDRP) Risk Factors

Health Care Associated Pneumonia (HCAP) Risk Factors:

- **Undergoing or recent chemotherapy/radiation therapy or any cancer therapy**
- Hospitalization for 2 or more days within 90 days
- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Chronic Dialysis within the last 30 days
- Home wound care
- Family member with MDRP

Hospital Acquired Pneumonia (HAP):

- Pneumonia that occurs 48 hours or more after admission, which was not present at the time of admission.

Community Acquired Pneumonia (CAP):

- Patient with pneumonia that does not fit criteria for HCAP, HAP or Ventilation Associated Pneumonia (VAP) without MDRP risk factors. At MD Anderson Cancer Center, this could be a patient in surveillance, an employee with no patient contact or a visitor.

Multi-Drug-Resistant Pathogen (MDRP) Risk Factors:

- **Immunosuppressive disease or therapy**
- Antibiotics within 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or specific hospital unit
- Presence of risk factors for HCAP

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

APPENDIX B: Pneumonia Severity Index (PSI)[1,2]

To obtain a total point score for a given patient add the patient's age in years (age minus 10 for women) plus the points for each applicable characteristic.

CHARACTERISTIC	POINTS ASSIGNED
• Nursing home resident	+10
• Coexisting illnesses[3]	
◦ Neoplastic disease	+30
◦ Liver disease	+20
◦ Congestive heart failure	+10
◦ Cerebrovascular disease	+10
◦ Renal disease	+10

CHARACTERISTIC	POINTS ASSIGNED
• Laboratory and radiographic findings	
◦ Arterial pH less than 7.35	+30
◦ BUN greater than or equal to 30 mg/dL (11 mmol/liter)	+20
◦ Sodium less than 130 mmol/liter	+20
◦ Glucose greater than or equal to 250 mg/dL (14 mmol/liter)	+10
◦ Hematocrit less than 30%	+10
◦ Partial pressure of arterial oxygen less than 60 mmHg	+10
◦ Pleural effusion	+10

CHARACTERISTIC	POINTS ASSIGNED
• Physical-examination findings	
◦ Altered mental status[4]	+20
◦ Respiratory rate greater than or equal to 30 minutes	+20
◦ Systolic blood pressure less than 90 mmHg	+20
◦ Temperature less than 35°C or greater than or equal to 40°C	+15
◦ Pulse greater than or equal to 125 beats per minute	+10

PSI Risk Score Interpretation	
I	Absence of all predictors: • Less than age 50 and • No neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease, and • No abnormalities on physical exam including: altered mental status, pulse greater than or equal to 125/minute, respiratory rate greater than or equal to 30/minute, systolic blood pressure less than 90 mmHg, temperature less than 35°C or greater than or equal to 40°C
II	Less than or equal to score of 70
III	71 – 90
IV	91 – 130
V	Greater than 130

[1] The use of this score is to facilitate site of care decisions for those patients that are classified as CAP, and have not been validated (requires prospective validation) for the HAP, HCAP or immunocompromised population that are the majority of patients seen at MDACC. This guideline is not meant to replace clinical judgment.

[2] The Pneumonia Severity Index may be found on the MDACC Intranet under Clinic Portal – Clinical Calculators.

[3] Coexisting illnesses definitions:
- Neoplastic disease - any cancer except basal- or squamous-cell cancer of the skin that was active at the time of presentation or diag-nosed within one year of presentation.
- Liver disease - a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease,such as chronic active hepatitis.
- Congestive heart failure - a systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest x-ray, echocardiogram, multiple gated acquisition scan, or left ventriculogram.
- Cerebrovascular disease – a clinical diagnosis of stroke or transient ischemic attack or stroke documented by MRI or CT.
- Renal disease - a history of chronic renal disease or abnormal BUN and creatinine concentrations documented in the medical record.

[4] Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic stupor or coma.

Department of Clinical Effectiveness V3
Approved by Executive Committee of the Medical Staff 12/15/2015

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

APPENDIX C:
Discharge Criteria

- Temperature less than 37.8°C
- Pulse less than 100 beats per minute
- Systolic BP greater than 90 mmHg
- Blood oxygenation greater than 90%
- Able to maintain oral intake

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

SUGGESTED READINGS

Abrahamian FM, Deblieux PM, Emerman CL, et al. (2008). Health care-associated pneumonia: identification and initial management in the ED. Am J Emerg Med.; 26(6 Suppl):1-11.

Anand N, Kollef MH. (2009). The alphabet soup of pneumonia: CAP, HAP, HCAP, NHAP, and VAP. Semin Respir Crit Care Med; 30(1):3-9. Epub 2009 Feb 6.

Baden LR, Bensinger W, Angarone M, et al. (2012). Prevention and treatment of cancer-related infections. Journal of the National Comprehensive Cancer Network, 10(11), 1412-1445.

Bratzler DW, Ma A, Nsa W. (2008). Initial antibiotic selection and patient outcomes: observations from the National Pneumonia Project. Clin Infect Dis; Suppl 3:S193-S201. doi: 10.1086/591404.

Brown SM, Jones BE, Jephson AR, et al. (2009). Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med; 37(12):3010-6.

Fine MF, Thomas EA, Yealy DM, et al. (1997). A prediction rule to identify low-risk patients with community acquired pneumonia. N Engl J Med; 336:243-50.

Gonzalez C, Johnson T, Rolston K, et al. (2014). Predicting pneumonia mortality using CURB-65, PSI, and patient characteristics in patients presenting to the emergency department of a comprehensive cancer center. Cancer Medicine 2014; 3(4): 962–970

Limper AH, Knox KS, Sarosi GA, et al. (2011). American Thoracic Society Fungal Working Group. Am J Respir Crit Care Med;1(83): pp96–128, 2011.

McCabe C, Kirchner C, Zhang H, et al. (2009). Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med; 169(16):1525-31.

Niederman MS. (2009). Making sense of scoring systems in community acquired pneumonia. Respirology; 14(3):327-35.

Niederman MS. (2007). Recent advances in community-acquired pneumonia: inpatient and outpatient. Chest; 131(4):1205-15.

Polverino E, Torres A. (2009). Current perspective of the HCAP problem: is it CAP or is it HAP? Semin Respir Crit Care Med; 30(2):239-48. Epub 2009 Mar 18.

Polverino E, Torres A. (2009). Diagnostic strategies for healthcare-associated pneumonia. Semin Respir Crit Care Med; 30(1):36-45. Epub 2009 Feb 6.

Vincent JL, Marshall JC. (2008). Surviving sepsis: a guide to the guidelines. Crit Care; 12(3):162. Epub 2008 Jun 30.

Seymann G, Barger K, Choo S, et al. (2008). Clinical judgment versus the Pneumonia Severity Index in making the admission decision. J Emerg Med; 34(3):261-8. Epub 2008 Jan 4.

The NCCN Clinical Practice Guidelines in Oncology™ Prevention and Treatment of Cancer-Related Infections (V2.2015). Available at: NCCN.org. Accessed [September 24, 2015].

Wachter RM, Holmboe ES. (2009). Diagnostic errors and patient safety. JAMA; 302(3):258; author reply 259-60.

Wachter RM, Flanders SA, Fee C, et al. (2008). Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. Ann Intern Med; 149(1):29-32.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Pneumonia in Adult Patients (18 years and older) with Cancer and on Therapy

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

DEVELOPMENT CREDITS

This practice consensus algorithm is based on majority expert opinion of the Pneumonia core development team at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following clinicians.

Samuel Aitken, PharmD, BCPS
Roy Chemaly, MD
Scott Evans, MD ₸
Carmen Gonzalez, MD ₸
Tami Johnson, PharmD, BCPS, FCCM ₸
Dimitrios P. Kontoyiannis, MD
Victor Mulanovich, MD
Issam Raad, MD
Kenneth V. Rolston, MD ₸
Samuel Shelburne, MD

₸ Core Development Team

APPENDIX IV. POTENTIAL DRUG-INDUCED LIVER INJURY/HY'S LAW

IDENTIFICATION

The Investigator is responsible for determining whether a patient meets the following potential Hy's law (PHL) criteria at any point after initiation of study therapy (IV or oral). For a PHL case to meet Hy's Law, the increases from baseline in AST or ALT and
total bilirubin values, in the Investigator's clinical judgment, should be temporally related to one another and to the administration of study drug, without an alternative explanation.

PHL

AST or ALT ≥ 3 × ULN; total bilirubin ≥ 2 × ULN and ALP < 2 × ULN

If there are increases from baseline in AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN:

- The Investigator must follow the instructions in this appendix
- The investigative site must complete the appropriate screen(s) of the eCRF with the local laboratory test results

FOLLOW-UP AND REPORTING

If the Investigator determines that the patient has not met PHL criteria (has not had increases from baseline in AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN, at any point after initiation of study drug), the Investigator is to perform follow-up on subsequent laboratory results as required for patient care and per protocol Section 9.5.2.9.2.

If the Investigator determines that the patient has met PHL criteria (has had AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, and ALP < 2 × ULN, elevated from baseline at any point after initiation of study drug):

- The Investigator should review the criteria for premature discontinuation of study drug due to elevated liver chemistry values, per protocol Section 9.3.3
- Any PHL case should be handled as an SAE associated with the use of the drug and reported as an SAE per protocol Section 9.5.2.5 (ie, even before all other possible causes of liver injury have been excluded). It should be promptly reported before doing a full workup on the patient to rule out other etiologies

- The Investigator will investigate the etiology of the event and establish if another explanation/alternative cause other than drug-induced liver injury caused by the study drug is possible. The Funder may be contacted to discuss the work-up.

- The investigative site must complete the appropriate screens of the eCRF

If there is an alternative explanation or the liver chemistry values increased from baseline arenot temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to reflect the attributed underlying illness and reassign an appropriate causality assessment, per protocol Sections 9.5.2.5 and 9.5.2.2, respectively.

If there is no alternative explanation and the liver chemistry values increased from baseline are temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to a Hy's Law case (reported term 'Hy's Law') and reassign a causality assessment of "related."

If, despite the Investigator's attempts to conduct follow-up and the guidance provided in this appendix, there is an unavoidable delay of > 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

REFERENCE

US Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: Premarketing clinical evaluation. 2009 Jul. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. Accessed 2014 Oct 28.

Table II

Trial description	*n*	Treatment regimens	Primary outcomes	Primary outcome results *n*/N (%)	Secondary outcomes	Secondary outcome results n/N (%)
Phase II treatment of cIAI (21) ClinicalTrials.gov ID: NCT01506271	351	Imipenem/relebactam 500/250 mg IV (t' 30 min) q6 h × 4–14 days Imipenem/relebactam 500/125 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem 500 mg IV (*t*' 30 min) q6 h × 4–14 days	Clinical response[a] in the ME[b]population at DCIV	Relebactam 250 mg: 78/81 (96.3) Relebactam 125 mg: 85/86 (98.8) Imipenem alone: 79/83 (95.2)	Clinical response[a] at EFU (ME[b])	Relebactam 250 mg: 75/79 (94.9) Relebactam 125 mg: 81/86 (94.2) Imipenem alone: 78/81 (96.3)
					Clinical response[a] at LFU (ME[b])	Relebactam 250 mg: 74/79 (93.7) Relebactam 125 mg: 81/85 (95.3) Imipenem alone: 75/79 (94.9)
					Microbiologic response[c] at DCIV (ME[b])	Relebactam 250 mg: 81/83 (97.6) Relebactam 125 mg: 86/86 (100) Imipenem alone: 82/84 (97.6)
					Global response[d] at 28 days after randomization (MITT[e])	Relebactam 250 mg: 77/89 (86.5) Relebactam 125 mg: 86/96 (89.6) Imipenem alone: 78/92 (84.8)
Phase II treatment of cUTI and AP (14) ClinicalTrials.gov ID: NCT01505634	302	Imipenem/relebactam 500/250 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem/relebactam 500/500/125 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem 500/500 mg IV (*t*' 30 min) q6 h × 4–14 days Optional oral step-down after 4 days (all regimens): ciprofloxacin 500 mg BID	Microbiological response[c] in the ME[b]population at DCIV	Relebactam 250 mg: 64/67 (95.5) Relebactam 125 mg: 70/71 (98.6) Imipenem alone: 74/75 (98.7)	Microbiological response[c] at EFU/LFU (ME[b])	Relebactam 250 mg: (61.5/68.3) Relebactam 125 mg: (68.1/65.2) Imipenem alone: (70.4/62.5)
					Clinical response[a] at DCIV/EFU/LFU (ME[b])	Relebactam 250 mg: (97.1/89.1/88.7) Relebactam 125 mg: (98.7/91.8/87.3) Imipenem alone: (98.8/93.4/88.2)
					Microbiological response[c] at DCIV for INS infections (ME[b])	Relebactam 250 mg: 10/10 (100) Relebactam 125 mg: 7/7 (100) Imipenem alone: 6/6 (100)

13.0 LITERATURE CITED

1. Prevention CfDCa. Antibiotic resistance threats in the United States 2013 [Available from: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
2. Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-Resistant Gram-Negative Bacterial Infections in the Hospital Setting: Overview, Implications for Clinical Practice, and Emerging Treatment Options. Microb Drug Resist. 2016;22(5):412-31.
3. Patel TS, Nagel JL. Clinical outcomes of Enterobacteriaceae infections stratified by carbapenem MICs. J Clin Microbiol. 2015;53(1):201-5.
4. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. Expert Rev Anti Infect Ther. 2013;11(3):297-308.
5. Rottier WC, Ammerlaan HS, Bonten MJ. Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae and patient outcome: a meta-analysis. J Antimicrob Chemother. 2012;67(6):1311-20.
6. American Thoracic S, Infectious Diseases Society of A. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171(4):388-416.
7. Livermore DM, Warner M, Mushtaq S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa. J Antimicrob Chemother. 2013;68(10):2286-90.
8. Organization WH. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics 2017 [Available from: https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/.
9. Rizk ML, Rhee EG, Jumes PA, Gotfried MH, Zhao T, Mangin E, et al. Intrapulmonary Pharmacokinetics of Relebactam, a Novel beta-Lactamase Inhibitor, Dosed in Combination with Imipenem-Cilastatin in Healthy Subjects. Antimicrob Agents Chemother. 2018;62(3).
10. Rizk ML JP, Lasseter K, et al, editor Pharmacokinetics of MK-7655, a novel b-lactamase inhibitor (BLI), in combination with imipenem/cilastatin (IPM/CIL) in subjects with impaired renal function. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2012; San Francisco, CA.
11. Centers for Disease C, Prevention. Vital signs: carbapenem-resistant Enterobacteriaceae. MMWR Morb Mortal Wkly Rep. 2013;62(9):165-70.
12. Jacob JT, Klein E, Laxminarayan R, Beldavs Z, Lynfield R, Kallen AJ, et al. Vital Signs: Carbapenem-Resistant Enterobacteriaceae. Mmwr-Morbid Mortal W. 2013;62(9):165-70.
13. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev. 2012;25(4):682-707.
14. Sims M, Mariyanovski V, McLeroth P, Akers W, Lee YC, Brown ML, et al. Prospective, randomized, double-blind, Phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. J Antimicrob Chemother. 2017;72(9):2616-26.
15. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in Klebsiella pneumoniae is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the foss of an outer membrane protein. Antimicrob Agents Chemother.

1997;41(3):563-9.
16. Crowley B, Benedi VJ, Domenech-Sanchez A. Expression of SHV-2 beta-lactamase and of reduced amounts of OmpK36 porin in Klebsiella pneumoniae results in increased resistance to cephalosporins and carbapenems. Antimicrob Agents Chemother. 2002;46(11):3679-82.
17. Quale J, Bratu S, Gupta J, Landman D. Interplay of efflux system, ampC, and oprD expression in carbapenem resistance of Pseudomonas aeruginosa clinical isolates. Antimicrob Agents Chemother. 2006;50(5):1633-41.
18. Zavascki AP, Carvalhaes CG, Picao RC, Gales AC. Multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii: resistance mechanisms and implications for therapy. Expert Rev Anti Infect Ther. 2010;8(1):71-93.
19. Karlowsky JA, Lob SH, Kazmierczak KM, Hawser SP, Magnet S, Young K, et al. In vitro activity of imipenem/relebactam against Gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme. J Antimicrob Chemother. 2018;73(7):1872-9.
20. Papp-Wallace KM, Barnes MD, Alsop J, Taracila MA, Bethel CR, Becka SA, et al. Relebactam Is a Potent Inhibitor of the KPC-2 beta-Lactamase and Restores Imipenem Susceptibility in KPC-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2018;62(6).
21. Lucasti C, Vasile L, Sandesc D, Venskutonis D, McLeroth P, Lala M, et al. Phase 2, Dose-Ranging Study of Relebactam with Imipenem-Cilastatin in Subjects with Complicated Intra-abdominal Infection. Antimicrob Agents Chemother. 2016;60(10):6234-43.
22. Motsch J, Murta de Oliveira C, Stus V, Koksal I, Lyulko O, Boucher HW, et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections. Clin Infect Dis. 2020;70(9):1799-808.
23. Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014) (RESTORE-IMI 2).
24. Wu J, Racine F, Wismer MK, Young K, Carr DM, Xiao JC, et al. Exploring the Pharmacokinetic/Pharmacodynamic Relationship of Relebactam (MK-7655) in Combination with Imipenem in a Hollow-Fiber Infection Model. Antimicrob Agents Chemother. 2018;62(5).
25. Al Shuaibi M, Bahu RR, Chaftari AM, Al Wohoush I, Shomali W, Jiang Y, et al. Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in febrile patients with hematologic malignancies. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2013;56(7):943-50.
26. Shomali W, Hachem R, Chaftari AM, Jiang Y, Bahu R, Jabbour J, et al. Can procalcitonin distinguish infectious fever from tumor-related fever in non-neutropenic cancer patients? Cancer. 2012;118(23):5823-9.
27. Shomali W, Hachem R, Chaftari AM, Bahu R, Helou GE, Jiang Y, et al. Can procalcitonin differentiate Staphylococcus aureus from coagulase-negative staphylococci in clustered gram-positive bacteremia? Diagnostic microbiology and infectious disease. 2013;76(2):158-61.
28. Chaftari AM, Hachem R, Reitzel R, Jordan M, Jiang Y, Yousif A, et al. Role of Procalcitonin and Interleukin-6 in Predicting Cancer, and Its Progression Independent of Infection. PloS one. 2015;10(7):e0130999.
29. Debiane L, Hachem RY, Al Wohoush I, Shomali W, Bahu RR, Jiang Y, et al. The utility of proadrenomedullin and procalcitonin in comparison to C-reactive protein as predictors of

sepsis and bloodstream infections in critically ill patients with cancer*. Crit Care Med. 2014;42(12):2500-7.
30. El Haddad H, Chaftari AM, Hachem R, Chaftari P, Raad, II. Biomarkers of Sepsis and Bloodstream Infections: The Role of Procalcitonin and Proadrenomedullin With Emphasis in Patients With Cancer. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018;67(6):971-7.
31. Haddad HE, Chaftari AM, Hachem R, Michael M, Jiang Y, Yousif A, et al. Procalcitonin Guiding Antimicrobial Therapy Duration in Febrile Cancer Patients with Documented Infection or Neutropenia. Sci Rep. 2018;8(1):1099.
32. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. The Lancet Infectious diseases. 2016;16(7):819-27.
33. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463-74.
34. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014;190(10):1102-10.
35. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. Intensive care medicine. 1998;24(8):888-9.