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Supplemental online content for:

Infusion-Compatible Antibiotic Formulations for Rapid Administration to Improve Outcomes in Outpatients With Cancer With Severe Sepsis and Septic Shock: The Sepsis STAT Pack

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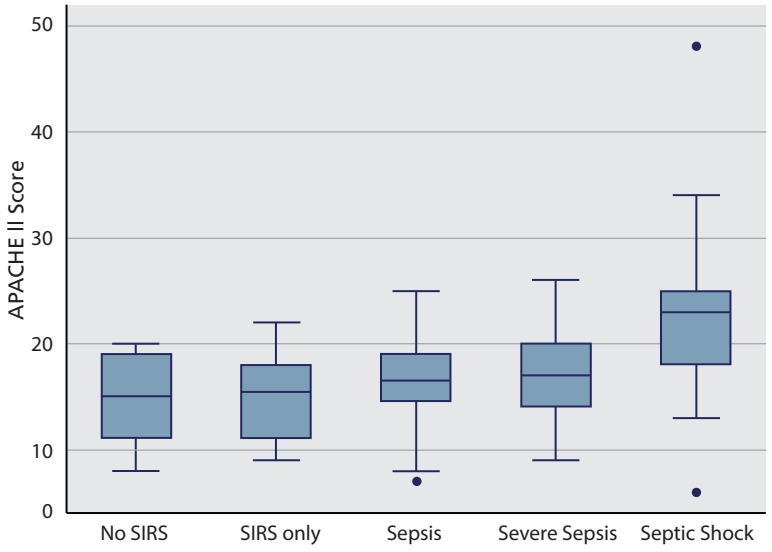
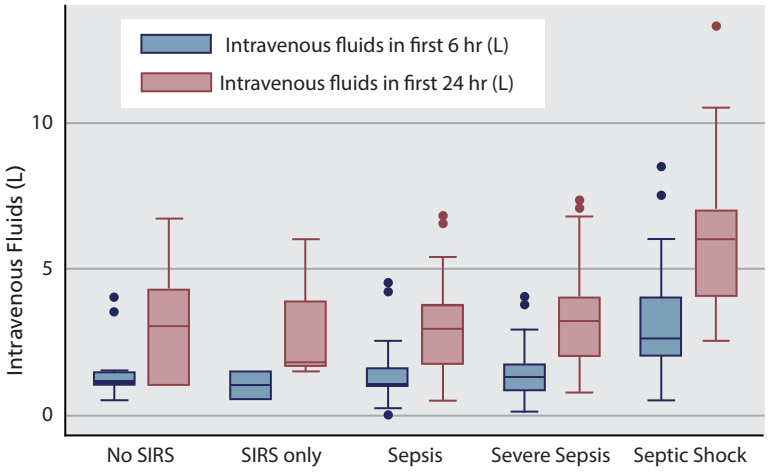
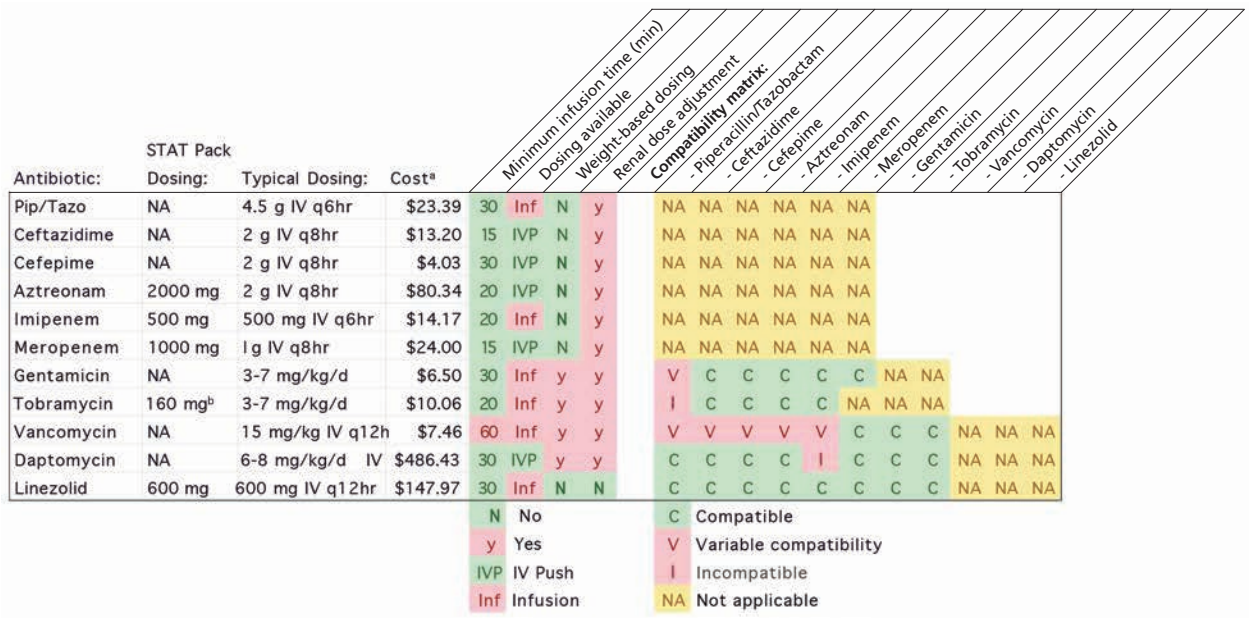


eFigure 1. APACHE II score by sepsis severity for Sepsis STAT Pack cohort.
Abbreviation: SIRS, systemic inflammatory response syndrome.



eFigure 2. Intravenous fluids administered in 6 and 24 hours by sepsis severity for Sepsis STAT Pack cohort.
Abbreviation: SIRS, systemic inflammatory response syndrome.



Antibiotic:	STAT Pack Dosing:	Typical Dosing:	Cost[a]	Minimum infusion time (min)	Dosing available	Weight-based dosing	Renal dose adjustment	Compatibility matrix: - Piperacillin/Tazobactam	- Ceftazidime	- Cefepime	- Aztreonam	- Imipenem	- Meropenem	- Gentamicin	- Tobramycin	- Vancomycin	- Daptomycin	- Linezolid
Pip/Tazo	NA	4.5 g IV q6hr	$23.39	30	Inf	N	y	NA	NA	NA	NA	NA	NA					
Ceftazidime	NA	2 g IV q8hr	$13.20	15	IVP	N	y	NA	NA	NA	NA	NA	NA					
Cefepime	NA	2 g IV q8hr	$4.03	30	IVP	N	y	NA	NA	NA	NA	NA	NA					
Aztreonam	2000 mg	2 g IV q8hr	$80.34	20	IVP	N	y	NA	NA	NA	NA	NA	NA					
Imipenem	500 mg	500 mg IV q6hr	$14.17	20	Inf	N	y	NA	NA	NA	NA	NA	NA					
Meropenem	1000 mg	I g IV q8hr	$24.00	15	IVP	N	y	NA	NA	NA	NA	NA	NA					
Gentamicin	NA	3-7 mg/kg/d	$6.50	30	Inf	y	y	V	C	C	C	C	C	NA	NA			
Tobramycin	160 mg[b]	3-7 mg/kg/d	$10.06	20	Inf	y	y	I	C	C	C	C	NA	NA	NA			
Vancomycin	NA	15 mg/kg IV q12h	$7.46	60	Inf	y	y	V	V	V	V	V	C	C	C	NA	NA	NA
Daptomycin	NA	6-8 mg/kg/d IV	$486.43	30	IVP	y	y	C	C	C	C	I	C	C	C	NA	NA	NA
Linezolid	600 mg	600 mg IV q12hr	$147.97	30	Inf	N	N	C	C	C	C	C	C	C	C	NA	NA	NA

N	No	C	Compatible
y	Yes	V	Variable compatibility
IVP	IV Push	I	Incompatible
Inf	Infusion	NA	Not applicable

eFigure 3. Dosing, timing of infusion, cost, and infusion compatibility matrix of potential components of the SSP.
Abbreviations: IV, intravenously; NA, not applicable; Pip/Tazo, piperacillin/tazobactam; SSP, Sepsis STAT Pack
[a]Cost: single dose by average wholesale price for 70 kg and 7 mg/kg/d when weight-based dose range is given.
[b]Equivalent does for 80 kg person = 2 mg/kg.

eTable 1. Univariate Association of Selected Characteristics With Time-to-Antibiotics

Characteristic	Time-to-ABx ≤110 min (n=80)	Time-to-ABx >110 min (n=80)	Total (Missing=2)	*P* Value[a]
Demographics				
Age, mean (SD), y	50.2 (15.6)	51.8 (15.1)	51.0 (15.3)	.517
Sex				.030
Female	21 (38.2%)	34 (61.8%)	55 (34.4%)	
Male	59 (56.2%)	46 (43.8%)	105 (65.6%)	
Race				.160
Caucasian	67 (53.6%)	58 (46.4%)	125 (82.8%)	
Other	10 (38.5%)	16 (61.5%)	26 (17.2%)	
Baseline clinical characteristics				
Oncologic diagnosis				.101
Heme malignancy	73 (52.5%)	66 (47.5%)	139 (86.9%)	
Other	7 (33.3 %)	14 (66.7%)	21 (13.1%)	
HSCT status				.752
Allo or auto	37 (48.7%)	39 (51.3%)	76 (47.5%)	
None	43 (51.2%)	41 (48.8%)	84 (52.5%)	
Immunosuppressives[b]				.288
Any	25 (56.8%)	19 (43.2%)	44 (27.5%)	
None	55 (47.4%)	61 (52.6%)	116 (72.5%)	
Neutropenia				.752
ANC <500 cells/mcL	39 (48.8%)	41 (51.3%)	80 (50.0%)	
ANC ≥500 cells/mcL	41 (51.3%)	39 (48.8%)	80 (50.0%)	
Antibiotics[b]				.316
Any	56 (52.8%)	50 (47.2%)	106 (66.3%)	
None	24 (44.4%)	30 (56.6%)	54 (33.8%)	
Clinical characteristics/concurrent therapies (current sepsis episode)				
Bacteremia				.265
Yes	39 (54.9%)	32 (45.1%)	71 (44.4%)	
No	41 (46.1%)	48 (53.9%)	89 (55.6%)	
Dexamethasone				.081
Yes	42 (57.5%)	31 (42.5%)	73 (45.6%)	
No	38 (43.7%)	49 (56.3%)	87 (54.4%)	

Time-to-antibiotics is given as time from first clinical encounter to administration of third Sepsis STAT Pack antibiotic, dichotomized at the median of 110 minutes.
Abbreviations: ABx, antibiotics; allo, allogeneic; ANC, absolute neutrophil count; auto, autologous; heme, hematopoietic; HSCT, hematopoietic stem cell transplant; SS, severe sepsis; SSh, septic shock.
[a]*P* value calculated using time-to-antibiotics variable dichotomized at the mean as the dependent variable. Test of association by type of independent variables: categorical: chi-square test; continuous: t test.
[b]Immunosuppressive therapies and antibiotics are listed in Table 1.

eTable 2. Univariate Association of Selected Characteristics With Combined Outcome of SSh or 30-Day Cumulative Mortality

Characteristic	No SSh or 30-Day Mortality (n=132)	SSh or 30-Day Mortality (n=30)	Total (Missing=0)	*P* Value[a]
Demographics				
Age, mean (SD), y	50.7 (14.9)	52.0 (16.7)	51.0 (15.2)	.668
Sex				.875
Female	46 (82.1%)	10 (17.9%)	56 (34.6%)	
Male	86 (81.1%)	20 (18.9%)	106 (65.4%)	
Race				.071
Caucasian	107 (84.3%)	20 (15.8%)	127 (83.0%)	
Other	18 (69.2%)	8 (30.8%)	26 (17.0%)	
Baseline clinical characteristics				
Oncologic diagnosis				.061
Heme malignancy	118 (83.7%)	23 (16.3%)	141 (87.0%)	
Other	14 (66.7%)	7 (33.3%)	21 (13.0%)	
HSCT status				.187
Allo or auto	66 (85.7%)	11 (14.3%)	77 (47.5%)	
None	66 (77.7%)	19 (22.4%)	85 (52.5%)	
Immunosuppressives[b]				.547
Any	38 (84.4%)	7 (15.6%)	45 (27.8%)	
None	94 (80.3%)	23 (19.7%)	117 (72.2%)	
Neutropenia				.742
ANC <500 cells/mcL	66 (82.5%)	14 (17.5%)	80 (49.4%)	
ANC ≥500 cells/mcL	66 (80.5%)	16 (19.5%)	82 (50.6%)	
Antibiotics[b]				.613
Any	86 (80.4%)	21 (19.6%)	107 (66.1%)	
None	46 (83.6%)	9 (16.4%)	55 (34.0%)	
Clinical characteristics/concurrent therapies (current sepsis episode)				
Bacteremia				.952
Yes	58 (81.7%)	13 (18.3%)	71 (43.8%)	
No	74 (81.3%)	17 (18.7%)	91 (56.2%)	
Dexamethasone				.489
Yes	62 (83.8%)	12 (16.2%)	74 (45.7%)	
No	70 (79.6%)	18 (20.5%)	88 (54.3%)	

Abbreviations: ABx, antibiotics; allo, allogeneic; ANC, absolute neutrophil count; auto, autologous; heme, hematopoietic; HSCT, hematopoietic stem cell transplant; SS, severe sepsis; SSh, septic shock.
[a]*P* value calculated using test of association by type of independent variables: categorical: chi-square test; continuous: t test.
[b]Immunosuppressive therapies and antibiotics are listed in Table 1.

eTable 3. Processes of Care Delivery: Clinic Time Flow in Recipients of the Sepsis STAT Pack

Time Elapsed	n (% Nonmissing)	Median (min)	IQR (min)
Time from first encounter to clinical encounter	162 (100)	26	0–70
Time from clinical encounter to antibiotics dispensed	162 (100)	74	31–123
Time from antibiotics dispensed to antibiotics administered	160 (98.8)	26	19–46
Time from antibiotics administered to inpatient admission	153 (94.4)	84	61–122
Time from clinical encounter to antibiotics administered	160 (98.8)	111	60–178
Time from blood culture to antibiotics administered	160 (98.8)	40	15–81
Time from first encounter to inpatient admission	155 (95.7)	260	188–385

Abbreviation: IQR, interquartile range.

eTable 4. Metrics of Sepsis Disease Severity for Sepsis STAT Pack Cohort

Disease Category	Patients n (%)	Number Organ Systems With Dysfunction: Number of Patients (%)[a]	APACHE II Score, Mean (SD)	Volume Intravenous Fluid Administration, Mean (SD)
No SIRS	13 (8.0)	0: 11 (84.6) 1: 2 (15.4)	14.6 (4.7)	6-hr: 1.5 (1.1) 24-hr: 3.0 (1.9)
SIRS only	6 (3.7)	0: 3 (50.0) 1: 3 (50.0)	15.2 (4.7)	6-hr: 1.0 (0.5) 24-hr: 2.8 (2.1)
Sepsis	71 (43.8)	0: 49 (68.1) 1: 23 (31.9)	16.4 (4.1)	6-hr: 1.3 (0.8) 24-hr: 2.7 (1.4)
Severe sepsis	47 (29.0)	0: 0 (0) 1: 28 (60.9) 2: 16 (34.8) 3: 1 (2.2) 4: 1 (2.2)	17.1 (4.2)	6-hr: 1.4 (0.9) 24-hr: 3.4 (1.6)
Septic shock	25 (15.4)	0: 0 (0) 1: 12 (48.0) 2: 4 (16.0) 3: 6 (24.0) 5: 3 (12.0)	23.0 (8.0)	6-hr: 3.3 (2.0) 24-hr: 6.1 (2.5)
Total	162 (100)	0: 63 (38.9) 1: 68 (42.0) 2: 20 (12.4) 3: 7 (4.3) 4: 1 (0.6) 5: 3 (1.9)	17.5 (5.5)	6-hr: 1.7 (1.3) 24-hr: 3.5 (2.1)

Abbreviation: SIRS, systemic inflammatory response syndrome.
[a]Percentages are across row.

eTable 5. Clinically or Microbiologically Diagnosed Infections and Alternative Diagnoses

Disease Category	Patients, n (%)	Diagnosis[a]		Other Infections and Alternative Diagnoses
No SIRS	13 (8.0)	Bacteremia	6	
		Other infection	3	Hepatic abscess (1), UTI (1) wound infection (1)
		Suspected infection	3	
		Alternative diagnosis	1	Drug reaction (1)
SIRS only	6 (3.7)	Alternative diagnosis	6	Drug reaction (2), tumor fever (2), dehydration (1), pancreatitis (1)
Sepsis	72 (43.8)	Bacteremia	24	
		Other infection	19	PNA (4), fungal PNA (3), viral PNA (6), C. diff (2), diverticulitis (1), peritonitis (1), UTI (1), meningitis (1)
		Cx-neg sepsis	29	
Severe sepsis	46 (29.0)	Bacteremia	29	
		Other infection	4	PNA (1), fungal PNA (1), CMV enteritis (1), UTI (1)
		Cx-neg sepsis	13	
Septic shock	25 (15.4)	Bacteremia	12	
		Other infection	7	PNA (3), viral PNA (2), CMV enteritis (1), UTI (1)
		Cx-neg sepsis	6	
Total	162 (100)	Bacteremia	71	
		Other infection:	33	PNA (8), fungal PNA (4), viral PNA (8), UTI (4), CMV enteritis (2), C. diff (2), diverticulitis (1), peritonitis (1), hepatic abscess (1), meningitis (1), wound infection (1)
		Cx-neg sepsis	48	
		Suspected infection	3	
		Alternative diagnosis	7	Drug reaction (3), tumor fever (2), dehydration (1), pancreatitis (1)

Abbreviations: C. diff, Clostridium difficile; CMV, cytomegalovirus; Cx-neg, culture negative; PNA, pneumonia; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection.
[a]Cx-neg sepsis: criteria for sepsis (or more severe sepsis) are met, but no alternative diagnosis or clinical/microbiological diagnosed infection is evident.

eTable 6. Unique Bacterial Bloodstream Isolates, Drug Susceptibility, and Intrinsic Resistance

Name	N	Drug Resistance Classification[a]	Antibiotic-Resistant Classes or Mechanism[b]
Gram-negative bacteria			
Achromobacter xylosoxidans	1	1 MDR	AG+MB+CHL
Acinetobacter baumanii	2	1 DR	ampC
Acinetobacter junii	1		
Acinetobacter ursingii	8	3 DR	3-ceph (2), 3-ceph+AG (1)
Aeromonas caviae	1		
Citrobacter freundii	1	1 DR	3-ceph+MB
Delftia acidovorans	1	1 DR	4-ceph, PMX
Enterobacter aerogenes	1		
Enterobacter asburiae	1		
Enterobacter cloacae	9	3 MDR, 1 MDR/XDR	ampC (3), ampC+AG+FQ (1)
Escherichia coli	8	1 DR, 3 MDR, 2 MDR/XDR	aPCN+FQ (1), aPCN/βLI+AG+FQ (2), aPCN+esPCN/βLI+AG+FQ (1), ESβL+FQ (1), aPCN/βLI+1,3-ceph+AG+FQ+FSI (1)
Klebsiella oxytoca	4		
Klebsiella pneumonia	4	1 DR, 1 MDR/XDR	FQ (1), ampC+AG+FQ (1)
Leptotrichia spp	1		
Pantoea spp	3	2 DR	aPCN (1), aPCN+1-ceph (1)
Proteus mirabilis	1		
Pseudomonas aeruginosa	9	4 DR, 1 MDR	FQ (1), esPCN/βLI (1), MB+esPCN/βLI (1), Carba (1), ESβL (1)
Rhizobium radiobacter	1	1 MDR	MB+3-ceph+AG+CHL
Serratia marcescens	3		
Stenotrophomonas maltophilia	3	2 DR	esPCN/βLI (2)
Gram-positive bacteria			
Clostridium perfringens	1		
Enterococcus faecalis	2	1 DR	Tetra
Enterococcus faecium	2	1 DR/MDR, 1 MDR	VRE (1), VRE+Tetra (1)
Rothia mucilaginosa	4	1 DR	AG+FQ
Staphylococcus aureus	2	1 MDR	MRSA+LCS
Staphylococcus, CoNS	13	2 MDR	MR-CoNS+LCS+FSI (2)
Streptococcus agalactiae	1		
Streptococcus bovis	1		
Streptococcus viridans	3	1 DR	FQ
Gram-positive cocci, not otherwise specified	1		
Unique isolates	93	37	Drug-resistant isolates

Abbreviations: 1,3-ceph, first- and third-generation cephalosporin; AG, aminoglycosides; ampC, AmpC β-lactamase; aPCN, amino-penicillin; βLI, β-lactamase inhibitor; Carba, carbapenem; ceph, cephalosporin, CHL, chloramphenicol; CoNS, coagulase-negative staphylococci; DR, drug-resistant; ECDC, European Centre for Disease Prevention and Control; ESβL, extended-spectrum β-lactamase; esPCN, extended-spectrum penicillin; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FSI, folate synthesis inhibitor; FQ, fluoroquinolone; LCS, lincosamide; MB, monobactam; MDR, multidrug-resistant; MR, methicillin-resistant; MRSA, methicillin-resistant *staphylococcus aureus*; PMX, polymyxin; Tetra, tetracycline; VRE, vancomycin-resistant enterococcus; XDR, extensively drug-resistant.

[a]Drug resistance definitions are determined from the EUCAST expert rules on antimicrobial susceptibility testing[1] and/or the ECDC consensus on drug resistance,2 and do not include antimicrobials to which the isolate is intrinsically resistant. Bridge categories of DR/MDR refers to possible MDR isolate, MDR/XDR refers to possible XDR isolate but without enough drug classes tested as per ECDC consensus on drug resistance.[2]

[b]The antimicrobial resistance mechanism is inferred from the agar disc diffusion antimicrobial susceptibility pattern.

Sources: [1]Leclercq R, Cantón R, Brown DF, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 2013;19:141–160; [2]Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–281.

eTable 7. Benchmark Mortality Data: Mortality Data for Patients With Cancer and Severe Sepsis/Septic Shock

Study	1) Setting 2) Population (identification) 3) Study design	Deceased/Total, N % (95% CI)
Williams, et al[1]	1) Hospitalized patients in 6 US states, 1999 2) Patients with cancer with SS/SSh, hospitalized (administrative data) 3) Retrospective cohort	Hospital mortality, SS/SSh Unknown/29,795 37.8% (cannot estimate)[a]
Larche et al[2]	1) Single-center ICU in Paris, France (St Louis), 1995–2000 2) Patients with cancer with SSh, ICU (clinical records) 3) Retrospective cohort	30-day mortality SSh 57/88 65.5% (54%–75%)
Legrand et al[3]	1) Single-center academic ICU in Paris, France (St Louis), 1998–2008 2) Neutropenic patients with cancer with SS/SSh, ICU (uncertain) 3) Retrospective cohort	Hospital mortality, SS/SSh 213/428 49.8% (45%–55%)
Pène et al[4]	1) Single-center ICU in Paris, France (Cochin), 1998–2005 2) Patients with cancer with SSh, ICU (uncertain) 3) Retrospective cohort	28-day mortality SSh 143/238 60.1% (54%–66%) ICU mortality, SSh 153/238 64.3% (58%–70%) Hospital mortality SSh 165/238 69.3% (63%–75%)
Mokart et al[5]	1) Single-center ICU in Marseille, France, 2008–2010 2) Neutropenic patients with cancer with SS or SSh, ICU (sequential patients enrolled) 3) Prospective cohort	ICU mortality SS/SSh 40/118 33.9% (25%–43%)
Azoulay et al[6]	1) Multicenter network of 17 academic ICUs in France and Belgium, 2010–2011 2) Hematologic malignancy patients with SS/SSh, ICU (sequential patients enrolled) 3) Prospective cohort, primary analysis	Hospital mortality SS 120/349 34.4% (29%–40%) Hospital mortality SSh 120/259 46.3% (40%–53%) Hospital mortality SS/SSh 240/608 39.5% (36%–43%)
Mokart et al[7]	1) Multicenter network of 17 academic ICUs in France and Belgium, 2010–2012 2) Neutropenic hematologic malignancy patients with sepsis, SS, or SSh, ICU (sequential patients enrolled) 3) Prospective cohort, post hoc analysis	Hospital mortality, sepsis/SS/SSh 104/230 45.2% (39%–52%)

Abbreviations: ICU, intensive care unit; SS, severe sepsis; SSh, septic shock.
[a]Count data not provided, so cannot accurately estimate 95% CI.
Sources: [1]Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. Crit Care 2004;8:R291–298; [2]Larche J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. Intensive Care Med 2003;29:1688–1695; [3]Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. Crit Care Med 2012;40:43–49; [4]Pene F, Percheron S, Lemiale V, et al. Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 2008;36:690–696; [5]Mokart D, Saillard C, Sannini A, et al. Neutropenic cancer patients with severe sepsis: need for antibiotics in the first hour. Intensive Care Med 2014;40:1173–1174; [6]Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en reanimation onco-hematologique study. J Clin Oncol 2013;31:2810–2818; [7]Mokart D, Darmon M, Resche-Rigon M, et al. Prognosis of neutropenic patients admitted to the intensive care unit. Intensive Care Med 2015;41:296–303.

eAppendix 1. Methods

Sepsis Definitions

Surviving Sepsis Campaign Guidelines[1]

Systemic Inflammatory Response Syndrome Criteria (≥2 of following)

- Body temperature >38.3°C or <36.0°C
- Heart rate >90 beats per minute (bpm)
- Respiratory rate >20/minute or partial pressure of carbon dioxide, arterial (Paco2) <32 mmHg (4.3 kPa)
- WBC count >12,000/mcL or <4,000/mcL or immature granulocytes >10%
- Altered mental status (Glasgow Coma Scale [GCS] <15 or objective assessment by clinician)

Note: Vital sign and laboratory abnormalities were assessed 24 hours before and after dispensing of the Sepsis STAT Pack antibiotics. Due to frequency of abnormalities to WBC counts in patients with cancer, systemic inflammatory response syndrome (SIRS) criteria for leukocytosis, leukopenia, or bandemia were considered fulfilled only if unequivocally due to the infection defining the septic episode by change from normal on most recent laboratory results and absence of other condition or treatment that could cause the abnormality in WBC count, including but not limited to cytotoxic or conditioning chemotherapy, irradiation, steroids, granulocyte colony-stimulating factor, calcineurin inhibitor, trimethoprim-sulfamethoxazole, or ganciclovir.

Sepsis Criteria (meeting SIRS criteria and ≥1 of following)

- Microbiologically confirmed infection
- Clinically diagnosed infection
- Suspected infection

Note: Patients were considered to have microbiologically confirmed infection if microbiologic cultures revealed an etiology consistent with the clinical syndrome. Patients were considered to have suspected infection based on the assessment of the treating clinicians or by non-microbiologic diagnostic testing, and absence of alternative diagnosis. Because clinical decisions in the outpatient setting were made in real-time and therapies were administered before all information is available to the treating clinician, we assumed that the initial treating clinicians made the correct assessment of suspected infection, unless later disproven by better alternative diagnosis. If better alternative diagnosis was made in hindsight (eg, drug allergy, infusion reaction), these cases were classified as SIRS only/alternative diagnosis. Culture-negative sepsis occurred when no clinically or microbiologically diagnosed infection or alternative diagnosis presented but when the initial treating clinician suspected sepsis.

Severe Sepsis Criteria (meeting Sepsis Criteria and ≥1 of the following definitions for organ dysfunction or decreased tissue perfusion)

- Arterial hypotension (systolic blood pressure [SBP] <90 mmHg or mean arterial pressure (MAP] <70 mmHg)
- Arterial hypoxemia (partial pressure of oxygen, arterial/fraction of inspired oxygen [Pao2/Fio2] <300)
- Acute oliguria (urine output <0.5 mL/kg/h for ≥2 hours despite adequate intravenous fluids)
- Acute kidney injury (AKI) (creatinine increase >0.5 mg/dL)
- Coagulation abnormalities (international normalized ratio [INR] >1.5, activated partial thromboplastin time [aPTT] >60 s or platelets <100,000/mcL)
- Ileus (absent bowel sounds on clinical examination or otherwise unexplained emesis temporally related to hypotension)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL)
- Hyperlactatemia (arterial lactate ≥1 mmol/L or venous lactate ≥4 mmol/L)
- Decreased capillary refill or skin mottling on clinical examination

Note: Patients were considered to have arterial hypotension only if the SBP or MAP criteria were fulfilled by repeated readings to exclude spurious measurements. Further, sepsis-related arterial hypotension was determined only if the hypotension was temporally related to the sepsis episode: patients with alternative explanations for hypotension (ie, low baseline blood pressure, hypotension only while sleeping) did not meet criteria for severe sepsis. Because few patients had arterial blood gas measurement, additional criteria for hypoxemia was determined by peripheral capillary oxygen saturation (Spo2) <90% with acute change from baseline. Evidence of other organ system dysfunction or poor tissue perfusion was determined to be sepsis-induced and fulfilled criteria for severe sepsis only if unequivocally due to the infection defining the septic episode by change from nor-

mal on most recent laboratory results and absence of other condition or treatment that could cause the abnormality. Specifically, thrombocytopenia was excluded as a cause of sepsis-related organ dysfunction due to the very high frequency of baseline thrombocytopenia in this population. Coagulation abnormality was considered fulfilled only if not explained by underlying disease or treatment with heparin, warfarin, or other anticoagulant. Ileus was considered strictly as clinician-diagnosed with or without supportive radiographic evidence; emesis alone did not fulfill this criteria, because patients undergoing treatments for malignancy have high frequency of treatment-related nausea and emesis. Sepsis-related ileus or skin changes were considered as evidence of organ dysfunction, but alone did not establish criteria for severe sepsis.

Septic Shock Criteria (meeting Severe Sepsis Criteria and ≥1 of the following)

- Refractory hypotension
- Vasopressor agents used to support blood pressure

Note: Refractory hypotension defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation (≥20 mL/kg crystalloid infusion[2,3]). Vasopressors considered included norepinephrine, epinephrine, vasopressin, dopamine, dobutamine, or phenylephrine.

APACHE II Score[4]

The following variables from a 48-hour window centered on the dispensing of the Sepsis STAT Pack antibiotics were extracted from the University of Washington Clinical Data Warehouse (Amalga). The highest and lowest values were assigned points, and the highest points for each variable were totaled for the Acute Physiology Score (APS) as per the initial report.[4]

- Body temperature (oC)
- Mean arterial pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (breaths/min)
- Oxygenation: alveolar-arterial oxygen gradient (AaDo2) if Fio2 >0.5 or Pao2 if Fio2 <0.5 (mmHg)
- Arterial pH, or serum HCO3-negative (mmol/L) if no arterial blood gas measurement
- Serum sodium (mmol/L)
- Serum potassium (mmol/L)
- Serum creatinine (mg/dL)
- Hematocrit (%)
- WBC count (x1,000 cells/mcL)
- GCS (points)

Note: Points for serum creatinine were doubled for AKI as per the initial APACHE II report,[4,5] with AKI defined as an increase in serum creatinine to >2.0 mg/dL from <1.4 mg/dL or elevated serum creatinine to >2.0 mg/dL that returns to <1.4 mg/dL. The total APACHE II score is the sum of APS + age points + 5 points for chronic organ insufficiency. Points for organ insufficiency based on immunosuppression were assigned if the patient had leukemia, lymphoma, neutropenia, or any immunosuppressive therapy (as listed in Table 1).

List of Variables (and Source) of Raw Data

- Demographics:
  - Date of birth (Amalga)
  - Sex (Amalga)
  - Race (Amalga)
- Administrative, time flow, and vital statistics:
  - Hospital admission and discharge date and time (Amalga)
  - Time and location of first encounter (electronic medical record [EMR])
  - Time and location of first clinical encounter (EMR)
  - Time of first laboratory and blood culture draw (EMR)
  - Time of antibiotic dispensing by pharmacy (PharmNet)
  - Time of antibiotic administration by nurse (EMR)
  - Date of death (Washington State Department of Health [WA DOH], Amalga, and hematopoietic stem cell transplant [HSCT])
  - Date of last UW Medicine encounter (Amalga)
- Clinical characteristics:
  - Oncologic diagnosis (HSCT or EMR)
  - Date of HSCT (HSCT)
  - Type of HSCT (HSCT)
  - Clinical diagnosis of ileus (EMR)
  - Clinical diagnosis of poor skin perfusion (EMR)
  - Clinical diagnosis of altered mental status (EMR)
  - Prophylactic antibiotics (EMR)
  - Immunosuppressive therapies (EMR)

- Adverse events (EMR)
- Intubation (Amalga and EMR)
- Microbiological data (EMR)
- Clinically diagnosed infection (EMR)
- Infectious disease consultation (EMR)
- Volume of intravenous crystalloid infusion in 6 and 24 hours (EMR)
- Urine output (EMR)
- Receipt of Seattle Cancer Care Alliance (SCCA) clinic antibiotics (EMR)
- Receipt of UW Medical Center hospital antibiotics (EMR)
- Receipt of dexamethasone in SCCA (PharmNet)
- Receipt of vasopressors (Amalga and EMR)
- Receipt of anticoagulants (EMR)

- Vital signs and laboratory data:
  - All APACHE II variables for APS as above (Amalga)
  - Clinician note documented vital sign data (EMR)
  - Weight (EMR)
  - Spo_2 and Fio_2 (EMR)
  - Absolute neutrophil count (EMR)
  - Immature granulocyte (EMR)
  - INR, aPTT (EMR)
  - Serum bilirubin (Amalga)
  - Arterial or venous lactate (EMR)

Note: Data sources: Amalga: UW Medicine clinical data repository; HSCT: Fred Hutchinson Cancer Research Center (FHCRC) Infectious Disease HSCT database; PharmNet: UW Medicine pharmacy informatics system; EMR: Citrix EMR; WA DOH: Washington Department of Health death data.

Data Collection and Assignment of Sepsis Disease Severity

Data were extracted from electronic data sources at FHCRC and UW Medicine, and variables identified above by "EMR" were abstracted by manual chart review by 2 reviewers (J.D.G., A.G.). Mortality was ascertained from 2 independent sources: WA DOH death certificate data and the UW Medicine clinical data repository. Assessments of sepsis disease severity criteria were determined through manual chart review by 1 reviewer. Logic definitions to distinguish syndromes were then applied to abstracted raw data to check the reviewer assessments with objective criteria of the Surviving Sepsis Campaign guidelines.[1] If discordance was present, charts were reexamined by the other reviewer to determine consensus. To determine adverse effects, the medical record was searched electronically for the following terms: "nephrotoxicity," "ototoxicity," "rash," and "serotonin syndrome," and hits to these search terms triggered review of relevant clinical notes. All cases of AKI were reviewed to determine temporal association to tobramycin administration.

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