Readily-Available Antibiotic Formulations to Improve Outcomes in Cancer Patients with Severe Sepsis and Septic Shock

Jason D. Goldman

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2015

Reading Committee:

Corey Casper, Chair

Stephen M. Schwartz

Program Authorized to Offer Degree:

Public Health- Epidemiology

University of Washington

Abstract

Readily-Available Antibiotic Formulations to Improve Outcomes in Cancer Patients with Severe Sepsis and Septic Shock

Jason D. Goldman, MD

Chair of the Supervisory Committee:
Corey Casper, MD, MPH
Professor, Department of Medicine
Adjunct Professor, Departments of Epidemiology and Global Health

Background: Cancer patients are at high risk for severe sepsis (SS) and septic shock (SSh) and delay to effective antimicrobial therapy (ABx) is strongly associated with increased mortality. Anti-pseudomonal beta-lactam intravenous monotherapy is equally effective and less toxic than combination therapy for uncomplicated neutropenic fever, but combination therapy may be superior for more severe disease.

Methods: We implemented a clinical algorithm to simplify timely and effective empiric ABx and other resuscitative care to cancer outpatients with SS/SSh prior to hospital admission. Triple therapy with meropenem, tobramycin and linezolid or alternatives such as aztreonam for penicillin-allergic patients can be co-administered and provides broad coverage for resistant

organisms typically encountered in this population. A pre-printed order form triggered dispensing of kits containing ABx, fluids and dexamethasone. We performed a retrospective cohort study to assess the impact of this strategy.

Results: From 1/1/08 through 1/31/12, 162 patients met inclusion criteria. Median age was 53 (IQR: 42 – 63) years and 65% were male. The majority of patients (87%) had hematopoietic malignancies. 77 (48%) were hematopoietic stem cell transplant recipients and 80 (49%) were neutropenic. SSh was diagnosed in 25 patients (15%), SS in 46 (28%), sepsis in 72 (44%) alternative diagnosis in 6 (4%) and infection without systemic inflammatory response syndrome in 13 (8%). Median time from clinical encounter to ABx administration was 111 (IQR: 60 – 178) minutes, 93% had blood cultures drawn prior to ABx, 46% received dexamethasone and 99% had crystalloid infusion started before hospital transfer. De-escalation on hospital day 1 occurred in 95% of persons admitted. 44% of 25 persons with SSh received vasopressors. 71 persons (44%) had bacteremia and 18% of 93 isolates were multidrug resistant. Possible nephrotoxicity occurred in 4 patients. 30 day mortality was 6/160 (4%) including 3/71 (4%) with SS/SSh. For each hour delay to administer antibiotics, there was an18% increased risk of developing SSh or death within 30 days (95% CI: 4 – 34%), p=0.01.

Conclusions: A program to simplify choice of aggressive empiric ABx among cancer patients presenting to an ambulatory clinic with suspected sepsis was associated with excellent survival in those with SS/SSh, without excessive adverse events or inappropriately long empiric ABx durations.

TABLE OF CONTENTS

List of Tables and Figures i

1. Background 1

2. Methods 2

2.1 Study Design 2
2.2 Study Setting and Programmatic Intervention 2
2.3 Study Participants 3
2.4 Categorization of Sepsis and Definitions 4
2.5 Data Collection 5
2.6 Statistical Analysis 6

3. Results 8

3.1 Study Participants 8
3.2 Processes of Care 8
3.3 Sepsis Disease Severity, Diagnoses and Mortality 9
3.4 Time to Antibiotics 10
3.5 Adverse Events 11
3.6 Microbiological Outcomes 12

4. Discussion 13

5. Tables and Figures 17

5.1 Table 1 17
5.2 Figure 1 18
5.3 Table 2 19
5.4 Table 3 20
5.5 Table 4 21

6. References 23

7. Appendix: Supplemental Material 25

List of Tables and Figures:

Table 1: Baseline Clinical Characteristics of Sepsis STAT Pack Cohort

Figure 1: Histogram of time from start of clinical encounter to nursing administration of third Sepsis STAT Pack antibiotic.

Table 2: Diagnoses and Outcome by Sepsis Disease Severity.

Table 3: Time to Antibiotics Regression Analysis.

Table 4: Unique bacterial bloodstream isolates, drug susceptibility and intrinsic resistance.

1. Background:

Cancer patients are at high risk for death from severe sepsis (SS) / septic shock (SSh),[1,2] a syndrome of inflammation caused by overwhelming bacterial infection. Mortality is poorly defined in cancer patients with SS/SSh presenting to outpatient care, where most cancer care in the United States is delivered. Empiric antimicrobial therapy (ABx) is prescribed to treat the presumed infection based on limited initial evaluation. Choice of empiric ABx needs to balance the increased toxicity of combination antimicrobial therapy[3] with the known survival benefit of initially effective ABx therapy.[4] Meta-analysis data show no benefit of combination ABx for uncomplicated neutropenic fever,[3] and limited data suggest that combination ABx therapy may be beneficial in more severely ill patients with cancer, namely those with SS/SSh.[5-7] However, severity of the sepsis syndrome is not fully assessed at the time when empiric ABx could be prescribed in the outpatient clinic. Thus, cancer patients presenting with symptoms that may reflect SS/SSh in the outpatient setting need to be treated rapidly and aggressively with ABx and other supportive therapies, even before the diagnosis of SS/SSh is established. The Infectious Disease Society of America (IDSA) guidelines strongly recommend monotherapy for uncomplicated neutropenic fever, but suggest additional ABx "may be added" for more serious infections, a weak recommendation reflecting equipoise in these sparse and conflicting data in cancer patients with SS/SSh.

We reasoned that intervening in the sepsis disease process prior to hospitalization with an aggressive approach initiated in the outpatient setting should reduce overall mortality. At the Seattle Cancer Care Alliance (SCCA) the "Sepsis STAT Pack" (SSP) program was implemented to simplify administration of timely and efficacious initial empiric antimicrobial therapy and expedite other supportive therapies for cancer outpatients with presumed SS/SSh. Triple therapy

with two ABx for treatment of gram negative (GN) and one ABx for gram positive (GP) bacterial infections was systematized to ensure that at least one active agent was initially provided in a population of cancer patients with high prevalence of antibiotic resistant microbes. We aim to determine the mortality experience of this unique cohort of cancer patients treated with the SSP for suspected SS/SSh, test the association of time-to-ABx with mortality or septic shock, ascertain adverse events, and determine what proportion of empiric therapy would have been inactive if a more limited regimen were instead prescribed.

2. Methods:

2.1. Study Design:

We conducted a retrospective cohort study of all cancer outpatients at the Seattle Cancer Care Alliance (SCCA) who received bundled care for the treatment of presumed severe sepsis or septic shock, the "Sepsis STAT Pack" (SSP). The study was approved by the Fred Hutchinson Cancer Research Center (FHCRC) institutional review board with a waiver of informed consent.

2.2. Study Setting and Programmatic Intervention:

The SCCA is affiliated with FHCRC, UW Medicine and Seattle Children's Hospital, which as a consortium, constitute an NCI-designated comprehensive cancer center. Outpatient cancer care is administered primarily at the SCCA outpatient clinic on the FHCRC campus with transfers to the adult inpatient unit at University of Washington Medical Center, located 3.0 miles from the SCCA outpatient clinic. While receiving certain specialized care, such as hematopoietic stem cell transplant (HSCT), patients stay in Seattle, often in SCCA housing, and are managed predominantly in the outpatient setting. The outpatient clinic has a full range of outpatient supportive care services for acutely ill but ambulatory cancer patients who are highly

immunosuppressed, have absolute neutropenia, and/or require intensive therapies such as daily infusions or blood products.

A clinical care algorithm termed the "Sepsis STAT Pack" (SSP) was developed and implemented in January, 2008 to simplify the ordering and administration of broad-spectrum antibiotics and other supportive care for cancer outpatients with presumed SS/SSh. Antibiotics include carbapenem (imipenem or meropenem), aminoglycoside (tobramycin) and oxazolidinone (linezolid) or suitable alternatives including but not limited to monobactam (aztreonam) for penicillin-allergic patients. This broad spectrum regimen includes double coverage for gram-negative bacteria which are frequently multi-drug resistant in this patient population. The antibiotics are "on-the-shelf" ready, prescribed in non-weight based doses, are infusion compatible, and can be co-administered in less than 30 minutes. These ABx were selected specifically for ease of co-administration as other common agents have prolonged infusion times (i.e. vancomycin) or infusion incompatibility with the other typical agents (i.e. gentamicin). A form containing check boxes was developed to facilitate quick ordering of a care bundle including broad-spectrum ABx, intravenous fluids, stress-dose steroids, laboratory tests, blood cultures drawn prior to administration of ABx and cues to the care team to arrange rapid transport for hospital admission.

2.3. Study Participants

We included all adult oncology patients at the SCCA with hematologic or solid malignancies if they were prescribed three classes of antibiotics for the treatment of presumed severe sepsis or septic shock (SS/SSh). Persons were identified by querying a pharmacy database for the following search terms: "imipenem", "meropenem", "tobramycin", "aztreonam", "linezolid" and "vancomycin" prescribed at the SCCA. Charts were reviewed for sequential subjects presenting

during the 4 year time period from January 1st, 2008 through January 31st, 2012 who were dispensed at least two classes of: carbapenem, monobactam, aminoglycoside, oxazolidinone, glycopeptide. Patients were included in the cohort if three antibiotics were administered or a reason was indicated to withhold one or more antibiotics (e.g., acute kidney injury (AKI) as cause to withhold aminoglycoside). Patients were excluded if <18 years of age, or receipt of <3 antibiotic classes without indication of rationale.

2.4. Categorization of Sepsis and Definitions

We used the Surviving Sepsis Campaign criteria to define the spectrum of sepsis disease severity.[8] Briefly, patients were considered to have systemic inflammatory response syndrome (SIRS) if two or more signs of systemic illness were present, sepsis if SIRS and suspected or confirmed infection was present, severe sepsis if sepsis and organ dysfunction or tissue hypoperfusion was present, and septic shock if severe sepsis and persistent hypotension was present despite adequate fluid bolus or need for vasopressor therapy. Given frequent hematologic and other abnormalities due to the underlying malignant condition or related therapies, a conservative approach was adopted to ascribing derangements as caused by the infection which defines the sepsis episode. Modification to the sepsis definitions for hematologic criteria were considered fulfilled only if unequivocally due to the infection defining the septic episode by change from normal on most recent labs and absence of other condition or treatment that could cause the abnormality (see eMethods supplement for detailed definitions). To define sepsis-related hypotension, patients were required to have hypotension temporally related to infection determined on repeated measurements. Confirmed infection included microbiological cultures supporting a consistent clinical syndrome or clinically diagnosed infection. Suspected infection

included any patient initially deemed by the treating clinician to have infection that was not later determined to be due to an alternative cause.

Acute kidney injury was defined as a rise in serum creatinine > 0.5mg/dL from most recent creatinine.[8] Aminoglycoside-related nephrotoxicity was excluded if AKI occurred prior to aminoglycoside and creatinine normalized after the first dose of aminoglycoside; nephrotoxicity was graded as "possible" if concurrent nephrotoxic therapies or sepsis-related hypotension were also present during aminoglycoside dosing which caused AKI and "confirmed" when the aminoglycoside therapy resulted in AKI in the absence of alternative causes. Neutropenia was defined as an absolute neutrophil count (ANC) < 500 cells/μL.[9] To further stratify acute severity of illness, the APACHE II score was calculated on all participants.[10] Bloodstream isolates were summarized as sensitive, drug resistant (DR), multi-drug resistant (MDR) or extensively DR (XDR) according to the European Centre for Disease Prevention and Control (ECDC) definitions,[11] which exclude intrinsic resistance of isolates based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) expert rules in antimicrobial susceptibility testing.[12] The designation of MDR requires non-susceptibility to at least 1 agent in ≥ 3 classes beyond patterns of typical intrinsic resistance. If sensitive to at least one SSP agent administered, the isolate was characterized as susceptible and otherwise was characterized as resistant.

2.5. Data Collection

Data were extracted from electronic data sources at the FHCRC and UW Medicine as well as abstracted by manual chart review (by the thesis author and a research staff member), see eMethods. Assessments of sepsis disease severity criteria were determined by manual chart review. Definitions to distinguish syndromes were then applied to abstracted raw data to check the reviewer assessments with objective criteria.[8] When 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.

2.6. Statistical Analysis

The primary outcomes of 30-day and hospital mortality were ascertained from two independent sources of death data including the Washington Department of Health death certificate data and UW Medicine clinical data repository which includes clinical and administrative data. Patients were assumed to be alive until the last recorded clinical visit in UW Medicine administrative databases and censored on that date. To test if mortality in cancer outpatients with confirmed SS/SSh treated with the SSP care bundle is lower than expected, we compared to mortality of 37.8% in a previously published population of cancer patients with hematologic or solid malignancies hospitalized for SS/SSh in 6 US states[1] by performing a binomial test of one proportion (i.e., H_0: mortality = 37.8 %, H_A: mortality ≠ 37.8%).

Secondary aims included assessing the association of time to antibiotics (ABx) with a combined outcome of SSh or 30-day mortality, assessing the risk of adverse events related to SSP ABx, and assessing the efficacy of the SSP ABx to isolated bloodstream microbes.

To test the association of time to ABx with development of septic shock (SSh) and 30-day mortality, we estimated the relative risk of 1) cumulative 30-day mortality 2) development of or septic shock (SSh) or 3) the combined outcome of cumulative 30-day mortality or development of SSh associated with the each 1 hour delay from first clinical encounter to administration of the 3rd antibiotic. A generalized linear regression model was specified with a Poisson distribution

for the dependent variable with a log-link function. Robust standard error estimates were used to allow for correlated observations within identified clusters. P-values and 95% confidence intervals (CIs) use Wald-based estimates. Multivariate models were constructed to control for pre-specified suspected confounding variables. Possible confounders were assessed in univariate analysis for association at the $p<0.20$ level with the exposure (time-to-ABx) dichotomized at the median, and in a separate univariate analysis with the combined outcome (30-day mortality or SSh). Possible confounders associated with *both* the exposure and the outcome were included in a parsimonious multivariate model and possible confounders associated with *either* the exposure or the outcome were included in a maximally adjusted model.

To determine efficacy of the SSP ABx, actual antimicrobial susceptibility was compared to a counterfactual scenario where isolated bloodstream bacteria were re-categorized as susceptible or resistant as if ABx were administered per the IDSA guidelines for neutropenic fever.[9] In this counterfactual scenario, combination antimicrobial therapy with glycopeptide (vancomycin) added to intravenous antipseudomonal beta lactam (piperacillin/tazobactam) would be given for hemodynamic instability, pneumonia or skin/soft tissue structure infections and piperacillin/tazobactam for all others in the Sepsis STAT Pack cohort who do not meet these criteria. The proportions of resistant microbes to the observed (SSP) and counterfactual (IDSA) scenarios were compared with the McNemar's test for correlated proportions with the bacterial isolate as the unit of comparison.

Summary data are presented as numbers and percentages, means with standard deviations (SD), medians and interquartile ranges (IQR), or proportions and 95% confidence intervals (CI). Accordingly, χ^2 tests for equal proportion, t-tests, or rank sum tests (Wilcoxon or Kruskal-Walis)

were used to test univariate associations for the multivariate model. Data analysis was performed in Stata v13.1.

3. Results:

3.1. Study Participants

During the study time period, at least 2 classes of antibiotics were prescribed and dispensed to 177 persons and of these, 15 patients were excluded from the cohort. Reasons for exclusion included <18 years old (5 patients), <3 antibiotic classes administered due to no presumed SS/SSh or without indication of rationale (9 patients), and transfer to Seattle Children's Hospital with no hospital chart available (1 adult patient). Of 162 included patients, 156 received 3 classes of antibiotics and 6 had a suitable reason indicated to withhold 1 antibiotic. The median (IQR) age of included persons was 55 (42 – 63), 106 (65%) were male and 127 (78%) were Caucasian, 8 (5%) Black, 8 (5%) Asian, 6 (4%) Hispanic, 4 (3%) other, and 9 not reported. Hematologic malignancies of leukemia, lymphoma and multiple myeloma accounted for the underlying oncologic diagnosis in 141 (87%), 80 (49%) were neutropenic, and 77 (48%) had received prior hematopoietic stem cell transplant (HSCT). At the time of SSP administration, 45 (28%) of persons were on immunosuppressive therapy and prophylactic antibiotics were prescribed in 105 (65%) (Table 1). Of the 77 HSCT patients, 38 were on immunosuppressive therapy, and 21 were < 14 days from HSCT, 8 were 14 – 28 days from HSCT, 27 were 29 – 100 days from HSCT and 21 were > 100 days from HSCT.

3.2. Processes of Care

Patients given the SSP ABx were also given other bundled resuscitative care and had a stereotypic movement through the clinic towards hospitalization (eTable 1). Primary antipseudomonal beta lactam ABx included imipenem in 107 (66%), meropenem 27 (17%),

aztreonam 24 (15%), ceftazidime 4 (2%); second GN coverage was tobramycin in 153 (94%), gentamycin 2 (1%), levofloxacin 1 (1%), and second agent held in 6 (3 for AKI, 1 for baseline hearing loss, 1 for pediatric protocol and 1 for allergy). GP coverage included linezolid in 154 (95%), vancomycin 6 (4%) and daptomycin 1 (1%). Dexamethasone was administered to 74 (46%) and crystalloid intravenous fluids (IVF) were started in clinic in 135/137 (99%) of patients for whom IVF status was known. All persons had blood cultures (BCx) drawn on the same day of SSP administration and 148/160 (93%, CI: 87 – 96%) had BCx drawn before administration of ABx, with median (IQR) time before ABx of 40 (15 – 81) minutes. Receipt of antibiotics within 1 hour occurred for 41 (26%), within 2 hours for 88 (55%), within 3 hours in 123 (77%), within 4 hours in 143 (89%), and >4 hours in 17 (11%) (Figure 1). 155 patients who received 3 SSP ABx were directly admitted to the hospital with median time from first encounter to hospital admission of 260 (IQR: 188 – 385) minutes. Of the 6 patients not directly admitted, 2 were not septic and were managed as outpatients and 4 returned for admission within the following days, 3 of which had SS/SSh upon presentation for this second encounter. For admitted patients, hospital teams empirically de-escalated ABx to a 1 or 2 drug regimen (usually dropping tobramycin) in 146/157 patients (93%, CI: 88 – 96%) on hospital day 1, prior to availability of culture results.

3.3. Sepsis Disease Severity, Diagnoses and Mortality

Of the patients administered the SSP ABx, 13 (8%) did not meet SIRS criteria, 6 (4%) met SIRS criteria or sustained organ dysfunction but were ultimately determined to have an alternative diagnosis, 72 (44%) had sepsis, 46 (29%) had severe sepsis and 25 (15%) had septic shock (Table 2). Vasopressors were used in 11 (44%) of those with SSh. The mean (SD) APACHE II score for patients without SS was 16 (4), SS was 17 (4) and SSh was 23 (8). Patients

with more severe disease along the spectrum of sepsis also received increasing 6- and 24-hour volumes of crystalloid infusion (eFigures 1-2 and eTable 2). All patients with confirmed SS/SSh had had least one organ system with dysfunction, and 22 patients with sepsis only had arterial hypotension that was not considered sufficient criteria for sepsis-related hypotension (eMethods, eTable 2). Bacteremia occurred in 71 patients (44%), other clinically or microbiologically diagnosed infections occurred in 33 patients without bacteremia, and culture-negative sepsis occurred in 48 (30%) persons (eTable 3).

Mortality was rare and only 1 person died during the hospitalization. Thirty day mortality occurred in 6 of 160 (3.8%) persons whose outcome could be measured to 30 days, 2 who had severe sepsis and 1 who had septic shock for 4.2% mortality in patients with SS/SSh. Based on a two-sided test of one proportion, we reject the null hypothesis that mortality is equal to the historical level of 37.8%[1] in favor of a lower mortality in the SSP cohort ($p<0.001$).

3.4. Time to Antibiotics

We modeled the association between time to antibiotics and each of three outcomes: 30-day mortality, development of septic shock (SSh) and the combination of 30-day mortality or SSh using a Poisson regression model. 30-day mortality was not associated with time to antibiotics ($p=0.35$). For each additional hour delay to administer antibiotics from the start of the clinical encounter, there was a 19% increased risk of developing SSh (95% CI: 3 – 39%), $p=0.02$ and an 18% increased risk of developing SSh or death within 30 days (95% CI: 4 – 34%), $p=0.01$. A parsimonious model adjusting for variables associated with *both* the time to antibiotics and the combined outcome (eTables 4 & 5) or a maximally adjusted model of all variables associated with *either* time to antibiotics or the combined outcome did not appreciably change the results (Table 3).

3.5. Adverse Events

Few adverse events could be specifically attributed to the Sepsis STAT Pack antibiotics due to multiple concurrent therapies and underlying disease. Of primary concern is the risk for nephrotoxicity due to tobramycin in a population of patients with potential for AKI due to sepsis-related hypotension and other potentially nephrotoxic concurrent therapies such as calcineurin inhibitors. In total, 7 patients had possible nephrotoxicity. Fifteen patients presented with AKI or developed AKI within the first 24 hours of hospitalization, 5 of these patients with AKI had possible nephrotoxicity. In the 10 patients presenting with AKI who did not have nephrotoxicity, AKI was diagnosed prior to tobramycin dosing and creatinine normalized following tobramycin (or tobramycin was withheld). In the 5 patients presenting with AKI who had continued rise in creatinine after tobramycin, kidney injury specifically due to tobramycin could not be determined due to concurrent sepsis-related hypotension. A further 2 patients developed rising creatinine indicating possible nephrotoxicity subsequently during hospitalization (after the first 24 hours). One of these patients had received 1 dose of tobramycin and 2 doses of gentamicin and was also on concurrent trimethoprim-sulfamethoxazole therapy; the other patient had 7 doses of tobramycin over the first 3 days of hospitalization with concurrent calcineurin inhibitor therapy with elevated serum tacrolimus level to 25ng/mL. Rash was thought due to SSP ABx in 6 cases and possibly due to SSP ABx in another 10 cases; these latter cases had alternative causes such as other ABx, cancer therapies or GVHD. Other possible reactions included itching with tobramycin, possible thrombocytopenia related to a single dose of linezolid, Red Man syndrome related to vancomycin. All cases of nephrotoxicity and rash resolved. There were no cases of ototoxicity, serious rashes (Steven Johnson syndrome or toxic epidermal necrolysis) or serotonin syndrome.

3.6. Microbiological Outcomes

Seventy one (44%, CI: 36 – 52%) of 162 patients had positive BCx (Table 4). Monomicrobial bacteremia occurred in 56 persons and polymicrobial bacteremia occurred in 15 persons with 37 additional isolates for a total of 93 unique isolates from 71 persons. Many highly pathogenic microbial isolates with significant intrinsic drug resistance caused sepsis syndromes including Pseudomonas aeruginosa (9 isolates), Acinetobacter baumanii (2), Enterobacter spp. (11) and Stenotrophomonas maltophilia (3). None of the bloodstream isolates were considered to be contaminants: of patients with coagulase-negative Staphylococcus (CoNS), all had high-grade bacteremias (in > 1 bottle), a central venous catheter associated skin infection, or evidence of sepsis. In patients with bacteremia who were not septic, 3 had GNRs and 3 had CoNS with clinically diagnosed central venous catheter infection. Isolates were graded according to the ECDC classification of drug resistance[11] which grades multi-drug resistance as non-susceptibility to at least 1 agent in ≥ 3 classes beyond patterns of typical intrinsic resistance (see EUCAST expert rules[12]). Of the 93 isolates, there were 20 DR, 1 possible MDR, 12 MDR, and 4 possible XDR isolates beyond what is predicted by intrinsic resistance.[11,12] The isolated bacteria and drug resistant patterns are given in Table 4.

Ninety (96.8%, CI: 90.9 – 99.3%) of 93 isolated microbes were susceptible to at least one Sepsis STAT Pack antibiotics administered (the "observed" scenario). The 3 resistant isolates were all Stenotrophomonas maltophilia. In a "counterfactual" (alternative scenario) analysis, microbiologic bloodstream isolates were reclassified as if the IDSA guidelines were followed using combination antimicrobial therapy with glycopeptide (vancomycin) added to intravenous antipseudomonal beta lactam (piperacillin/tazobactam) for hemodynamic instability, pneumonia or skin/soft tissue structure infections and intravenous monotherapy with antipseudomonal beta

lactam (piperacillin/tazobactam) for all others in the Sepsis STAT Pack cohort who do not meet these criteria. 76/92 (82.6%) isolated microbes would have been susceptible to ABx given under counterfactual scenario following the IDSA guidelines. Under the observed and competing scenarios, concordant pairs included 3 isolates which were resistant to both ABx regimens and 76 isolates which were sensitive to both regimens, leaving 13 isolates (14.1%) in 12 patients with discordant susceptibility in the competing scenarios, all 13 of which were susceptible to the observed SSP ABx administered and resistant to the IDSA scenario (p=0.0002).

4. Discussion:

Cancer patients are at high risk of death from SS/SSh,[1] especially those with disease-related or iatrogenic immunosuppression.[2] Delay to effective ABx is strongly associated with mortality,[4,13,14] and high prevalence of microbial resistance exists in populations of heavily ABx treated cancer patients.[15] This study assesses a novel care bundle comprising three antibiotics (meropenem, tobramycin and linezolid) and other supportive treatments that can be rapidly and simultaneously administered in an outpatient care setting en route to more definitive inpatient care. Of note, other possible substitutes for these ABx can introduce delays as vancomycin typically takes 2 hours to infuse and gentamicin is not compatible for simultaneous administration with many other agents. Bundled care for SS/SSh has been shown to improve outcomes in multiple settings,[16-18] but cancer outpatients have not been the focus of prior studies. The uniquely identified population of high-risk cancer outpatients with presumed SS/SSh was treated with this novel care bundle (the "Sepsis STAT Pack") and those with confirmed SS/SSh realized excellent survival compared to the best previously reported mortality data from comparable populations. Since there is no contemporaneous comparison group of outpatient

cancer patients, it cannot be known for certain what the cohort would have experienced in the absence of SSP program.

Epidemiology of SS/SSh in cancer patients has largely been confined to studies of hospitalized patients and usually by identifying patients treated in the intensive care unit.[19] ICU, hospital or 30-day mortality in these studies ranges from 34 – 69%[1,2,14,20-22] (eTable 6). Compared against these data, the mortality we observed in the subset of cohort patients with SS/SSh treated with the Sepsis STAT Pack of 4.2% is considerably lower. While sepsis-related mortality is decreasing in cancer[14,22] and non-cancer patients[23], we think the excellent survival experience in the SSP cohort is unlikely to be due only to secular trends in management of critically ill patients with SS/SSh. Further, though patients were identified in the outpatient setting, they all required hospitalization acutely and the few who did not receive rapid transport to the hospital had poor outcomes. Very conservative definitions of SS and SSh were applied to carefully extracted clinical data (eMethods) making it unlikely that these patients had less severe disease compared to prior studies[1,2,14,20-22] (especially Williams et al,[1] mortality = 37.8%).

Rather, we ascribe the low mortality seen in this cohort to the standardization of timely and effective antimicrobial therapy and other supportive care through the SSP bundle. These interventions were delivered very proximal in the disease course prior to the development of multisystem organ failure which is characteristic of SS/SSh left untreated. Indeed, each hour delay in ABx within the SSP cohort was associated with a statistically significant higher risk of developing SSh or 30-day mortality. While only a quarter of patients in this cohort were treated with ABx within one hour (as recommended by guidelines[8,24]), two thirds received effective ABx within 3 hours, leaving room for further quality improvement. The high prevalence of intrinsically drug-resistant and MDR bacterial isolates underscores the need for broad effective

coverage: the sensitivity analysis showed that 14% of isolates responsible for bacteremia would not be covered by an approach recommended by the IDSA guidelines.

Appropriate empiric ABx for cancer patients with SS/SSh is controversial. Meta-analyses in cancer patients with neutropenic fever[3] and non-cancer patients with sepsis[25] found no mortality difference between beta-lactam monotherapy vs. beta-lactam plus aminoglycoside combination therapy. However, nephrotoxicity was more common with combination therapy.[3] Sparse evidence suggests a mortality benefit to combination therapy in the most severely ill non-cancer patients with SS/SSh.[5-7] These data lend further evidence that combination therapy is beneficial in the most severely ill cancer patients with SS/SSh, especially in settings of high prevalence of microbial drug resistance. We did not find evidence for excessive nephrotoxicity with a short course of tobramycin, an observation supported by recent retrospective studies[22,26] and an animal model[27]. We also carefully looked at the inappropriate use of broad antibiotics and found that except in a few cases where SIRS criteria were not met, the resource was not overused, and hospital-based teams promptly de-escalated therapy based on clinical response, even prior to maturity of microbiologic cultures.

The main limitation of this study is the lack of randomization and lack of contemporaneous control group as discussed above. While we enrolled sequential patients receiving the SSP care bundle, it is possible that potentially eligible patients who had SS/SSh did not receive the intervention and were hence not included in the cohort. While the SSP care bundle was rolled out clinic-wide, patients could have missed receiving the intervention due to incomplete penetrance of the educational program, failure of clinicians to recognize SS/SSh or subjective patient factors not easy to ascertain in a retrospective study.

Our results suggest that a short course of empiric very broad coverage ABx and other resuscitative care initiated in the outpatient setting is beneficial for survival in cancer patients with SS/SSh. These data extend what we know about need for timely ABx to the outpatient setting, and multicenter trials should study a comparable approach in other clinic-based practices of immunocompromised patients such as cancer outpatients, solid organ transplant recipients or patients receiving disease-modifying anti-rheumatic agents or other iatrogenic immunosuppressive therapy.

5. Tables and Figures:

Table 1: Baseline Clinical Characteristics of Sepsis STAT Pack Cohort.

Clinical Characteristics	N (%):*
Oncologic Diagnosis:	
- **Leukemia**	- 67 (41.4%)
- **Lymphoma**	- 48 (29.6%)
- **Multiple Myeloma**	- 26 (16.0%)
- **Myelodysplastic Syndrome**	- 11 (6.8%)
- **Solid Tumors**	- 6 (3.7%)
- **Other ****	- 4 (2.5%)
Received HSCT:	77 (47.5%)
- **Allogeneic**	- 50 (64.9%)
- **Autologous**	- 27 (35.1%)
Neutropenia:	80 (49.4%)
Immunosuppressive Therapy: †	45 (27.8%)
- **Tacrolimus**	- 21 (46.7%)
- **MMF**	- 18 (40.0%)
- **Cyclosporin**	- 18 (40.0%)
- **Sirolimus**	- 2 (4.4%)
- **Predisone (≥ 20mg daily)**	- 16 (35.6%)
Prophylactic Antibiotics:	105 (64.8%)
- **Levofloxacin**	- 45 (41.9%)
- **TMP-SMX**	- 39 (37.1%)
- **Dapsone**	- 9 (8.6%)
- **Other ††**	- 34 (32.4%)

Abbreviations: HSCT: hematopoietic stem cell transplant; MMF: Mycophenolate mofetil; TMP-SMX: trimethoprim-sulfamethoxazole.
* Data given as: N (%) and data available on all 162 participants. Sub-categories are not mutually exclusive for Immunosuppressives and Antibiotics.
** Oncologic Diagnosis: "Other" includes Aplastic Anemia (2), Lymphoproliferative Disease, NOS (1), and Hemophagocytic Lymphohistiocytosis (HLH, 1).
† Immunosuppressive therapy in persons without HSCT: HLH on cyclosporine (1), Post-transplant lymphoproliferative disease on tacrolimus (1), Lymphoproliferative disease NOS on tacrolimus and MMF (1), and predisone ≥ 20mg daily for reasons of asthma (1), rash (1) and unknown (2).
†† Patients on other antibiotics for prophylaxis or treatment of prior infection.

Figure 1: Histogram of time from start of clinical encounter to nursing administration of the third Sepsis STAT Pack antibiotic.

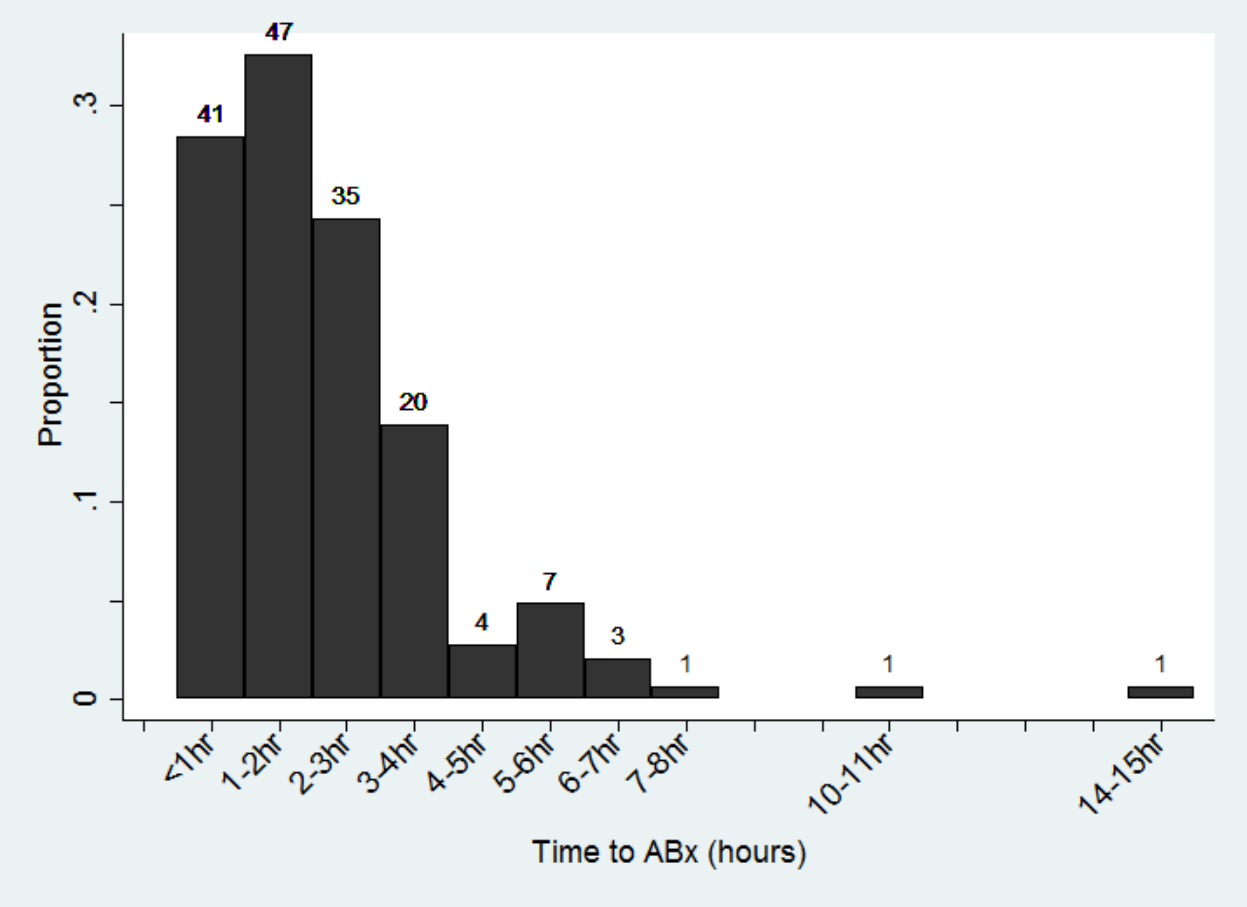


Table 2: Diagnoses and Outcome by Sepsis Disease Severity.

Disease Category	Patients, N (%) *	Neutropenia, n (%)	Diagnosis, n (%): **		30-day mortality, n (%) [missing]
No SIRS	13 (8.0)	7 (53.9)	Bacteremia:	6 (46.2)	0 (0)
			Other Infection:	3 (23.1)	[0]
			Suspected Infection:	3 (23.1)	
			Alternative Dx:	1 (7.7)	
SIRS only	6 (3.7)	2 (33.3)	Alternative Dx:	6 (100)	0 (0)
					[1]
Sepsis	72 (43.8)	40 (56.3)	Bacteremia:	24 (33.3)	3 (4.2)
			Other Infection:	19 (25.4)	[1]
			Cx Neg Sepsis:	29 (40.8)	
Severe Sepsis	46 (29.0)	19 (41.3)	Bacteremia:	29 (63.0)	2 (4.3)
			Other Infection:	4 (10.4)	[0]
			Cx Neg Sepsis:	13 (29.2)	
Septic Shock	25 (15.4)	12 (48.0)	Bacteremia:	12 (48.0)	1 (4.0)
			Other Infection:	7 (29.2)	[0]
			Cx Neg Sepsis:	6 (20.8)	
Total:	162 (100)	80 (49.4)	Bacteremia:	71 (43.8)	6 (3.8)
			Other Infection:	33 (20.4)	[2]
			Cx Neg Sepsis:	48 (29.6)	
			Suspected Infection:	3 (1.9)	
			Alternative Dx:	7 (4.3)	

Abbreviations: SIRS: systemic inflammatory response syndrome, Dx = diagnosis, CxNS = culture-negative sepsis.
* Percent over all patients (columns). Other proportions in table over disease category (rows).
** Diagnosis categorization is mutually exclusive. When bacteremia and source are both known, patient is characterized only as bacteremia.

Table 3: Time to Antibiotics Regression Analysis. Unadjusted and adjusted relative risk for each successive hour delay in time to receipt of 3rd antibiotic for developing the outcomes of 30-day mortality, septic shock (SSh), or the combined outcome of either 30-day mortality or SSh among cancer outpatients treated with the Sepsis STAT Pack.

Model adjustment * - Outcomes:	**Relative Risk (95% CI):**	**P-value:**
Unadjusted:		
- **30-day Mortality**	1.10 (0.90 – 1.36)	0.35
- **Septic Shock**	1.19 (1.03 – 1.39)	0.02
- **Either SSh or 30-day Mortality**	1.18 (1.04 – 1.34)	0.01
Adjusted for hematologic malignancy and race: †		
- **30-day Mortality**	1.09 (0.88 – 1.35)	0.45
- **Septic Shock**	1.18 (1.01 – 1.38)	0.04
- **Either SSh or 30-day Mortality**	1.16 (1.02 – 1.33)	0.03
Adjusted for sex, race, hematologic malignancy, history of HSCT, receipt of dexamethasone: ††		
- **30-day Mortality**	1.02 (0.85 – 1.23)	0.83
- **Septic Shock**	1.18 (1.01 – 1.38)	0.03
- **Either SSh or 30-day Mortality**	1.16 (1.02 – 1.32)	0.02

Abbreviations: CI: confidence interval; SSh: septic shock; HSCT: hematopoietic stem cell transplant;

* All models have the same number of 13 patients excluded if any variables are missing from the maximally adjusted model, i.e. time to antibiotics (n=2), survival to 30-days confirmed (n=2), race (n=9).

† Parsimonious multivariate model is adjusted for covariates associated with *both* the exposure (time to antibiotics) *and* the combined outcome (SSh or cumulative 30-day mortality).

†† Maximally adjusted model is adjusted for covariates associated with *either* the exposure (time to antibiotics) *or* the combined outcome (septic shock or cumulative 30-day mortality.

Table 4: Unique bacterial bloodstream isolates, drug susceptibility, and intrinsic resistance.

Name:	Num:	Isolate Drug Resistance:*	Intrinsic Resistance:*
Gram Negative Bacteria:			
Achromobacter xylosoxidans	1	1 MDR	AG, aPCN, 1,2-Ceph, Erta
Acinetobacter baumanii	2	1 DR	aPCN, 1,2-Ceph, Erta, Fos, TMP[28]
Acinetobacter junii	1		
Acinetobacter ursingii	8	3 DR	[29]
Aeromonas caviae	1		
Citrobacter freundii	1	1 DR	aPCN, aPCN+βLI, 1,2-Ceph
Delftia acidovorans	1	1 DR	
Enterobacter aerogenes	1		aPCN, aPCN+βLI, 1,2-Ceph
Enterobacter asburiae	1		aPCN, aPCN+βLI, 1,2-Ceph
Enterobacter cloacae	9	3 MDR, 1 MDR/XDR	aPCN, aPCN+βLI, 1,2-Ceph
Escherichia coli	8	1 DR, 3 MDR, 2 MDR/XDR	
Klebsiella oxytoca	4		aPCN
Klebsiella pneumonia	4	1 DR, 1 MDR/XDR	aPCN
Leptotrichia spp.	1		
Pantoea spp.	3	2 DR	[30]
Proteus mirabilis	1		
Pseudomonas aeruginosa	9	4 DR, 1 MDR	aPCN, aPCN+βLI, 1,2,3-Ceph, Erta, Phen, Tetra, TMP
Rhizobium radiobacter	1	1 MDR	
Serratia marcescens	3		aPCN, aPCN+βLI, 1,2-Ceph
Stenotrphomonas maltophilia	3	2 DR	AG, aPCN, aPCN+βLI, PsA-PCN+βLI, Ceph, Carba, Fos[31]
Gram Positive Bacteria:			
Clostridium perfringens	1		
Enterococcus faecalis	2	1 DR	Streptogramin
Enterococcus faecium	2	1 DR/MDR, 1 MDR	Carba
Rothia mucilaginosa	4	1 DR	AG, Erythro, Fos[32,33]
Staphylococcus aureus	2	1 MDR	Ceftaz
Staphalococcus, coag neg	13	1 DR, 1 MDR	Ceftaz, Fos
Streptococcus agalactiae	1		
Streptococcus bovis	1		
Streptococcus, viridans	3	1 DR	
GP cocci, NOS	1		
Unique Isolates:	93	37	

Abbreviations: AG: aminoglycosides; aPCN: amino-penicillins; βLI: beta lactamase inhibitor; Carba: carbapenem; 1,2-ceph: 1st and 2nd generation cephalosporins; Ceftaz: ceftazidime; Erta: ertapenem; Erythro: erythromycin; Fos: fosphomycin; Phen: phenicols; PsA: anti-pseudomonal; Tetra: tetracyclines; TMP: trimethoprim; DR: drug resistant; MDR: multidrug resistant; XDR: extensively drug resistant.
* Intrinsic resistance and drug resistance definitions are determined from the EUCAST expert rules on antimicrobial susceptibility testing[12] and/or the ECDC consensus on drug resistance.[11] Additional references provided as needed when microbe not sufficiently addressed in EUCAST and ECDC. 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.[11]

References:

1. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Critical care.* Oct 2004;8(5):R291-298.
2. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 1 2013;31(22):2810-2818.
3. Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *The Cochrane database of systematic reviews.* 2013;6:CD003038.
4. Lin MY, Weinstein RA, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: impact of severe neutropenia. *Antimicrobial agents and chemotherapy.* Sep 2008;52(9):3188-3194.
5. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. *Critical care medicine.* Aug 2010;38(8):1651-1664.
6. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Critical care medicine.* Sep 2010;38(9):1773-1785.
7. Diaz-Martin A, Martinez-Gonzalez ML, Ferrer R, et al. Antibiotic prescription patterns in the empiric therapy of severe sepsis: combination of antimicrobials with different mechanisms of action reduces mortality. *Critical care.* 2012;16(6):R223.
8. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical care medicine.* Feb 2013;41(2):580-637.
9. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* Feb 15 2011;52(4):427-431.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical care medicine.* Oct 1985;13(10):818-829.
11. 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. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Mar 2012;18(3):268-281.
12. Leclercq R, Cantón R, Brown DF, et al. EUCAST expert rules in antimicrobial susceptibility testing. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* Feb 2013;19(2):141-160.
13. Elting LS, Rubenstein EB, Rolston KV, Bodey GP. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis.* Aug 1997;25(2):247-259.
14. 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. *Critical care medicine.* Mar 2008;36(3):690-696.
15. Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. *Clin Infect Dis.* Nov 15 2014;59 Suppl 5:S335-339.
16. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Critical care medicine.* Apr 2007;35(4):1105-1112.

17. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Critical care medicine.* Aug 2014;42(8):1749-1755.
18. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. *Critical care medicine.* Feb 2010;38(2):668-678.
19. Cohen J, Vincent JL, Adhikari NK, et al. Sepsis: a roadmap for future research. *The Lancet. Infectious diseases.* May 2015;15(5):581-614.
20. Mokart D, Saillard C, Sannini A, et al. Neutropenic cancer patients with severe sepsis: need for antibiotics in the first hour. *Intensive care medicine.* Aug 2014;40(8):1173-1174.
21. Larche J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. *Intensive care medicine.* Oct 2003;29(10):1688-1695.
22. Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Critical care medicine.* Jan 2012;40(1):43-49.
23. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA : the journal of the American Medical Association.* Apr 2 2014;311(13):1308-1316.
24. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 20 2013;31(6):794-810.
25. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *The Cochrane database of systematic reviews.* 2006(1):CD003344.
26. Picard W, Bazin F, Clouzeau B, et al. Propensity-based study of aminoglycoside nephrotoxicity in patients with severe sepsis or septic shock. *Antimicrobial agents and chemotherapy.* Dec 2014;58(12):7468-7474.
27. Lipcsey M, Carlsson M, Larsson A, et al. Effect of a single dose of tobramycin on systemic inflammatory response-induced acute kidney injury in a 6-hour porcine model. *Critical care medicine.* Oct 2009;37(10):2782-2790.
28. Fishbain J, Peleg AY. Treatment of Acinetobacter infections. *Clin Infect Dis.* Jul 1 2010;51(1):79-84.
29. van den Broek PJ, van der Reijden TJ, van Strijen E, Helmig-Schurter AV, Bernards AT, Dijkshoorn L. Endemic and epidemic acinetobacter species in a university hospital: an 8-year survey. *J Clin Microbiol.* Nov 2009;47(11):3593-3599.
30. Mardaneh J, Dallal MM. Isolation, identification and antimicrobial susceptibility of Pantoea (Enterobacter) agglomerans isolated from consumed powdered infant formula milk (PIF) in NICU ward: First report from Iran. *Iranian journal of microbiology.* Sep 2013;5(3):263-267.
31. Safdar A, Rolston KV. Stenotrophomonas maltophilia: changing spectrum of a serious bacterial pathogen in patients with cancer. *Clin Infect Dis.* Dec 15 2007;45(12):1602-1609.
32. Ramanan P, Barreto JN, Osmon DR, Tosh PK. Rothia bacteremia: a 10-year experience at Mayo Clinic, Rochester, Minnesota. *J Clin Microbiol.* Sep 2014;52(9):3184-3189.
33. von Eiff C, Herrmann M, Peters G. Antimicrobial susceptibilities of Stomatococcus mucilaginosus and of Micrococcus spp. *Antimicrobial agents and chemotherapy.* Jan 1995;39(1):268-270.

Appendix: Supplementary Online Content

eMethods: Sepsis Definitions, as per the Surviving Sepsis Campaign (SSC) guidelines,[1] and APACHE II score,[2] with modifications noted.

eMethods: List (and source) of raw data.

eMethods: List of variables (and source) of raw data.

eTable 1: Clinic time flow in recipients of the Sepsis STAT Pack.

eFigure 1: APACHE II score by Sepsis Severity for Sepsis STAT Pack cohort.

eFigure 2: Intravenous Fluids administered in 6 and 24 hours by Sepsis Severity for Sepsis STAT Pack cohort.

eTable 2: Metrics of Sepsis Disease Severity for Sepsis STAT Pack cohort.

eTable 3: Clinically or microbiologically diagnosed infections and alternative diagnoses for Sepsis STAT Pack cohort.

eTable 4: Univariate association of selected characteristics with Time-to-Antibiotics among cancer outpatients with presumed SS/SSh.

eTable 5: Univariate association of selected characteristics with combined outcome of Septic Shock or 30 Day Cumulative Mortality among cancer outpatients with presumed SS/SSh.

eTable 6: Previously published mortality data for cancer patients with Severe Sepsis / Septic Shock.

Supplemental References

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Sepsis Definitions, as per the Surviving Sepsis Campaign (SSC) guidelines,[1] and APACHE II score,[2] with modifications noted.

Systemic inflammatory response syndrome (SIRS) criteria: meeting ≥ 2 of:

- Body temperature > 38.3°C or < 36.0°C
- Heart rate > 90 beats/minute
- Respiratory rate > 20/minute or PaCO2 lower than 32 mmHg (4.3 kPa)
- White blood cell count > 12,000 cells/μL or < 4,000 cells/μL or immature granulocytes > 10%
- Altered mental status (GCS<15 or objective assessment by clinician)

* Note: Vital sign and lab abnormalities were assessed 24 hours before and after dispensing of the Sepsis STAT Pack antibiotics. Due to frequency of abnormalities to white blood cell counts in cancer patients, 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 labs and absence of other condition or treatment which could cause the abnormality in white blood cell 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:

- 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. Since 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 later by better alternative diagnosis. If better alternative diagnosis was made in hindsight (e.g. 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 (SBP < 90 mm Hg or MAP < 70 mm Hg)
- Arterial hypoxemia (PaO_2/FiO_2 < 300)
- Acute oliguria (urine output < 0.5 mL/kg/hr for ≥ 2 hours despite adequate IVFs)
- Acute kidney injury (Cr increase > 0.5 mg/dL)
- Coagulation abnormalities (INR > 1.5, aPTT > 60s or platelets < 100k/μL)

- Ileus (absent bowel sounds on clinical exam 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 exam

* Note: Patients were considered to have arterial hypotension only if the systolic blood pressure (SBP) or mean arterial blood pressure (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 (i.e. low baseline blood pressure, hypotension only while sleeping) did not meet criteria for severe sepsis. Since few patients had arterial blood gas measurement, an 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 normal on most recent labs and absence of other condition or treatment which 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 as 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: meeting criteria for Severe Sepsis and ≥ 1 of:
- Refractory hypotension
- Vasopressor agents used to support blood pressure

* Note: Refractory hypotension defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation (≥ 20 cc/kg crystalloid infusion[3,4]). Vasopressors considered included norepinephrine, epinephrine, vasopressin, dopamine, dobutamine or phenylephrine.

APACHE II score: The following variables from a 48 hour window centered on the dispensing of the SSP ABx were extracted from the UW Medicine clinical data repository (Amalga). The highest and lowest values were assigned points and the highest points for each variable totaled for the Acute Physiology Score (APS) as per the initial report.[2]
- Body temperature (^{o}C)
- Mean arterial pressure (mm Hg)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)
- Oxygenation: $AaDO_2$ if $FiO_2 > 0.5$ or PaO_2 if $FiO_2 < 0.5$ (mm Hg)
- Arterial pH, or serum HCO_3^- (mmol/L) if no arterial blood gas measurement
- Serum sodium (mmol/L)

- Serum potassium (mmol/L)
- Serum creatinine (mg/dL)
- Hematocrit (%)
- White blood cell count (x 1000 cells/μL)
- Glascow Coma Score (points)

* Note: Points for serum creatinine were doubled for acute kidney injury as per the initial APACHE II report,[2,5] with acute kidney injury defined as rise 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).

eMethods: 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 (EMR)
  - Time and location of first clinical encounter (EMR)
  - Time of first lab and blood culture draw (EMR)
  - Time of antibiotic dispensing by pharmacy (PharmNet)
  - Time of antibiotic administration by nurse (EMR)
  - Date of death (WA DOH, Amalga & 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 & 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)

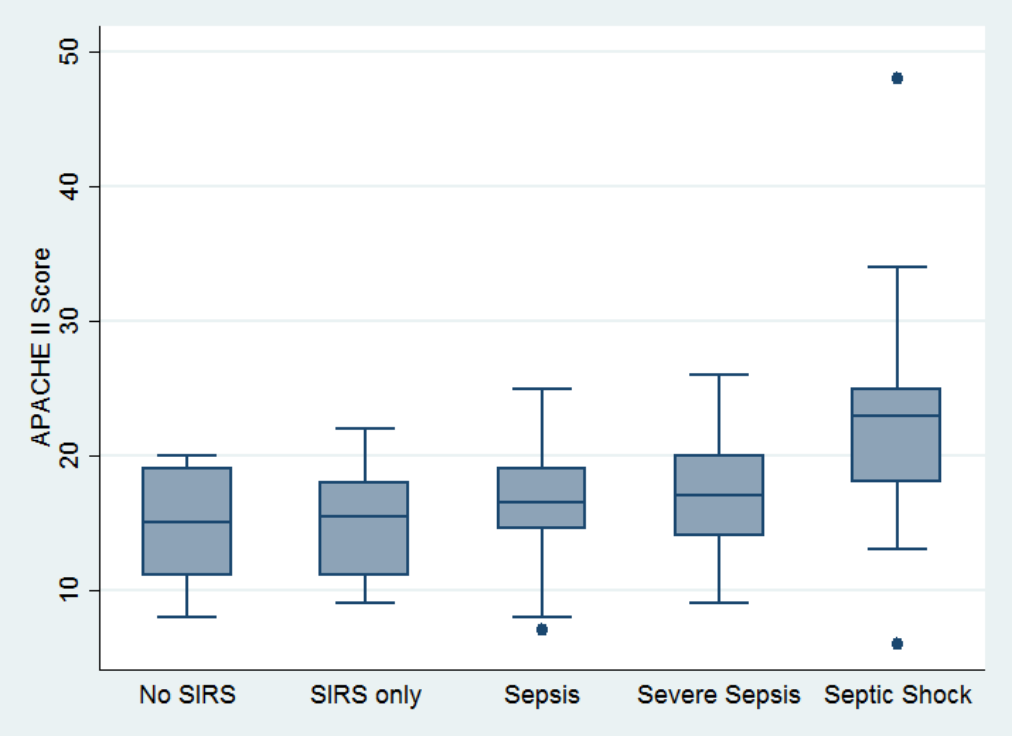
    - Receipt of SCCA clinic antibiotics (EMR)
    - Receipt of UWMC hospital antibiotics (EMR)
    - Receipt of dexamethasone in SCCA (PharmNet)
    - Receipt of vasopressors (Amalga & EMR)
    - Receipt of anticoagulants (EMR)
- Vital Signs (VS) & Laboratory Data:
    - All APACHE II variables for APS as above (Amalga)
    - Clinician note documented VS 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: FHCRC Infectious Disease HSCT database; PharmNet- UW Medicine pharmacy informatics system; EMR- Citrix electronic medical record; WA DOH: Washington Department of Health death data.

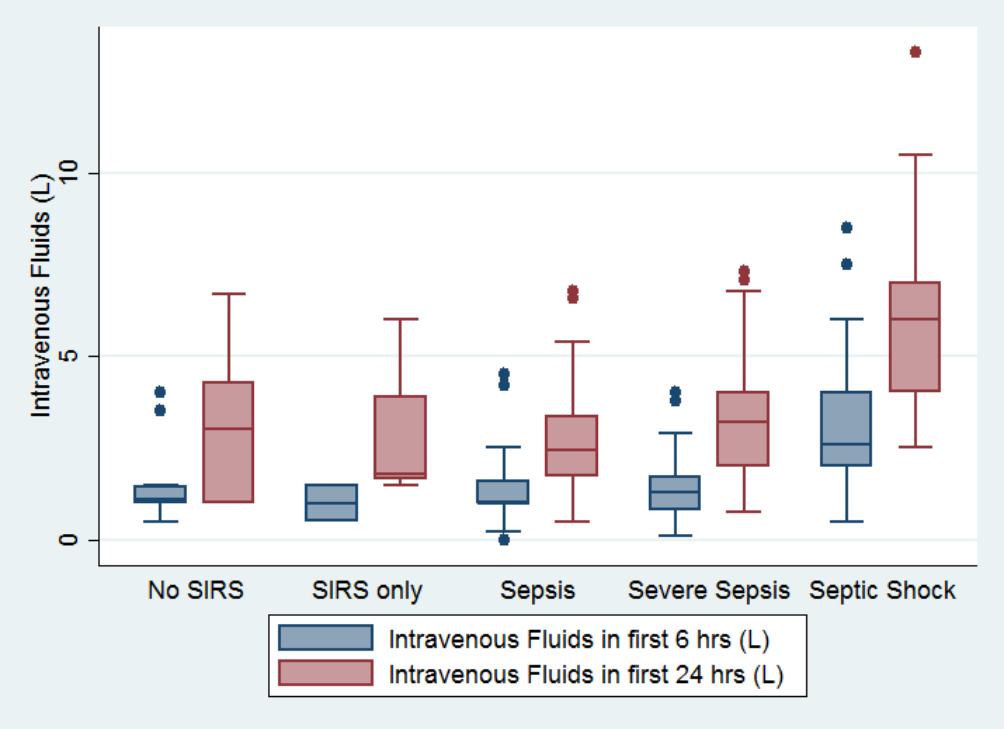
eTable 1: Clinic time flow in recipients of the Sepsis STAT Pack.

Time Elapsed:	n (% non-missing)	Median (minutes)	IQR (minutes)
Time First Encounter to Clinical Encounter	162 (100)	26	0 – 70
Time Clinical Encounter to Antibiotics Dispensed	162 (100)	74	31 – 123
Time Antibiotics Dispensed to Antibiotics Administered	160 (98.8)	26	19 – 46
Time Antibiotics Administered to Inpatient Admission	153 (94.4)	84	61 – 122
Time Clinical Encounter to Antibiotics Administered	160 (98.8)	111	60 –178
Time Blood Culture to Antibiotics Administered	160 (98.8)	40	15 – 81
Time First Encounter to Inpatient Admission	155 (95.7)	260	188 – 385

eFigure 1: APACHE II score by Sepsis Severity for Sepsis STAT Pack cohort.



eFigure 2: Intravenous Fluids administered in 6 and 24 hours by Sepsis Severity for Sepsis STAT Pack cohort.



eTable 2: Metrics of Sepsis Disease Severity for Sepsis STAT Pack cohort.

Disease Category	Patients: n (%)	Number organ systems with dysfunction: number of patients (%) *	APACHE II score: mean (SD)	Volume intravenous fluid administration, 6-hour, mean (SD) 24-hour, mean (SD)
No SIRS	13 (8.0)	0: 11 (84.6) 1: 2 (15.4)	14.6 (4.7)	1.5 (1.1) 3.0 (1.9)
SIRS only	6 (3.7)	0: 3 (50.0) 1: 3 (50.0)	15.2 (4.7)	1.0 (0.5) 2.8 (2.1)
Sepsis	71 (43.8)	0: 49 (68.1) 1: 23 (31.9)	16.4 (4.1)	1.3 (0.8) 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)	1.4 (0.9) 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)	3.3 (2.0) 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)	1.7 (1.3) 3.5 (2.1)

* Percentages are across row.

eTable 3: Clinically or microbiologically diagnosed infections and alternative diagnoses for Sepsis STAT Pack cohort.

Disease Category	Patients, n (%)	Diagnosis: *		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 Dx:	1	Drug Rxn (1)
SIRS only	6 (3.7)	Alternative Dx:	6	Drug Rxn (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 Dx:	7	Drug Rxn (3), Tumor Fever (2), Dehydration (1), Pancreatitis (1)

Abbreviations: PNA: Pneumonia; UTI: Urinary Tract Infection; CMV: Cytomegalovirus; C. diff: Clostridium difficile; Cx Neg: culture negative, Rxn: reaction.

* Culture-negative (Cx Neg) sepsis occurs when criteria for sepsis (or more severe sepsis) is met, but no apparent clinically or microbiologically infection nor alternative diagnosis is evident.

eTable 4: Univariate association of selected characteristics with Time-to-Antibiotics among cancer outpatients with presumed SS/SSh. 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.

Characteristic	Time-to-ABx ≤ 110 min (n=80)	Time-to-ABx > 110 min (n=80)	Total (missing=2)	P-value†
Demographics:				
Age, mean (SD)	50.2 (15.6)	51.8 (15.1)	51.0 (15.3)	0.517
Sex				0.030
- **Female**	21 (38.2%)	34 (61.8%)	55 (34.4%)	
- **Male**	59 (56.2%)	46 (43.8%)	105 (65.6%)	
Race				0.160
- **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				0.101
- **Heme Malignancy**	73 (52.5%)	66 (47.5%)	139 (86.9%)	
- **Other**	7 (33.3 %)	14 (66.7%)	21 (13.1%)	
HSCT status				0.752
- **Allo or Auto**	37 (48.7%)	39 (51.3%)	76 (47.5%)	
- **None**	43 (51.2%)	41 (48.8%)	84 (52.5%)	
Immunosuppressives*				0.288
- **Any**	25 (56.8%)	19 (43.2%)	44 (27.5%)	
- **None**	55 (47.4%)	61 (52.6%)	116 (72.5%)	
Neutropenia				0.752
- **ANC < 500 cells/uL**	39 (48.8%)	41 (51.3%)	80 (50.0%)	
- **ANC ≥ 500 cells/uL**	41 (51.3%)	39 (48.8%)	80 (50.0%)	
Antibiotics*				0.316
- **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):				
Bacteremic				0.265
- **Yes**	39 (54.9%)	32 (45.1%)	71 (44.4%)	
- **No**	41 (46.1%)	48 (53.9%)	89 (55.6%)	
Dexamethasone				0.081
- **Yes**	42 (57.5%)	31 (42.5%)	73 (45.6%)	
- **No**	38 (43.7%)	49 (56.3%)	87 (54.4%)	

Abbreviations: ABx: Antibiotics; Heme: hematopoietic; HSCT: hematopoietic stem cell transplant; Allo: allogeneic; Auto: autologous; ANC: absolute neutrophil count

* Immunosuppressive drugs and Antibiotics are listed in Table 1.

† 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-squared test; continuous: t-test.

eTable 5: Univariate association of selected characteristics with combined outcome of Septic Shock or 30 Day Cumulative Mortality among cancer outpatients treated with Sepsis STAT Pack at the SCCA, 2008 - 2012.

Characteristic	No SSh or 30-day Mortality (n=132)	SSh or 30-day Mortality (n=30)	Total (missing=0)	P-value†
Demographics:				
Age, mean (SD)	50.7 (14.9)	52.0 (16.7)	51.0 (15.2)	0.668
Sex				0.875
- **Female**	46 (82.1%)	10 (17.9%)	56 (34.6%)	
- **Male**	86 (81.1%)	20 (18.9%)	106 (65.4%)	
Race				0.071
- **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				0.061
- **Heme Malignancy**	118 (83.7%)	23 (16.3%)	141 (87.0%)	
- **Other**	14 (66.7%)	7 (33.3%)	21 (13.0%)	
s/p HSCT				0.187
- **Allo or Auto**	66 (85.7%)	11 (14.3%)	77 (47.5%)	
- **None**	66 (77.7%)	19 (22.4%)	85 (52.5%)	
Immunosuppressive*				0.547
- **Any**	38 (84.4%)	7 (15.6%)	45 (27.8%)	
- **None**	94 (80.3%)	23 (19.7%)	117 (72.2%)	
Neutropenia				0.742
- **ANC < 500 cells/uL**	66 (82.5%)	14 (17.5%)	80 (49.4%)	
- **ANC ≥ 500 cells/uL**	66 (80.5%)	16 (19.5%)	82 (50.6%)	
Antibiotics*				0.613
- **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				0.952
- **Yes**	58 (81.7%)	13 (18.3%)	71 (43.8%)	
- **No**	74 (81.3%)	17 (18.7%)	91 (56.2%)	
Dexamethasone				0.489
- **Yes**	62 (83.8%)	12 (16.2%)	74 (45.7%)	
- **No**	70 (79.6%)	18 (20.5%)	88 (54.3%)	

Abbreviations: ABx: Antibiotics; HSCT: hematopoietic stem cell transplant; Allo: allogeneic; Auto: autologous; ANC: absolute neutrophil count

* Immunosuppressive drugs and Antibiotics are listed in Table 1.

† P-value calculated using test of association by type of independent variables: categorical: Chi-squared test; continuous: t-test.

eTable 6: Previously published mortality data for cancer patients with Severe Sepsis / Septic Shock.

Study:	1) Setting: 2) Population (identification): 3) Study design:	By mortality outcome: Deceased / Total, % (95% CI)
Williams, et al.[6]	1) Hospitalized patients in 6 US states, 1999. 2) CA patients with SS/SSh, hospitalized (administrative data) 3) Retrospective cohort	Hospital Mortality, SS/SSh: unknown / 29,795, 37.8% (cannot estimate)*
Larche, et al.[7]	1) Single center ICU in Paris, France (St Louis), 1995 – 2000 2) Cancer patients with SSh, ICU (clinical records) 3) Retrospective cohort	30-day Mortality SSh: 57 / 88, 65.5% (54 – 75%)
Legrand, et al.[8]	1) Single center academic ICU in Paris, France (St Louis), 1998 – 2008. 2) Neutropenic cancer patients with SS/SSh, ICU (uncertain) 3) Retrospective cohort	Hospital Mortality, SS/SSh: 213 / 428, 49.8% (45 – 55%)
Pène, et al.[9]	1) Single center ICU in Paris, France (Cochin), 1998 – 2005. 2) Cancer patients 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.[10]	1) Single center ICU in Marseille, France, 2008 – 10. 2) Neutropenic cancer patients with SS or SSh, ICU (sequential patients enrolled) 3) Prospective cohort	ICU Mortality SS/SSh: 40 / 118, 33.9% (25 – 43%)
Azoulay, et al.[11]	1) Multicenter network of 17 academic ICUs in France & Belgium, 2010 – 11 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.[12]	1) Multicenter network of 17 academic ICUs in France & Belgium, 2010 – 12 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: CI: confidence interval; ICU: intensive care unit; SS: severe sepsis; SSh: septic shock.

* Count data not provided, so cannot accurately estimate 95% CI.

Supplemental References:

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical care medicine.* Feb 2013;41(2):580-637.
2. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical care medicine.* Oct 1985;13(10):818-829.
3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* Nov 8 2001;345(19):1368-1377.
4. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* May 2014;370(18):1683-1693.
5. Sweet SJ, Glenney CU, Fitzgibbons JP, Friedmann P, Teres D. Synergistic effect of acute renal failure and respiratory failure in the surgical intensive care unit. *American journal of surgery.* Apr 1981;141(4):492-496.
6. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Critical care.* Oct 2004;8(5):R291-298.
7. Larche J, Azoulay E, Fieux F, et al. Improved survival of critically ill cancer patients with septic shock. *Intensive care medicine.* Oct 2003;29(10):1688-1695.
8. Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Critical care medicine.* Jan 2012;40(1):43-49.
9. 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. *Critical care medicine.* Mar 2008;36(3):690-696.
10. Mokart D, Saillard C, Sannini A, et al. Neutropenic cancer patients with severe sepsis: need for antibiotics in the first hour. *Intensive care medicine.* Aug 2014;40(8):1173-1174.
11. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 1 2013;31(22):2810-2818.
12. Mokart D, Darmon M, Resche-Rigon M, et al. Prognosis of neutropenic patients admitted to the intensive care unit. *Intensive care medicine.* Feb 2015;41(2):296-303.