DR. MEGAN CRANE (Orcid ID : 0000-0001-6630-7177)

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Title

Impact of a hospital-wide sepsis pathway on improved quality of care and clinical outcomes in surgical patients at a comprehensive cancer center

Running heading

Sepsis pathway for patients with cancer

Authors

Alison Hiong¹ • Karin A. Thursky^{1,2,3} • Georgina Venn¹ • Benjamin W. Teh^{1,2} • Gabrielle M. Haeusler^{1,2}
• Megan Crane² • Monica A. Slavin^{1,2} • Leon J. Worth^{1,2,4}

Corresponding author

megan.crane@petermac.org

Affiliations

¹ Department of Infectious Diseases and Infection Prevention, Peter MacCallum Cancer Centre, Melbourne, VIC

² National Centre for Infections in Cancer, National Health and Medical Research Council Centre for Research Excellence, The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

³ National Centre for Antimicrobial Stewardship, National Health and Medical Research Council Centre for Research Excellence, Doherty Institute, Melbourne, VIC

⁴ Victorian Healthcare Associated Infection Surveillance System (VICNISS), Doherty Institute, Melbourne, VIC

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Abbreviations

SSI, surgical site infection; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit; CRP, C-reactive protein

ABSTRACT

Purpose: Sepsis is a significant complication following cancer surgery. Although standardised care bundles improve sepsis outcomes in other populations, the benefits in cancer patients are unclear. The objectives of this study were to describe the epidemiology of sepsis in cancer patients post-surgery, and to evaluate the impact of a clinical sepsis pathway on management and clinical outcomes.

Methods: A standardised hospital-wide sepsis pathway was developed in 2013, and all cases of sepsis at the Peter MacCallum Cancer Centre in 2014 were retrospectively evaluated. Inclusion criteria were sepsis onset during the 100-day period following a surgical procedure for cancer diagnosis. Patients were identified using ICD-10-AM sepsis discharge codes, audit documentation, and the hospital's antimicrobial approval system. Sepsis episodes were classified as managed on- or off-pathway.

Results: 119 sepsis episodes were identified. Of these, 71 (59.7%) were managed on the sepsis pathway. Episodes managed on-pathway resulted more frequently in administration of appropriate antibiotics compared to those off-pathway (94.4% vs. 66.7%, $p<0.001$), and had shorter time to first-dose antibiotics (median 85 vs. 315 minutes, $p<0.001$). Pathway utilisation was associated with significant reductions in need for inotropes (7% vs. 13%, $p=0.023$), ventilation (3% vs. 10%, $p=0.006$), and length of hospitalisation (median 15 vs. 30 days, $p=0.008$). The most frequent source of infection was organ-space surgical site infection (24.4% of instances).

Conclusions: A dedicated hospital-wide sepsis pathway had significant impact on the quality of care and clinical outcomes of sepsis in cancer surgery patients. Cost-benefit analysis of sepsis pathways for cancer patients is required.

Keywords: sepsis, cancer, surgery, infection

Introduction

Sepsis is a significant complication of cancer management (Avritscher et al., 2014, Mulvey et al., 2017, Aquina et al., 2017), with severe sepsis estimated to account for 8.5% of all cancer deaths in the United States at a cost of \$3.4 billion for the year of 2004 (Azoulay et al., 2013). Cancer patients are at increased risk of sepsis related to multiple factors (Sood et al., 2017, Mokart et al., 2016), including immunocompromise from underlying malignancy, immune dysfunction following chemotherapy, recurrent hospitalization, and the requirement for interventions and invasive procedures that predispose to infection (Hiong et al., 2016). Survival of cancer patients admitted to intensive care units (ICUs) with sepsis has improved from approximately 20% to 50% over recent decades (Azoulay et al., 2013, Jackson et al., 1998), this being ascribed largely to early recognition and treatment of sepsis and utilisation of standardised clinical pathways (Burrell et al., 2016). However, despite the availability of evidence-based guidelines for sepsis management, the applicability to cancer surgery patients in hospital ward settings is not known.

Early intervention improves sepsis outcomes. Delays in the administration of antibiotic therapy are associated with increased mortality (Kumar et al., 2006), particularly in patients with septic shock (Yealy et al., 2014). A major barrier to early intervention is the correct identification of

sepsis. This can be challenging in patients who have recently undergone surgery, as clinical features of sepsis may be non-specific (Kaukonen et al., 2015), and signs of sepsis in the early post-operative period, such as oliguria, tachycardia and altered mental status, may mistakenly be attributed to non-infective post-operative complications (Ou et al., 2016).

In March 2013, a hospital-wide clinical sepsis pathway based on international guidelines, was implemented at the Peter MacCallum Cancer Centre (PMCC). The objectives of this study were to describe the epidemiology of surgical sepsis in cancer patients and to evaluate the impact of the sepsis pathway.

Methods

Development of sepsis pathway

International and national evidence-based guidelines were reviewed by clinical stakeholders (medical, nursing, ICU clinicians) to formulate a nurse-led standardised clinical pathway for sepsis management. Patients were eligible for the pathway if two or more of the systemic inflammatory response syndrome (SIRS) criteria or a systolic blood pressure of less than 100mmHg were present in a ward setting. Key components of the pathway included establishing intravenous access, drawing two sets of blood cultures prior to administration of antibiotics, and performing venous lactate measurements and a full blood examination (Burrell et al., 2016, Kumar et al., 2015, Morneau et al., 2017, Mattison et al., 2016) (Box 1). Following organisation-wide education and development of a dedicated checklist for pathway components (embedded in patient medical record), the program was implemented across all wards in March 2013. Development and implementation of the pathway has been outlined in detail elsewhere (Thursky et al., 2018).

Study population

The study population was defined as all patients at PMCC with onset of sepsis between 1 January and 31 December 2014, who had undergone surgery for cancer within the 100-day period prior to sepsis onset. PMCC is a tertiary cancer hospital where a range of surgical procedures are performed, including colorectal, gastrointestinal, head and neck, skin and soft tissue, urological and breast surgeries. Orthopaedic surgery, neurosurgery and cardiothoracic surgery are not performed. Institutional policy at time of study was for intravenous cefazolin and metronidazole or intravenous cefoxitin to be administered 1-hour prior to procedures for surgical antibiotic prophylaxis.

Episodes of sepsis were retrospectively identified using three different sources: ICD-10-AM hospital discharge codes for sepsis, sepsis pathway audit documentation, and the hospital's antimicrobial approvals system (Guidance®, Melbourne Health). Following identification, patient records were then assessed for clinical signs and symptoms of sepsis. Patients who fulfilled the definition of sepsis were deemed eligible for inclusion in the study. Cases were excluded if sepsis management was commenced at another facility before transfer to PMCC, or if the resected tumour was histologically confirmed to be non-malignant.

Outcome measures

The primary evaluable outcome was hospital length of stay. Secondary outcomes were ICU admission, length of stay in ICU, acute kidney injury, use of inotropes, need for ventilation, unplanned hospital readmission within 30 days of discharge, 30-day all-cause mortality and 90-day all-cause mortality. For each sepsis episode, data pertaining to patient demographics, comorbidities, cancer diagnosis, surgical history, infection diagnosis, and outcomes were captured. Standardised information regarding sepsis management, including the antibiotic(s) administered, time elapsed between sepsis onset and the first antibiotic first dose, and fluid resuscitation measures, were also collected.

Definitions

Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine criteria (Levy et al., 2003) as infection in the presence of more than one of the following: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats per minute, hyperventilation (respiratory rate >20 breaths per minute), or a white blood cell count >12000 cells/ μL or <4000 cells/ μL . The onset of sepsis was recorded as the time at which these diagnostic criteria were first present. Patients were considered to have subsequent episodes of sepsis if events meeting sepsis criteria were separated by a continuous period of at least 48 hours during which sepsis criteria were not fulfilled.

Surgery was defined as an operative procedure involving at least one incision through skin or mucous membrane. For the purposes of this study, only patients who underwent surgery directly related to primary cancer diagnosis were eligible. Surgical site infections (SSIs) were classified as either superficial incisional, deep incisional, or organ-space, according to Centers for Disease Control/National Healthcare Safety Network definitions (Centers for Disease Control and Prevention, Worth et al., 2015).

Sepsis pathway. A patient was classified as being on the sepsis pathway if the patient's records contained completed sepsis pathway documentation, if entry into the sepsis pathway was explicitly mentioned in the patient's notes, or if a customised audit sheet was available. Uniform data regarding each sepsis episode were captured. Physical examination and investigation findings carried out at the onset of sepsis were recorded. Vital signs and lactate levels were captured if measured within two hours of sepsis onset, and white blood cell count and C-reactive protein (CRP) values were captured if taken within 24 hours of sepsis onset. The peak CRP was defined as the highest CRP value within seven days of sepsis onset. The first antibiotic administered after the onset of sepsis was recorded, as well as all subsequent antibiotics given within 12 hours of onset. The choice of antibiotic was considered to be appropriate if it adhered to sepsis pathway recommendations (Box 1). If a patient was not given any antibiotics, this was considered to be inappropriate. If a patient was already on intravenous antibiotics prior to meeting sepsis criteria, the time of the next dose administered after the onset of sepsis was documented.

Primary site of infection. Clinical records, microbiological results and imaging tests were reviewed to determine if a primary site of infection present. Infection was deemed to be a microbiologically-documented infection if it was clinically detectable and microbiologically proven, a clinically-documented infection if clinically diagnosed but not proven microbiologically, or infection of unknown source if neither microbiologically nor clinically documented infection was present (Teh et al., 2015). The diagnosis was recorded as SIRS of non-infectious origin only if an alternative aetiology was confirmed.

The age-adjusted Charlson comorbidity index was calculated for each patient according to Charlson *et al.* (Charlson et al., 1987). Neutropenia was defined as an absolute neutrophil count $<1.0 \times 10^9/L$. Acute kidney injury was defined according to Mehta *et al.* (Mehta et al., 2007) as an increase in serum creatinine to more than three-fold from baseline.

Ethics

The study was a retrospective evaluation of clinical care, and no identifiable patient-level data were captured. Criteria for a National Health and Medical Research Council quality assurance program were fulfilled, and ethics approval was not required.

Statistical analysis

Differences between the on-sepsis pathway and off-pathway groups were tested using the chi-square or Fisher's exact tests for categorical variables. The Mann-Whitney U-test was used to evaluate continuous variables, given the non-normal distribution of the data. Continuous variables were expressed as median and interquartile range (IQR). In all instances, a p-value <0.05 was deemed statistically significant. Stata, version 11 (StataCorp, Tx) was used for analyses.

Results

Characteristics of sepsis episodes

Overall, 119 episodes of sepsis occurring in 101 patients fulfilled inclusion criteria. Of these, 71 (59.7%) were managed in accordance with the sepsis pathway and 48 (40.3%) were not. The most frequent underlying diagnosis was lower gastrointestinal malignancy. Of all surgical procedures, 112 (89.1%) were electively-performed procedures. Characteristics of sepsis episodes are summarised in Table 1.

There were no differences between on-pathway and off-pathway groups with regard to age, sex, Charlson comorbidity index, cancer status, or recent exposure to chemotherapy, steroids or radiotherapy, and the proportion of neutropenic patients was not significantly different these groups ($p=0.472$). The proportion requiring percutaneous drainage or open procedures as a component of post-operative care was not significantly different in the two groups (Table 1). The on-pathway cohort had a higher proportion of head and neck cancers than the off-pathway group (12.7% vs. 2.1%, $p=0.048$), and higher median temperature (38.2°C vs. 38.1°C, $p=0.007$) and heart rate (106 bpm vs. 95 bpm, $p=0.012$) at sepsis onset.

Sepsis management

The utilisation of key evidence-based components of sepsis management is presented in Table 2. A significantly higher proportion of patients on the sepsis pathway had at least two sets of blood cultures taken when compared to those not managed on the pathway (52% vs. 33%, $p=0.043$) and a lactate level measured within two hours of developing sepsis (77.5% vs. 48%, $p=0.001$). The total time elapsed between the onset of sepsis and administration of intravenous antibiotics was significantly shorter in the on-pathway group (median 85 minutes, IQR 50-135 minutes), compared to the off-pathway group (median 315 minutes, IQR 120-1220 minutes) ($p<0.001$). Within the on-pathway group, the median time to antibiotic administration from entry into the sepsis pathway was 60 minutes (IQR 50-135 minutes). 94.4% of patients on the sepsis pathway were administered

appropriate initial antibiotics for sepsis, which was a significantly higher proportion than the off-pathway cohort, for whom appropriate antibiotics were initially administered to 66.7% of patients ($p<0.001$).

Clinical outcomes

Clinical outcomes are summarised in Table 3. A significantly lower proportion of patients on-pathway required inotropic support (7% vs. 13%, $p=0.023$) and ventilation (3% vs. 10%, $p=0.006$), compared to the off-pathway cohort. There was also a trend towards a lower rate of ICU admission in the on-pathway group, but this was not statistically significant. A lower median peak CRP level was observed in patients who were on the sepsis pathway (259.5 vs. 214.0 mg/L, $p=0.048$) and those managed on the pathway had a median duration of hospitalisation of 15 days (IQR 7-34 days), which was significantly shorter than those not managed on the pathway (median duration 30 days, IQR 12.5-49.0 days) ($p=0.008$). There were no differences in rates of acute kidney injury, unplanned hospital readmissions within 30 days of discharge, or in 30-day or 90-day all-cause mortality between the two groups (Table 3).

Type and site of infection

Overall, 39 sepsis episodes were associated with microbiologically-documented infection and 47 episodes with clinically-documented infection. Of microbiologically-confirmed infections, *Pseudomonas aeruginosa* was the most frequently isolated pathogen (23%), followed by *Escherichia coli* (14%), methicillin-sensitive *Staphylococcus aureus* (12%), methicillin-resistant *S. aureus* (8%), *Bacteroides* spp. (5%), *Klebsiella* spp. (5%), and *Proteus* spp. (5%).

The most frequently identified primary sites of infection were organ-space SSI and post-operative pneumonia, responsible for 29 (24.2%) and 27 (22.7%) of sepsis episodes, respectively (Figure 1). The on-pathway group had a significantly lower proportion of post-operative organ-space SSIs compared to those not managed on the pathway (15.3% vs. 34.6%, $p=0.012$). However, the proportion of patients with pneumonia was comparable in on- and off-pathway groups (22.5% vs. 22.9%, $p=0.961$). There were no significant differences in the relative frequencies of other infection diagnoses (bloodstream infection, urinary tract infection, deep incisional SSI) when the two cohorts were compared (Figure 1). No studied patients developed *Clostridium difficile* infection in the post-operative period.

Discussion

The importance of early recognition and intervention in sepsis is well-established (Kumar et al., 2006, Rivers et al., 2001, Yealy et al., 2014, Moore and Moore, 2013, Thursky and Worth, 2015). Timely and standardised management reduces mortality (Burrell et al., 2016) and this is particularly important in cancer patients who are at increased risk of developing septic shock (Hiong et al., 2016). Identifying sepsis in the surgical setting is particularly challenging as sepsis may present with non-specific findings, or be misclassified as a non-infectious complication (Kaukonen et al., 2015). This study evaluated the use of a sepsis pathway in the post-operative setting in cancer patients. Importantly, we demonstrated improved clinical outcomes - a significant reduction in the need for inotropic support and ventilation, a shorter median hospital length of stay and more appropriate antibiotic usage - amongst those managed on the pathway, demonstrating a clear advantage of early sepsis recognition and aggressive treatment in cancer surgery patients.

Our sepsis pathway was utilised in 59.7% of eligible cases, despite the fact that all cases met diagnostic criteria for sepsis (Levy et al., 2003). This reflects the fact that recognition of sepsis is challenging in surgical populations. Normal physiological parameters may be masked in the postoperative period, and onset of sepsis may occur insidiously (Kaukonen et al., 2015). The significantly higher proportion of organ-space SSIs in the off-pathway group (Figure 1) suggests that recognition of sepsis is potentially more challenging in those patients with deep-seated infections. These patients may not present with overt clinical signs and the diagnosis may only be revealed by imaging studies many days following surgery. In the absence of distinct clinical features consistent with infection, clinicians may fail to recognise infection. Furthermore, the higher median temperature and higher heart rate observed at onset of sepsis in those managed on the pathway compared to those who were not (Table 1), suggests that clinical staff place a heavy reliance on obvious signs of fever as an indicator of infection and sepsis. We also observed that the on-pathway cohort had a higher proportion of patients with head and neck cancers, which may reflect variable uptake of the pathway by staff in individual surgical departments.

The median time to sepsis onset (days post-procedure, Table 1) was significantly longer in those managed on-pathway, suggesting that early recognition of sepsis and utility of the pathway in the early post-operative setting is most challenging. The post-operative setting therefore remains an area for ongoing educational campaigns at our facility to improve early recognition of sepsis and adherence to sepsis management guidelines. Although we observed increased drawing of blood cultures in instances where patients were managed on the sepsis pathway (Table 2), we

acknowledge the need for ongoing education and improved practices to ensure the drawing 2 or more blood cultures for all sepsis episodes. We postulate that delivery of palliative or end-stage cancer care (e.g. goals of care not documented in all cases) may also impact upon uptake of the pathway. Indeed, a program to improve documentation of goals of care has subsequently been instituted at our organisation.

Our hospital-wide pathway was developed specifically for patients with cancer, some of whom were neutropenic at time of sepsis onset. As such, the pathway was aligned to national and international recommendations for management of febrile neutropenia, with vancomycin reserved for targeted therapy of patients with antimicrobial-resistant infections. Epidemiology at our centre is such that the incidence of infections due to methicillin-resistant organisms is very low (<1 infection per month hospital-wide). Indeed, only three microbiologically-confirmed infections in the studied cohort were due to methicillin-resistant *Staphylococcus aureus*, and we believe this to be a low rate of discordance between microbiological isolates and appropriate antibiotic therapy. In those cases where methicillin-resistant pathogens were responsible for infection, vancomycin was commenced as targeted therapy when confirmatory results were available. Regular review of local epidemiology, including antibiotic susceptibilities of infecting pathogens is important to ensure that empiric antibiotic regimens for sepsis are appropriate for individual hospital settings.

Initiation of the sepsis pathway does not guarantee full adherence to all evidence-based components of sepsis management (Hiong et al., 2016). However, on the basis of previously evaluated quality improvement programs, several core components of the pathway can be identified as minimum requirements for a sepsis management bundle. These include: having 2 or more sets of blood cultures taken, lactate measurements, a time of less than 30 minutes to first dose of antibiotics from sepsis onset and/or from time of entry into sepsis pathway and appropriate use of first line antibiotics (Levy et al., 2015, Dellinger et al., 2013, Kumar et al., 2006, Yealy et al., 2014). We therefore evaluated compliance with these key components at our center. Patients on the sepsis pathway were more likely to have a lactate level measured, have two or more blood cultures taken and to receive appropriate antibiotics than patients not on the pathway. These three steps, in addition to administration of intravenous fluids (for patients with hypotension or elevated lactate levels), formed the basis of the first evidence-based sepsis management bundle outlined by the Surviving Sepsis Campaign (Dellinger et al., 2013). We note, however, that the median time elapsed between commencing the sepsis pathway and the first dose of antibiotics at our center was 60 minutes, twice the recommended time to affect improved patient mortality (Dellinger et al., 2013). This represents an area for further improvement and education. A target of less than 30 minutes to

first-dose of antibiotics from sepsis onset has now been set by clinical stakeholders in our organisation (Dellinger et al., 2013).

Evaluation of clinical outcomes revealed a reduced need for ventilation and inotrope support in those placed on the sepsis pathway. Significantly, the median length of hospitalisation for patients not managed on the sepsis pathway was double the median length of stay for those on the pathway (Table 3). We were not able to demonstrate an impact on mortality with initiation of the sepsis pathway in our study. However, this is likely to be related to the fact overall mortality in our study was 11% (Table 3), considerably lower than that reported in other studies (Moore et al., 2011, Sammon et al., 2015). Moore *et al.* (Moore et al., 2011) reported 18% in-hospital mortality in a general surgical cohort with a relatively high rate of severe sepsis and/or septic shock (82%). This study also included a very high proportion of patients who underwent emergency surgery (66.7%). Similarly, Sammon and colleagues (Sammon et al., 2015) reported a mortality of 31.5% in sepsis following cancer surgery, but in an elderly population with a high proportion of cases having severe sepsis. Similarly, acute kidney injury was observed to have a low incidence in our cohort, potentially related to the fact that a large proportion of studied patients underwent elective surgical procedures, with opportunity to reduce risks of renal impairment (e.g. optimisation of fluid balance and hydration in the perioperative period). Further, we did not demonstrate a difference in the proportion of patients requiring unplanned readmission to hospital when on- and off-pathway groups were compared. Reasons for this are not clear, but could include the fact that management of primary sites of infection (e.g. open surgical procedure or percutaneous drainage) was comparably performed for the two groups during the hospitalisation period in which the sepsis event was observed (Table 1).

Our study was limited by the retrospective study design. Our sepsis pathway was implemented at a single center, and although a broad range of surgical procedures are performed at PMCC, a small number of specialty surgical services are not provided (neurosurgery, cardiothoracic surgery and orthopaedic surgery). Also, the majority of surgical procedures were performed electively, rather than in emergency settings. These factors may impact upon generalizability of findings, and are also likely to have contributed to the observed low overall mortality rates. Identification of eligible patients for inclusion in the study was complicated by poor correlation between ICD-10-AM discharge codes for sepsis and true sepsis. However, we attempted to minimise any ascertainment bias by supplementing our means of patient identification using customised sepsis pathway audit forms and the hospital's antimicrobial approvals system. Consistent with all retrospective studies, we were unable to imply direct causation between processes and patient outcomes.

A major strength of this study was the ability to capture findings in the unique population of cancer surgery patients with sepsis, and to investigate the utility of a dedicated sepsis pathway in this population. Furthermore, our program is the first hospital-wide sepsis management pathway to be developed and implemented in Australia. We were able to demonstrate improved clinical outcomes with early management of sepsis, and to gain insight into relative uptake of individual components of our sepsis management bundle. Future studies are required to estimate the cost-benefit of this program.

In conclusion, we demonstrate that a dedicated sepsis pathway is associated with improved management and clinical outcomes of sepsis in cancer surgery patients, including improved antibiotic usage and decreased hospital length of stay. Adherence and widespread adoption of key evidence-based steps in sepsis management may be enhanced by further education and increasing awareness of the pathway to improve sepsis-related outcomes in this at-risk patient population.

References

- Ethical considerations in quality assurance and evaluation activities. National Health and Medical Research Council. Published: March 2014. URL: https://www.nhmrc.gov.au/files/nhmrc/publications/attachments/e111_ethical_considerations_in_quality_assurance_140326.pdf [accessed 28 June 2017].
- AQUINA, C. T., MOHILE, S. G., TEJANI, M. A., BECERRA, A. Z., XU, Z., HENSLEY, B. J., ARSALANI-ZADEH, R., BOSCOE, F. P., SCHYMURA, M. J., NOYES, K., MONSON, J. R. & FLEMING, F. J. 2017. The impact of age on complications, survival, and cause of death following colon cancer surgery. *Br J Cancer*, 116, 389-397.
- AVRITSCHER, E. B., COOKSLEY, C. D., ROLSTON, K. V., SWINT, J. M., DELCLOS, G. L., FRANZINI, L., SWISHER, S. G., WALSH, G. L., MANSFIELD, P. F. & ELTING, L. S. 2014. Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume. *Support Care Cancer*, 22, 527-35.
- AZOULAY, E., MOKART, D., PENE, F., LAMBERT, J., KOUATCHET, A., MAYAUX, J., VINCENT, F., NYUNGA, M., BRUNEEL, F., LAISNE, L. M., RABBAT, A., LEBERT, C., PEREZ, P., CHAIZE, M., RENAULT, A., MEERT, A. P., BENOIT, D., HAMIDFAR, R., JOURDAIN, M., DARMON,

- M., SCHLEMMER, B., CHEVRET, S. & LEMIALE, V. 2013. 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*, 31, 2810-8.
- BURRELL, A. R., MCLAWS, M. L., FULLICK, M., SULLIVAN, R. B. & SINDHUSAKE, D. 2016. SEPSIS KILLS: early intervention saves lives. *Med J Aust*, 204, 73 e1-7.
- CENTERS FOR DISEASE CONTROL AND PREVENTION. *Guideline for Prevention of Surgical Site Infection*, 1999 [Online]. Atlanta: Centers for Disease Control and Prevention. Available: http://www.cdc.gov/hicpac/SSI/002_SSI.html [Accessed February 10 2015].
- CHARLSON, M. E., POMPEI, P., ALES, K. L. & MACKENZIE, C. R. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*, 40, 373-83.
- DELLINGER, R. P., LEVY, M. M., RHODES, A., ANNANE, D., GERLACH, H., OPAL, S. M., SEVRANSKY, J. E., SPRUNG, C. L., DOUGLAS, I. S., JAESCHKE, R., OSBORN, T. M., NUNNALLY, M. E., TOWNSEND, S. R., REINHART, K., KLEINPELL, R. M., ANGUS, D. C., DEUTSCHMAN, C. S., MACHADO, F. R., RUBENFELD, G. D., WEBB, S., BEALE, R. J., VINCENT, J. L. & MORENO, R. 2013. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*, 39, 165-228.
- HIONG, A., THURSKY, K. A., TEH, B. W., HAEUSLER, G. M., SLAVIN, M. A. & WORTH, L. J. 2016. Sepsis following cancer surgery: the need for early recognition and standardised clinical care. *Expert Rev Anti Infect Ther*, 14, 425-33.
- JACKSON, S. R., TWEEDDALE, M. G., BARNETT, M. J., SPINELLI, J. J., SUTHERLAND, H. J., REECE, D. E., KLINGEMANN, H. G., NANTEL, S. H., FUNG, H. C., TOZE, C. L., PHILLIPS, G. L. & SHEPHERD, J. D. 1998. Admission of bone marrow transplant recipients to the intensive care unit: outcome, survival and prognostic factors. *Bone Marrow Transplant*, 21, 697-704.
- KAUKONEN, K. M., BAILEY, M. & BELLOMO, R. 2015. Systemic Inflammatory Response Syndrome Criteria for Severe Sepsis. *N Engl J Med*, 373, 881.
- KUMAR, A., ROBERTS, D., WOOD, K. E., LIGHT, B., PARRILLO, J. E., SHARMA, S., SUPPES, R., FEINSTEIN, D., ZANOTTI, S., TAIBERG, L., GURKA, D., KUMAR, A. & CHEANG, M. 2006. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*, 34, 1589-96.

- KUMAR, P., JORDAN, M., CAESAR, J. & MILLER, S. 2015. Improving the management of sepsis in a district general hospital by implementing the 'Sepsis Six' recommendations. *BMJ Qual Improv Rep*, 4.
- LEVY, M. M., FINK, M. P., MARSHALL, J. C., ABRAHAM, E., ANGUS, D., COOK, D., COHEN, J., OPAL, S. M., VINCENT, J. L., RAMSAY, G. & SCCM/ESICM/ACCP/ATS/SIS 2003. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*, 31, 1250-6.
- LEVY, M. M., RHODES, A., PHILLIPS, G. S., TOWNSEND, S. R., SCHORR, C. A., BEALE, R., OSBORN, T., LEMESHOW, S., CHICHE, J. D., ARTIGAS, A. & DELLINGER, R. P. 2015. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med*, 43, 3-12.
- MATTISON, G., BILNEY, M., HAJI-MICHAEL, P. & COOKSLEY, T. 2016. A nurse-led protocol improves the time to first dose intravenous antibiotics in septic patients post chemotherapy. *Support Care Cancer*, 24, 5001-5005.
- MEHTA, R. L., KELLUM, J. A., SHAH, S. V., MOLITORIS, B. A., RONCO, C., WARNOCK, D. G. & LEVIN, A. 2007. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*, 11, R31.
- MOKART, D., GIAOUI, E., BARBIER, L., LAMBERT, J., SANNINI, A., CHOW-CHINE, L., BRUN, J. P., FAUCHER, M., GUIRAMAND, J., EWALD, J., BISBAL, M., BLACHE, J. L., DELPERO, J. R., LEONE, M. & TURRINI, O. 2016. Postoperative sepsis in cancer patients undergoing major elective digestive surgery is associated with increased long-term mortality. *J Crit Care*, 31, 48-53.
- MOORE, L. J., MCKINLEY, B. A., TURNER, K. L., TODD, S. R., SUCHER, J. F., VALDIVIA, A., SAILORS, R. M., KAO, L. S. & MOORE, F. A. 2011. The epidemiology of sepsis in general surgery patients. *J Trauma*, 70, 672-80.
- MOORE, L. J. & MOORE, F. A. 2013. Early diagnosis and evidence-based care of surgical sepsis. *J Intensive Care Med*, 28, 107-17.
- MORNEAU, K., CHISHOLM, G. B., TVERDEK, F., BRUNO, J. & TOALE, K. M. 2017. Timing to antibiotic therapy in septic oncologic patients presenting without hypotension. *Support Care Cancer*.
- MULVEY, C. L., BRANT, J. A., BUR, A. M., CHEN, J., FISCHER, J. P., CANNADY, S. B. & NEWMAN, J. G. 2017. Complications Associated with Mortality after Head and Neck Surgery. *Otolaryngol Head Neck Surg*, 156, 504-510.

- OU, L., CHEN, J., BURRELL, T., FLABOURIS, A., HILLMAN, K., BELLOMO, R. & PARR, M. 2016. Incidence and mortality of postoperative sepsis in New South Wales, Australia, 2002-2009. *Crit Care Resusc*, 18, 9-16.
- RIVERS, E., NGUYEN, B., HAVSTAD, S., RESSLER, J., MUZZIN, A., KNOBLICH, B., PETERSON, E., TOMLANOVICH, M. & EARLY GOAL-DIRECTED THERAPY COLLABORATIVE, G. 2001. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*, 345, 1368-77.
- SAMMON, J. D., KLETT, D. E., SOOD, A., OLUGBADE, K., JR., SCHMID, M., KIM, S. P., MENON, M. & TRINH, Q. D. 2015. Sepsis after major cancer surgery. *J Surg Res*, 193, 788-94.
- SOOD, A., ABDOLLAH, F., SAMMON, J. D., ARORA, N., WEEKS, M., PEABODY, J. O., MENON, M. & TRINH, Q. D. 2017. Postoperative sepsis prediction in patients undergoing major cancer surgery. *J Surg Res*, 209, 60-69.
- TEH, B. W., HARRISON, S. J., WORTH, L. J., SPELMAN, T., THURSKY, K. A. & SLAVIN, M. A. 2015. Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. *Br J Haematol*, 171, 100-8.
- THURSKY, K., LINGARATNAM, S., JAYARAJAN, J., HAEUSLER, G. M., TEH, B., TEW, M., VENN, G., HIONG, A., BROWN, C., LEUNG, V., WORTH, L. J., DALZIEL, K. & SLAVIN, M. A. 2018. Implementation of a whole of hospital sepsis clinical pathway in a cancer hospital: impact on sepsis management, outcomes and costs. *BMJ Open Qual*, 7, e000355.
- THURSKY, K. A. & WORTH, L. J. 2015. Can mortality of cancer patients with fever and neutropenia be improved? *Curr Opin Infect Dis*, 28, 505-13.
- WORTH, L. J., BULL, A. L., SPELMAN, T., BRETT, J. & RICHARDS, M. J. 2015. Diminishing surgical site infections in Australia: time trends in infection rates, pathogens and antimicrobial resistance using a comprehensive Victorian surveillance program, 2002-2013. *Infect Control Hosp Epidemiol*, 36, 409-16.
- YEALY, D. M., KELLUM, J. A., HUANG, D. T., BARNATO, A. E., WEISSFELD, L. A., PIKE, F., TERNDROP, T., WANG, H. E., HOU, P. C., LOVECCHIO, F., FILBIN, M. R., SHAPIRO, N. I. & ANGUS, D. C. 2014. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*, 370, 1683-93.

Table 1. Baseline characteristics of studied sepsis episodes (N = 119)

Characteristic	Not on sepsis pathway n = 48	On sepsis pathway n = 71	p-value

Age (years) – median (IQR)	63.9 (52.5-73.1)	61.0 (47.9-72.9)	0.470
Male – n (%)	37 (77.1)	46 (64.8)	0.152
Charlson comorbidity index – median (IQR)	7 (4-9)	6 (4-8)	0.308
Cancer diagnosis – n (%)			
Breast	1 (2.1)	3 (4.2)	0.468
Head and neck	1 (2.1)	9 (12.7)	0.048
Lower gastrointestinal	25 (52.1)	28 (39.4)	0.173
Melanoma	4 (8.3)	4 (5.6)	0.713
Sarcoma	4 (8.3)	7 (9.9)	1.000
Upper gastrointestinal	4 (8.3)	3 (4.2)	0.438
Other	10 (20.8)	18 (25.4)	0.325
Metastatic cancer – n (%)	24 (50.0)	34 (47.9)	0.821
Relapse/refractory cancer status – n (%)	15 (31.3)	27 (38.0)	0.448
Open surgical procedure – n (%)	33 (68.8)	36 (50.7)	0.050
Radiotherapy in last 30 days – n (%)	2 (4.2)	8 (11.3)	0.312
Chemotherapy in last 30 days – n (%)	11 (22.9)	19 (27.1)	0.433
Mean daily steroid dose in last 30 days (mg) [†]	4.0	3.4	
Neutropenia – n (%)	2 (4.2)	6 (8.5)	0.472
Time to sepsis onset - median days post-procedure (range)	6 (1-95)	12 (1-96)	0.040
Findings at sepsis onset – median (IQR)			
Temperature (°C)	38.1 (36.6-38.3)	38.2 (38.1-38.5)	0.007
Systolic blood pressure (mmHg)	125 (110-140)	130 (115-140)	0.530
Heart rate (bpm)	95 (91-110)	106 (99-118)	0.012
Respiratory rate (bpm)	18 (16-22)	18 (16-20)	0.275
White blood cells (×10 ⁹ /L)	10.4 (7.7-13.7)	10.1 (5.8-15.1)	0.154
Lactate level (mmol/L)	1.5 (0.9-2.7)	1.3 (0.9-1.7)	0.141
CRP (mg/L)	174 (102-246)	154 (81-212)	0.170
Fluid resuscitation required – n (%)	3 (6.3)	3 (5.3)	0.363
Post-operative interventions – n (%)			
Percutaneous drainage	10 (20.8)	9 (12.7)	0.334
Open procedure or debridement	5 (10.4)	5 (7.0)	0.515

IQR, inter-quartile range; CRP, C-reactive protein

[†] Expressed in prednisolone equivalent dose.

Table 2. Uptake of evidence-based components of sepsis management

Sepsis bundle component	Not on sepsis pathway n = 48	On sepsis pathway n = 71	p-value
2 or more sets of blood cultures drawn – n (%)	16 (33.3)	37 (52.1)	0.043
At least 1 set of blood cultures drawn – n (%)	38 (79.2)	71 (100)	<0.001
Lactate measured – n (%)	23 (47.9)	55 (77.5)	0.001
Time to first dose of antibiotics from sepsis onset (min) – median (IQR)	315 (120-1220)	85 (50-135)	<0.001
Time to first dose of antibiotics from entry into sepsis pathway (min) – median (IQR)	†	60 (30-90)	N/A
Appropriate first antibiotic – n (%)	32 (66.7)	67 (94.4)	<0.001

IQR, inter-quartile range

† Time to first dose of antibiotics not available for patients not managed on pathway.

Table 3. Clinical outcomes in cancer surgery patients with sepsis

Outcome	Not on sepsis pathway n = 48	On sepsis pathway n = 71	p-value
ICU admission – n (%)	17 (35.4)	15 (21.1)	0.085
Inotropes given – n (%)	13 (27.1)	7 (9.9)	0.023
Ventilated – n (%)	10 (20.8)	3 (4.2)	0.006
Acute kidney injury – n (%)	2 (4.2)	1 (1.4)	0.564
Peak CRP (mg/L)	259.5 (190-364)	214.0 (148-282)	0.048
Length of stay in ICU (days) – median (IQR)	1.4 (1.0-4.0)	1.7 (1.4-2.8)	0.509
Length of stay in hospital (days) – median (IQR)	30 (12.5-49.0)	15 (7.0-34.0)	0.008
Unplanned readmission within 30 days – n (%)	9 (18.8)	16 (23.5)	0.232
30-day mortality (all cause) – n (deaths per 100-sepsis episodes)	2 (4.2)	0 (0)	0.161
90-day mortality (all cause) – n (deaths per 100-sepsis episodes)	8 (16.7)	4 (5.6)	0.065

ICU, intensive care unit; CRP, C-reactive protein; IQR, inter-quartile range

Box 1. Key components of hospital-wide sepsis pathway

A: Recognise sepsis

- Patient eligibility for pathway: ≥ 2 SIRS criteria* or SBP < 100 mmHg

B: Immediate resuscitation

- Maintain $\text{SaO}_2 > 95\%$
- Obtain large-bore intravenous access
- Draw 2 sets of blood cultures prior to commencing antibiotic therapy
- Fluid resuscitation if SBP < 90 mmHg or lactate ≥ 4 mmol/L: rapid bolus Hartmann's 10-20 mL/kg
- Commence first-dose intravenous antibiotics within 30 minutes:
 - piperacillin/tazobactam 4.5g IV in 0.9% normal saline over 30 mins
 - cefepime 2g IV over 5 mins if non-life threatening penicillin allergy
 - ciprofloxacin 400mg IV followed by vancomycin if life-threatening penicillin allergy
- Investigations: full blood examination, urea and electrolytes, INR, APTT, glucose, lactate
- Commence 30 minute monitoring and documentation of vital signs for two hours

*SIRS criteria: temperature $< 36^\circ\text{C}$ or $> 38^\circ\text{C}$, heart rate > 90 bpm, respiratory rate $> 20/\text{min}$, white cell count < 4 or $> 12 \times 10^9/\text{L}$.

SIRS, systemic inflammatory response syndrome; IV, intravenous; SBP, systolic blood pressure; INR, international normalised ratio; APTT, activated prothrombin time; bpm, beats per minute

Figure 1. Primary infections responsible for sepsis[†]

SSI, surgical site infection

* Organ-space surgical site infections were responsible for 15.3% and 34.6% episodes of sepsis in on- and off-pathway groups, respectively ($p=0.012$).

[†] >1 primary site of infection could be ascribed to a single sepsis episode if criteria for >1 infection diagnosis were met.

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Author/s:

Hiong, A;Thursky, KA;Venn, G;Teh, BW;Haeusler, GM;Crane, M;Slavin, MA;Worth, LJ

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