A 10-Year Longitudinal Analysis of Protocol-Based Sepsis Management in a Philippine Tertiary ICU

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Objectives: To compare the outcomes of sepsis management using protocol-based therapy versus non-protocolized care, assessed over 10 years.

Design: Retrospective cohort study, analyzed longitudinally with risk-adjusted control charts, referenced against hospital- and unit-level programs or interventions.

Setting: Private, tertiary teaching hospital ICU in the Philippines.

Patients: Nine-hundred fifty adult patients (19 yr old or older) diagnosed with severe sepsis or septic shock, using 2001 consensus definitions, admitted to the ICU from September 2007 to August 2017.

Interventions: Three iterations of a standard clinical pathway (including early antibiotics, prescribed fluid resuscitation, and hemodynamic management) versus concurrent non-protocolized care.

Measurements and Main Results: Seven-hundred sixty patients were in the protocol-based care group versus 190 in the non-protocolized care group. Protocol-based management was associated with lower hospital mortality (28.4% vs 44.7%; \( p = 0.00 \)) and ICU mortality (24.2% vs 31.6%; \( p = 0.038 \)). There were no differences in ICU or hospital length-of-stay, mechanical ventilator days, or vasoactive days. Risk-Adjusted Cumulative Sum and Risk-Adjusted Exponentially Weighted Moving Average control charts showed that a survival advantage was achieved after 1 year and was sustained over the duration of the study.

Conclusions: Protocol-based management was associated with sustained improvements in the survival of sepsis patients over 10 years in this hospital setting, after a run-in period of 1 year. Hospital- and unit-level interventions may have measurable impacts on the efficacy of sepsis clinical pathways.

Key Words: intensive care unit; quality improvement; resuscitation; retrospective; sepsis

Sepsis remains one of the major causes of ICU admissions worldwide. Early recognition, early resuscitation with IV fluids and vasoactive drugs, control of the source of infection, and early administration of appropriate antibiotics are key actions to decrease mortality and improve survival among patients (1).

Several studies have attempted to estimate the global incidence of sepsis. Current estimates of 30 million new cases and 6 million deaths per year come from a systematic review of national and local population studies. The majority of data come from high-income countries, comprising only 13% of the world population (1). Data on mortality, burden, and prevalence of sepsis in low- and middle-income countries are scarce.

The World Health Organization has urged member states to develop policies for early recognition and treatment of sepsis (2). Several of these, such as Rory’s Regulation in New York State, Sepsis Kills in New South Wales, Australia, and Surviving Sepsis Campaign (SSC) (3), have reduced sepsis mortality in high-income states. Sadly, these policies and practices may not be easily applied in low and lower-middle-income countries (LMICs) (4). It then becomes necessary for clinicians and policymakers to lead local initiatives to improve sepsis-related mortality. These include public health or even hospital-based programs for sepsis prevention, early detection, and delivery of early treatment (2).
Protocol-based (PB) care for sepsis, advocated since the Rivers trial of early goal-directed therapy (EGDT) (5), has since been questioned following the publication of larger studies: the Protocolized Care for Early Septic Shock (ProCESS) trial (6), Protocollated Management in Sepsis trial (7), and Australasian Resuscitation in Sepsis Evaluation (8). These trials did not show any significant improvement in mortality using EGDT over usual care. However, the “usual care” practiced in high-resourced regions that were represented in those trials may not be the norm in LMICs. Indeed, the value of this complex intervention may be different across healthcare settings.

In 2007, a Sepsis Alert Pathway was operationalized in our center. Over 10 years, this pathway had three iterations and was influenced by changes in sepsis guidelines, hospital policies, accreditation standards, and the availability of technology and personnel. In this study, we aim to illustrate the relationship between mortality of patients with sepsis and the implementation and evolution of local PB management in a Philippine tertiary hospital. Secondary outcomes include ICU mortality and length of stay (LOS), hospital LOS, duration of mechanical ventilation, and duration of vasoactive use. To examine mortality trends over time, risk-adjusted control charts were used.

**MATERIALS AND METHODS**

**Population and Sample**

We performed a retrospective cohort of sepsis patients in The Medical City (TMC), a 500-bed private tertiary teaching hospital in Pasig City, Philippines. The TMC ICU is an 18-bed mixed-use unit that follows a semi-closed model of care (intensivists automatically co-manage severely ill patients, including those with sepsis).

All medical records of adult patients 19 years old and above who were admitted in the ICU between October 2007 and September 2017 with a discharge diagnosis that included severe sepsis or septic shock were reviewed. Criteria for inclusion were as follows: 1) suspected infection, 2) at least two of the systemic inflammatory response syndrome (SIRS) criteria, and 3) signs of end-organ damage. Patients who were not admitted in the ICU and those with requested limitations to intensive care (such as do not resuscitate [DNR] status, and refusing intubation, central line insertion, or renal replacement therapy) prior to, or immediately upon, ICU admission, were excluded (Appendix A, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

Data elements extracted included age, gender, and comorbid status. Baseline physiologic variables for calculation of the Acute Physiology and Chronic Health Evaluation (APACHE) II score were obtained. The primary outcome was hospital mortality. Secondary outcomes included ICU mortality, ICU and hospital LOS, and the duration of mechanical ventilation and vasoactive medication use.

The research protocol was approved by the Institutional Review Board with a waiver of informed consent.

**The Sepsis Alert Clinical Pathway**

A multi-professional working group (Appendix B, Supplemental Digital Content 1, http://links.lww.com/CCX/A117), including specialists and trainees from intensive care, infectious diseases and internal medicine, nurses, pharmacists, and administrators constructed the first TMC Sepsis Alert Pathway in September 2007. This pathway was activated upon identification of two of four SIRS criteria and suspected infection (9). It included automatic referrals to Infectious disease and Critical Care services, bundled laboratory tests (such as lactate and cultures) performed immediately upon activation, early broad-spectrum antibiotics within 30 minutes of activation, and fluid resuscitation for hypotensive patients (Appendix C, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

Per hospital policy, clinical pathway activation was dependent on the agreement of admitting physicians, and the activation rate was tracked monthly.

A second iteration of the pathway was developed in January 2011 that expanded on organ dysfunction criteria, the need to treat sepsis-induced hypoperfusion (lactate > 4 mmol/L) as septic shock, and steroid use based on interim guideline updates. Central access and invasive hemodynamic monitoring were considered if initial resuscitation efforts failed to meet targets (Appendix D, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

In August 2013, the pathway underwent revision after the release of the 2012 SSC Guidelines (10). Changes included fluid boluses of 30 mL/kg using balanced electrolyte solutions, and the use of dynamic variables to predict response to further fluid resuscitation.

**Analysis**

Chi-square or Mann-Whitney U tests were used to compare categorical or continuous data. Multiple logistic regression was performed to determine clinical factors associated with hospital mortality.

For mortality trend analysis, control charts were made using two techniques: Risk-Adjusted Cumulative Sum (RA-CUSUM) and Risk-Adjusted Exponentially Weighted Moving Average (RA-EWMA). These two techniques were found to be the most useful for detecting small trend changes with the shortest lag-time (11–13).

Control limits (CLs) for the RA-CUSUM were set to detect a 50% increase or decrease in mortality, with an average run length (ARL) of 60 cases (~6 mo). For the RA-EWMA, variables were set to detect a deviation of mortality beyond the CLs at an ARL of 50 cases (~5 mo). A detailed discussion of these techniques is in Appendix E (Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

Events or policy changes lasting for at least 6 months that had a potential effect on mortality were plotted against the control charts. These included the hospital-wide launches of the three sepsis protocols, the beginning of training programs in Critical Care Medicine (2010) and Emergency Medicine (2014), and the availability of new technology (such as point-of-care ultrasound).

For all statistical tests, p value of less than 0.05 was considered to indicate statistical significance. SPSS 23 (IBM, Chicago, IL) was used for statistical analysis.

**RESULTS**

From October 2007 to September 2017, 1,782 patients were diagnosed with severe sepsis and septic shock, of which 832 patients were excluded (Fig. 1). Nine-hundred fifty patients were included...
in the analysis, 760 in the PB group and 190 in the non-protocolized (NP). Baseline characteristics showed a lower male-to-female ratio, greater number of patients with no comorbidities, and a higher temperature upon presentation in the PB group (Table 1; and Appendix F, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

Table 1. Baseline Characteristics of the Population

| Patient Characteristics               | Protocol-Based, n = 750 | Non-Protocolized, n = 190 | p   |
|---------------------------------------|-------------------------|---------------------------|-----|
| Demographics                          |                         |                           |     |
| Median age, median (IQR)              | 69 (55–80)              | 67 (56–79)                | 0.84a|
| Female, n (%)                         | 433 (57)                | 81 (42.6)                 | 0.00b|
| Septic shock, n (%)                   | 615 (80.9)              | 144 (75.8)                | 0.12a|
| Focus of infection, n (%)             |                         |                           |     |
| Respiratory                           | 501 (65.9)              | 121 (63.7)                | 0.56a|
| Skin/soft tissue                      | 107 (14.1)              | 17 (8.9)                  | 0.06a|
| Genitourinary                         | 274 (36.1)              | 42 (22.1)                 | 0.00a|
| Blood                                 | 53 (7)                  | 17 (8.9)                  | 0.35a|
| Gastrointestinal                      | 109 (14.3)              | 45 (23.7)                 | 0.002a|
| CNS                                   | 12 (1.6)                | 3 (1.6)                   | 0.10a|
| Baseline laboratory and clinical variables, median (IQR) | | | |
| WBC (× 10⁹ cells/mm³)                 | 14.5 (8.9–20.2)         | 14.6 (8.9–22)             | 0.56a|
| Temperature (°C)                      | 38.0 (37.2–39.0)        | 37.9 (36.9–38.8)          | 0.01a|
| Lactate (mmol/L)                      | 2.76 (1.66–4.30)        | 2.82 (1.84–5.01)          | 0.46a|
| Creatinine (mg/dL)                    | 1.36 (0.84–2.47)        | 1.21 (0.71–2.6)           | 0.08a|
| Mean arterial pressure (mm Hg)        | 63 (56–70)              | 60 (55–71)                | 0.76a|
| Heart rate (beats/min)                | 105 (88–120)            | 104 (88–121)              | 0.80a|
| Acute Physiology and Chronic Health Evaluation II score | 20 (14–27)              | 21 (16–28)                | 0.13a|

IQR = interquartile range.

χ² test.

Mann-Whitney U test.

Median age was 69 years (interquartile range [IQR], 55–80 yr) for PB and 67 years (IQR, 56–79 yr) for the NP group. Majority of sepsis patients were identified at the emergency room (60.9% in PB, 53.2% in NP) and required vasopressor therapy (80.9% in PB, 75.8% in NP). The respiratory tract was the most common site of infection in both groups (65.9% in PB, 63.7% in NP).

Hospital mortality was higher for the NP group (44.7%) compared with the PB group (28.4%; odds ratio [OR], 0.5; p = 0.00) (Table 2).

As cohort characteristics showed differences in the proportions of female patients, cirrhosis and urosepsis, and because pathway activation rate varied over time, a propensity-matched analysis was performed post hoc. Using program year, gender, comorbid status, initial vital signs, patient origin, and sepsis source as predictors for protocolized therapy, a propensity-matched cohort of 380 patients was developed (Appendix G, Supplemental Digital Content 1, http://links.lww.com/CCX/A117). Analysis of mortality rates showed 43.2% for NP, and 33.2% for PB (p = 0.045), consistent with the primary outcome analysis.

ICU mortality was also higher in the NP group (31.6% vs 24.2%; OR, 0.69; p = 0.038). There were no significant differences in the other secondary outcomes (Table 2): ICU stay was 3–4 days (IQR, 2–7 d), hospital stay was 8–9 days (IQR, 4–17 d), duration of mechanical ventilation was 3–4 days (IQR, 2–8 d), and duration of vasoactive therapy was 2 days (IQR, 1–4 d).
Logistic regression showed that an APACHE II score greater than or equal to 25 and lactate greater than or equal to 4 mmol were independently associated with mortality, with OR 5.3 (95% CI, 3.9–7.2; $p = 0.00$) and 2.6 (95% CI, 1.9–3.7; $p = 0.00$), respectively. PB management was independently associated with decreased mortality, OR 0.5 (95% CI, 0.4–0.7; $p = 0.00$; Appendix H, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

The RA-CUSUM chart of the whole population (Fig. 2) revealed a halving of mortality rate in July 2009 until May 2011, then in April 2012 until the end of the study period. This second downward inflection of the slope of RA-CUSUM appeared six months following the introduction of a radiofrequency identification (RFID)-based solution for improving hand hygiene in ICU. There was a decrease in mortality below the lower CL for the PB group starting June 2009 until the end of the study (Appendix E, Supplemental Digital Content 1, http://links.lww.com/CCX/A117; and Fig. 2).

The RA-EWMA chart showed that the expected mortality of the entire population decreased over time. Actual mortality remained below the upper CL since May 2008, and breached the lower CL starting January 2015 (Fig. 3). However, the observed mortality of the NP group remained above the upper CL throughout the study (Appendix E, Supplemental Digital Content 1, http://links.lww.com/CCX/A117).

**DISCUSSION**

This single-center retrospective cohort study represents the largest dataset of sepsis patients in the Philippines. We found that PB management was associated with decreased hospital mortality (OR, 0.5; $p = 0.00$) and ICU mortality (OR, 0.69; $p = 0.038$) in patients with sepsis admitted to ICU. This association was consistent over 10 years, over three protocol iterations.

EGDT, the first model of PB sepsis management, achieved lower mortality and less severe organ dysfunction compared with standard therapy (5). However, three large multicenter studies (6–8) done to validate EGDT showed no survival benefit over usual care, but only an increased patient exposure to invasive procedures. It has been argued that the differences in results may be attributed to the 15-year gap between Rivers and the newer trials, such that the “usual care” in the studies were not comparable.

The ProCESS trial reported a third patient group, who were randomized to receive “Protocol-Based Standard Therapy” (6). This differed with EGDT in some aspects: central venous catheter placement only if peripheral access was insufficient, fluids and vasoactive agents titrated to goals for systolic blood pressure and shock index, and conservative red cell transfusions.

During the first years of implementation, our clinical pathway was patterned after EGDT. Its most recent iteration is similar to the Protocol-Based Standard Therapy in ProCESS: initial fluid resuscitation of 30 mL/kg followed with standard therapy (5). However, three large multicenter studies (6–8) done to validate EGDT showed no survival benefit over usual care, but only an increased patient exposure to invasive procedures. It has been argued that the differences in results may be attributed to the 15-year gap between Rivers and the newer trials, such that the “usual care” in the studies were not comparable.

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**Figure 2.** Risk-Adjusted Cumulative Sum chart of entire population. Blue series—maximum function with $R_A$ of 1.5 ($R_A$ is the odds ratio for mortality that the chart is designed to detect). Orange series—minimum function with $R_A$ of 0.5. Red series—quarterly pathway activation rates. Dashed lines indicate control limits at 1.5 and −1.5. Implementation of institutional changes and events are marked as follows: A, pilot study of sepsis alert pathway (September 2007), B, hospital-wide launch of first version of the sepsis alert pathway (May 2008), C, start of fellowship in Critical Care Medicine (April 2010), D, implementation of rapid response system (October 2010), E, implementation of radiofrequency identification in ICU (January 2011), F, start of residency in emergency medicine (September 2014), G, purchase of ultrasound machine dedicated to the ICU (September 2014), and H, management directive regarding pathway activation (July 2016). Pathway version in implementation differentiated by the background: blue—version 1, yellow—version 2, red—version 3.
In the RA-EWMA charts, the observed mortality of the NP group exceeded predicted mortality throughout the duration of the study (Appendix E, Supplemental Digital Content 1, http://links.lww.com/CCX/A117; and Fig. 6). This suggests that unlike in other settings, where “institutional learning” was posited as a mechanism for better outcomes in “usual care” groups, patients in our system seemed to benefit from a degree of protocolization or, conversely, appeared to be harmed by “usual care.”

### TABLE 2. Primary and Secondary Outcomes

| Outcome                                    | Protocol-Based, n = 750 | Non-Protocolized, n = 190 | \( p \) |
|--------------------------------------------|-------------------------|----------------------------|--------|
| Primary outcome, \( n \) (%)               |                         |                            |        |
| Hospital mortality                         | 216 (28.4)              | 85 (44.7)                  | 0.00*  |
| Secondary outcomes                         |                         |                            |        |
| ICU mortality, \( n \) (%)                 | 184 (24.2)              | 60 (31.6)                  | 0.038* |
| Days in the ICU, median (IQR)              | 3 (2–6)                 | 3 (2–7)                    | 0.13*  |
| Days in the hospital, median (IQR)         | 8 (5–16)                | 9 (5–15)                   | 0.38*  |
| Need for mechanical ventilation, \( n \) (%) | 399 (53.2)              | 110 (57.9)                 | 0.18*  |
| Days on mechanical ventilation, median (IQR) | 4 (2–8)                 | 3 (2–7)                    | 0.15*  |
| Need for vasopressor, \( n \) (%)         | 615 (80.9)              | 144 (75.8)                 | 0.11*  |
| Days on vasopressor, median (IQR)          | 2 (1–4)                 | 2 (1–4)                    | 0.47*  |

*IQR = interquartile range.

*\( \chi^2 \) test.

*Mann-Whitney \( U \) test.
Our findings also differ from the study on hypotensive septic patients in Zambia, where protocolized hemodynamic resuscitation led to significantly increased in-hospital mortality (14). This has led to the suggestion that protocolization may be harmful in resource-limited settings. Our results suggest that the benefits of protocolization follows a nonlinear curve whose inflection points reflect differences in baseline healthcare delivery capability.

APACHE II scores in this study (20, IQR 14–27 in PB and 21, IQR 16–28 in NP) are similar to that of the three groups on ProCESS (mean ± sd 20.8 ± 8.1 in EGDT, 20.6 ± 7.4 in protocol-based standard therapy, and 20.7 ± 7.5 in usual care) (6), indicating similar severity of illness. Mortality in ProCESS was only 19.3% (vs 32% in our population); 18.2% for their protocol-based standard therapy (28.4% in PB), suggesting that further gains are still possible for our model of protocolized care, while also recognizing that some attributable mortality lies outside the scope of the clinical pathway.

There were no significant differences in ICU or hospital LOS, mechanical ventilation days, or duration of vasoactive therapy between groups.

There are several limitations of this study beyond those intrinsic to a single-center retrospective cohort design:

The annual pathway activation compliance was 75–87% of all eligible patients throughout the study (Appendix I, Supplemental Digital Content 1, http://links.lww.com/CCX/A117). Clinician resistance to the complete pathway did not appear to influence the early administration of broad-spectrum antibiotics: 74.7% of the NP and 77.1% PB patients received broad-spectrum antibiotics within 30 minutes of sepsis diagnosis (p = 0.4), suggesting that at least this component was widely accepted.

The most cited reasons for nonactivation included perceived costs of care, healthcare being a substantial out-of-pocket expenditure for many in the Philippines (15), perceived poor prognosis upon admission, and physician disagreement with the sepsis diagnosis. Nonactivation occurred in spite of hospital policies requiring reporting (and administrative sanction) of physician noncompliance with clinical pathways, continuous education programs regarding sepsis, and advocacy activities (such as the World Sepsis Day). This illustrates the challenge faced by healthcare organizations in our setting to administer a complex clinical pathway.

A substantial number of patients (n = 609) in the ICU had limitations to therapy (including DNR or do-not-intubate orders) requested upon or shortly after admission and were excluded from our analysis, as our original intent was to compare the outcomes of patients with full commitment to critical care. However, we recognize that these excluded patients could be the subject of a follow-up report.

This study was also not designed to identify the specific components of the Sepsis Alert Pathway that were critical in improving mortality. Besides the stipulated therapies within the pathways, many treatments or procedures (e.g., stress-dose steroids, recruitment maneuvers for acute respiratory distress syndrome) were performed or foregone in a nonsystematic fashion over a decade. Furthermore, the 2001 International Sepsis Definitions (9) were used throughout the duration of the study. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (16) have not yet been applied.

CONCLUSIONS

This 10-year single-center retrospective cohort showed that the use of PM management of severe sepsis and septic shock was associated with a decreased hospital mortality for patients. This mortality benefit was preserved over time and through three iterations of the protocol. Protocolized management of sepsis appears to be advantageous, while a reliance on “usual care” may be detrimental, in our setting. Finally, unit- or hospital-level interventions can impact the performance of our clinical pathways.

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