Critical Illness-Related Corticosteroid Insufficiency (CIRCI) among Patients with Refractory Shock at a Tertiary Hospital: A Look into Clinical Practices and Patient Outcomes

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ABSTRACT

Introduction. A significant number of critically ill patients, as high as 60% among patients with septic shock, suffer from critical illness-related corticosteroid insufficiency (CIRCI), which refers to an inadequate corticosteroid response to the level of stress.

Objectives. This study aimed to determine the strategies employed in managing patients with critical illness-related corticosteroid insufficiency and the outcomes of these patients at a tertiary hospital.

Methods. This was a single-center, mixed-methods study which consisted of a review of charts of patients 19 years old and above admitted for shock or developed refractory hypotension from January 2017-December 2019, and key informant interviews and focus group discussion among clinicians who have experience in managing CIRCI.

Results. A total number of 362 patient charts reviewed showed a relatively low rate of initiation of corticosteroids for patients with refractory shock, at just 28.57% of the entire population. After corticosteroids were initiated, patients were in shock for a median of just one day and the median blood pressure improved to 100/60 mm Hg. In this cohort, patients who were started on steroids had more severe illness, as measured by the Mortality Probability Model (MPM) score, which had a median of 43.65% for the group on steroids and just 25.0% for the non-steroid group ($p \leq 0.0001$). Patients who were started on steroids had a statistically significant longer median days on a ventilator, 5 days vs. 3 days for the non-steroid group ($p = 0.0297$); longer median length of intensive care unit (ICU) stay, 8 days vs. 5 days for the non-steroid group ($p = 0.0410$), and a higher morbidity and mortality rate. The need for steroids, the presence of septic shock, and a higher MPM score were significant predictors of mortality.

Discussions among clinicians revealed significant variability in practices in the management of CIRCI.

Conclusion. The presence of clinical features of CIRCI is a poor prognostic factor. Timely recognition, work-up, and interventions to address CIRCI are paramount in critical care.

Key Words: critical illness-related corticosteroid insufficiency, shock

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INTRODUCTION

A significant number of critically ill patients suffer from critical illness-related corticosteroid insufficiency (CIRCI), which refers to an inadequate corticosteroid response to the level of stress. The incidence of CIRCI can be as high as 60% in patients experiencing septic shock.[1] In various in-hospital populations, the incidence of CIRCI among patients with sepsis ranged from 12% to as high as 75%.[2] These critically ill patients usually present with refractory hypotension and are at increased risk for prolonged vasopressor and ventilator dependence and mortality. Dysregulated systemic inflammation contributes to organ dysfunction and poorer health outcomes. Corticosteroids, by addressing the pro-inflammatory state, initiate tissue repair and improve tissue and organ perfusion. Clinical studies such as CORTICUS have demonstrated that patients started on corticosteroids had a reduced period on vasopressor therapy, were weaned off earlier from the mechanical ventilator, leading to a shorter length of hospital stay.[3]

CIRCI stems from three major pathophysiologic defects: dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis; altered cortisol metabolism; and tissue resistance to glucocorticoids. Acute conditions such as sepsis, septic shock, severe community-acquired pneumonia, acute respiratory distress syndrome (ARDS), cardiac arrest, head injury, trauma, burns, and post-major surgery can present with CIRCI.[3] One report states a twenty-fold higher incidence of symptomatic adrenal insufficiency in critically ill patients being managed in the intensive care unit for more than two weeks.[4]

Due to the complexity of the conditions of patients suffering from CIRCI, establishing the diagnosis itself presents a challenge. The 2008 Consensus statements for the Diagnosis and Management of CIRCI in Adult and Pediatric patients recommend that the diagnosis should be established by an increase in total cortisol at 60 minutes from baseline to <9 μg/dL after a 250-μg cosyntropin (ACTH) stimulation test or random total cortisol <10 μg/dL.[4] In 2017, a guideline on the diagnosis and management of CIRCI released by the Society of Critical Care Medicine and European Society of Intensive Care Medicine stated that delta cortisol (change in baseline cortisol at 60 min of <9 μg/dL) after cosyntropin (250 μg) administration and random plasma cortisol of <10 μg/dL might be utilized by physicians for diagnosing CIRCI.[5] In one study, it was found that a cortisol value of less than 15 μg/dL correlated with an abnormal response to the ACTH test, while a cortisol level of more than 34 μg/dL predicted a normal reaction to the ACTH test.[2] The diurnal variation of cortisol is lost during critical illness. In patients with septic shock, a decreased response to the ACTH test marked by a serum cortisol level less than 9 μg/dL is associated with an increased mortality rate.[6] These laboratory findings, along with a clinical setting for CIRCI, and the presence of refractory hypotension or increasing vasopressor requirements, make the diagnosis of CIRCI highly likely.

Corticosteroids are an essential aspect in the management of CIRCI. Recent evidence has demonstrated that low dose corticosteroids (200-300 mg of hydrocortisone per day) given for a prolonged period (greater than or equal to 3 days) are sufficient in addressing the dysregulated inflammatory response in CIRCI and in improving hemodynamic stability and survival with no significant risk of adverse events.[5]

A timely response to the presence of CIRCI is vital in reducing morbidity and mortality among critically ill patients. Even if a patient is only suspected of having CIRCI, management must commence because of the high mortality rate associated with this condition. Various studies have demonstrated that CIRCI is a harbinger of poor outcomes. CIRCI patients with delta cortisol of less than 9 mcg/dL had a significantly higher 28-day mortality (39.3%) compared to those with a baseline cortisol level of less than 10 mcg/dL (10%) and non-CIRCI patients (6.3%), according to an investigation by Yang et al.[7] In a local study done at the Philippine General Hospital (PGH) which included 50 patients, patients with CIRCI as defined by non-responders to the ACTH test had a longer duration of vasopressor dependence (5.9 days in patients with CIRCI vs. 3.5 days in patients without CIRCI) and had a significantly higher rate of mortality (75% in patients with CIRCI vs. 33.3% in patients without CIRCI).[8]

Currently, in many institutions worldwide, there is variation and inconsistency in clinical practice in the evaluation and management of patients with CIRCI. For instance, Karir et al. found in their investigation of a tertiary institution (Harborview Medical Center in Seattle, USA) that only 58% of the 81 patients who met the vasopressor-dependent septic shock criteria were evaluated and managed for CIRCI.[9] At another University Medical Center in the United States, which included 47 patients diagnosed with severe sepsis or septic shock, only 13% were started on corticosteroids in the emergency room. In contrast, only 49% were given corticosteroids in the intensive care unit.[10] In a local study done at the Medical Intensive Care Unit of the PGH, only less than half (46.6%) of the non-survivors and 60% of the survivors with adrenal insufficiency were given glucocorticoids, which is the cornerstone of management in patients with CIRCI.[8]

Addressing CIRCI is vital in ensuring the optimal care of critically ill patients because of the high prevalence of this condition. More than half of patients with septic shock have CIRCI, and sepsis and septic shock remain the leading causes of mortality across the different areas of the hospital – comprising 40.51% of emergency room mortalities and 42% of ward mortalities based on the area census reports of the Department of Medicine of the PGH. Sepsis presents a significant challenge to health service delivery in many institutions such as the PGH. Reducing morbidity and mortality from sepsis entails holistic management of the critical condition, which includes targeting CIRCI, a key contributor to the deterioration of patients. This study, which

is the first phase of a research initiative on the development and pilot testing of an in-hospital protocol for CIRCI, aims to determine the strategies employed in managing patients with CIRCI and the outcomes of these patients at the PGH. Such an initiative seeks to provide baseline data on the management of CIRCI at PGH, which is vital in formulating a protocol that addresses the challenges of responding to this life-threatening condition.

METHODS

Study Design

This was a single-center, mixed methods, retrospective observational study that involved a qualitative assessment of the management of patients with refractory shock suspected to have CIRCI at the PGH. It consisted of a chart review conducted on patients 19 years old and above admitted for shock or developed refractory hypotension from January 2017-December 2019. The qualitative aspect of the research comprised of key informant interviews and focus group discussions among clinicians from various specialties who have experience in managing CIRCI. This mixed-methods study is a preliminary study to a research endeavor that aims to create an in-hospital protocol for the diagnosis and management of CIRCI.

Study Population

For the retrospective chart review, all patients aged 19 years old and above with an admitting diagnosis of shock or developed refractory hypotension during the admission (i.e., requiring at least 0.2 mcg/kg/min of Norepinephrine or its equivalent dose with another vasopressor or with increasing vasopressor requirement) were assessed for the management of suspected CIRCI. Refractory hypotension or shock is defined as systolic blood pressure of persistently < 90 mm Hg after hypovolemia is addressed through adequate fluid resuscitation for at least 30 minutes, need for a vasopressor to maintain adequate organ perfusion, and signs of hypoperfusion such as tachycardia, altered mental status, confusion or encephalopathy, cold extremities, oliguria, and blood lactate > 2 mmol/L.[6]

Clinicians, both residents from Internal Medicine and subspecialty fellows who have direct experience in managing patients suspected to have CIRCI, were asked to participate in key informant interviews and focus group discussions.

Data Collection

To ensure that all eligible patients were included in the retrospective analysis, various hospital-generated reports were screened to detect cases of interest in this study. The list of patients was obtained from the manual review of the Department of Medicine's disease indices and census reports. Data collectors also utilized the ICD-10 (International Classification of Diseases) codes of septic shock (R65.21), cardiogenic shock (R57.0), and adrenal insufficiency (E27.2-E27.4) to thoroughly search for the admissions records so that cases of probable CIRCI would not be missed. All patients with available medical records fulfilling the conditions previously stated were included in this retrospective chart review. Upon retrieval of records, patients on vasopressors during the admission who were started on corticosteroids and those who were not given corticosteroids were both included in the analysis. Patients listed in the medical census but with no available medical records were excluded from this study. Upon retrieval of the records, patients who were weaned off vasopressors immediately upon additional fluid resuscitation or loading of antibiotics were excluded from the analysis because such patients were less likely to have suffered from CIRCI.

Residents and subspecialist fellows with experience in managing patients with probable CIRCI were asked to participate in the key informant interview and focus group discussion. The participants' inquiries focused on the management of patients with refractory shock, when CIRCI should be suspected, how CIRCI is diagnosed and managed, and the possible impact on patient care of an institutional protocol for managing CIRCI. Investigators facilitated the discussion through the questions set before the interviews. The proceedings of the discussion were recorded and subjected to thematic analysis.

Outcomes

This retrospective cohort study determined baseline characteristics such as the median age, proportion of males and females, median blood pressure, the top etiologies of shock, vasopressor dose, number of days on vasopressors, ventilator days, length of intensive care unit (ICU) stay, length of hospital stay, and morbidity and mortality rates of patients admitted at PGH from 2017-2019 for refractory shock, in whom, CIRCI was suspected.

The rates of using corticosteroids, along with the type of corticosteroid initiated and the dose, for patients with probable CIRCI were determined. Clinical outcomes such as the number of days in shock, blood pressure, and vasopressor dose, that ensued after corticosteroids were initiated were obtained.

A comparison of the clinical outcomes regarding the number of days on vasopressors, ventilator days, vasopressor requirement, length of ICU stay, length of hospital stay, morbidity and mortality rate, and the ICU severity of illness score in the form of Mortality Probability Model (MPM) of the patients in refractory shock who were started on steroids and who were not started on steroids was made.

Within the group of patients who were started on steroids, a comparison of the clinical outcomes regarding the number of days on vasopressors, ventilator days, vasopressor requirement, length of ICU stay, length of hospital stay, morbidity and mortality rate, and the ICU severity of illness score in the form of MPM of the patients who were given hydrocortisone and those who were given other types of

corticosteroids such as dexamethasone, prednisone and methylprednisolone were made. The same clinical outcomes were measured for patients who were started on different doses of hydrocortisone: <200 mg/day, exactly 200 mg/day, and >200 mg/day.

Qualitative information on clinicians' baseline knowledge and practices regarding diagnosing and managing CIRCI was obtained from key informant interviews and focus group discussions.

Statistical Methods

The analysis of the data obtained from the retrospective chart review was performed using Stata Version 15.1. In determining the baseline characteristics of patients with CIRCI, the median and range were used as summary measures because almost all quantitative variables were not normally distributed. The distribution was tested using the Shapiro-Wilk test of normality. Qualitative variables were reported using count and proportion or rate. In comparing the groups started on steroids and those who were not started on steroids, and between the hydrocortisone group and the non-hydrocortisone group, the Mann-Whitney U test of the difference between the medians of two groups and the Z test of two proportions were employed. The groups utilizing various doses of hydrocortisone were analyzed using the Kruskal-Wallis test of the difference between medians of more than two groups and the Chi-square test of homogeneity (proportion) of more than two groups. A multivariate logistic regression analysis was employed to determine the predictors of mortality among patients with CIRCI.

Ethical Issues

This retrospective, mixed methods, observational study was approved as the Phase 1 arm of the research on "The Development and Pilot Testing of a Protocol for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency for Patients Admitted with Shock at the Philippine General Hospital" by the University of the Philippines Manila Research Ethics Review Board with the UPMREB code 2019-505-01. There is a waiver of consent for patients who satisfy the criteria for probable CIRCI for inclusion into the registry of the study for the retrospective chart review as no personal data was collected. For key informant interviews and focus group discussions, participation was voluntary, and informed consent was obtained. The reporting of the findings of these discussions was anonymized to protect participant identities.

RESULTS

Study Population

A comprehensive review of all the patient lists and census yielded 440 patients admitted for shock during the years 2017-2019 at the different sites of care (emergency room, wards, and intensive care unit) of the PGH. Only those with the vasopressor requirement for norepinephrine or epinephrine reaching at least 0.2 mcg/kg/min were included in the final analysis. After excluding patients who were weaned off from vasopressors immediately or brought out of shock rapidly in less than 24 hours after instituting fluid resuscitation or loading of antibiotics for septic shock or administration of an inotrope such as dobutamine for cardiogenic shock, the total number of patients analyzed was 362. Table 1 shows the profile and outcomes of patients with probable CIRCI admitted at PGH from 2017-2019. The median age of the patients was about 53 years old (range of 19-89 years old), and the population cohort predominantly consisted of males, at 60.5% of the population. The top three etiologies of shock were septic, cardiogenic, and multifactorial. Patients in the study were either on one, two, or three vasopressors, with the median doses of the vasopressors ranging from 0.4-0.55 mcg/kg/min. The included patients in the study were on vasopressors for a median of 3 days (range of 0-33 days). For the 107 patients who had acute respiratory failure, the median number of days on a ventilator was 4 days (range of 1-97 days). The median length of an ICU stay was 5 days (range of 1-24 days), and the median length of the entire hospital stay was 10 days (range of 1-136 days). The mortality rate for the entire study population, which consisted of critically ill patients, was relatively high at 32.60%.

Due to the inconsistent availability of the reagent for random serum cortisol, which was obtained through the

Table 1. Clinical Characteristics and Outcomes of Patients with Probable Critical Illness-Related Corticosteroid Insufficiency Admitted at PGH from 2017-2019

Age (years), median (range)	53.5 (19 – 89)
Sex, count (percent)	
Males	219 (60.50%)
Females	143 (39.50%)
Blood Pressure, count (percent)	
Hypotensive (<90/60)	270 (74.59%)
Not Hypotensive (≥90/60)	92 (25.41%)
Top 3 Diagnoses	
Top 3 Etiologies of Shock, count (percent)	
Septic	203 (56.08%)
Cardiogenic	135 (37.29%)
Multifactorial	19 (5.25%)
Vasopressor Dose (mcg/kg/min), median (range)	
On 1 vasopressor	0.4 (0.1 – 10)
On 2 vasopressors	0.55 (0.1 – 16.85)
On 3 vasopressors	0.55 (0.3 – 17.8)
Number of Days on Vasopressors, median (range)	3 (0 – 33)
Number of Days on Ventilator, median (range)	4 (1 – 97)
Length of ICU Stay, median (range)	5 (1 – 24)
Length of Entire Hospital Stay, median (range)	10 (1 – 136)
Morbidity, count (rate)	107 (29.56%)
Mortality, count (rate)	118 (32.60%)

radioimmunoassay method during the years 2017-2019 in this resource-limited setting, there was low utilization of this diagnostic exam. Random serum cortisol level results were only found among four patients in this study cohort, and the range of cortisol levels was from 12.29 mcg/dL to 23.27 mcg/dL, with a median of 17.68 mcg/dL. All of them presented with symptoms and signs consistent with CIRCI.

Use of Corticosteroids for Refractory Shock

There was a relatively low rate of initiation of corticosteroids for patients with refractory shock, at just 28.73% of the entire study population. Variation in the type and dose of corticosteroid used was also observed. Some patients were started on hydrocortisone ranging from 50 mg-300 mg/day, while others were treated with other types of corticosteroids such as prednisone, dexamethasone, and methylprednisolone. Among patients started on hydrocortisone, less than half, at 45.35%, was at exactly 200 mg/day of hydrocortisone, which is the recommended dose for CIRCI. This dose of 200 mg/day of hydrocortisone for CIRCI is equivalent to about 0.8-1 mg/kg body weight of prednisone. In this cohort, steroids were initiated in 78.45% of the patients, corresponding to 284 out of the 362 patients in the cohort, in less than 24 hours of vasopressor-dependent shock. About 9.67% of the cohort were given steroids within 24 hours of vasopressor-dependent shock. However, as many as 42 patients, making up 11.6% of the cohort, were started on steroids beyond 24 hours from the onset of shock. Several patients received corticosteroids at 14 days and even at 18 days of vasopressor dependence. There was also variation in the duration of administration of steroids, with a median of just two days and a range of 0-14 days. The loading doses for the corticosteroids also varied; some were given a loading dose of 50 mg, 100 mg, and 200 mg of hydrocortisone. Patients who were started on prednisone had doses ranging from 10-40 mg of prednisone/day, while those given methylprednisolone were at 1 g of methylprednisolone per day. For the dexamethasone group, there was significant variation in the mode of administration and the dosing of the drug; with some patients receiving the oral form, while others were receiving the intravenous form, with the dose ranging from 4 mg-15 mg/day. After corticosteroids were initiated, the patients were in shock for a median of just one day, the median vasopressor dose was at 0.4 mcg/kg/min (from an initial median dose of 0.4 mcg/kg/min for those with one vasopressor and 0.55 mcg/kg/min for those with two or three vasopressors), and the median blood pressure improved to 100/60 mm Hg. Table 2 summarizes the use of corticosteroids for this cohort group.

Table 2. Use of Corticosteroids for Patients with Probable Critical Illness-Related Corticosteroid Insufficiency Admitted at PGH from 2017-2019

Corticosteroid Use, count (rate)	104 (28.73%)
Hydrocortisone	86 (83.50%)
<200 mg/day	20 (23.26%)
200 mg/day	39 (45.35%)
>200 mg/day	27 (31.40%)
Non-hydrocortisone	17 (16.50%)
Number of Days in Shock when Corticosteroids were Initiated, median (range)	1 (0 – 18)
Days on Corticosteroids, median (range)	2 (0 – 14)
Blood Pressure after Corticosteroids were Initiated, count (percent)	
Improved	8 (8.70%)
Still Hypotensive	84 (91.30%)
Dose of Vasopressors (mcg/kg/min) after Corticosteroids were Initiated, median (range)	0.4 (0.1 – 17.8)

Use of Corticosteroids and Patient Outcomes

Patients who were started on steroids had a statistically significant longer median days on a ventilator at 5 days vs. 3 days for the non-steroid group ($p = 0.0297$), a longer median length of ICU stay at 8 days vs. 5 days for the non-steroid group ($p = 0.0410$), and a higher morbidity rate at 49.04% vs. 21.71% for the non-steroid group and a higher mortality rate at 50.0% vs. 25.58% for the non-steroid group (Table 3). No statistically significant difference was detected in terms of the number of days on vasopressors, the highest vasopressor requirement reached, and the entire hospital stay. However, it is notable that patients who were started on steroids had more severe illness, as measured by the MPM score, which had a median of 43.65% for the group on steroids and just 25.0% for the non-steroid group ($p \leq 0.0001$).

The patients in the hydrocortisone group and the non-hydrocortisone group did not exhibit any statistically significant difference in terms of clinical outcomes. Similarly, comparisons between those who were started on different doses of hydrocortisone (<200 mg/day, 200 mg/day, and >200 mg/day) did not also reveal any statistically significant differences in patient outcomes.

A multivariate logistic regression analysis was done to establish the predictors of mortality among patients with refractory shock admitted at this tertiary hospital. The analysis revealed that the need for steroids, the presence of septic shock, and a higher MPM score are significant predictors of mortality among patients with CIRCI (Table 4).

Baseline Clinical Practices and Clinicians' Perspectives and Practices on CIRCI

Four clinicians with direct experience in managing critically ill patients with refractory shock in this tertiary hospital participated in the focus group discussions and key informant interviews. The respondents consisted of three clinicians who completed their Internal Medicine training and one fellow in Pulmonary and Critical Care Medicine. This pool of participants enabled us to reach saturation point. These clinicians were asked to share their inputs on the following questions:

Table 3. Comparison of Groups of Patients Started on Corticosteroids and Those Without Use of Corticosteroids (n = 362)

	With Use of Steroids (n = 104)	Without Use of Steroids (n = 258)	p-value
Number of Days on Vasopressors, median (range)	4 (0 – 33)	3 (0 – 30)	0.0716
Number of Days on Ventilator, median (range)	5 (1 – 97)	3 (1 – 64)	0.0297
Highest Vasopressor Requirement, median (range)			
Vasopressor 1	0.5 (0.1 – 11.9)	0.5 (0.1 – 30)	0.1036
Vasopressor 2	0.8 (0.13 – 22)	0.8 (0.1 – 20)	0.7163
Vasopressor 3	10 (8.5 – 10)	7.5 (0.3 – 15)	0.5896
Length of ICU Stay, median (range)	8 (1 – 24)	5 (1 – 21)	0.0410
Length of Entire Hospital Stay, median (range)	11 (1 – 105)	10 (1 – 136)	0.9486
Morbidity, count (rate)	51 (49.04%)	56 (21.71%)	<0.0001
Mortality, count (rate)	52 (50.00%)	66 (25.58%)	<0.0001
MPM score (%), median (range)	43.65 (2.6 - 90.7)	25.0 (6.7 – 98.4)	<0.0001

Table 4. Factors Associated with Mortality in Patients with Critical Illness-Related Corticosteroid Insufficiency Admitted at PGH from 2017-2019

Factors	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Steroid use	2.91	[1.91, 4.68]	<0.001	2.01	[1.16, 3.49]	0.013
Etiology of shock						
Septic	Reference			Reference		
Cardiogenic	0.25	[0.15, 0.43]	<0.001	0.50	[0.28, 0.91]	0.024
Multifactorial	0.46	[0.16, 1.32]	0.147	0.48	[0.15, 1.55]	0.222
Others	0.85	[0.14, 5.22]	0.864	0.34	[0.04, 2.86]	0.325
Days in shock when steroids were started	0.99	[0.89, 1.11]	0.886	-	-	-
Days on steroids	0.88	[0.77, 1.01]	0.066	-	-	-
Hypoglycemia	2.08	[0.13, 33.5]	0.606	3.34	[0.2, 56.39]	0.402
MPM score	1.04	[1.03, 1.06]	<0.001	1.04	[1.03, 1.05]	<0.001

1. How do you manage patients with increasing vasopressor requirements or refractory hypotension?
2. When should we suspect that a patient has critical illness-related corticosteroid insufficiency?
3. When do you usually start steroids for patients with critical illness-related corticosteroid insufficiency?
4. How do you initiate steroids in patients with CIRCI? At what dose and over how many days?
5. What laboratory tests do you usually send for patients suspected of having CIRCI?
6. How do you taper the dose of steroids in patients with CIRCI?
7. How do you evaluate such patients for discontinuation of steroids?
8. Do you think a protocol for managing patients suspected to have CIRCI will help you in clinical decision-making and management of such patients?
9. What are the outcomes of patients with CIRCI that you have encountered in clinical practice here at PGH?
10. What issues, gaps, or barriers to adherence to the protocol on managing patients with CIRCI do you think are present in our institution?

Substantial variability in the threshold for suspecting CIRCI was observed among clinicians. Some clinicians would consider working up for CIRCI when the patient is already on a second or third vasopressor. In contrast, others would immediately facilitate an investigation for the presence of CIRCI when a critically ill patient failed to respond to adequate fluid resuscitation and other management strategies such as the administration of antibiotics for septic shock or inotropes for cardiogenic shock. Most clinicians initiate management for CIRCI late into the course of the disease; after all other etiologies of shock have been addressed. The majority of the respondents diagnosed CIRCI based on a favorable hemodynamic response to the administration of steroids rather than by obtaining the random cortisol level. The lack of availability of the random cortisol diagnostic exam at the time specified was a major reason for the failure to facilitate this necessary work-up. There were times when the reagent for running the cortisol assay at the radioimmunoassay laboratory was not available. This special laboratory within the hospital was also closed on weekends during the time included in this cohort. Some clinicians were unaware of methods to store the blood specimen for cortisol for subsequent testing once the laboratory could run the

test. A lack of access to funds to send random serum cortisol testing in other diagnostic centers was also a significant barrier. A few respondents did not perceive the random serum cortisol as an essential tool in the diagnosis of CIRCI because they felt that evaluating for the therapeutic response was already adequate to confirm the diagnosis of CIRCI. One participant was not aware that random serum cortisol was available at the institution during that time.

The respondents in this study had consistent knowledge regarding the proper dosage and administration of steroids for CIRCI; all of them said that they gave hydrocortisone at a 100 mg loading dose intravenously, followed by 50 mg of hydrocortisone every 6 hours. Consistency in knowledge was defined as adherence to recommendations stipulated in the latest guidelines on managing CIRCI from the Society of Critical Care Medicine and European Society of Intensive Care Medicine - such a quality was present in all the clinicians who participated in the focus group discussion. However, there was practice variation in terms of the number of days that the patient should be on corticosteroid and the indications for discontinuing the corticosteroid. Some clinicians expressed that they gave steroids only for three days, while one respondent said he gave steroids for as long as five days. The clinicians utilized different criteria for discontinuing steroids– the majority of them discontinued steroids if clinical improvement, in terms of blood pressure rise, was seen, with no specific quantitative parameters used. At the same time, another clinician also considered changes in sensorium and resolution of hypoglycemia as part of the criteria for discontinuing steroids. Among the respondents, the experience regarding managing patients with CIRCI was similar— most patients with CIRCI had a high rate of morbidity and mortality and a poor prognosis. The respondents unanimously agreed that an in-hospital protocol for managing patients with CIRCI would aid clinicians, especially since there is currently practice variability in diagnosing and managing this life-threatening condition.

DISCUSSION

An essential aspect of critical care is suspecting CIRCI in patients with unexplained refractory shock, in whom other etiologies of shock have already been addressed.[4] In the population cohort in this study, there was a high threshold before considering CIRCI as an etiology of shock. CIRCI appears to be underdiagnosed because in cases where it was warranted to suspect if CIRCI was present in the patient, there was relatively low usage of steroids among patients with shock (at 28.73%). Among 362 patients with shock, only four patients had random cortisol results. Only a few patients were evaluated for CIRCI in patients with vasopressor-dependent septic shock in this cohort. CIRCI can be present in as much as 75% of patients with septic shock; therefore, it is vital to recognize this condition in a timely manner.[2] The prevalence of probable CIRCI is at least 28.73% among patients with shock during this period at PGH, based on the number of cases wherein there was initiation of corticosteroids for refractory shock, and this is likely an underestimation. In cases where an evaluation for the presence of CIRCI was absent even if it was warranted, there was an inability to detect and confirm the presence of CIRCI. The true prevalence of CIRCI cannot be extrapolated from the data because of the lack of diagnostic confirmation from random cortisol results in this cohort. Findings of this study also underscore the need to ensure the consistent availability of the random serum cortisol diagnostic exam in all institutions catering to critically ill patients, which is the most objective parameter for confirming the diagnosis of CIRCI compared to just a favorable hemodynamic response to a therapeutic trial of corticosteroids.

The cortisol results of patients from this study ranged from 12.29 mcg/dL to 23.27 mcg/dL, with a median of 17.68 mcg/dL, all of which were accompanied with symptoms and signs consistent with CIRCI. Since random serum cortisol was only obtained for a few patients, a random serum cortisol level of <10 mcg/dL was not seen in this cohort. This is a limitation of this retrospective cohort— most of the patients in this study were clinically diagnosed with CIRCI, with lacking random serum cortisol results. Still, it is vital to recognize that not all patients with CIRCI have cortisol results less than 10 mcg/dL; some have elevated cortisol levels due to decreased cortisol metabolism during critical illness. The phenomenon of reduced cortisol metabolism and clearance is caused by suppressed levels of A-ring reductases and 11-βHSD2. The adrenocorticotrophic hormone is also transiently increased in these patients, and cortisol levels remain elevated, exhibiting a paradoxical dissociation.[11] Other mechanisms that could increase cortisol levels even in patients with CIRCI are the direct production of cortisol from the adrenal glands and the activation of a form of ACTH-independent cortisol synthesis.[2]

Partly due to the variation in the timing of initiation and dosing of steroids, the cohort examined in this study could not demonstrate an overarching improvement in outcomes with using steroids. Patients started on steroids appeared to have worse outcomes than those who were not started on steroids in this retrospective chart review (longer time on ventilator, longer ICU stay) because the patients on the steroid group had more severe illness (MPM score 43.65% for the steroid group and 25.0% for the non-steroid group). There was a selection bias regarding the administration of steroids observed because those given steroids in this cohort mainly were patients with more severe disease (ex. with multi-organ failure, longer time in shock, and longer ventilator days) to begin with. Clinicians who participated in the FGDs expressed that their practices mostly involved initiating steroids as a form of "last resort" when patients were already on maximal doses of vasopressors or already deteriorating. Thus, for this cohort, more adverse outcomes were inevitably seen in the steroid group. This cohort study also highlighted the

importance of examining more precise timestamps, from the onset of refractory shock to the initiation of steroids, to assess the benefits of such intervention fully. The lack of significant difference regarding outcomes between the hydrocortisone and non-hydrocortisone group and the groups with different dosing and administration of hydrocortisone could be accounted for by the relatively small number of patients on steroids in the cohort, so the study was not powered enough to detect a difference among these groups.

Different cohort studies exhibited varying results regarding the benefits of corticosteroids in shock. The findings of the Corticosteroid Therapy of Septic Shock (CORTICUS) study are similar to the results of this retrospective cohort at PGH, which found no mortality benefit for patients with septic shock who were started on corticosteroids. In the CORTICUS study, steroids were initiated for patients who were in shock for the past 24-72 hours.[12] The timing of the initiation of steroids in the CORTICUS study was almost identical to the PGH cohort, where in the median time for starting corticosteroids was within 24 hours of shock. This contrasts with the retrospective study of 178 patients done by Park et al., where a mortality benefit was seen using corticosteroids. The median time to initiation of corticosteroids was within 8.5 hours of shock. In this cohort study by Park, those who had a longer time of shock before initiation of corticosteroids, that is, more than 6 hours from the onset of shock, had higher 28-day mortality rates, at adjusted OR = 2.142. Those patients in whom corticosteroids were given within 6 hours from the onset of shock had a reduction in the 28-day mortality by as much as 37%.[13] These observations suggest that delayed administration of steroids in patients with septic shock may significantly attenuate the benefits of this treatment.[13] Indeed, early recognition of CIRCI is essential because once patients go into multi-organ failure, interventions like steroids may not significantly improve outcomes. The logistic regression analysis emphasizes the need to address septic shock on time because its presence is a significant predictor of mortality. As shock progresses, multi-organ failure ensues, increasing the MPM score, thus markedly increasing the patient's risk for morbidity and death.

Currently, in this tertiary hospital, there is variation in the practice of the specific circumstances or indications for which corticosteroids are initiated for critically ill patients and what type of corticosteroid regimen should be used. There are also differences in the duration of corticosteroid treatment and the utilization of criteria for the discontinuation of corticosteroid treatment. The clinicians who participated in the focus group discussions and key informant interviews were adequately equipped to manage critically ill patients because they all had internal medicine and critical care training. Differences in clinical practice stem from a lack of overarching local guidance reconciling conflicting recommendations in the various international guidelines. The lack of awareness on the utility of the random cortisol test in the management of CIRCI and the inconsistent availability of this important diagnostic test in this resource-limited setting during the years included in this cohort also contributed to the practice variation observed in managing CIRCI.

The variability in clinical practices underscores the need to harmonize recommendations and develop an in-hospital protocol to standardize the management of CIRCI in critically ill patients. Once an in-hospital protocol for CIRCI is established, dissemination of this clinical pathway to clinicians taking care of critically ill patients is key to improving awareness on the management of this often overlooked condition. To enhance the quality of care in this tertiary hospital that attends to a significant number of critically ill patients, the availability of the random cortisol diagnostic test must be ensured. Clinicians must have access to the results of this exam on time to have better guidance for further management. An in-hospital protocol will formalize the institution of timestamps so that patients can reap the maximum benefit of crucial interventions. Such an initiative will lead to better healthcare delivery for patients at the highest risk for morbidity and mortality.

CONCLUSION

The presence of clinical features of CIRCI is a poor prognostic factor. Variation in clinical practice in the recognition and management of CIRCI can have an impact on patient outcomes. Timely recognition, work-up, and interventions to address CIRCI are paramount in critical care. Random cortisol is an important diagnostic exam in the management of CIRCI, which must be readily available in critical care settings. An in-hospital protocol that would standardize the recommendations for the recognition, diagnosis, and management of CIRCI, will aid clinicians and improve patient outcomes.

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Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

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REFERENCES

1. Ok YJ, Lim JY, Jung SH. Critical Illness-Related Corticosteroid Insufficiency in Patients with Low Cardiac Output Syndrome after Cardiac Surgery. Korean J Thorac Cardiovasc Surg. 2018; 51:109-13.
2. Cutillar CS, Ramirez J, Ardena JR, Lantion-Ang L, Jimeno C, Laurel MT. Prevalence of Adrenal Insufficiency using Random Cortisol Level among Patients with Sepsis and Septic Shock Admitted at the Philippine General Hospital. 2005; Unpublished.
3. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA. Guidelines for the Diagnosis and Management of Critical Illness-related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med. 2017; 43:1751–63.
4. Huang X, Hu W, He X, Zhang G. A Potential Diagnostic Protocol for Critical illness-related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients. J Emerg Crit Care Med. 2018; 2:86.
5. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A. Critical Illness-related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Med. 2017; 17: 4914.
6. Peng YS, Wu CY, Chen YC, Lien JM, Tian YC, Fang JT, et al. Critical Illness-related Corticosteroid Insufficiency in Patients with Severe Acute Biliary Pancreatitis: A Prospective Cohort Study. Critical Care. 2009; 13:R123.
7. Yang Y, Liu L, Jiang D, Wang J, Ye Z, Ye J, et al. Critical Illness-related Corticosteroid Insufficiency after Multiple Traumas: A Multicenter, Prospective Cohort Study. J Trauma Acute Care Surg 2014 Jun; 76(6):1390-6.
8. Cutillar CS, Fojas M, Ramirez J, Ardena JR, Lantion-Ang L, Jimeno C, Laurel MT. Adrenal Responsiveness to the 10-mcg ACTH Stimulation Test Among Critically Ill Patients on Inotropic Support Admitted at the Philippine General Hospital. 2005; Unpublished.
9. Karir V, Cooke CR, Andersson L, Caldwell E, Rubenfield G. Practice Variability in the Assessment and Treatment of Critical Illness-related Corticosteroid Insufficiency. J Crit Care. 2010; 25(2):363.
10. Pacheco G, Hypes C, Joshi R, Mosier J. Emergency Department Recognition of Critical Illness Related Corticosteroid Insufficiency. Crit Care Med. 2015; 43: 12.
11. Boonen E, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, et al. Reduced Cortisol Metabolism during Critical Illness. N Engl J Med. 2013;368(16):1477-88. Doi:10.1056/NEJMoa1214969.
12. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone Therapy for Patients with Septic Shock. New England Journal of Medicine, 2008; 358(2), 111–124. doi:10.1056/nejmoa071366.
13. Park HY, Suh GY, Song JU, Yoo H, Jo IJ, Shin TG, et al. Early Initiation of Low-dose Corticosteroid Therapy in the Management of Septic Shock: A Retrospective Observational Study. Crit Care. 2012;16(1):R3. Published 2012 Jan 7. doi:10.1186/cc10601.