

The Development of a Protocol for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) at a Tertiary Hospital

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Abstract

Objectives. The diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) remains a challenge. This initiative aimed to develop a protocol for the diagnosis and management of CIRCI which will facilitate informed decision-making among clinicians through consensus-building among a multi-disciplinary team.

Methodology. This was a single-center, qualitative study which utilized the modified Delphi method, consisting of a sequential iterative process with two rounds of voting. A cut-off value of 70% was set as the threshold for reaching consensus.

Results. The protocol on the diagnosis and management of CIRCI was approved after two rounds of voting, with all the components reaching 83.3%-100% agreement. This protocol on CIRCI provided a framework for the clinical approach to refractory shock. It was advocated that all cases of probable CIRCI should immediately be started on hydrocortisone at 200 mg/day. The definitive diagnosis of CIRCI is established through a random serum cortisol <10 mcg/dL or increase in cortisol of <9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test in patients with indeterminate random cortisol levels.

Conclusion. The presence of refractory shock unresponsive to fluid resuscitation and vasopressors should warrant the clinical suspicion for the existence of CIRCI and should trigger a cascade of management strategies.

Key words: critical illness-related corticosteroid insufficiency, shock, corticosteroid, cortisol

INTRODUCTION

Critical illness-related corticosteroid insufficiency or CIRCI, which refers to an inadequate and blunted corticosteroid response to the level of stress, is an underrecognized condition in the critical care arena.¹ It occurs in about 30-70% of critically ill patients² and can be as high as 77% in patients with sepsis.³ The clinical presentation of CIRCI is ominous, commonly manifesting with shock refractory to fluid resuscitation and vasopressors. Hypoglycemia, metabolic acidosis and eosinophilia may also be signs of relative adrenal insufficiency.⁴ Indeed, CIRCI is a challenging disease plaguing critically ill patients.

To this day, the diagnosis of CIRCI remains a challenge. Guidelines from various societies differ in terms of the proposed criteria for diagnosis. The Society of Critical

Care Medicine and the European Society of Intensive Care Medicine recommended in their consensus statements that in patients with putative signs and symptoms of CIRCI such as refractory shock that is unresponsive to catecholamines, a random cortisol level of less than 10 mcg/dl or a delta cortisol at 60 minutes of less than 9 mcg/dl after administration of 250 mcg cosyntropin or ACTH may be utilized by physicians to diagnose CIRCI.⁴ On the other hand, local sepsis guidelines advocate that the use of random cortisol is not a prerequisite to diagnosing CIRCI, that the presence of shock refractory to fluid resuscitation and the finding of increasing vasopressor requirements are enough to establish the diagnosis.⁵ This lack of consensus underscores the need to formulate a protocol that can be adapted to the local setting, and which can guide clinicians in managing critically ill patients.

Practice variation is an important issue to be reckoned with in managing CIRCI. Such differences in clinical practice likely stem from differences in local and international guidelines. For instance, in a tertiary care center, the presence of CIRCI was investigated in only 58% of patients with refractory shock, and among these patients, only 47% received corticosteroids.⁶

This trend in clinical practice is also seen locally. In a study done at the Medical Intensive Care Unit of the Philippine General Hospital, 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 of patients with CIRCI,⁷ hence the exigency to improve its recognition and timely management.

A protocol in the clinical setting refers to a recommended course of action for a particular situation and serves as a guide for healthcare providers. The protocol is formulated based on updated evidence-based research to facilitate better health service delivery.⁸ An important component is a clinical algorithm, which consists of a series of steps involved in clinical decision-making. Algorithms help to standardize practice when it comes to important clinical scenarios and are a product of expert consensus.⁹ These algorithms facilitate the provision of optimal high-quality care when a clinical pathway responsive to the health problem is activated upon contact with the healthcare system, and provides guidance for decision-making that is evidence-based.¹⁰ Deming's quality improvement theory illustrates a strong basis for the creation and implementation of clinical pathway algorithms. These pathways enable standardization of clinical processes and reliable measurement of clinical outcomes.¹¹

Consensus-building is an integral aspect of protocol development. The Delphi method, originally proposed by Dalkey and Helmer, is a validated means for arriving at a consensus in clinical settings.¹⁰ It has been used in many studies which involve the development of clinical pathway algorithms. The Delphi method is iterative and the participants, who are experts in the field, engage in several rounds of voting to arrive at a consensus. In the modified Delphi method, experts vote to agree or disagree on a set of statements communicated through email questionnaires. Similar to the original Delphi method in terms of its objective, the modification refers to initiating the discussion with set issues from literature review.¹² This modified method is appropriate in situations where the evidence surrounding disease management is inconclusive, and expert opinion to adjudicate the current pool of literature is paramount,¹⁰ such as in the case of CIRCI.

The lack of local guidance on the diagnosis and management of CIRCI needs to be urgently addressed with a clinical pathway in the care of critically ill patients with refractory shock. A tertiary hospital, which is a national referral center for patients warranting intensive care, is a

suitable location to initiate a vital protocol that will shape clinical practice.

This research aims to develop a protocol for the diagnosis and management of critical illness-related corticosteroid insufficiency through consensus-building among a multi-disciplinary team of experts. To date, this is the first initiative of its kind on this topic in the country.

METHODOLOGY

Identification of key issues

The authors identified pressing inquiries on the diagnosis and management of CIRCI that need to be addressed. These questions were deemed pertinent for the identification of patients with CIRCI in whom treatment is indicated. Such questions reflect processes that entail crucial decision-making. The following key issues in the diagnosis and management of CIRCI were identified:

1. When should CIRCI be suspected?
2. How should cases of probable CIRCI be managed?
3. How should patients be managed after the initiation of steroids for probable CIRCI?
4. How long should corticosteroids be given for patients with CIRCI?
5. How should steroids be tapered for patients with CIRCI?
6. What blood glucose levels should be maintained for patients on steroids?
7. How is the definitive diagnosis of CIRCI made?
8. How should patients be managed after the cessation of steroid therapy?
9. Do you approve of this algorithm for the initiation and use of corticosteroids for patients admitted with shock at this tertiary hospital?

Formulation of recommendations

The authors reviewed published literature and existing guidelines on critical illness-related corticosteroid insufficiency and key clinical trials were identified. The following selection criteria were applied to determine inclusion of the literature for creating recommendations: validity, feasibility, and adaptability.¹³ Seminal works on CIRCI were also included.^{1,4,6,14-20}

Since septic shock is the most common etiology of shock among patients with CIRCI,¹⁴ recommendations for managing patients with sepsis were also critically appraised. From this review of evidence, responses to the inquiries were constructed by the authors to serve as recommendations for the diagnosis and management of CIRCI. The authors, who belong to different fields (two authors from Endocrinology, one author from Pulmonology and Critical Care, and one author from Infectious Diseases), independently examined and approved all the recommendations that they formulated from the systematic

review of literature. These recommendations were then forwarded to the experts for consensus-building to develop a protocol for the diagnosis and management of CIRCI.

Selection of experts

A multi-specialty panel of clinicians directly involved in managing patients with refractory shock was formed. These experts have a wide range of knowledge and clinical experience that can contribute to the decision-making process. They also fulfill the criteria for panel selection of being able to implement the recommendations of the body.²¹ Deemed as content experts, the participants in the consensus-building process were clinicians from the Divisions of Endocrinology, Diabetes, and Metabolism (18 participants), Pulmonary Medicine and Critical Care (1 participant), Infectious Disease (1 participant) and Cardiology (1 participant). All stages of the study involved participants from various specialties, ensuring that diverse inputs were reflected in all the processes. A letter detailing the objectives and nature of the procedure was sent to all the invited experts.

There has been substantial variation in the panel size for the Delphi method. Several protocols advocate that about 5-10 experts are sufficient for consensus-building.¹⁰ A minimum of 12 respondents is considered adequate for the Delphi method.²² For the development of a protocol for CIRCI, more than 20 experts were invited, which exceeded the minimum required number of participants for the Delphi method. The expected dropout rate is around 20% based from previous studies.²² Because the number of participants invited exceeded the number of participants required, the validity of the consensus-building procedure was unlikely to be affected by drop-outs. The number of experts in this study enabled us to reach saturation point.

Modified Delphi Method

A sequential process consisting of two rounds of voting was instigated for the development of a protocol for the diagnosis and management of CIRCI. Informed consent was obtained from the invited experts. Upon signifying their consent to join the consensus-building process, the first set of recommendations for the diagnosis and management of CIRCI was sent through electronic mail to the participants' encrypted institutional webmail address for all the exchanges about the consensus-building process to ensure data privacy.

The online tool utilized in this modified Delphi method was Google forms, which had secure sockets layer (SSL) encryption, which guaranteed that the transmitted data were secure. Since this study was conducted in 2020 during the surge of the COVID-19 pandemic, the modified Delphi method was done virtually through this secure online tool because face-to-face meetings were discouraged to ensure the participant's safety. The Google forms questionnaire

was checked by the investigators before every Delphi round to ascertain its operability to a diverse pool of participants.

For the first round of voting, the experts were asked to indicate if they "agree or disagree" with the stipulated provisions and were instructed to submit any comments and suggestions through the free-text response feature on Google forms. After the first round of voting, the feedback was incorporated and the recommendations revised.

During the second round of voting, the experts were asked to scrutinize the recommendations and indicate "agree," "disagree with minor modifications," and "disagree with major modifications," and "redo algorithm." Both rounds of voting utilized a Likert-type scale to gauge the expert responses and level of agreement and was deemed sufficient to determine which components of the protocol should be retained, discarded or modified.²³ The protocol for the diagnosis and management of CIRCI was modified after the second round of voting.

This amended protocol was again disseminated to the experts. A third round of voting was only reserved for any major disagreements that would arise in the second round of voting. This strategy is compliant with the recommended two to three rounds for Delphi procedures.²⁴ Reminders were regularly sent to experts to improve response time.

The method for establishing consensus that was applied for this study was based on the proportion of experts showing agreement with the recommendations. A cut-off value of 70% was set as the threshold for reaching consensus, the same level of agreement used in a large number of studies.^{22,25,26}

Data analysis

Pooled results from all the experts were generated after every round. Descriptive statistics were employed based on the level of agreement set at 70% for establishing consensus. The stability of the consensus was assessed if there was variation after each round of voting in just 10% or less of the statements. For each statement, the investigators produced a statistical representation of the viewpoints of the experts.²³ Based on the feedback for every recommendation stipulated in the free text response, qualitative content analysis²⁷ was pursued. The responses of the experts were categorized by themes, which addressed the various aspects of the diagnosis and management of CIRCI.

Protocol development

The results acquired from all the rounds of voting were synthesized. A statistical representation of all the responses of the experts and the feedback of all the experts were sent

to all the participants after every round. All statements that reached consensus were incorporated in the final form.

The protocol format for the diagnosis and management of CIRCI was a set of key inquiries followed by responses, accompanied by the evidence that served as the basis for such recommendations. An algorithm for CIRCI among patients with refractory shock was presented at the end of the protocol. The experts received a copy of the protocol prior to dissemination so that they could corroborate the recommendations made in the final form.

Dissemination

This protocol, which was a product of a thorough consensus-building process, was disseminated to trainees and consultants of the Department of Medicine, who are the main users of this clinical pathway. The document, accompanied by a cover letter, was submitted to the Department Chair and Assistant Vice-Chair for Patient Services for review. Upon approval, the protocol on the diagnosis and management of CIRCI was disseminated. A consultation session to reinforce awareness about the protocol and to address inquiries about the recommendations was attended by the residents of the Department of Medicine.

Ethical considerations

The protocol development phase was a component of the mixed methods study entitled, "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," approved by the University of the Philippines Manila Research Ethics Review Board with the UPMREB code 2019-505-01. For the consensus-building procedure, participation was voluntary and informed consent was obtained.

RESULTS

Consensus-building

To initiate the development of a protocol for CIRCI, twenty-seven experts from the Divisions of Endocrinology, Infectious Disease, Pulmonology and Critical Care and Cardiology were invited to participate in the consensus-building process. Out of the 27 experts invited, 21 experts participated. This corresponds to a 78% response rate, which was satisfactory because this was more than the minimum target number of participants. In an earlier study, a 61% response rate was already considered sufficient for a Delphi consensus.²⁸ The consensus-building process for the diagnosis and management of CIRCI consisted of two modified Delphi rounds, and all experts participated in both rounds, thereby corresponding to a 100% response rate in the second round. There were no dropouts during the entire consensus-building process.

Inclusivity of the consensus-building process was upheld. Detailed instructions and reminders on the modified Delphi rounds were disseminated and all experts were given an adequate time to respond. For the first round of voting, the experts were given 21 days to evaluate the proposed recommendations on the diagnosis and management of CIRCI. The average response time was 2.1 days, with the shortest turnaround time of less than one day, and the longest turnaround time of 19 days. The feedback from all the participants were synthesized and circulated among the participants. A revised version of the protocol was sent. Another 21 days were allotted to assess the revisions. This three-week period for evaluation for each round is sufficient for reviewing the protocol, the recommended length of time of modified Delphi rounds is at least 10 days and up to 10 weeks.¹³

Consensus building was facilitated through two rounds of voting using the modified Delphi method. Participants were asked to give their responses on each component of the protocol. During the first round of voting, the participants indicated "agree" or "disagree" for each component of the protocol and indicated their reasons for doing so. There was an 84.2%-100% agreement for all the components of the proposed protocol.

The expert's feedback were consolidated and the following revisions in the protocol were made: 1) Simplified the algorithm for benefit of the user; 2) Clarified the timing of the ACTH stimulation testing; 3) Included hydrocortisone infusion as a means of administering steroids for CIRCI; and 4) Incorporated a protocol for tapering steroids. This proposed protocol for CIRCI was also reviewed for consistency with local and international sepsis guidelines.

During the second round of voting, the respondents were asked to evaluate each component of the protocol by indicating "agree," or "disagree-minor modification needed," "disagree-major modification needed, redo algorithm." All the components of the protocol reached 83.3%-100% agreement, exceeding the threshold of at least 70% agreement among participants. No disagreement calling for major modification of the algorithm was encountered during the second round of voting. All experts gave feedback on the proposed modifications. The process of consensus-building was completed after the second round because a convergence on viewpoints was achieved.²³ Both rounds also showed no significant difference in the level of consensus.²⁴ A table detailing the level of agreement for every recommendation in the protocol for both rounds is found in Appendix 1.

The protocol on the diagnosis and management of CIRCI, a product of consensus-building among experts from different fields, was approved by the Department of Medicine, which served as a form of external validation. It was then disseminated to all residents, fellows and consultants of the Department of Medicine prior to pilot testing and implementation.

Final form of the protocol

Presented below is the final form of the protocol on the diagnosis and management of CIRCI:

Protocol for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) for Patients Admitted with Shock at a Tertiary Hospital

When should Critical Illness-Related Corticosteroid Insufficiency (CIRCI) be suspected ?

All patients aged 19-years-old and above with an admitting diagnosis of refractory shock or developed **refractory hypotension or shock** during the admission should be managed as a case of **probable CIRCI**. Refractory shock is defined as any of the following:

- **Systolic blood pressure of persistently <90 mm Hg after hypovolemia is addressed through adequate fluid resuscitation (at least 30 ml/kg if without signs of congestion)⁵ for at least 30 minutes** with a need for a vasopressor to maintain adequate organ perfusion, accompanied by signs of hypoperfusion such as tachycardia, altered mental status, confusion or encephalopathy, cold extremities, oliguria, or blood lactate > 2mmol/L¹⁵ or
- **requiring at least 0.2 mcg/kg/min of norepinephrine (or any other vasopressor)²⁹ or**
- **with increasing vasopressor requirement²⁹ or**
- **requiring a second vasopressor to maintain MAP of ≥65 mm Hg).**⁵
- Adequate fluid resuscitation, of at least 30 ml/kg of fluid (if the patient is not at risk of pulmonary congestion), should have been administered and the patient should have been assessed for other etiologies of shock (hypovolemic, septic, cardiogenic) and adequate management (i.e., antibiotics for septic shock, inotrope such as dobutamine for cardiogenic shock) should already have been initiated for the patient.

How should cases of probable CIRCI be managed?

As soon as CIRCI is suspected, prior to initiating steroids, obtain a blood sample for random serum cortisol (at least 4 ml of blood sample in a red top vial).^{*} **Subsequently, immediately start hydrocortisone as 100 mg intravenous (IV) loading dose followed by 50 mg IV every 6 hours or a 200 mg continuous infusion in isotonic saline to run for 24 hours** even if the result of the random cortisol is not yet available.^{5,16} Treat a case of probable CIRCI even prior to establishing a definitive diagnosis based on the laboratory result. Testing should not cause any delay in the delivery of appropriate, life-saving management in the form of steroids.

^{*} At least 4 ml of blood in a red top vial is needed for random serum cortisol. The test must be submitted to a laboratory for radioimmunoassay. If the test cannot be submitted on the same day of collection, the sample must be stored in the refrigerator (at 4°C for up to 72 hours) and brought to the laboratory once it is open.

How should patients be managed after the initiation of steroids for probable CIRCI?

Continue hydrocortisone at a dose of 200 mg/day for at least 72 hours and up to 7 days for patients:

- whose norepinephrine or vasopressor requirement are reduced by ≥50% within 72 hours of initiating hydrocortisone or
- have a random serum cortisol of <10 mcg/dL or <275.9 nmol/L⁴ or
- with septic shock⁵

Discontinue hydrocortisone for patients who have random serum cortisol of >34 mcg/dL or >938.06 nmol/L or an increase in cortisol of at least 9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test^{4**} unless given for other indications [e.g., Acute Respiratory Distress Syndrome (ARDS) or Chronic Obstructive Pulmonary Disease (COPD) in Acute Exacerbation or autoimmune disease].

How long should corticosteroids be given for patients with CIRCI?

Hydrocortisone at 200 mg/day should be given for **at least 72 hours and up to 7 days**, to have significant benefit.^{4,5}

How should steroids be tapered for patients with CIRCI?

Steroids may be tapered in the following instances:

- Vasopressor requirements decrease by at least 50% for at least 72 hours³⁰ or
- Patient is off vasopressors for at least 72 hours,³⁰ and
- There are no other indications for maintaining patient on corticosteroids (i.e. ARDS, COPD or bronchial asthma in exacerbation, autoimmune disease, etc.)

Hydrocortisone may be tapered as follows: decrease dose to 50 mg IV every 8 hours for one day, then 50 mg IV every 12 hours the next day, then may discontinue the following day.³⁰

What blood glucose levels should be maintained for patients on steroids?

Target blood glucose at **140-180 mg/dl**, which is the recommended range for critically ill patients,³¹ with or without underlying diabetes mellitus. Refer to Endocrinology for difficulty in managing diabetes mellitus or steroid-induced hyperglycemia.

How is the definitive diagnosis of CIRCI made?

CIRCI is likely to be present if **random serum cortisol <10 mcg/dL or <275.9 nmol/L.**⁴ Thus, patient is likely to benefit from corticosteroids.

For patients with an **indeterminate result of random cortisol (random cortisol of 11-34 mcg/dl or 304.49-938.06 nmol/L)** but with clinical features of CIRCI, an adrenocorticotrophic hormone (ACTH) stimulation test using high dose ACTH (250 mcg) with determination

^{**} Unlikely to be CIRCI, therefore, corticosteroids are not proven to be of benefit in such cases.

of the baseline cortisol, and peak cortisol response at 60 minutes after ACTH administration should be undertaken. An **increase in cortisol of <9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test** is indicative of CIRCI.^{4***} This test should be done 24-hours after the last dose of hydrocortisone.

How should patients be managed after the cessation of steroid therapy?

A random cortisol should be drawn 24-hours after the last dose of hydrocortisone. If the results still meet the criteria for CIRCI (random serum cortisol <10 mcg/dL or <275.9 nmol/L), a low dose oral steroid should be initiated in the form of prednisone tablet at 5-7.5 mg/day, which is equivalent to the physiologic dose of hydrocortisone at 10-12 mg per square meter of body surface area for clinically stable patients.¹⁷

For patients who remain critically ill, maintain the corticosteroid dose at least twice as high as the physiologic dose, which is about 40-60 mg of hydrocortisone or 10-15 mg of prednisone while optimizing work-up and management of the underlying conditions (i.e., adequate hydration, microbiologic diagnosis and source control for sepsis, two-dimensional echocardiography with cardiac index for cardiac dysfunction, initiation of work-up for causes of primary or secondary adrenal insufficiency if indicated****).

The clinical algorithm for the initiation and use of corticosteroids for patients admitted with shock is found in Figure 1.

DISCUSSION

The pressing need to address both practice variations in treating critical illness and the lack of local guidance on this condition fueled the development of the protocol for the diagnosis and management of CIRCI. Through the modified Delphi method, a consensus among experts from different fields was achieved and divergent points in international and local guidelines on both CIRCI and sepsis were reconciled to increase adaptability in the local setting.

All recommendations were evaluated through a rigorous process through the modified Delphi method, subscribing

*** Refer to Endocrinology for administration of the standard ACTH stimulation test. Clinicians may also refer patients with probable CIRCI for guidance in optimizing diagnostics and management, even if the patient is not a candidate for ACTH stimulation testing. The standard ACTH stimulation test with 250 mcg ACTH (the optimal dose that overcomes ACTH resistance) is done by first obtaining a baseline serum cortisol level, then administering 1 ampule containing 250 mcg of ACTH in the form of tetracosactrin (Synacthen) intramuscularly or intravenously, and then drawing blood again for serum cortisol after 60 minutes.³² An increase in serum cortisol of <9 mcg/dl is highly indicative of CIRCI.⁴ This test will be done 24-hours after the last dose of hydrocortisone for patients with an indeterminate random cortisol result.

**** Refer to Endocrinology for assessment for possible primary or secondary adrenal insufficiency.

to the CREDES (Conducting and Reporting for Delphi Studies) standards.¹³ The modified Delphi method is a reliable method that upholds shared responsibility among the experts²⁷ in the development of a clinical pathway. This initiative featured a highly motivated set of experts who analyzed the current body of literature and screened the proposed clinical pathway and algorithm for CIRCI for validity and clarity.

Setting the criteria for diagnosis

This protocol on CIRCI provides a framework for the clinical approach to refractory shock, which will aid in the management of critically ill patients in the local setting. The definition of refractory shock was comprehensive and specific, incorporating key components of the Surviving Sepsis guidelines and the Philippine Society of Microbiology and Infectious Diseases (PSMID) guidelines.^{5,33} Indeed, a large number of studies have shown that CIRCI is likely present in patients with refractory shock, with patients in septic shock comprising a significant proportion of these cohorts.¹⁸

A major contribution of this protocol is the emphasis on the utility of random cortisol as a vital tool in diagnosing CIRCI. During critical illness, the circadian rhythm of cortisol production is lost, therefore, random serum cortisol is the appropriate laboratory examination to diagnose CIRCI.¹⁹ Assays for serum cortisol are more accessible in local diagnostic centers than plasma cortisol and both methods for determining cortisol levels are comparable. There is also no advantage in utilizing free cortisol levels to detect relative adrenal insufficiency in the clinical setting.³⁴ Though random cortisol is an important tool for diagnosis, its value should not be used to decide whether corticosteroids should be given or not.¹⁸ Patients afflicted with refractory shock with a clinical setting for relative adrenal insufficiency should immediately be started on corticosteroids. The pool of experts emphasize that awaiting the cortisol result is not a reason to delay treatment.

The role of ACTH stimulation testing was also stipulated in this protocol. It is an important adjunct in the diagnosis of CIRCI and it is also useful in guiding subsequent management after the acute phase. For patients with indeterminate result of random serum cortisol (11-34 mcg/dl), an incremental increase in serum cortisol of less than 9 mcg/dl after administration of 250 mcg ACTH is indicative of CIRCI, thus warranting further treatment with corticosteroids. The use of the high dose 250 mcg ACTH, rather than the low dose 1 mcg ACTH, for definitive testing for adrenal insufficiency, has been validated among critically ill patients.²⁰ Once the patient has been stabilized, ACTH stimulation testing facilitates a definitive diagnosis if the relative adrenal insufficiency has already been reversed. For critically ill patients, the absolute increase in cortisol levels is used rather than the peak cortisol level, for the latter is more appropriately used in non-critically ill patients.³⁵

Algorithm for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) for Patients Admitted with Shock at PGH

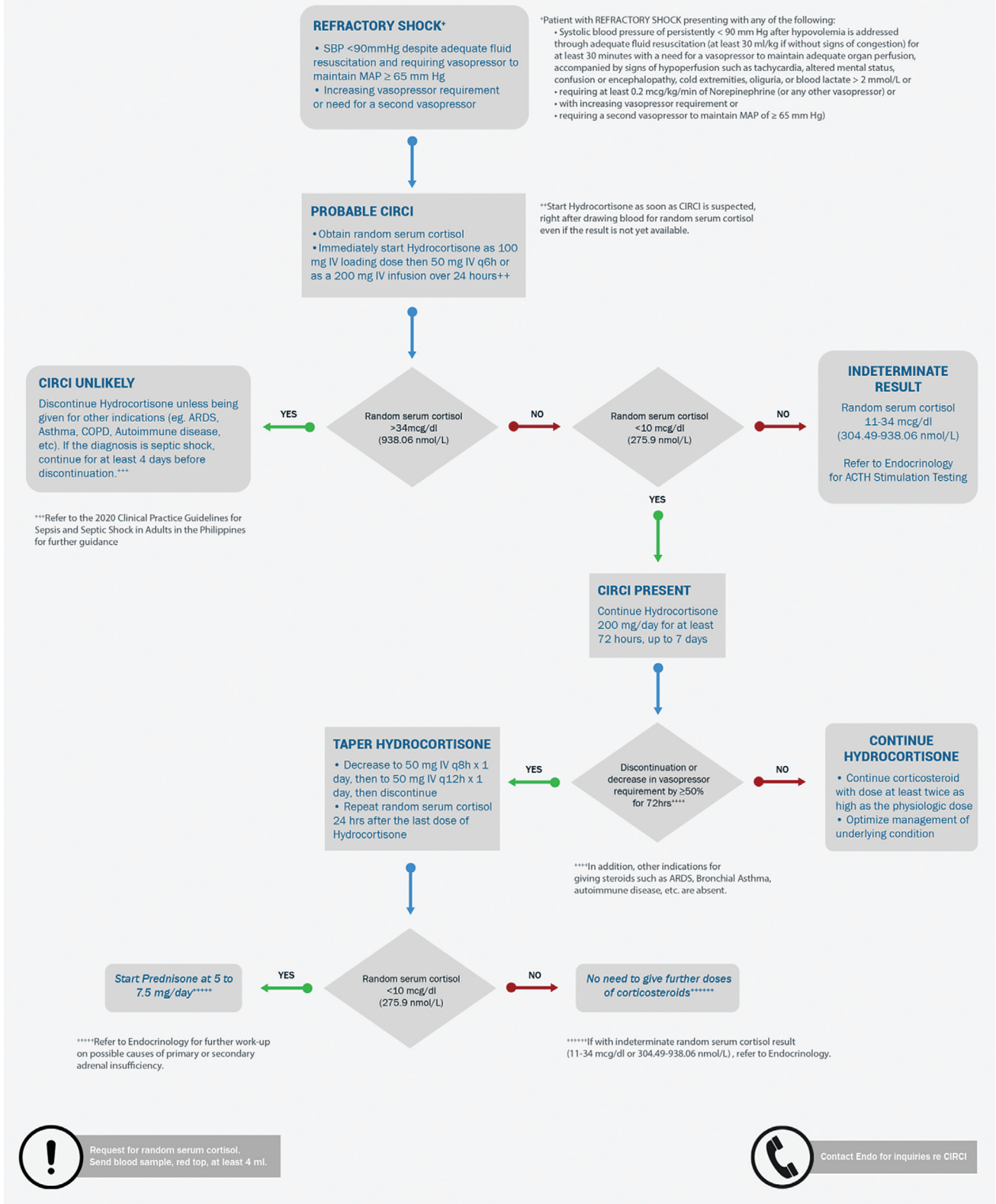


Figure 1. Algorithm for the diagnosis and management of CIRCI.

The experts also advocate for the use of a modified protocol for ACTH stimulation testing, which involves obtaining the serum cortisol at baseline and 60 minutes after ACTH stimulation because this methodology is adequate to diagnose CIRCI, even for late responders,²⁰ and is more adaptable in the local, resource-limited setting.

Addressing management issues

A comprehensive approach to management, incorporating the appropriate treatment regimen is a key component of this protocol. The optimal dose of hydrocortisone was set at 200 mg/day, in line with the recommendations of various societies of critical care and infectious diseases.^{4,20} This stress dose did not lead to increased risk of infections and other adverse events such as hypernatremia and hypercoagulability, as seen in several trials such as the HYPOLYTE study.^{18,36} Higher doses exceeding 200 mg/day, on the other hand, did not result in better patient outcomes.¹⁸

Pertinent issues in the management of CIRCI were also addressed in this clinical pathway. The criteria for the discontinuation of steroids, specifically those used to ascertain clinical improvement, are included to guide clinicians in the initiation and maintenance of the corticosteroid dose. A tapering protocol was incorporated in this clinical pathway to reduce the risk of hypotension and rebound inflammation.¹⁸

Future challenges

A standardized approach to the diagnosis and management of CIRCI was forwarded by this protocol. The institution of this clinical pathway underscores the need to evaluate the impact of this protocol on patient outcomes and in optimizing the care of critically ill patients in the local setting.

CONCLUSION

Using the modified Delphi method, a systematic and validated tool for consensus-building, we were able to create a protocol for the diagnosis and management of CIRCI. The presence of refractory shock unresponsive to fluid resuscitation and vasopressors should warrant the clinical suspicion for the existence of CIRCI and should trigger a cascade of management strategies. This stepwise clinical pathway and algorithm aids in the prompt recognition of CIRCI. The timely initiation of corticosteroids is paramount. This clinical pathway, tailored for the local setting, provides guidance on the management of a challenging condition afflicting critically ill patients.

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Statement of Authorship

All the authors fulfilled the ICJME criteria for authorship.

Author Disclosure

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APPENDIX

Recommendation	Round 1 Percent Agreement	Round 2 Percent Agreement
When should CIRCI be suspected? 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) should be managed as a case of probable CIRCI.	94.7%	94.4%
How should cases of probable CIRCI be managed? Prior to initiating steroids, obtain a blood sample for random serum cortisol. Immediately start hydrocortisone (as soon after blood sample is drawn, even if result is not yet available) as 100 mg intravenous (IV) loading dose followed by 50 mg IV every 6 hours for at least 72 hours, but not longer than 7 days.	84.2%	94.4%
How should patients be managed after the initiation of steroids for probable CIRCI? Continue hydrocortisone for patients whose norepinephrine or vasopressor requirement are reduced by more than 50% or have a random serum cortisol of < 10 mcg/dL or < 275.9 nmol/L.	100%	100%
How should patients be managed after the initiation of steroids for probable CIRCI? Discontinue corticosteroids for patients whose vasopressor requirements are not decreasing or have random serum cortisol of > 34 mcg/dL or > 938.06 nmol/L or a peak cortisol at 60 minutes of > 18 mcg/dL unless given for other indications (ex. Acute Respiratory Distress Syndrome (ARDS) or Chronic Obstructive Pulmonary Disease (COPD) in Acute Exacerbation).	94.7%	94.4%
How long should corticosteroids be given for patients with CIRCI? Hydrocortisone should be given for at least 72 hours, to have significant benefit, but not longer than 7 days.	100%	94.4%
How should steroids be tapered for patients with CIRCI? Steroids may be tapered in the following instances: <ul style="list-style-type: none"> • Vasopressor requirements decrease by at least 50% for at least 72 hours, or • Patient is not on vasopressors anymore for at least 72 hours, and • there are no other indications for maintaining patient on corticosteroids (i.e. ARDS, COPD or Bronchial Asthma in exacerbation, autoimmune disease, etc.) <p>Hydrocortisone may be tapered as follows: decrease dose to 50 mg IV every 8 hours for one day, then 50 mg IV every 12 hours the next day, then may discontinue the following day.</p>	94.7%	100%
At what levels should blood glucose be maintained for patients started on steroids? Target blood glucose 140-180 mg/dl, which are the recommended levels for critically ill patients.	94.7%	100%
How is the definitive diagnosis of CIRCI made? CIRCI is likely to be present if random serum cortisol < 10 mcg/dL or < 275.9 nmol/L. Thus, patient is likely to draw benefit from corticosteroids. For patients with indeterminate result of random cortisol (random cortisol of 11-34 mcg/dl or 304.49-938.06 nmol/L) but with clinical features of CIRCI, an adrenocorticotrophic hormone (ACTH) stimulation test using high dose ACTH (250 mcg) with determination of the baseline cortisol, and peak cortisol response at 60 minutes after ACTH administration should be employed. An increase in cortisol of < 9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test is indicative of CIRCI. This test will be done at 24 hours after the last dose of hydrocortisone.	100%	100%
How should patients be managed after the cessation of steroid therapy? A random cortisol test will be performed after the cessation of the steroid therapy. If the results still meet the criteria for CIRCI (random serum cortisol < 10 mcg/dL or <275.9 nmol/L), a low dose oral steroid should be resumed in the form of prednisone tab at 5-7.5 mg/day.	84.2%	94.4%
Algorithm	84.2%	83.3%