

Hydrocortisone Therapy for Critically Ill Trauma Patients to Decrease Ventilator Use in Pneumonia Patients

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ABSTRACT

Secondary infections such as nosocomial pneumonia are one of the highest causes of mortalities for critically ill trauma patients in a hospital. Prevention practices have been appropriately placed in order to lower infection rates. However, clinical data suggests that little improvement of nosocomial pneumonia infections have occurred because of prevention practices. New groundbreaking research of hydrocortisone therapy for trauma patients has shown to be successful in improving not only patient outcomes, but decreasing time with mechanical ventilation and decrease in total hospital days. Hydrocortisone therapy is effective because critically injured patients suffer from a condition called critical injury-related corticosteroid insufficiency (CIRCI). In this condition, the natural pro-inflammatory response is heavily exaggerated and takes an exacerbated toll on the body of a patient. The natural anti-inflammatory steroids that are normally produced in stress events such as cortisol is severely diminished or nonexistent. Therefore, with the exaggerated inflammatory response, the chances of contracting secondary infections such as nosocomial or ventilator-acquired pneumonia are heightened drastically. Data from clinical research studies have shown that stress dose levels of cortisol therapy for critically injured patients have shown to be efficacious in lowering risks of secondary infection. Furthermore, due to fewer days in the hospital, there is less stress on the limited capacity of an emergency department of a hospital. Moreover, patients are saving \$5,000 to \$20,000 from avoiding excessive medical expenses that would result from more hospital stays.

Keywords

Trauma patients, Pneumonia, Infections, Hydrocortisone therapy.

Introduction

Trauma patients are seen in the hospital for injuries that are critically life threatening. However, patients in the intensive care unit are not only at risk of dying from the traumatic injury but also secondary infections such as nosocomial pneumonia (NP). Nosocomial and ventilator-acquired pneumonia (VAP) is the second most common nosocomial infection in intensive care units. NP and VAP both affect 27% of all critical patients in ICUs [1]. NP and VAP are only behind urinary tract infections for common secondary infections in the ICU [2]. VAP is defined to be pneumonia that occurs more than 48 hours after a patient has received mechanical ventilation and been intubated [1]. 86% of all nosocomial pneumonia cases

are related to mechanical or ventilator-associated pneumonia. Between 250,000 and 300,000 cases occur each year in the U.S. alone [1]. Late-onset of VAP can pose higher risks of mortality than the early onset of VAP [3]. The higher risks of mortality are associated with greater chances of antibiotic-resistant bacterial infections. Research has shown that the chances of death resulting from VAP can range between 0-50% [1]. The type of organisms causing the infection will also have an effect on the prognosis of pneumonia. For example, as stated earlier, late-onset will likely be resistant to commonly used antibiotics, which may lead to physician use of a broad-spectrum antibiotic in order to help combat the infection [4]. Higher mortality rates are seen with specific bacteria, namely, *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. This is because these bacteria are more resistant to antibiotics [1]. Beyond heightened

chances of death from nosocomial pneumonia infections, there is a massive economic expense that accumulates with increased length of ICU stays due to secondary infections. For example, the study by Koenig and Truitt showed that each diagnosis of VAP costs the patient between \$5,000 to \$20,000 due to increases in stays and more resources required to treat secondary infections [1]. Conventional treatment of nosocomial pneumonia is done by a spectrum of antibiotics. However, with prolonged use resistance will develop from highly infectious bacteria; therefore, careful implementation and cycling of antibiotics is imperative to produce favorable outcomes [1]. The rate of death in VAP and NP is very high.

One study by Sibila and Agusti showed that the chances of mortality range from 20-50% [5]. This is very dangerous and can leave many patients with already high chances of mortality due to critical illness or trauma to die from secondary infections. The paper also discussed that despite antibiotic therapy and other corresponding and appropriate treatment for NP, the rate of infection and mortality remains the same throughout the years. The researchers deduce that the unwavering rates are attributable to an abnormal increase in systemic and local inflammatory responses from the patient [5]. This response can be a factor that is hindering further advancement in treating NP. Furthermore, there is evidence that the treatment of patients with stress-dose corticosteroids decreases the exaggerated inflammatory response that results from critical illness and is shown to decrease mortality and infections from NP and VAP [4]. The reasoning behind the use of corticosteroids, such as prednisone, is that they led to a decrease in mortality rate in critically injured patients, which comes from a new finding of a condition called Critical illness-related corticosteroid insufficiency (CIRCI). CIRCI has been shown to be a major role in increasing chances for secondary infection from pneumonia like NP and VAP. CIRCI is defined to be insufficient corticosteroid production and activity for the comparative severity of an illness [6]. When there is insufficient activity and production of cortisol the body undergoes exaggerated systemic inflammation that can incite tissue damage and increase chances of disease progression. Research has shown that in patients in the ICU with critical illness when treated with stress dose corticosteroids have shown lower rates of NP and VAP when compared with placebo [7]. This paper seeks to find out the status of nosocomial and ventilator-acquired pneumonia in the context of the ICU and possibilities of reducing and treating secondary infections to improve survival rates from traumatic injury via glucocorticoid steroid therapy.

What is Cortisol and how does it work in the body?

Cortisol is a glucocorticoid steroid that is produced naturally in the human body. Commonly referred to as the stress hormone, cortisol is produced from the zona fasciculata in the adrenal gland. One of the main roles that cortisol plays in the body is to supply glucose to the brain. Heightened levels of cortisol lead to an increase in the process of gluconeogenesis. Gluconeogenesis is a process that reverses the reaction of glycolysis [8]. Gluconeogenesis is the pathway that produces glucose from lactate and glucogenic amino acids. In the existence of cortisol muscle cells decrease

glucose uptake and use and instead break down proteins for use in gluconeogenesis. In fatty tissues like adipose cortisol initiates lipolysis, which increases concentrations of glycerol and fatty acids for use in gluconeogenesis [8]. Cortisol is produced continuously throughout the day and is highest in the morning and lowest in the night. Cortisol is a normal steroid that is produced in the regulation of homeostasis. Glucocorticoids like cortisol have several different functions in the body that range from inducing apoptosis to reducing neutrophil movement during inflammation. Cortisol can induce apoptosis of proinflammatory T cells and reduce neutrophil migration during inflammation. This is a vital aspect of cortisol as apoptosis and neutrophil movement inhibition is a crucial part of cortisol's anti-inflammatory properties [8].

The production of cortisol starts from the amygdala which evokes the fight or flight response. When the amygdala responds to fear or danger the amygdala immediately releases signals to produce catecholamines like norepinephrine and epinephrine. After the catecholamines are released into the body the catecholamine's increase heart rate, produce hypertension, and tachypnea [8]. Furthermore, the effect of catecholamines is proinflammatory in order to fight foreign invaders and pathogens. After the initial onslaught of catecholamine is that produces the initial stage of stress response, the amygdala signals the hypothalamus-pituitary-adrenal axis (HPA) to release corticotrophin-releasing hormone (CRH). The CRH binds to the anterior pituitary. Then adrenocorticotropic hormone or ACTH is released from the anterior pituitary in response to stress. ACTH increases low-density lipoproteins and increases the reactivity and activity of cholesterol desmolase which transforms cholesterol into pregnenolone. ACTH acts on the adrenal cortex and stimulates the production of cortisol [8]. Cortisol is a steroid that is derived and synthesized from cholesterol. Cortisol is normally in circulation in the body inactivated and attached to albumin and corticosteroid-binding globulin. The inactive form is only converted to an active form after being reacted with 11-beta-HSD1. After the production of cortisol, the levels of cortisol remain elevated in response to stress for multiple hours after the initial stress response. The resulting high levels of cortisol suppress the function of non-vital organ systems such as the gastrointestinal tract in favor of giving fuel to vital organs like the heart. Furthermore, cortisol has anti-inflammatory properties that counteract the catecholamines, which will help reduce inflammation.

Cortisol is a steroid hormone that acts as a primary messenger. The cortisol molecules can freely cross the cytoplasm membrane in body cells because cortisol is a fat-soluble nonpolar molecule. The cortisol molecule passes through the membrane and attaches to specific receptors that are located in the cytoplasm. After the receptors and cortisol, molecules bind together the cortisol-receptor complex breaks into the nucleus and change the transcription of genes [6].

In the event, the human body is exposed to high levels of cortisol for a long period of time a syndrome called Cushing syndrome occurs. There are different types of Cushing syndromes. For

example, there are ACTH dependent and ACTH independent. For ACTH dependent there is excessive production of ACTH. The overproduction of ACTH stimulates the adrenal gland to produce a large quantity of cortisol. In ACTH independent, the cause can be corresponded to a pituitary tumor or can be caused by excessive intake by mouth or IV corticosteroid usage. One such oral corticosteroid that is commonly taken is prednisone, which can increase the amount of cortisol in the body. Common symptoms of Cushing's syndrome are weight gain in the face and abdomen commonly called moon face. There are also commonly fat deposits between the shoulder blades. Other symptoms are hypertension, diabetes, and osteoporosis. Common treatments for this condition involve using glucocorticoid receptor antagonists to help decrease the concentration of cortisol in the body [7]. Although there are surgical intervention options for severe cases, medication therapy is the most common treatment option.

Insufficient concentration and production of cortisol can result in a condition called Addison's disease. Common causes of Addison's disease are adrenal hemorrhage, infection, autoimmune adrenalitis, and malignancy. Pituitary disease and HPA axis inhibition can cause a decrease in the production of ACTH from the anterior pituitary. Another cause can be the lack of CRH released from the hypothalamus, which will decrease the production of cortisol. Symptoms of Addison's disease are weight loss, fatigue, hypotension, and hyperpigmentation of the skin.

Treatment for Addison's disease includes supplemental glucocorticoid therapy like hydrocortisone [6]. As shown by the two diseases the production of cortisol must strike a fine balance and cannot go too much into either of the extremes.

The blood in the human body carries a large portion of cortisol. However, the vast majority of the cortisol in the bloodstream is inactive and bound to corticosteroid-binding globulin (CBG). While the rest of the proportion of cortisol is bound to albumin or free-floating and active. The adrenal gland does not store cortisol but increases production in response to ACTH. The half-life while circulating in the bloodstream is 70-120 minutes for cortisol [9]. While the biological half-life is 6-8 hours. The metabolism of cortisol is mainly concentrated in the liver and kidneys.

Traumatic injuries, the effects on steroid production in the body, and critical illness-related corticosteroid insufficiency

Traumatic injuries impose great levels of stress onto the body, which, at times, can have stress responses that are inappropriate. In 2008, the Society of Critical Care medicine named the term critical illness-related corticosteroid insufficiency (CIRCI). The term CIRCI is used to describe the malfunction of the HPA axis during critical injury and illness. Recent clinical findings suggest that the exaggerated proinflammatory response that is produced by the catecholamines suppresses the HPA axis and produces adrenal failure. Moreover, corticosteroid tissue resistance may play a role in CIRCI [7]. CIRCI arises with insufficient anti-inflammatory factories. Like type II diabetes, CIRCI comes from a corticosteroid

tissue resistance that often is compounded by insufficient levels of free cortisol. CIRCI is also known to be inadequate corticosteroid activity for the severity of a given patient's current condition. CIRCI can occur in several conditions like septic shock, pneumonia, acute respiratory distress syndrome, sepsis, trauma, burns, and major surgery [6].

While the traditional stress response is adequate to help combat pathogens and foreign invasions, the prolonged inflammation can be detrimental in a long-term response. In the event of excessive epinephrine, production that causes severe inflammatory responses when it is during a critical injury the production of cortisol may not be adequate to quell the inflammatory response. Thus, persistent system-wide inflammation can lead to tissue destruction and heighten disease progression [6]. The heightened systemic inflammation is driven partly by an imbalance of inflammatory pathways like nuclear factor-kappa B (NF-kB) signaling and dysregulated HPA axis response [6]. The glucocorticoid receptor plays a fundamental role in the maintenance of both resting and stress-related physiologic adaptations for stress responses. The glucocorticoid receptor affects the activity of nDNA and mtDNA, which affect the response to stress by affecting numerous genes that affect stress response. In critically injured patients increased cortisol levels are not evident which may be attributable to an increase in adrenocortical sensitivity to the ACTH molecule.

There are several physiological changes in critically ill patients that can include changes in levels of blood concentration of inactive cortisol. In critically injured patients both free and active and bound and inactive forms of cortisol are severely diminished. CBG and albumin-bound cortisol is decreased in trauma patients. The decrease is directly proportional to the severity of the injury. Septic patients can be seen with plasma interleukin that is directly proportional to CBG bound levels of cortisol in the body [6]. The function of the HPA axis has been shown in clinical studies to be decreased from 10-20% in trauma patients and can be decreased by 60% for septic patients. This shows that the responses that are natural and productive to combat stress may be ineffective when the body encounters severe stress. An increase in inflammatory cytokines on admission to the ER and during the patient's stay in the ER can be a prevalent indicator of the severity of the patient's condition. Moreover, the higher the inflammatory cytokines the higher the probability the patient may die.

The molecules TNF-alpha and IL-1 are known to be responsible for dysfunction of the HPA axis in the event of critical illness. TNF-alpha can reduce cortisol synthesis in the adrenal glands by inhibiting the actions of ACTH and angiotensin II on adrenal cells. TNF-alpha also negatively affects CRH-caused ACTH production. This is further shown by clinical studies that have shown low concentrations of ACTH in patients with sepsis [7]. Substrate insufficiency can decrease the creation of cortisol during acute illness. The acute illnesses that can be a cause range from myocardial infarctions, sepsis, and burns. CIRCI is a dangerous condition that can compound the present condition and illness of the patient. The exaggerated immune response that creates the

excessive systemic inflammation is dangerous as it can further destroy tissue and progress disease. The excessive inflammatory response can also increase chances for secondary infections like nosocomial pneumonia to take place, which can worsen a patient's condition rapidly if not controlled rapidly. CIRCI should be of utmost concern for all physicians in the ER. Physicians should also carefully pay attention to patients that require vasopressors as patients may have the hyperactive circulation that may worsen the dynamic circulation of the patient with sepsis.

What is hospital-acquired nosocomial and ventilator-acquired pneumonia and how is it caused?

The consensus conference statement defines pneumonia as a lung infection of the distal portion that is caused by microbial pathogens. Nosocomial pneumonia is pneumonia that develops in a span of 48 hours upon admission to a hospital. Nosocomial pneumonia is not an infection that was prevalent prior to hospital admission. Nosocomial is the second most common hospital-acquired secondary infection at 27% infection rate only behind urinary tract infections coming in at 31% of all hospital infections [2]. The various passages that bacteria can take to reach the distal portions of the lung range from hematogenous seeding, contiguous spread, aspiration, and inhalation.

The most frequent route as determined by clinical data suggests that the risk of aspiration of gastric or oropharyngeal contents. Nevertheless, other routes can serve as paths for pathogens to take to reach the distal lung. For example, improper ventilator circuit setup or maintenance can lead to pathogens being aerosolized into the breathing apparatus and sent into the distal lungs. Furthermore, in the presence of an endotracheal tube aspiration risk is high because the tube inherently works by opening the vocal cords. When the vocal cords are held open, coughing and other natural reflexes are hindered. Other natural methods of pathogenic defense systems of the body include filtration and humidification of air when passing through the nasopharyngeal passages. The epiglottis and cough reflexes are hindered. When the natural reflexes for foreign body expulsion are suppressed, secretions can pool above the cuff that is inflated in the endotracheal tube. In the case of nosocomial pneumonia patients without risk factors for pneumonia have a 1% chance of contracting a pneumonia infection during a hospital stay [2]. However, the chances of a pneumonia infection increase to 20% when the patient is mechanically ventilated and intubated. Nosocomial pneumonia commonly affects critically injured or ill-intubated patients [2]. In a study by Feldman and colleagues, a bio membrane that was infected with pathogenic bacteria called biofilm was found in the lower portion of the endotracheal tube in intubated patients. The research concludes that nearly all patients that were intubated for more than 96 hours had biofilm on the endotracheal tubes.

The stomach and oropharynx are known to be breeding grounds for potentially harmful gram-negative bacteria. When the pH of the stomach and gastric acids are increased, the naturally bactericidal environment will no longer be effective in killing pathogens. The pH changes are most commonly caused by prophylaxis stress

ulcer medication treatment [2]. This, when combined with alkaline feeding can cause potentially a perfect breeding ground for gram-negative enteric bacteria. Furthermore, the oropharynx has natural flora that can be aspirated into the lungs or the stomach, which will then cause the pathogens to colonize, multiply, and cause infection. The natural bactericidal gastric acid will no longer be effective in eradicating bacteria due to pH changes.

Signs and symptoms of pneumonia include a variety of bodily and systemic changes. One notable symptom is the onset of fever. This, when combined with tachypnea, respiratory secretions and excessive sputum, and leukocytosis can be an indicator of a pneumonia infection. Furthermore, a physician can auscultate for lung sounds and determine if there are diminished lung sounds from distal lung areas as infection can be a valid cause. The physician can auscultate for diminished breath sounds and rales. Rales can be heard as crackles, which are caused by fluid buildup in the lungs as caused by a pathogenic infection like pneumonia. New clinical findings suggest that the new presence of a radiologic opacity may indicate a possible pneumonia infection. However, recent studies suggest that there is merely a 68% accuracy of diagnosis when using radiologic opacity, especially when used on patients with an acute lung injury [2].

The timing of infection and type of pneumonia can greatly affect the prognosis of the condition. Early-onset of VAP or NP can be seen to be caused by aspiration of community-acquired pathogens. The early onset is typically within 48 hours of hospital admission. Late-onset is typically defined to be after 48 hours of hospital admission. Pathogens that typically are caused by early-onset NP are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and *Haemophilus influenzae* [2]. However, late-onset of NP is associated with higher morbidities. This is because more commonly in late-onset NP antibiotic-resistant pathogens are more likely to cause infection. The types of pathogens that commonly infect in late-onset infections are bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Acinetobacter* species [2]. The late types of infection are typically more resistant to antibiotics and must be treated with a wide spectrum of antibiotics for a chance to effectively eradicate the infection. However, for early infections, the spectrum of antibiotics can be much smaller due to the nature of the pathogen.

Patient pre-existing health conditions can heighten risks and comorbidities associated with NP. Research has shown that older patients are typically more at risk of contracting infections due to a weakened immune system. Men are typically more likely to be infected than women. If the patient was in a traumatic injury or a burn incident the patient may be at heightened risk of becoming infected with NP. The severity of the patient's condition is also directly proportional to the increase in risk for pathogenic infection. Other risk factors include diabetes mellitus, pulmonary disease, CHF, acute lung injury, and head injury. The risks for VAP can be seen rising steadily from the first day and peaking on the fifth day of mechanical ventilation. However, on day 15 of mechanical

ventilation the risk of VAP plateaus and declines drastically [2]. This shows that patients that are receiving long-term mechanical ventilation assistance can have low incidences of VAP. It is only in the initial phase of ventilation that infection risks are heightened.

What are some methods to conventionally combat VAP and NP?

Currently, there are several methods that are implemented for critically injured mechanically ventilated patients to reduce infections like VAP and NP. One prominent method is to continuously drain the secretions from the subglottis region. Furthermore, maintenance of a proper ET tube cuff, which will prevent cuff leaks, can help to prevent infections. The threshold of pressure is between 25 cm H₂O and 30 cm H₂O [2]. The cuff should not be inflated past 30 to prevent tracheal injury. Prophylactic administration of antibiotics is common practice in the ER in order to prevent early-onset NP. Albeit, antibiotic treatment in prolonged use cases can heighten risks for late-onset NP with antibiotic-resistant pathogens. Furthermore, good hygiene practices can help prevent any excessive contamination and the introduction of pathogens to a patient. Hand disinfection with antibacterial soap and water with adequate scrubbing can help to reduce pathogens. Furthermore, the use of hand sanitizers and alcohol can be effective in reducing but not as effective as traditional handwashing. Furthermore, to prevent the spread of nosocomial infections hand disinfection with chlorhexidine has been shown to be effective in reducing risks of pathogen infection. Moreover, the use of appropriate PPE such as gowns, gloves, and sterile equipment will reduce the chances of infection.

Other methods of preventing NP can vary from the positioning of the patient to using different types of ET tubes. Topical administration of prophylactic antibiotics in the oropharyngeal cavity can help prevent oral flora from colonizing and aspirating into the stomach. Furthermore, frequent suctioning of oral secretions will decrease the risks of aspiration. Oral rinses with chlorhexidine can reduce the chances of oral flora developing biofilm on ET tubes [2]. Hand hygiene will also help prevent cross-contamination between patients. In a clinical study by Myrianthefs et al., the use of sucralfate has been shown to decrease rates of NP infections. This is shown to be superior to the traditional ranitidine treatment. This is because the H₂-antagonists that are normally used may increase the risk of infection due to a change of pH in the stomach. However, this should only be implemented in patients with low risks for GI bleeding. Furthermore, the researchers found that glutamine-enriched diets that promote immunity have decreased incidences of NP in patients in the ER. The prevention of NP has been estimated to save \$1872 per patient [2]. Furthermore, positioning of the patient in a semi-recumbent position or semi-fowler as opposed to supine has been shown to be effective in reducing infection risks. The reduction in risks is attributable to the lowered risk of aspiration that is allowed by a slight elevation of the body, which is preferable to the 0-degree elevation that is produced by a supine position.

Antibiotic treatment for early versus late-onset NP varies due to the

inherent qualities of the types of infections. According to the ATS guidelines, with severe early-onset NP, the suggested treatment is a third or second-generation cephalosporin combined with a beta-lactamase inhibitor, a fluoroquinolone, and aztreonam [2]. However, in late-onset NP the recommended treatment changes. The recommended treatment is ciprofloxacin in addition to an antipseudomonal broad-spectrum antibiotic such as penicillin and a third-generation cephalosporin. If an MRSA infection is, suspected clinical studies strongly recommend that vancomycin, a glycopeptide, be added to the treatment in order to suppress the infection earlier.

How does corticosteroid therapy benefit trauma patients?

In times of critical illness and trauma, CIRCI can disable many of the body's natural mechanisms for stress response. In the HYPOLYTE study, the researchers found that when giving patients with multiple trauma stress dose bolus of corticosteroids, which were 200-350 mg per day there has been demonstrably improved patient outcomes when compared to placebo [7].

In the study, the researchers showed results that produced patients with more ventilator-free days. The study concluded that the stress dose steroid therapy has been shown to be efficacious in increasing short-term survival probabilities in patients with critical illness and trauma [10]. This is due partly to the fact that CIRCI exaggerates the proinflammatory response and suppresses the natural production of cortisol in response to high stress. Thus, by supplementing the cortisol the patient is better able to achieve homeostasis and negate any of the negative properties of excessive catecholamines in the system.

Hydrocortisone therapy is also shown to be efficacious in reducing mortality related to sepsis. In an article by Nafae et al., the use of hydrocortisone was shown to be an effective manner of reducing sepsis-related complications and pathogenic infections [10]. This is attributable to the anti-inflammatory properties of cortisol and due to the CIRCI that happens during critical illness, a patient may not be able to naturally produce the cortisol needed to counterbalance the catecholamine's produced initially in response to the stress. This counterbalance effect is highly desired as it can reduce the mortality associated with pathogenic infections. However, it should be noted that Nafae et al. showed a prominent side effect of hypokalemia [10]. The hypokalemia that was associated with the hydrocortisone therapy was attributable to the mineralocorticoid mechanism of hydrocortisone. Mineralocorticoids act by increasing renal sodium retention. However, as a side effect, there is fluid retention that, in extreme cases, can cause weight gain as seen in Cushing's syndrome. In Cushing's syndrome, a patient will experience excessive fluid retention in the face and abdomen. The fluid retention in the face is referred to as moon face. However, a side effect of renal sodium retention is potassium loss. However, this can be offset during acute hydrocortisone therapy by supplementing the patient with IV potassium.

The use of corticosteroid therapy in critically injured patients can offset the negative side effects of CIRCI and improve patient

outcomes. Due to the inherent characteristics of corticosteroids, the anti-inflammatory properties work at the molecular level. The cortisol combined with the CBG will enter the nucleus of a body cell and down-regulate the production of genes that produce inflammatory cytokines. Instead the CBG and cortisol complex upregulate the production of anti-inflammatory cytokine transcription. By reducing proinflammatory cytokine response the anti-inflammatory cytokines will instead be able to reduce systemic inflammation. Furthermore, by decreasing inflammation the early stages of NP will be reduced drastically. Thereby leading to an earlier resolution of the NP infection. In a clinical analysis by Nafae et al., when compared to placebo the mean duration assisted ventilation in hydrocortisone groups was significantly shorter. The mean time for the placebo group was (4.3 ± 7.83) days while the hydrocortisone group had a mean time of 1.2 ± 3.75 days of mechanical ventilation [10]. This shows that hydrocortisone therapy is efficacious in reducing the risks of infection and accelerating the healing process. Furthermore, the use of hydrocortisone therapy is shown to save a significant amount of time under mechanical ventilation and ultimately hospital days. This is not only beneficial to limited hospital resources, but it is also significantly beneficial to the patient that may save thousands of dollars in medical expenses.

The dangers of excessive or improper hydrocortisone use

In several clinical studies, including the HYPOLYTE, the dosage and appropriate administration had differing outcomes. According to Myrianthefs et al, when patients were given a high dose therapy of hydrocortisone (10,000- 40,000 mg in >24 hours) the patients did not receive any beneficial effects [8]. Instead, it was shown in the clinical data that patients with severe sepsis failed to improve conditions and instead suffered other complications. It was concluded that supra-physiologic doses of corticosteroids negate any beneficial effects of the steroid therapy [11]. In fact, the ultra-high doses of steroids created severe adverse effects, which lead to some patients in the study obtaining life-threatening infections and suppression of the HPA axis. The clinical data also shows that there is a direct correlation between increasing dose and symptoms of Cushing's syndrome. The clinical data showed that patients with high doses of hydrocortisone showed fluid retention and ecchymosis. However, using too little hydrocortisone will not yield any results as the effect will not be evident on the patient. Instead, it is imperative that physicians administer a stress dose that ranges between 200-350 mg a day [7].

Conclusion and Future Trends

The important role of glucocorticoids like cortisol has been known in the medical community for years. However, recent advancements due to new clinical data and research suggest that CIRCI is a prevalent condition that affects critically injured patients. In order to best treat critically ill patients, it is imperative that the role of cortisol supplementation be further explored in order to reduce secondary infections such as nosocomial pneumonia. However, drugs and the metabolism of them within an individual can vary greatly from one patient to another. This means that the same dose and same administration time period for two different patients can result in two completely different outcomes. The specific

pharmacokinetics of a patient must be taken into consideration in order to treat a patient for the most favorable outcome. Future studies should be undertaken to further understand the reasons behind why CIRCI occurs and if there are other methods in treating critically ill patients. Perhaps research can be done in order to explore the opportunity of implementing other types of glucocorticoid steroids in lieu of cortisol. Moreover, more research should be undertaken to explore the physiological effects of supra-physiological doses of hydrocortisone and why the results occur to involve the patients experiencing severe adverse reactions. The role of nosocomial pneumonia especially in critically ill patients is very dangerous and highly prevalent. Even with the present methods of prevention nosocomial pneumonia is one of the most prevalent secondary infections from a hospital. Future research can also be completed on how different types of endotracheal tubes can minimize the occurrence of biofilm. By understanding the mechanism of how and why biofilm buildup occurs during mechanical ventilation medical equipment manufacturers and researchers can better create more efficacious equipment that may have bactericidal properties that may, on its own, decrease chances for infection drastically. Furthermore, by using hydrocortisone, physicians can help offset the natural inflammatory mechanisms of the stress response system by introducing increased level of cortisol into the body which helps limit and ultimately lower inflammation drastically which is shown to help reduce secondary infections. Future research should be conducted with regards to dosage, route of administration, and side effects concerning hydrocortisone therapy. The use of hydrocortisone therapy in trauma patients has also been shown to be efficacious in reducing days with mechanical ventilation and total hospital day stays. Not only will the effect of reducing hospital days reduce the limited resources of an emergency department, but it can also drastically save patients in medical expenses. Furthermore, by allowing patients to have a speedy recovery the patient will ultimately experience a higher improvement in quality of life especially with reduced chances of contracting secondary infections. The Hippocratic oath says to do no harm and if healthcare professionals desire to help patients to the best of their abilities, then using and further researching hydrocortisone therapy to reduce mortality and increasing the quality of life should be further investigated and purported.

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