Glucocorticosteroids: as Adjuvant Therapy for Bacterial Infections

WONDIM MELKAM*, HAGAZI GEBREMEDHIN, SOLOMON ABRHA,
BRHANETENSAY MASRESHA, FANTAHUN MOLLA

Mekelle University, College of Health Sciences,
Department of pharmacy, PO. Box 1871, Mekelle, Ethiopia.
E-mail: neyilign@yahoo.com

ABSTRACT

Glucocorticoids (GCs), synthetic analogues of the natural steroid hormones, are well known for their anti-inflammatory and immunosuppressive properties in the periphery. They are widely and successfully used in the treatment of autoimmune diseases, chronic inflammation, and transplant rejection. Nowadays, GCs are claimed to have a beneficial role being as adjunct therapy in various infections. Different studies have been conducted to investigate their use as adjuvant therapy for different bacterial infection. This review, therefore, summarizes various bacterial infections for which glucocorticoids are reported to be used as adjuvant therapy, strategies for administration of glucocorticoids, and challenges of using glucocorticoids as adjuvant therapy.

1. INTRODUCTION

Glucocorticoids (GCs) are synthetic analogues of the natural steroid hormones produced by the adrenal cortex. Like the natural hormones, these compounds have glucocorticoid and/or mineralocorticoid properties [1].Cortisol is a naturally occurring glucocorticoid that predominantly involved in carbohydrate, fat and protein metabolism, and regulation of inflammation. However, sometimes the levels of cortisol are not enough to counter sudden, chronic, or severe inflammation, therefore; synthetic GCs are important which act in a similar way to stop inflammation [2]. GCs are well known for their anti-inflammatory and immunosuppressive properties in the periphery. As a result, they are widely and successfully used in the treatment of autoimmune diseases, chronic inflammation, and transplant rejection [3].

GCs exert many pharmacologic effects through cytosolic receptors which are the member of the nuclear hormone receptor super family. Upon ligand activation, glucocorticoid receptor is released from the protein complex, dimerizes and translocates in the nucleus where it binds to specific DNA sequences called glucocorticoid response elements [4]. Thus, glucocorticoid receptor function has a ligand dependent transcription factor. Through this pathway GCs induce anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects [1]. Their anti-infalmatory effect is brought by preventing or suppressing the inflammatory reaction to infectious, physical, or immunologic agents through inhibition of early inflammatory events such as edema, cellular exudation, fibrin deposition, capillary dilatation, and migration of leukocytes into the area. However, the major effect of GCs on the inflammatory process is inhibition of recruitment of neutrophils and monocytes. They dampen the ability of neutrophils to adhere to capillary endothelial cells by blocking the normal increase in expression of extracellular adhesion molecule-1(ECAM-1) and intracellular adhesion molecule-1 (ICAM-1) and inducing expression of lipocortin, a protein inhibitor of phospholipase A2 (PLA2) which is one of the enzymes that are involved in production of inflammatory mediator prostaglandins [5].

In addition, they inhibit the production of pro-inflammatory cytokines either directly or indirectly [6]. Direct inhibition may entail GR-mediated transcriptional repression and GCs regulated cytokine expression which augment production of proteins that destabilise cytokine mRNA, which in turn diminishes expression of these cytokines. Whereas, their indirectly inhibition is by hindering cytokine production through induction of synthesis of glucocorticoid-induced leukine zipper, IκB, and lipocortin-1. Both IκB and glucocorticoid-induced leukine zipper act by inhibiting the activity of pro-inflammatory transcription factors.

Glucocorticoids'immunosupressive effect is due to induction of apoptosis in mature T-lymphocytes, monocytes, and eosinophils and inhibition of T-cell response to activating stimuli through interference with T-cell receptor-mediated signalling pathways [6]. GCs mediated inhibition of cytokine production may account for inhibition of T-cell and macrophage activation and reduction in T-cell proliferation. Besides, they decrease the secretion of interlukin-1(IL-1) and other mediators of immune response, inhibit lymphocyte participation in delayed hypersensitivity reactions, and interfere with the rejection of immunologically incompatible graft tissue [5]. From the preceding, therefore, it can easily be understood that GCs have different pharmacologic effect. Due to this fact, many researchers have conducted an experiment to look into the use of GCs as adjuvant therapy to decrease the inflammation and related pain induced by the inflammatory reactions for different infectious and non-infectious diseases. Hence, in this review the use of GCs as adjuvant therapy for bacterial infections is discussed.

2. CORTICOSTEROIDS AS ADJUVANT THERAPY IN THE TREATMENT OF BACTERIAL INFECTIONS

2.1. Acute bacterial meningitis (ABM)

Acute bacterial meningitis (ABM) is a severe infection of the meninges which is associated with high mortality and morbidity rates despite optimal antibiotic therapy and advances in critical care [7]. The most common causative agents of ABM in adulthood are *N.meningitides* and *S.pneumonia*. Whereas, the major pathogens associated with newborn meningitis are *S.pneumonia*, *L.monocytogenes*, *E.coli*, and other gram-negative bacilli [8]. The pathogens colonize the nasopharynx, penetrate the epithelial cells of the upper respiratory tract, invade the CNS, and generate an intense inflammatory response in the subarachnoid space [9].

Cerebrospinal fluid (CSF) is an area of impaired host resistance due to the virtual absence of antibodies and complement. This allows rapid bacterial proliferation [10]. The brain damage associated with ABM is not simply dependent on the presence or amount of viable bacteria, but rather occurs as a consequence of host immune response to bacterial components [11]. The inflammatory response to bacterial infection in the CSF has substantial clinical impact with associated morbidity and mortality.

Inflammation of the subarachnoid space is largely responsible for the pathological consequences and clinical features of ABM including increased permeability of blood brain barrier (BBB), cerebral oedema, increased intracranial pressure (ICP), cerebral vasculitis, loss of auto-regulation of cerebral blood flow, cortical hypoxia and CSF acidosis [10]. Subarachnoid space inflammation is induced by certain bacterial constituents like gram positive cell wall peptidoglycans , teichoic acid and endotoxins of gram negative bacteria. These constituents in the meninges provoke the release of cytokines such as interleukins, tumour necrosis factor-α (TNF-α) and platelet aggregation factor which in turn flare an inflammatory cascade [12]. In addition, the administered antibiotics intended to treat this particular infection exaggerate the formation of inflammatory exudates from tissue destruction and endotoxins from bacterial lysis, resulting in edema formation [13].

Administration of GCs as adjunctive treatment in ABM may attenuate the acute inflammatory process while antibiotics clear the pathogenic microorganisms. This might improve clinical outcomes both in the short and long term [12]. Adjuvant GCs are claimed to be useful in both adult and paediatric meningitis as it is evident from experimental studies and vast growing clinical data [13]. Since dexamethasone has superior penetration in the CSF and lower mineralocorticoid activity, it is particularly considered to be the corticosteroid of choice in ABM [7]. Although findings suggest that two days and four-day regimens are equally effective, the four days regimen has been used in most clinical trials involving children with ABM. The four day regimen is recommended, with dexamethasone therapy started before or with the first dose of antibiotics [14].

Even though GCs are very helpful as adjuvant therapy, there are some concerns like reduction in CSF penetration of antibiotics and their potential to mask antimicrobial failure by preventing secondary fever [15]. For instance, treatment failures have been reported in adults who received standard doses of vancomycin and adjunctive dexamethasone. The suggested reason for the aforementioned incidence is due a reduction in penetration of vancomycin into the subarachnoid space associated with the BBB integrity maintaining effect of dexamethasone. However, treatment failure has not been reported in children with BM treatment with dexamethasone because dexamethasone has not been reported to reduce vancomycin levels in CSF [14]. Higher permeability of the BBB in children might be the reason for the better outcome of the combination as opposed to the outcome in adults.

The above finding is well supported by a placebo-controlled, blinded clinical trial conducted among infants and children aged between six weeks and 12 years in Costa Rica to investigate the impact of dexamethasone on childhood meningitis. From the result, it was found that overall neurological and audiological sequelae were significantly lower [12]. The findings forwarded by a randomized trial study on adults and adolescents with bacterial meningitis in Vietnam are also promising, as adjuvant GCs were found to decrease mortality in those patients with culture- confirmed bacterial meningitis, but had no significant effect on those with probable meningitis [15].

The effect of adjuvant GCs on mortality, hearing loss and neurological sequelae in participants of all ages with ABM was conducted utilizing a total of 24 randomised clinical trials (RCTs). The review reported that using adjuvant GCs decreased mortality, hearing loss and short-term neurologic sequelae in adults. In addition, for children with meningitis caused by H. influenzae, hearing loss was significantly reduced by corticosteroids but, for children with meningitis caused by bacteria other than H. influenzae, no significant beneficial effect was seen [7].

Ahsan and his co-workers also conducted an open, interventional cohort study utilizing 68 adult patients who were admitted in Medical Unit and diagnosed to have ABM. Patients who were given adjuvant therapy in addition to antibiotics were reported to have early resolution of fever, headache, and altered consciousness as well as well reduced inflammatory response as compared to patients with no adjuvant therapy. Besides, no complications attributable to the adjuvant CSs were observed [10]. Similar findings were also revealed in another prospective randomized, double blinded, multicentered trials aiming at investigating the effect of dexamethosone as compared to placebo in adults with ABM [14]. Eight weeks after enrolment, the percentage of patients with an unfavourable

outcome and the number of mortality incidents were significantly smaller in the dexamethasone group than in the placebo group.

In conclusion, although there are some concerns regarding reduction in CSF penetration of some antibiotics, majority of the studies reviewed in this paper has shown promising results of using of GCs as adjuvant therapy for patients with ABM.

2.2. Tubercular Meningitis (TBM)

Tubercular Meningitis (TBM) is an inflammation of the meninges, caused by infection with *M.tuberculosis* [16]. It is the most severe extrapulmonary complication of TB which is resulted from haematogenous spread of primary or post-primary pulmonary disease [17]. Despite of the advent of the newer anti-tuberculosis drugs and modern imaging techniques, mortality and morbidity remain high. In fact, most studies have suggested that combination of various factors like delayed diagnosis and treatment, extremes of ages, associated chronic systemic diseases and advanced stage of disease at presentation may contribute to this high morbidity and mortality rate [18].

TBM needs to be treated by two different points of view: both the microbiological and the inflammatory ones. Indeed, anti-TB therapy alone does not improve outcome significantly despite reductions in bacillary load. Rather, after initiation of therapy, patients often progress to severe neurologic signs and death. This is due to antibiotic killing of mycobacteria and release of cell wall products which further induces meningeal inflammation by stimulating the production of inflammatory cytokines, resulting in damage of the vessels accompanied by infarcts, brain edema, and necrosis. For this reason, in order to reduce the inflammation accompanying TBM, standard anti-TB therapy usually includes anti-inflammatory treatment, such as adjuvant GCs [17].

GCs are commonly used in addition to anti-tuberculosis drugs for treating those conditions; they help to reduce inflammation, especially in the subarachnoid space; reduce cerebral and spinal cord oedema and ICP; and reduce inflammation of small blood vessels and therefore reduce damage from blood flow reduction to the underlying brain tissue [16]. The rationale behind the use of adjuvant GCs lies in reducing the harmful effects of inflammation as the antibiotics kill the organisms [19]. However, steroids also have immunosuppressive effects, and concerns remain that their use might worsen outcome in TBM because of failure of immune response against the organism. Moreover, the reduced inflammation of the meninges achieved by GCs treatment could reduce the ability of drugs to seep into the subarachnoid space [17].

A significant number of clinical trials have been conducted on the impact of adjutants on the treatment morbidity and mortality of TBM. A Cochrane systematic review was conducted to evaluate the effects of GCs as an adjunct to anti-tuberculous treatment on death and severe disability in people with TBM. This review identified seven RCTs involving 1140 participants comparing a corticosteroid plus anti-tuberculous treatment with anti-tuberculous treatment alone in people with clinically diagnosed TBM. With respect to death or disabling residual neurological deficit, the overall estimate showed a significant reduction in the risk of death or disabling residual neurological deficit with CSs. Only one trial evaluated the effects of CSs in HIV-positive people, but the effects were unclear. Given the results of the review, all HIV-negative people with TBM should receive CSs, but more trials are needed in HIV- positive people [16].

Another prospective randomized clinical trial has been done on children with moderate to severe TBM to study the effect of high-dose prednisone on ICP, cranial computed tomographic findings, and clinical outcome for 6 months. From the result, it was found that both the course of tuberculomas that were present at admission and the incidence of new tuberculomas were significantly improved by steroid therapy. Mortality rate before completing 6 months of anti-tuberculosis therapy, in children with stage III TBM, was significantly smaller in the steroid group than the non-steroid group. No significant difference was found between the steroid and non-steroid groups in the incidence of motor deficit, blindness, or deafness and infract size [20].

Unlike the aforementioned studies, a randomized, placebo-controlled trial conducted on patients over the age of 14 years with TBM in Vietnam showed no significant difference for the combined outcome of death or severe neurological disability between cases treated with dexamethasone or placebo. However, patients treated with steroids had less hepatitis when taking anti-TB drugs and this resulted in reduced interruption and changes in antibiotic regimen [17].

2.3. Acute bacterial pharyngitis (ABP)

Acute bacterial pharyngitis (ABP) is described as an inflammation of the pharynx and surrounding lymphoid tissue. The most common bacteria causing pharyngitis is group A β-haemolytic streptococcus (GABHS) [21]. In general, inflammation benefits hosts with an infectious diseases because it is useful for eliminating the infecting pathogens. However, an excessive amplification of the inflammatory response may worsen the clinical course of infectious diseases, leading to significant tissue damage and development of systemic effects. This indicates that CSs can be useful in infectious diseases when the inflammation is particularly severe, but dangerous when the activation of inflammatory processes remains within the normal range [22].

Bacterial infections that cause ABP generate pain through inflammation of the pharynx and the surrounding lymphatic tissue. Although antibiotic treatment may shorten the duration of symptoms in a bacterial throat infection, the benefits are considered moderate. The anti-inflammatory action of steroids might be effective to relieve symptoms caused by inflammation [23]. Given the fact that inflammation is associated with pharyngitis, moderating the inflammatory cascade may assist in both relieving the acute attack and preventing complications. A variety of anti-inflammatory agents may provide benefit in the treatment of sore throat through the mitigation of inflammation. GCs are an appealing, inexpensive, and familiar agent with which the inflammation can be mitigated [24].

GCs inhibit the transcription of pro- inflammatory mediators in human airway endothelial cells that cause pharyngeal inflammation and ultimately symptoms of pain. It has been, therefore, suggested that GCs could offer symptomatic relief from sore throat and could be used in the treatment of ABP. A number of clinical trials have evaluated the effect of adjuvant GCs in patients with ABP [21, 22, 23, 24]. In most cases, they are beneficial in patients with ABP because the treatment was associated with a significantly faster reduction in pain or complete pain relief [22].

Whether steroids can serve as treatment of pain related to pharyngeal inflammation is a question clinicians have been asking for more than half a century. Health care providers are at times reluctant to give steroids owing to their potential long-term side effects. However, no corticosteroid induced long-term side effects were observed when steroids were used for acute pharyngitis [23]. Studies in adults and children [21, 23, 25] confirmed that GCs in combination with antibiotic treatment provide symptomatic relief of pain and faster recovery, mainly in patients with severe or exudative sore throat. For children with severe symptoms and bacterial pathogens confirmed by rapid streptococcal tests, a single dose of oral and intramuscular dexamethasone can be considered a safe adjunctive treatment with antibiotics [26]. In addition, GCs adjuvant therapy was also reported to provide relief of symptoms in acute exudative pharyngitis in adult patients [21].

2.4. Community acquired pneumonia (CAP)

Community acquired pneumonia (CAP) is the most common type of pneumonia and occurs when one is infected by pathogens without being recently hospitalized. The most common causative agents are *S. pneumonia*, *M. pneumonia*, *H. influenzae*, viruses and atypical bacteria [27]. Although antibiotics and vaccines have greatly reduced the morbidity and mortality associated with CAP, it remains a significant clinical problem worldwide. Additional therapeutic interventions are, therefore, urgently needed [22].

The inflammatory response triggered by the entry of pathogens into the alveolar space is useful for controlling and eliminating primary CAP, provided that it remains localised. However, when the cytokine response is unbalanced and excessively amplified, the clinical course can worsen and lead to severe community acquired pneumonia (SCAP) with systemic effects. It has, consequently, been suggested that systemic GCs could be used as adjunctive therapy in order to accelerate the resolution of systemic and pulmonary inflammation in the early phase of the disease [22].

Excessive cytokine response in patients with SCAP has been linked with deleterious effects and poor prognosis [28]. Despite optimal antibiotic and supportive treatment, SCAP remains associated with exceedingly high mortality rates. For this legitimate reason, investigators have worked for decades in numerous clinical trials aiming to identify adjunctive strategies for this condition. In this sense, GCs are the prototypical ‘ideal candidate’. They present anti-inflammatory properties that may reduce the intense proinflammatory cytokine response and thus modify the occurrence and severity of organ failures [29]. They are obvious adjunctive agents for infections and have been studied in CAP for many years [30]. For instance, in a small, multicentered trial, 46 patients with SCAP randomised to receive hydrocortisone (200 mg bolus followed by 10 mg/h infusion for 7 days) showed significant improvements in gas exchange, resolution of organ failure and reduction in hospital stay. It was then recommended to consider hydrocortisone in SCAP [31]. Besides, retrospective evaluation of the effect of prednisolone and methylprednisolone in children with CAP or documented *M.pneumoniae* infection, whose clinical and radiographic findings progressively worsened, found that GCs were associated with a marked improvement in all of the signs and symptoms of disease in most cases [22].

Another randomized, double blinded, placebo-controlled trial was conducted to analyse the effect of adjuvant GCs on the clinical course and outcome of CAP needing hospital admission, as well as on the profile of the host inflammatory response. The results of this study showed good results on favourable evolution of the pO2/FiO2 ratio and faster decrease of fever, as well as greater radiological improvement at seven days. However, no differences in mortality were found between test and placebo groups [28].

A variety of arguments support a beneficial effect of GCs in pneumonia. Nevertheless, the available data do not permit to draw firm conclusions on the use of GCs in the treatment of this disease. The administration of GCs in mild to moderate CAP cases cannot be recommended. The open point is the use of these drugs in very severe cases, particularly those requiring admission to the ICU [22]. In addition, CSs appeared to be both safe and efficacious in patients with obstructive airways disease complicated by CAP and should not be withheld in these patients [30]. Despite this fact, further studies are needed in order to better define the characteristics of the patients and pathogens

for whom this addition is really needed, the type of drug and dosage to prescribe, as well as to precisely discover the real safety and tolerability of the treatment [22].

2.5. Tubercular pericarditis (TBP)

Tubercular pericarditis (TBP) is a life threatening infection of the pericardial membrane that results in a build-up of fluid around the heart, which in turn constrains its pumping action (tamponade). Besides, the infection can sometimes cause a thickening of the pericardium without an effusion, and this can also constrain the pumping action [32]. TBP presents clinically in 3 forms, namely, pericardial effusion, constrictive pericarditis, and a combination of effusion and constriction. The treatment of TBP involves the use of standard anti-tuberculosis drugs for 6 months and pericardiectomy for persistent constriction in the face of drug therapy [33].

Persistent TBP will lead to pericardial constriction due to chronic inflammation of the pericardium, which leads to pericardial scarring, thickening, and fibrosis. Use of CSs as an adjuvant therapy has been recommended for patients with TBP and in the presence of large amount of pericardial effusion to suppress inflammation, reduce effusion and the accumulation of fluid or development of adhesions in the pericardium [34]. CSs as anti-inflammatory agents are expected to reduce the accumulation of fluid or development of adhesions in the pericardium that are induced by the tuberculosis infection. Some authors recommend the routine use of steroids in all cases of TBP. In contrast, other experts advise that CSs should be reserved for people who are critically ill with recurrent large effusion and who do not respond to pericardial drainage and anti-tuberculous drugs alone [32]. Despite the use of steroids is remaining controversial, a meta-analysis of patients with effusive and constrictive TBP suggested that tuberculosis treatment combined with steroids might be associated with fewer deaths, and less frequent need for pericardiocentesis or pericardiectomy, and anti-tuberculosis treatment combined with CSs is recommended if no clear contraindication is present [35].

The above findings are in agreement with a randomised trial conducted on 383 South African patients to assess the effect of prednisolone on mortality, functional status and need for repeated pericardiocentesis. From their findings, the prednisolone group showed a trend towards improved overall survival, but it did significantly decrease the composite endpoint of death and adverse outcome, mainly as it reduced the need for pericardectomy and its associated mortality. This study recommended prednisolone tapering from 60 mg daily over 11 weeks to be given in TBP [31].

According to a double-blinded, randomised clinical trial conducted in Transkei comparing prednisolone with placebo as a supplement to 6 months of anti-tuberculosis chemotherapy in the treatment of active constrictive TB, prednisolone was reported to have been effective in increasing the rate of clinical improvement, reducing the risk of death and the need for pericardiectomy [36]. The above study is supported by a double-blinded, randomised clinical trial study done in Zimbabwe on 58 HIV-seropositive patients with tuberculous pericardial effusion aimed at investigating the effect of prednisolone on treatment outcomes. From their finding, more rapid clinical improvement and fewer deaths during 18 months of follow up were reported even though no difference in radiographic or ecocardiographic resolution of pericardial effusion was showed [37]. Similar results also revealed in a double-blinded, randomized, controlled trial done in South Africa [33].

In conclusion, most of the studies conducted on the use of CSs on the treatment of TBP as adjuvant therapy, has positive result. Hence, it would not be wrong to recommend the use of CSs to improve the clinical complications and mortality rates associated with TBP.

2.6. Severe sepsis and septic shock

Septic shock, the most severe manifestation of sepsis, is defined as infection-induced hypotension refractory to fluid replacement that is accompanied by organ dysfunction or hypoperfusion [38]. It is characterized by uncontrolled systemic inflammation that contributes to the progression of organ failures and eventually death. There is now ample evidence that the inability of the host to mount an appropriate Hypothalamus-Pituitary-Adrenal axis response plays a major role in overwhelming systemic inflammation during infections [39].

Stress states such as septic shock causes the corticotrophin levels to increase, but the adrenal glands may be unable to produce sufficient cortisol to meet the added stress needs. Administration of low dose CSs in septic shock is thought to make up this cortisol deficit to produce a beneficial effect on shock reversal, the immune system, and the hemodynamic profile. Low dose CSs should only be administered to a subset of patients with septic shock who are unresponsive to fluid replacement and vasopressor therapy [38].

The rationale for using CSs in septic shock relies on the concept of critical illness associated corticosteroid insufficiency. Hydrocortisone should be preferred to synthetic CSs for the following reasons. First, most of the experience with low dose corticosteroid treatment in septic shock has been with the use of hydrocortisone. Second, treatment with hydrocortisone directly replaces cortisol, independent of metabolic transformation. Third, hydrocortisone has intrinsic mineralocorticoid activity. Different mechanisms provide rationale for the use of low dose CSs in patients with septic shock: relative adrenal insufficiency (RAI), peripheral steroid resistance, effects on the vascular tone, and prolongation of survival time. RAI is considerably more common, in patients with septic shock. Hydrocortisone 200–300 mg/ day, for 7 days in three or four divided doses or by continuous infusion are

recommended in patients with septic shock who requires adequate fluid replacement and vasopressor therapy to maintain adequate blood pressure [40].

The preceding has been confirmed by different studies done on the benefit of combining CSs adjuvant therapy with standard therapy for sepsis. For instance, Annane et al organized a multicentered, placebo-controlled, randomized trial in 19 ICUs in France. A total of 299 patients were randomized within 8 hours of the onset of septic shock to receive hydrocortisone or placebo intravenously for 7 days. The primary finding was a significant reduction in 28-day mortality in non-responders treated with low dose steroid compared to non-responders receiving placebo. The reported 28-day mortality rate was 55% in patients receiving steroid and 61% in the placebo group. The median time to vasopressor withdrawal was 9 days in the placebo group and 7 days in the steroid group. These results indicated that patients in septic shock with RAI may benefit from corticosteroid therapy continued for 7 days after the outcome of the cortisol stimulation test is determined [38].

Complementary result of the above study was reported in a placebo-controlled, randomized, double-blinded study performed at the department of medical intensive care unit and the department of infectious diseases of Erciyes University. The aim of the study was to assess the prognostic importance of basal cortisol concentrations and cortisol response to corticotrophin, and to determine the effects of physiological dose steroid therapy on mortality in patients with sepsis. One group received standard therapy for sepsis and physiological-dose of IV prednisolone for 10 days. The mortality rates in patients with occult adrenal insufficiency were 40% in the steroid therapy group and 55.6% in the standard therapy group, respectively. No statistically significant difference was found in organ failure between the steroid group and the standard therapy group in survivors [41].

On contrary to the above-mentioned findings, a retrospective cohort study conducted on paediatric severe sepsis concluded that no definitive improvement in outcomes was attributable to adjunctive steroids in this largest paediatric sepsis trial conducted to date. Their conclusion is made due to the fact that there was no significant difference between test and placebo groups on factors such as vasoactive-inotropic infusions, mechanical ventilation, ICU length of stay as well as mortality attributable to adjunctive CSs [42].

To sum up, although some studies attach negative connotations to the use of CSs for septic shock, it is evident by a significant number of literatures that CSs have a role in helping the standard treatment modalities of septic shock in combating complications, morbidities and mortalities associated with it. However, like other bacterial infections further studies are needed to characterize the patients, the type of drugs and dosage to prescribe, as well as to precisely spot on the real tolerability of the treatment appropriate dose of CSs used for septic shock.

3. Conclusions

Glucocorticoids are well known for their anti-inflammatory and immunosuppressive properties. Considering the presence of inflammation in bacterial infections, studies have been conducted in both children and adults to investigate their clinical benefit as adjuvant therapy in the treatment of different bacterial infections. Majority of the studies showed the benefits of adding GCs to antibiotics in the treatment of acute bacterial meningitis, tubercular meningitis, acute bacterial pharyngitis, community acquired pneumonia, tubercular pericarditis, severe sepsis and septic shock. However, there are few studies that did not support the benefit of adding GCs especially to antibiotics used for treatment of acute bacterial meningitis. This might be due to the fact that GCs repair the integrity of BBB and combining GCs with low BBB permeable/polar antibiotics could limit the CNS level of the antibiotics. The dosage, duration, and time to initiate corticosteroids as adjuvant therapy in most bacterial infections remain argumentative. Therefore, it is apparent to say that further studies are needed to be done in order to draw a firm conclusion on appropriate dosage, duration, time to initiate, and the beneficial role of adjuvant corticosteroids.

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