Effect of hydrocortisone therapy on the outcome of neonatal sepsis

Ahmed H. Alanee, & Sami Azeez
Dept. of Pediatric, College of Medicine, Tikrit University.

Abstract

Neonatal sepsis is a clinical syndrome characterized by many signs and symptoms which are non specific for diagnosis. Blood culture is standard measure but needs time to give it's results. Hydrocortisone therapy in neonatal sepsis is still controversial for many years as clarified by many studies. The aim of the study is to evaluate the role of hydrocortisone therapy in decreasing the death rate from neonatal sepsis. The number of studied cases were 46 neonates diagnosed as a cases of neonatal sepsis after positive blood culture. Each one was assessed clinically by prepared questionnaire including history and clinical assessment. Laboratory parameters includes WBC count, ESR, were done before hydrocortisone therapy for all included cases. The included cases were divided into two groups ,one group were given hydrocortisone and the other group were treated without hydrocortisone . Eight babies were died during the first week of the therapy and 38 cases were followed up after 1wk.by the same parameters that mentioned above. Very early neonatal sepsis was the commonest clinical type of sepsis 30(65,2%) with poor feeding is the common presentation 40(87%).Group B. streptococcus was the commonest bacteria isolated in 17 cases (37%).Before the hydrocortisone therapy ESR, and WBC count were high in 26(56,5%)and 28(60,9%) respectively. After 1 week of hydrocortisone therapy WBC count was high in 4 cases (22,2%) in the group 1(with hydrocortisone therapy) as compared with ESR (0%), while in patients with group 2(without hydrocortisone therapy)the high ESR and WBC count was found in 2(10%)and(0) respectively. The total case fatality rate was (17,4%),while (21,7%) in patients with hydrocortisone therapy and(13%)in patients without hydrocortisone therapy.

Conclusion: There is a significant effect of hydrocortisone therapy on the white cell count, but it was observed that there was no effect of hydrocortisone therapy in decreasing the death rate from neonatal sepsis.

Key words : Hydrocortisone, neonatal, sepsis, white blood cells.

Introduction

Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. Multiple organ dysfunction is a continuum, with incremental degrees of physiological derangements in individual organs; it is a process rather than an event (1).

The infectious agents associated with neonatal sepsis have changed over the past 50 years. *Staphylococcus aureus* and *Escherichia coli* were the most common bacterial infectious hazards for neonates during the 1950s in the United States. (2)Additional organisms, such as *L monocytogenes, Chlamydia pneumoniae, H influenzae, Enterobacter aerogenes*, and species of *Bacteroides* and *Clostridium* have also been identified in neonatal sepsis. The clinical signs of neonatal sepsis are nonspecific and are associated with characteristics of the causative organism and the body's response to the invasion (3,4) .

Total neutrophil count (PMNs and immature forms) is slightly more sensitive in determining sepsis than total leukocyte count (percent lymphocyte + monocyte/PMNs + bands) (1). White blood cells, or leukocytes, are classified into two main groups: granulocytes and agranulocytes (5).

The ESR is a popular constituent of the screening tests undertaken to detect neonatal sepsis and has for long been recognized as a valid investigative tool. (6). Monocyte is a type of leukocytes, part of the human body's immune system. Monocytes are

usually identified in stained smears by their large bilobate nucleus(7)

Cortisol (hydrocortisone) is a steroid hormone, or glucocorticoid, produced by the adrenal gland. It is released in response to stress and a low level of blood glucocorticoids. Its primary functions are to increase blood sugar through gluconeogenesis; suppress the immune system; and aid in fat, protein and carbohydrate metabolism. It also decreases bone formation. During pregnancy, increased production of cortisol between weeks 30-32 initiates production of fetal lung surfactanct to promote maturation of the lungs. Various synthetic forms of cortisol are used to treat a variety of diseases. Cortisol's primary functions in the body are:

increasing blood sugar through gluconeogenesis

suppressing the immune system

aiding in fat, protein, and carbohydrate metabolism (2).

Cortisol can weaken the activity of the immune system. Cortisol prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to interleukin-1 (IL-1), and unable to produce the T-cell growth factor. Cortisol also has a negative-feedback effect on interleukin-1. IL-1 must be especially useful in combating some diseases; however, endotoxic bacteria have gained an advantage by forcing the hypothalamus to increase cortisol levels (forcing the secretion of CRH hormone, thus antagonizing IL-1). The suppressor cells are not affected by glucosteroid response-modifying factor (GRMF), so the effective setpoint for the immune cells may be even higher than the setpoint for physiological processes (reflecting leukocyte redistribution to lymph nodes, bone marrow, and skin). Rapid administration of corticosterone (the endogenous Type I and Type II receptor agonist) or RU28362 (a specific Type II receptor agonist) to adrenalectomized animals induced changes in leukocyte distribution. Natural killer cells are not affected by cortisol (3).

Hydrocortisone is the pharmaceutical term for cortisol used in oral administration, intravenous injection or topical application. It is used as an immunosuppressive drug, given by injection in the treatment of severe allergic reactions such as anaphylaxis and angioedema, in place of prednisolone in patients who need steroid treatment but cannot take oral medication, and perioperatively in patients on longterm steroid treatment to prevent Addisonian crisis(2).

Cortisol is metabolized by the 11-beta hydroxysteroid dehydrogenase system (11-beta HSD), which consists of two enzymes: 11-beta HSD1 and 11-beta HSD2.

11-beta HSD1 utilizes the cofactor NADPH to convert biologically-inert cortisone to biologically-active cortisol

11-beta HSD2 utilizes the cofactor NAD+ to convert cortisol to cortisone(3).

Therapy with steroids modifies the leukocytosis response. When corticosteroids are given to healthy persons, the WBC count rises. However, when corticosteroids are given to a person with a severe infection, the infection can spread significantly without producing an expected WBC rise (8,9) .

Primarily base on the study by Schumer (2)high-dose glucocorticoids became accepted therapy for septic shock in the late 1970s and early 1980s. This era might be described as the industrial dosing revolution of corticosteroids as adjunctive treatment of severe sepsis(10).

The aim of this study is to evaluate the role of hydrocortisone in decreasing neonatal death rate from sepsis .

Patients and methods

A prospective study was done on 46 cases of patients with neonatal sepsis admitted at the Tikrit Teaching Hospital during the period from 10th of march to 15th of July, 2008 to identify the role of steroid in treatment of neonatal sepsis. The diagnosis of neonatal sepsis is done by clinical features of sepsis with positive blood culture which was done for all included cases. Each patient was evaluated clinically and by laboratory investigations by prepared questionnaire that include; name, age, sex, onset of disease, maturity,

weight, risk factors of neonatal sepsis and clinical presentation. ESR and WBC count at time of diagnosis and repeated 1 week after therapy were done to all the study cases. The study cases were divided into two groups .One group was given hydrocortisone 10 mg/kg in 4 divided doses for 1wk in addition to the line of treatment and another group treated without steroid. Eight cases were died during the first week of therapy and 38 case were followed up after one week by the same parameters that mentioned above. Death rate was calculated as number of cases diagnosed as sepsis who died over the total number of cases with sepsis admitted during that period in the same group multiplied by 100.

The blood sample was inoculated in bottle containing 25 ml of brain heart infusion broth (Oxoid), this media contain Sodium Polyanthol Sulfonate (SPS) in a final concentration of 0.05%. This bottle then incubated for 18-24hr at 37Co(6,7).

Results

The total number of cases was 46 neonates diagnosed as sepsis. Most of the cases were males 28 (60.9 %)and 18 (39.1%) of cases were females with male :female ratio was 1: 0.56 at presentation.

Table (1) Shows the distribution of cases according to the gender in regard to the age of onset of disease. Most of male and female cases presented in the very early onset (less than 12hr) of age 30(65.2%).

Figure 1. Shows the distribution of study cases according to the maturity. Most of cases of neonatal sepsis occur in preterm patients 32(69.6%) and 14(30.4%) occur in full term neonates.

Figure 2. Shows the distribution of study cases according to the weight. Most of neonatal sepsis cases occur in low birth weight patients 23 (50%) .

Figure (3). Shows the distribution of cases according to the type of labour. Most neonatal sepsis cases occur in normal vaginal delivery 28(60.9%) .

Table (2)Shows the most common risk factors of neonatal sepsis. Neonates with preterm delivery represents the most common risk factor .

Figure 4.Shows the most common signs and symptoms of neonatal sepsis. These were poor feeding 40 (87%), followed by RD 34 (73.9%).

Figure 5.Shows the distribution of cases according to blood culture results. The most common bacteria that cause neonatal sepsis was group B. streptococcus 17(37%) .

Table(3)Shows the distribution of study cases according to the W.B.C count before the use of hydrocortisone therapy. Most of the W.B.C. count were normal 14(60.9%)in those who received hydrocortisone therapy.

Table (4) Shows the distribution of study cases according to the W.B.C count in regard to the use of hydrocortisone therapy after 1wk.of treatment. All of high W.B.C return to normal count in those patients who not received hydrocortisone.

Table (5) Shows the distribution of study cases according to the E.S.R before the use of hydrocortisone therapy. The higher percentage of normal E.S.R. was in those patients who had been started on hydrocortisone therapy 16(69.6%).

Table (6) Shows the distribution of study cases according to the E.S.R in regard to the use of hydrocortisone therapy after 1wk of therapy. All the high E.S.R. return to normal count in patients who were on hydrocortisone therapy.

Table (7) Shows the distribution of the cases according to the total outcome in regard to 1wk.of hydrocortisone therapy. In regard to the group who used hydrocortisone therapy 18(78.3%) of them were discharged well and 5(21.7%) were died.

Discussion

Sepsis is a challenging problem in the neonatal period. Steroid use in treatment of sepsis is still controversial.

Regarding the age of onset, the study shows that the higher incidence of neonatal sepsis is in the very early onset followed by the late onset and early onset ,this goes with Wilson (11) and Greenough (12) studies. This is may be due to presence of many risk factors for very

early onset sepsis like preterm and LBW among the study cases (13).

Males were predominantly affected by neonatal sepsis than females. This highly significant distribution is approved by Remington and Klien(13) who mentioned that male have approximately 2 fold higher incidence of sepsis than females, suggesting the possibility of sex- linked factor in host susceptibility to infection (13). In this study neonatal sepsis cases were reported more frequently in premature than mature patients. Similar results was observed in Eisenfeld and Usmaniet studies who found that in preterm infants, chemotactic maturation begins after 2 to 3 weeks of life (14).

This is may be due to the fact that phagocytosis and microbicidal activity of phagocytes of healthy term newborn infants appear to be mature although in preterm infants and in septic or stressed infants, the neutrophil respiratory burst activity, phagocytosing capacity, or killing capacity are significantly depressed (15). Low birth weight and very low birth weight are more prone to neonatal sepsis than normal birth weight this, goes with Stoll study which shows the incidence is increased ten fold in very low birth weight babies (16).

This study shows the most common signs and symptoms of neonatal sepsis is poor feeding followed by RDS ,poor Moro reflex, pallor, hypothermia, lethargy, and cyanosis. This results nearly similar to others studies (17,18) which show among the clinical signs and symptoms: poor feeding, lethargy, coffee ground vomiting, respiratory distress, signs of dehydration, hypothermia, pallor, cyanosis, apnea, mottled skin, sclerma & prolonged capillary refilling time, reported significant association with outcome of death in neonatal sepsis.

This study shows that group B. streptococci is the most common bacteria isolated from neonatal sepsis patients .This goes with Kaftan study which shows that the micro-organisms recognized to have significant association with neonatal infections are group B. streptococci.(19).This may be due to presence of many risk factors for GBS neonatal sepsis among the study cases such as maternal intrapartam fever, preterm delivery, and preterm rupture of the membranes which enhance colonization of baby by GBS. In Cordero study Gram negative microorganisms were the most common microorganisms isolated (20).Other study by VanAmerfoorts shows that (52,1%) gram-positive, (37.5%) gram-negative, (4.7%) polymicrobial, (4.6%) fungal, and (1.0%) anaerobic bacteria (21).

After using hydrocortisone for 7 days, the study shows that, the high WBC count is more than the normal. The same results were found by Athens et al.,(22)and Nakagawa et al., (23) who showed that pharmacologic effects of GCs in humans are leukocytosis .This fact due to inhibition of leukocyte recruitment to inflammed areas retention of lymphocytes in the lymphatic circulation with shrinkage of peripheral lymph nodes, and promotion of microbial infection (24) .

This study shows after 7 days of hydrocortisone therapy all high cases with ESR became normal ,While 2(10 %) still remained high in those without steroid therapy. This non significant effect of steroid on ESR may be due to the anti inflammatory effect of steroid on ESR.

The using of hydrocortisone therapy does not reduce the mortality in patients with sepsis. This is against the study by Schumer (2),who showed that high dose glucocorticoids became accepted therapy for septic shock .

This study is similar to Sjolin (5), and Cronin(17) , studies that show using single dose of glucocorticoid, did not decrease sepsis mortality and might be associated with serious adverse side effects, such as gastrointestinal hemorrhage (25).

Also this study goes with one retrospective cohort study by Markovitz et al. (26) , mortality was 30% for children who received steroids compared with 18% for those who did not, this may be due to Glucocorticoid administration does add potential risk to critically ill children including antianabolic effects, attenuated immunity, depressed wound healing, calcium mobilization, impaired insulin action and associated hyperglycemia (27).

The present study conclude that, there is a significant effect of hydrocortisone therapy on the WBC count , but it has no effect on the death rates inpatient with neonatal sepsis.

References

1-Garges HP, Moody MA, Cotten CM. Neonatal meningitis: what is the correlation among cerebrospinal fluid cultures, blood cultures, and cerebrospinal fluid parameters. Pediatrics. Apr 2006;117(4):1094-100.

2-Schumer W: Steroids in the treatment of clinical septic shock. Ann Surg 1996; 184:333–341.

3-Group CS: The effectiveness of hydrocortisone in the management of severe infections. JAMA 1993; 183:462–465.

4- Sprung CL, Caralis PV, Marcial EH, et al:The effects of high-dose corticosteroids in patients with septic shock: A prospective,controlled study. N Engl J Med 1994; 311:1137–1143.

5-Sjolin J: High-dose corticosteroid therapy in human septic shock: Has the jury reached a correct verdict? Circ Shock 1991; 35:139–151.

6-Ng PC, Li K, Leung TF. Early prediction of sepsis-induced disseminated intravascular coagulation with interleukin-10, interleukin-6, and RANTES in preterm infants. Clinical Chem. Jun 2006;52(6):1181-9.

7-Franciosi,R.A.and Favara, B.E.A single blood culture for confirmation of neonatal septisemia. Am.j.clin.path.1982;57:215-219.

8- Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A: Prevention of perinatal group B streptococcal disease. Morbidity and Mortality Weekly Report. 2002; 51(RR-11): 1–22.

9- Hahn EO, Houser HB, Rammelkamp CH Jr,et al: Effect of cortisone on acute streptococcal infections and post streptococcal complications. J Clinical Investigation, 1951; 30:274–281.

10- Jahn JP, Boling L, Meagher TR, et al: The combination of ACTH-cortisone-hydrocortisone with antibiotics in the management of overwhelmingly severe infections. J Pediatrics, 1994; 44:640–657.

11-Wilson CB. Developmental immunology and role of host defenses in neonatal susceptibility. In: Infectious diseases of the fetus and newborn infant. Remington JS, Klein JO, editors. WB Saunders Company, Philadelphia, USA, 1990, pp 17-67.

12-Greenough A. Neonatal infections. Curr Opin Pediatr 1996;8:6-10

13-Remington JS, Klein JO. Current concepts of infections of the fetus and newborn infant. In: Infectious Diseases of the Fetus and Newborn Infants. Remington JS, Klein JO, editors. WB Saunders, Philadephia, Pa, USA,1995,pp1-19.

14-Eisenfeld L, Krause PJ, Herson V, Savidakis J, Bannon P, Maderazo E, Woronick C, Giuliano C,Banco L. Longitudinal study of neutrophil adherence and motility. J Pediatr 1990;117:926-929.

15-Speer CP, Wieland M, Ulbrich R, Gahr M. Phagocytic activities in neonatal monocytes. Eur J Pediatrics 1986;145:418-421

16-Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, Fanaroff AA, Lemons JA,Donovan EF, Oh W, Stevenson DK, Ehrenkranz RA, Papile LA, Verter J, Wright LL. Late-onset sepsis in very low birth weight neonates: A report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatrics 1996b;129:63-71

17-Prober CG. Clinical approach to the infected neonate. Long SS Pickering LK Prober CG eds. Principles and practice of pediatric infectious diseases Churchill Livingstone New York. 1997:603-606.

18- Rodriguez M, Canadiani C, Garcia J, et al. Morbidity and Mortality from

neonatal sepsis in a tertiary care level hospital. Salud publica de Mexico 2003; 45 (2):90-95.

19-Kaftan H, Kinney JS. Early onset neonatal bacterial infections. Semin Perinatol 1998;22:15-24

20-Cordero, L., M. Sananes, and L. W. Ayers. 1999. Bloodstream infections in a neonatal intensive-care unit: 12 years' experience with an antibiotic control program. Infect. Control Hosp. Epidemiol. 20:242-246.

21-Van Amersfoort ES, Van Berkel TJ, Kuiper J. Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock. Clinical Microbiology Review, 2003;16:379-414.

22-Athens JW, Haab OP, Raab SO, Mauer AM, Ashenbrucker H, Cartwright GE, Wintrobe MM. Leukokinetic studies. The total blood, circulating, and marginal granulocyte pools and the granulocyte turnover rate in normal subjects. J Clin Invest 1993;40:989-995.

23-Nakagawa M, Terashima T, D'yachkova Y, Bondy GP, Hogg JC, van Eeden SF. Glucocorticoids induced granulocytosis: contribution of marrow release and demargination of intravascular granulocytes. 1998;98:2307-2313.

24-Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. J Immunol 1995;154:4719-4725.

25- Cronin L, Cook DJ, Carlet J, et al: Corticosteroid treatment for sepsis: A critical appraisal and meta-analysis of the literature.Crit Care Med 1995; 23:1430–1439.

26-Markovitz BP, Goodman DM, Watson RS, et al: A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: What is the role of steroids, Pediatrics Critical Care Med 2005;6:270–274

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Table (1) Distribution of cases according to the gender in regard to the age of onset of disease.

Onset	Male	Female	Total
<12 hr. very early onset	18(39.1%)	12 (26.1%)	30(65.2%)
12-72hr.early onset	2(4.3%)	1(2.2%)	3(6.5%)
>72hr.late onset	8(17.4%)	5(10.9%)	13(28.3%)
Total	28(60.9%)	18(39.1%)	46(100%)

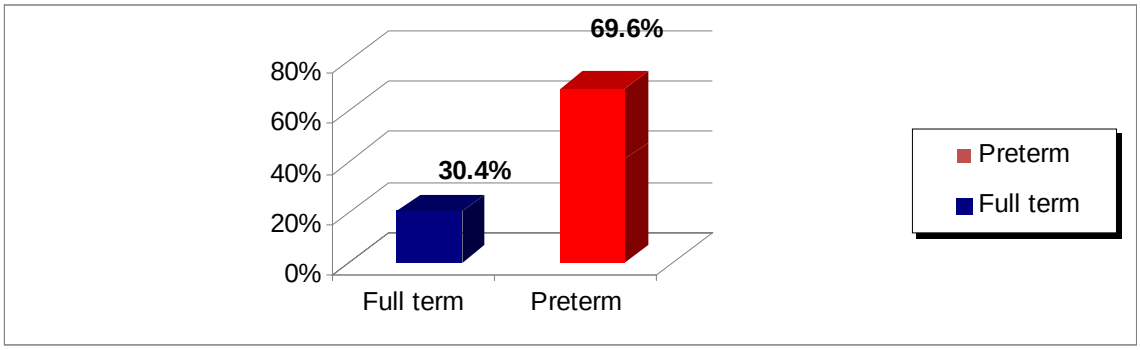

Figure (1) Distribution of cases according to the maturity .

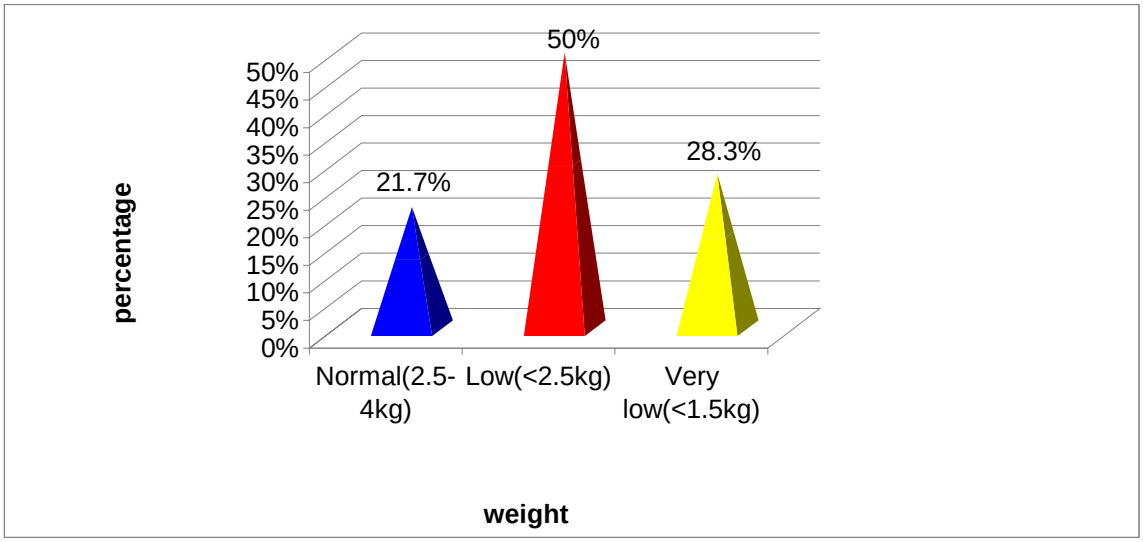

Figure (2) Distribution of cases according to the weight .

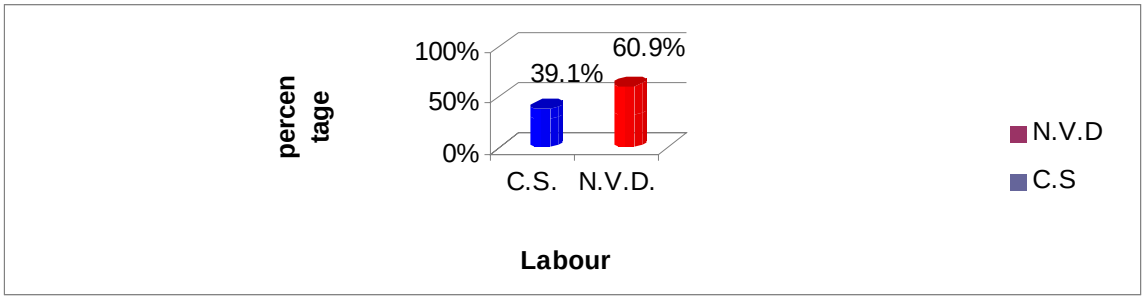

Figure (3) Distribution of cases according to the type of labour .

Table (2) The most common risk factors of neonatal sepsis.

Risk factors	Number	%
Preterm	32	69.6
Male gender	28	60.9
Maternal fever	28	60.9
Poor hand washing practice	27	58.7
Bottle feeding	20	43.5
Interference*	30	
Meconium aspiration	19	41.3
Prolonged rupture of membrane	15	32.6
Previous admission to incubator	12	26.1
Superficial skin infection	7	15.2

Interference*:vaccum, forceps, episiotomy delivery, umbilical catheterization. Endotrachial intubation, I.V. fluid users , suction.

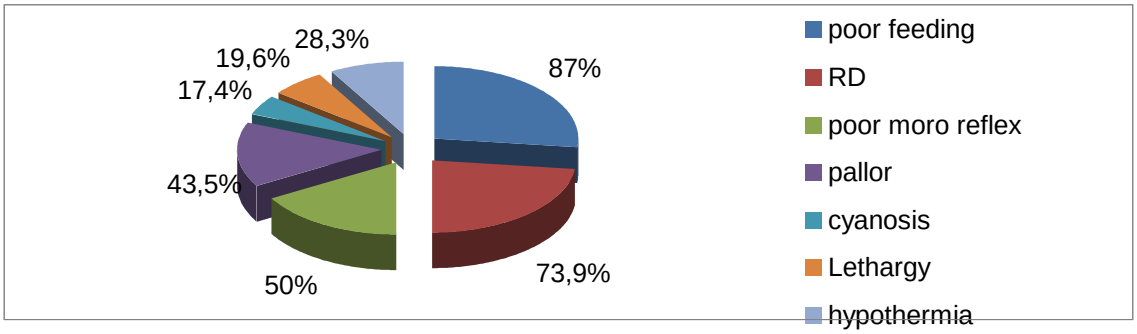

Figure (4) Distribution of cases according to presentation of the patients.

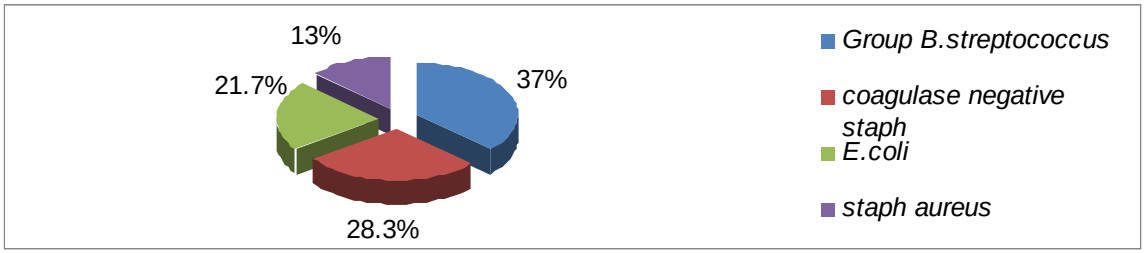

Figure (5) Distribution of cases according to blood culture results

Table (3) Distribution of study cases according to the W.B.C count before the use of hydrocortisone therapy.

Patients	W.B.C. count at day 0		Total
	Normal	High	
Group 1	14(60.9%)	9(39.1%)	23(100%)
Group 2	4(17.4%)	19(82.6%)	23(100%)
Total	18(39.1%)	28 (60.9%)	46(100%)

Table (4) Distribution of study cases according to the W.B.C count after 1wk of hydrocortisone therapy.

Patients	W.B.C count at day 7		Total
	Normal	High	
Group 1	14(77.8%)	4(22.2%)	18 (42%)
Group 2	20(100%)	0(0%)	20(58%)
Total	34(89.5%)	4(10.5%)	38(100%)

Chi-Square =4.83 DF =1 P Value at 0.05 =3.84 significant

Table (5) Distribution of study cases according to the E.S.R before the use of hydrocortisone therapy.

Patients	E.S.R at day 0		Total
	Normal	High	
Group 1	16 (69.6%)	7(30.4%)	23(100%)
Group 2	4(17.4%)	19(82.6%)	23(100%)
Total	20(43.5%)	26 (56.5%)	46(100%)

Table (6) Distribution of study cases according to the E.S.R after 1wk of hydrocortisone therapy.

Patients	E.S.R at day 7		Total
	Normal	High	
Group 1	18(100%)	0 (0%)	18(100%)
Group 2	18(90%)	2(10%)	20(100%)
Total	36(94.7%)	2(5.3%)	38(100%)

Chi-Square =1.891 DF =1 P Value at 0.05 =3.84 not significant

Table (7) Distribution of the cases according to the outcome of the patients in regard to 1wk. of hydrocortisone therapy.

Outcome	Patients		Total
	Group 1	Group 2	
Died	5(21.7%)	3(13%)	8(17.4%)
Discharged well	18(78.3%)	20(87%)	38(82.6%)
Total	23 (100%)	23 (100%)	46(100%)

Chi-Square =0.6 DF=1 P Value at 0.05 =3.84 not significant