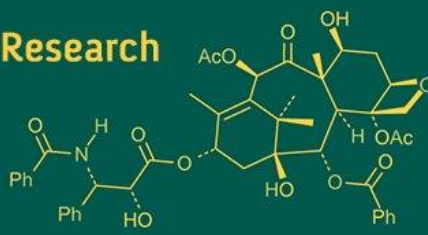
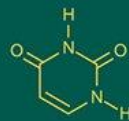
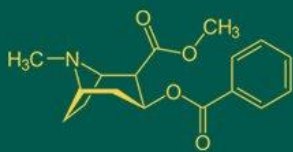


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Incidence and aetiopathogenesis of sepsis in bovine calves: Evaluating the immunoglobulin g levels and its prognostic implications

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Abstract

Sepsis is a major cause of mortality in young calves, still its diagnosis and treatment remain a challenge in Veterinary Medicine. Aim of this study was to determine the incidence and etiopathogenesis of sepsis along with the changes in serum IgG levels and hematobiochemical parameters in bovine calves affected with sepsis and the role of IgG as a prognostic marker. Total 306 bovine calves below the age of 6 months were screened for sepsis irrespective of their breed and sex. Screening was done on the basis of clinicopathological signs and diagnosis was confirmed by measuring the sepsis biomarkers (procalcitonin and neopterin). Blood and serum samples were taken on the day of presentation from affected animals. Control group consisted of 6 healthy animals. The incidence of sepsis was determined to be 13.4% in calves under 6 months of age. *E. coli* and *Staphylococcus sp.* were most frequently isolated from cases of sepsis in calves. Serum IgG and albumin levels were significantly lower in affected animals ($p < 0.05$). Serum GGT, SGOT were also significantly elevated ($p < 0.05$), creatinine was also elevated but it was not statistically significant ($p > 0.05$). Hematology revealed leukocytosis with neutrophilia and lymphopenia. IgG levels were significantly decreased in calves affected with sepsis and were associated with poor outcomes. Decreased serum IgG concentration in calves with sepsis may be used to predict the prognosis of sepsis and may aid in introduction of novel therapeutic approaches like intravenous immunoglobulin transfusion or fresh plasma transfusion for management of sepsis in calves.

Keywords: Calves, IgG, Neopterin, Procalcitonin, sepsis, SIRS

Introduction

In India, livestock farming is an integral part of people's lives especially in rural areas. Livestock sector contributes significantly to the agricultural GDP (Gross Domestic Product) in India. Young calves are most frequently affected with diarrhoea accompanied by respiratory affections and omphalitis (Fentie *et al.*, 2020) [16]. These morbidities along with poor hygiene, under-nutrition and insufficient colostrum feeding predispose neonatal calves towards sepsis. Sepsis is a prime cause of mortality in calves. The term "Sepsis" was introduced for the first time by Hippocrates in 4th century B.C., which means "putrefaction" or "putridity". Sepsis is a process of decomposition of organic matter (Majno, 1991; Kumar, 2018) [25, 28]. Since then, the definition of sepsis has been evolving and has been revised from time to time. In 1992, American College of Chest Physicians/Society of Critical Care Medicine defined sepsis as "the systemic inflammatory response syndrome (SIRS) caused by microbial infection". Diagnosis of sepsis is made if more than 2 SIRS criteria are met in presence of suspected or confirmed infection. The SIRS criteria in calves include: fever ($>39.5^{\circ}\text{C}$ or 103.1°F), or hypothermia ($<36^{\circ}\text{C}$ or 98.6°F), leukopenia ($<4000/\text{mm}^3$) or leucocytosis ($>12000/\text{mm}^3$), heart rate (>160 or $<100/\text{min}$) and respiratory rate ($>45/\text{min}$) (Beydilli and Gökçe, 2019) [8]. In 2016, sepsis was redefined as serious organ failure or dysfunction caused by the inappropriate response of host towards infection. While septic shock was defined as the subgroup of septic patients having metabolic, circulatory and cellular abnormalities which need vasopressor drugs to sustain a MA $p > 65$ mmHg or having serum lactate $>2\text{mmol/L}$ (Singer *et al.*, 2016) [35]. Sepsis is one of the major causes of mortality in neonatal period in animals as well as humans, but very few studies have been

Done regarding the same in farm animals. Few older studies suggest that 30% of the neonatal calves having diarrhoea or any other illness may develop sepsis (Fecteau *et al.*, 1997; Lofstedt *et al.*, 1999) [14, 26]. Various etiological agents may be involved in the aetiology of diarrhoea in calves including bacteria, viruses, protozoa (Ok *et al.*, 2009) [31]. During 1st month, diarrhoea in calves is more commonly caused by *E. coli*, rotavirus, coronavirus and cryptosporidium (Lorenz *et al.*, 2011) [27]. Clinicopathological changes associated with sepsis include changes in heart-rate, rectal temperature, respiration-rate, mucus membrane colour, capillary refill time, total leucocyte count, decreased blood pressure, generalised weakness and absent suckling reflex (House *et al.*, 2015) [24]. Diagnosis of sepsis can be confirmed only by isolation of causative pathogen on blood culture examination, although its sensitivity can be low (Fecteau *et al.*, 2009) [15]. The present focus of research is towards the sepsis-specific biomarkers. Procalcitonin and neopterin are proven markers for diagnosis of sepsis in human as well as Veterinary medicine (Afsar and Senar, 2015; Giunti *et al.*, 2010; Pergialiotis *et al.*, 2018) [1, 19, 33]. Thus, their estimation can increase the diagnostic accuracy and help to provide timely treatment to the patients at risk (Fecteau *et al.*, 2009; Fielding and Magdesian, 2015; Ercan *et al.*, 2016) [13, 15]. This research seeks to elucidate the incidence and etiopathogenesis of sepsis along with the alterations in Immunoglobulin G (IgG) and its role as prognostic marker in calves affected with sepsis.

Materials and Methods

The present scientific study was conducted at Cattle and Buffalo (C and B) farm, under the division of Livestock Production Management, Indian Veterinary Research Institute, Bareilly, India. Screening of animals for sepsis was undertaken for a period of 6 months (February 2023 to August 2023). Bovine calves irrespective of sex and breed, under the age of 6 months were selected based on clinical signs, haematology, biochemical parameters and sepsis-specific biomarkers (Neopterin and procalcitonin). All the calves affected with fever, diarrhoea, navel ill, joint ill and other morbidities were screened for sepsis based on the SIRS criteria and animals found to be positive for >2 SIRS criteria were selected for our study. Further diagnosis of sepsis was confirmed on the basis of changes sepsis-specific biomarkers (Neopterin and Procalcitonin) as compared with the healthy control group consisting of 6 animals. Following the diagnosis, serum IgG levels were determined along with the hematobiochemical parameters of calves affected with sepsis.

Haematology and serum biochemistry

For estimation of haematological parameters, 2-3 ml of blood was collected by puncturing the jugular vein aseptically by using a sterile syringe into anticoagulant (K₃-EDTA) containing vacutainers and for estimation of serum biochemical parameters, 3-4 ml of blood was collected into vacutainers containing clot activator. Following collection vacutainer was placed at an angle of 45° for half an hour. After coagulation of blood, it was centrifuged at 2500-3000 RPM for 10 minutes to separate serum from RBCs. Haematological parameters including Hb, TLC, DLC, PCV, Platelets were estimated using an automated haematology analyser (Model no. MEK 6450K by Nihon Kohden, Japan). Serum biochemical parameters including BUN, creatinine, total protein, albumin, SGOT, ALP, GGT, sodium and

potassium were estimated using commercially available kits (Tulip Diagnostics (P) Ltd, Goa, India) by spectrophotometry. Immunoglobulin G (IgG) concentration was estimated in the serum samples by competitive ELISA using commercial ELISA kit procured from Cusabio, USA. Procalcitonin concentration was estimated in the serum samples of animals screened for sepsis by quantitative sandwich ELISA using commercial ELISA kit manufactured by Cusabio, USA. Neopterin concentration was estimated by competitive ELISA using commercial ELISA kit manufactured by Finetest, China.

Microbiological culture to identify pathogens causing sepsis

Various samples including blood, pus (from navel ill, joint ill cases), faeces (from diarrhoea cases) were collected from cases suspected for sepsis using sterile swab and/or vacutainers. Pus and faecal samples were directly streaked on basal media i.e., nutrient agar, while blood samples were haemolyzed prior to streaking followed by incubation @ 37 °C for 18-24 hours. Samples were subjected to gram's staining if growth was apparent on basal media otherwise samples were discarded if no growth was visible on the agar plate. Then based on the gram's staining, samples were streaked on to differential media such as MLA agar, BP agar, HE medium etc. Finally, the identification of bacteria was done based on its colonial characteristics.

Statistical analysis

Statistical relationship in various parameters among animals with sepsis and healthy animals was analysed using one way ANOVA and post-hoc analysis using tukey test at 5% level of significance, with the help of IBM SPSS statistics 26.0 software.

Results

Out of the total 306 animals screened for sepsis, 61 were positive for sepsis based on SIRS criteria. 41 out of 61 were having elevated levels of procalcitonin (PCT) and were confirmed cases of sepsis. Thus, the incidence of sepsis in calves under 6 months of age was found to be 13.4%. In relation to breed and sex wise incidence of sepsis among calves reared at C and B farm, under division of LPM, ICAR-IVRI the incidence was found to be highest in the crossbred Vrindavani cattle (18.25%) followed by Sahiwal cattle (16.13%), tharparker cattle (11.54%) and murrah buffalo (5.81%). In this study, clinical signs shown by affected animals include fever, tachycardia, tachypnoea, diarrhoea, omphalitis, joint swelling, pallor of mucus membranes, increased CRT, dullness, weak suckling reflex (Fig. 1 & 2). Table 1 represents the differences in clinical parameters (heart rate, temperature and respiratory rate) between healthy animals and animals affected with sepsis. Respiratory rate and temperature were found to be significantly elevated in animals with sepsis ($p < 0.05$). Among the etiological agents isolated from affected calves, *E. coli* (9/14) was the primary pathogen isolated from diarrheic faeces followed by *Staphylococcus* (3/14). Among these cases of diarrhoea, some cases were positive for both *Staphylococcus* sp. and *E. coli* (6/14) were isolated. From pus samples obtained from navel ill and joint ill cases *Staphylococcus* sp. (3/7) was primarily isolated pathogen (Fig. 3). Table 2 represents the variations in hematological parameters between healthy animals and affected animals. Noteworthy increase was seen

in Total Leucocyte Count (TLC) and neutrophils (%) and a notable reduction was observed in lymphocyte (%) count in septic animals as opposed to healthy animals ($p < 0.05$). Among serum biochemical parameters, no notable variation was detected in concentrations of serum electrolytes (Na^+ and K^+), blood urea and alkaline phosphatase. However, noteworthy increase was seen in levels of GGT, SGOT/AST, whereas albumin was reduced saliently in serum of septic animals as compared to healthy animals ($p < 0.05$). Levels of creatinine were on the higher side in septic animals however it was not significant from statistical viewpoint.

Mean immunoglobulin G concentration in serum of animals affected with sepsis was determined to be 12.03 ± 0.37 mg/ml whereas that of healthy animals from control group was 20.14 ± 0.90 mg/ml, which was significantly different ($p < 0.05$). Among sepsis-biomarkers, both procalcitonin (PCT) and neopterin (NPT) were elevated notably in septic animals ($p < 0.05$).

Discussion

In the present study, the incidence of sepsis was found to be highest in calves of Vrindavani cattle followed by Sahiwal, Tharparkar and Murrah buffalo. This can be explained on the basis of the fact that indigenous cattle and buffaloes are hardier and disease resistance as compared to the crossbreds. Among etiological agents, *Escherichia coli* was the primary pathogen isolated from diarrheic faeces followed by *staphylococcus* sp. From pus samples obtained from navel ill and joint ill cases *Staphylococcus* sp. was primarily isolated pathogen. From certain cases of diarrhoea, both *Staphylococcus* sp. and *E. coli* were isolated. In study conducted by Pas *et al.* (2023) [32], *E. coli* was most frequently isolated microorganism from septic calves followed by *Salmonella*, *Klebsiella*, *Enterobacter* and *Staphylococcus*. Common pathogens reported to cause sepsis in other calves include *E. coli*, *klebsiella*, *Salmonella* (Çitil and Gökçe, 2013; Akyüz and Gökçe, 2021) [3, 11]. In two studies conducted by Fecteau and coworkers in 1991 and 1993, *E. coli* was the predominant bacteria to be isolated from critically ill calves followed by other gram negative enterics (*Klebsiella*, *Salmonella*), gram negative anaerobes, gram positive cocci and gram-positive rods (Fecteau *et al.*, 1997) [14]. Most calves affected with localized infections like omphalitis, joint ill, diarrhoea etc. develop sepsis when the pathogen gains entry in the blood stream. Most of the animals affected with diarrhoea are dehydrated, also the entry of pathogen in blood stream activates the SIRS leading to an increase in heart rate (Naseri, 2017; Yildiz *et al.*, 2018; Akyüz and Gökçe, 2021) [3, 30, 41]. Respiratory rate increases due to compensatory mechanisms (Naseri, 2017) [30]. Prolonged CRT is due to harmful effects of sepsis on Cardiovascular System (CVS) (Fecteau *et al.*, 2009) [15].

On hematology, leukocytosis with neutrophilia and lymphopenia was observed in calves affected with sepsis. One study on neonatal calves affected with sepsis, TLC count in sepsis group was higher than in control group, however this increase in TLC in sepsis group was not reported to be statistically significant (Akyüz and Gökçe, 2021) [3]. But this study by Akyüz and Gökçe was conducted on 15 calves which had sepsis out of which 4 had leucopenia but in the present scientific study majority of the calves had leucocytosis. Another study by Ercan *et al.*, (2016) [13] on neonatal calves suffering from septicaemic-colibacillosis reported a significant increase in TLC ($12.4 \pm 1.4 \times 10^3/\mu\text{l}$) in

septicaemic calves as compared to non-septicaemic calves ($5.2 \pm 0.0 \times 10^3/\mu\text{l}$). This finding is similar to findings of present study. Another study on septicaemia in diarrheic calves reported a significant increase in band neutrophils in septicaemic calves (Lofstedt *et al.*, 1999) [26]. In the study conducted by Garcia *et al.*, (2022) [18] on bacteremic calves, segmented neutrophils in bacteremic calves were higher than in non bacteremic calves however this difference was not statistically significant. This leucocytosis with neutrophilia indicates the general inflammatory response of the body in sepsis. Among serum biochemical parameters, GGT, SGOT/AST were significantly increased, whereas albumin was reduced notably in serum of septic animals as compared to healthy animals. Decreased albumin may be the result of impaired hepatic function in sepsis. Creatinine levels were also increased in septic calves but could not be interpreted statistically. Lofstedt *et al.*, (1999) [26] also reported a decrease in TP and albumin concentration in septicaemic calves as compared to non-septicaemic calves. Garcia *et al.*, (2022) [18] reported that 66% of bacteremic calves had a total protein concentration of less than 6.2g/dl in their study. Another study by Ercan *et al.*, (2016) [13] on neonatal calves suffering from septicemic-colibacillosis did not report any significant variation in total protein and albumin concentration between septicaemic and non-septicaemic calves. Akyüz and Gökçe, (2021) [3] also reported a decrease in albumin concentration along with increment in ALT/SGPT, AST/SGOT, GGT, ALP, BUN and creatinine concentration in septic calves which may be a consequence of inflammation and infection (Talkhan *et al.* 2009) [37]. Other studies have also reported increased liver enzymes (AST, ALT, ALP, GGT) in neonatal calves suffering from diarrhea (Bozokluhan *et al.* 2017; Naseri, 2017) [9, 30]. Another study conducted on neonatal sepsis in calves which reported a significant increase in ALT/SGPT, AST/SGOT, GGT, ALP in calves affected with sepsis (Akyüz and Gökçe, 2021) [3]. This may be caused by adverse effects of sepsis and SIRS on liver function (Akyüz *et al.*, 2022) [4], additionally this might be a reflection of multiple-organ dysfunction due to sepsis (Akyüz and Gökçe, 2021) [3]. Renal dysfunction may also be a consequence of multiple-organ dysfunction due to sepsis. In diarrhea, there is severe fluid loss and dehydration leading to hypoperfusion to the kidneys causing increased serum urea (BUN) and creatinine concentrations (Dratwa-Chalupnik *et al.*, 2012) [12].

Serum IgG levels were significantly decreased in affected calves which might be caused by decreased production, enhanced consumption and leakage from vascular endothelium (Almansa *et al.*, 2015) [5] or it may be due to failure of passive transfer of antibodies via colostrum, predisposing the calves to sepsis. Low IgG concentration is related with poor outcomes (Akatsuka *et al.*, 2021). Bovine calves don't receive any IgG in-utero because of the syndesmochorial placenta thus sufficient colostrum intake with 36 hours of life is essential to attain optimal IgG levels (Weaver *et al.*, 2000) [38]. IgG concentration of >16 mg/ml indicates normal transfer of antibodies, 8-16 mg/ml indicates partial failure of transfer of immunoglobulins and a concentration less than 8 mg/ml signifies failure of immunoglobulin transfer (Wittum and Perino, 1995; Hopkins *et al.*, 1984) [23, 40]. Basoglu *et al.*, (1999; 2014) [6, 7] have reported a significantly low level of IgG in neonatal diarrheic calves suspected for sepsis. However, administration of immunoglobulins intravenously is controversial as some

studies have not found any association between serum IgG levels and outcomes of septic patients (Werdan *et al.*, 2007; Tagami *et al.*, 2015) [36, 39]. On the contrary, Goto *et al.*, have found that IV immunoglobulin therapy (IVIG) had favourable effect in septic patients irrespective of hypogammaglobulinemia (Goto *et al.*, 2022) [20]. No studies have been published demonstrating the effect of serum or plasma transfusion on serum IgG levels in calves. Thus, further research is required regarding the effects of IVIG therapy on serum IgG levels and their correlation with outcome of sepsis.

Sepsis biomarkers (Procalcitonin and Neopterin) were significantly elevated in animals affected with sepsis. This is consistent with the findings of Akyüz and Gökce, (2021) [3] which have reported a significant increase in neopterin (NPT) and procalcitonin (PCT) concentrations in calves affected with sepsis. The level of neopterin rises more in septic shock,

this it can be utilised to differentiate between septic-shock and sepsis (Ruokonen *et al.*, 2002; Sönmezer and Tülek, 2015) [34]. Neopterin can also differentiate patients having SIRS caused by infection from those without an infectious aetiology (Ruokonen *et al.*, 2002) [34]. Ercan *et al.*, (2016) [13] also reported significant increase in procalcitonin levels in septic calves. A continuous rise in procalcitonin levels throughout the course of infection is a poor prognostic sign (Hacımustafaoğlu, 2017) [21]. Thus, procalcitonin can be used as diagnostic and prognostic marker of sepsis. Unlike other sepsis markers, PCT remains stable at room temperature in blood samples (Carrol *et al.*, 2002) [10]. PCT may also differentiate between infectious and non-infectious aetiologies of SIRS (Harbarth *et al.*, 2001) as well as infections of bacterial and viral origin (Ahn *et al.*, 2011) [2]. PCT is considered as the most sensitive marker for bacterial sepsis.

Table 1: Changes in clinical parameters in animal with sepsis

Parameter	Control group (Healthy animals)	Sepsis group	P-value
Temperature (°F)*	101.48 ± 0.22	103.69 ± 0.19	0.001
Heart rate (per minute)	109.66 ± 2.70	124.68 ± 3.17	0.156
Respiration rate (per minute)*	27.66 ± 2.33	53.42 ± 2.65	0.004

Difference is statistically significant at 5% level of significance (Mean ± SE)

Table 2: Haematological parameters in bovine calves affected with sepsis and in healthy control group

Parameter	Healthy control group	Sepsis group	P-value
Haemoglobin (g/dl)	9.4 ± 0.26	8.09 ± 0.34	0.154
TLC (×1000/μL)*	6.88 ± 0.38	13.01 ± 0.76	0.017
TEC (×10 ⁶ /μL)	6.45 ± 0.34	7.60 ± 0.28	0.143
PCV (%)	27.88 ± 1.59	27.29 ± 1.09	0.844
Platelets (×10 ³ /μL)	409.51 ± 41.47	491.36 ± 45.42	0.501
Lymphocytes (%)*	68.68 ± 1.62	47.81 ± 2.74	0.006
Neutrophils (%)*	31.78 ± 1.47	48.90 ± 2.69	0.018
Monocytes (%)	1.95 ± 0.78	1.30 ± 0.29	0.442
Eosinophils (%)	2.11 ± 0.57	5.03 ± 1.39	0.434

*Difference is statistically significant at 5% level of significance (Mean ± SE)

TLC- Total Leukocyte count, TEC- Total Erythrocyte count, PCV- Packed cell volume

Table 3: Different serum biochemical parameters in bovine calves affected with sepsis and in healthy control group

S.N.	Parameter	Healthy Control group	Sepsis group	P-value
1	Urea (mg/dl)	48.28 ± 6.90	41.70 ± 2.63	0.454
2	Creatinine (mg%)	1.67 ± 0.07	2.08 ± 0.11	0.274
3	Sodium (mmol/L)	147.72 ± 5.05	150.69 ± 2.38	0.707
4	Potassium (mmol/L)	4.56 ± 0.09	4.69 ± 0.18	0.832
5	Alkaline phosphatase	23.17 ± 2.54	18.70 ± 1.22	0.271
6	SGOT (I.U./L)*	55.59 ± 5.34	139.26 ± 8.62	0.004
7	GGT (I.U./L)*	11.58 ± 1.88	26.64 ± 2.06	0.028
8	Total protein (g/dl)	6.24 ± 0.26	5.97 ± 0.13	0.530
9	Albumin (g/dl)*	3.64 ± 0.13	1.82 ± 0.10	0.000
10	Neopterin (ng/ml)*	2.70 ± 0.37	7.94 ± 1.02	0.043
11	Procalcitonin (pg/ml)*	24.62 ± 2.30	143.54 ± 3.85	0.00
12	IgG (mg/dl)*	20.14 ± 0.90	12.03 ± 0.37	0.00

*Difference is statistically significant at 5% level of significance (Mean ± SE)

SGOT- Serum glutamic oxaloacetic transaminase, GGT- Gamma Glutamyl Transferase, IgG- Immunoglobulin G

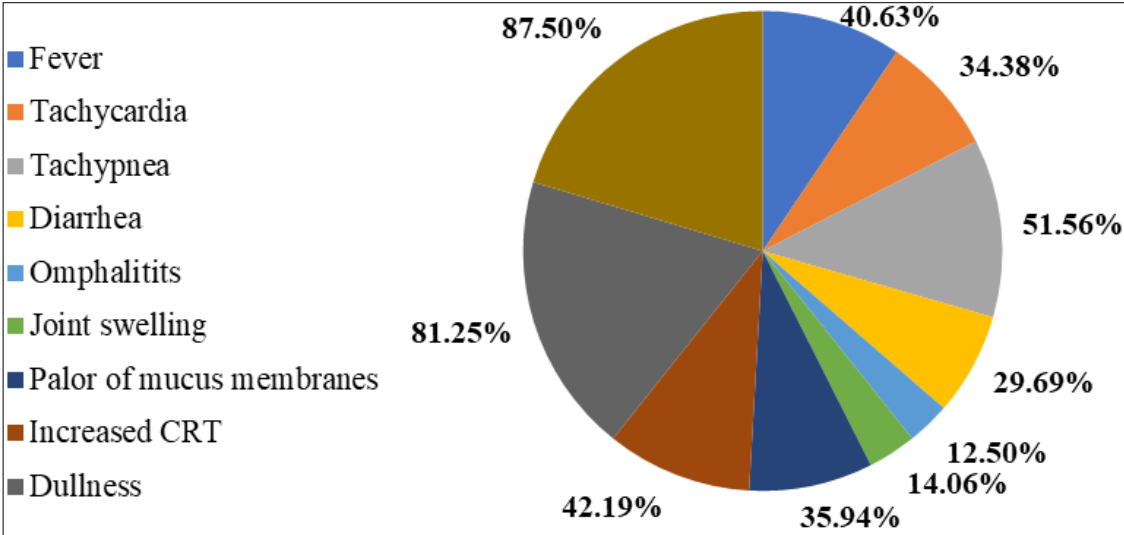


Fig 1: Graphical depiction illustrating the proportion of animals affected with sepsis exhibiting a specific clinical sign



Fig 2: Clinical signs of sepsis in bovine calves

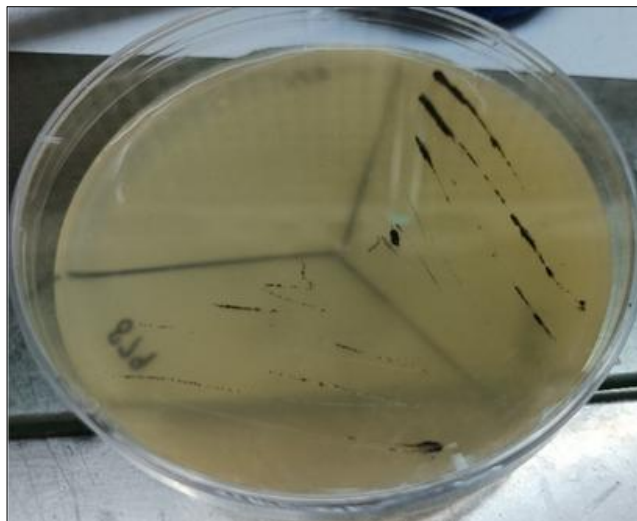


Fig 3: *Staphylococcus* colonies on baird-parker agar



Fig 4: *Escherichia coli* colonies on EMB agar

Conclusion

This study provides further evidence for reliability of procalcitonin and neopterin as diagnostic markers of sepsis in bovine calves. Increase in other biochemical parameters indicate the adverse effects of sepsis on multiple organs of the body. To our knowledge, this is the only study in which serum IgG levels were estimated in calves affected with sepsis, which were found to be significantly lower in animals affected with sepsis and were associated with poor outcomes. However, further research is required to establish the effect of intravenous immunoglobulin transfusion or fresh plasma transfusion on survival of calves with sepsis.

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Conflict of interest

The authors affirm that there are no conflicts of interest to disclose.

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