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Comparative therapeutic effects of tilmicosin phosphate and amoxicillin on clinical outcomes and hematobiochemical variables in buffalo calves with acute respiratory disease: A randomized clinical trial

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ABSTRACT

Acute respiratory disease (ARD) in buffalo calves is a major health concern in tropical and subtropical regions, particularly in developing countries. It contributes significantly to calf morbidity and mortality, affecting productivity and economic returns in livestock farming. The objective of the present investigation was to evaluate the comparative therapeutic efficacy of tilmicosin and amoxicillin for the treatment of the acute respiratory disease in buffalo calves. For this purpose, 18 buffalo calves were randomly assigned into two treatment groups (9 each). Group 1 was treated with subcutaneous injection of tilmicosin phosphate at a dosage of 10 mg/kg body weight, and Group 2 was treated with amoxicillin LA at a dosage of 15 mg/kg body weight. Buffalo calves were examined clinically and clinical index scores were recorded before treatemt and at 7 and 14 days post-treatment. Additionally, hematological and biochemical investigations were done for each calf. Calves of group 1 showed significant improvements in their clinical index scores ($p < 0.01$), and a reduction of total leukocyte count in comparison with group 2. However, there was a significant increase in RBCs count, hemoglobin and MCHC% ($p < 0.05$). There was a significant decrease in the serum globulin and copper ($p < 0.05$) in group 1 in comparison with group 2 after 14 days post-treatment. However, haptoglobin showed non-significant variation. Moreover, albumin and albumin/globulin ratio showed a significant increase in tilmicosin treated group in comparison with amoxicillin treated one. The results of the present study indicate superior efficacy of tilmicosin for treatment of acute respiratory disease in buffalo calves. More investigations are needed to evaluate the efficacy of tilmicosin on specific microorganism in this locality.

Introduction

Bovine respiratory disease is a broad term for respiratory diseases in cattle and is the most common disease worldwide. Besides being one of the leading causes of illness and mortality, bovine respiratory disease produces significant financial losses for the cattle sector since it reduces output, labor, feed time, and prophylactic and metaphylactic therapies (Abutarbush *et al*., 2012; Ramadan *et al*., 2019). Acute respiratory disease (ARD) in buffalo calves is the highest priority health problem in tropical and subtropical regions of most developing countries. The complexity of the ARD etiology at the levels of infectious agents, environmental stressors, and management practices makes its control complicated and challenging.

Macrolides are those antibiotics with spectrum includes both Gram-positive and Gram-negative bacteria, such as Pasteurella multocida and *Mannheimia haemolytica*, and they are effective against significant animal diseases (Williams, 2003). Besides their antibacterial action, macrolides show important immunomodulatory actions. As such, they have been described to enhance phagocytosis, diminish local inflammation, and increase the host's pro-inflammatory response (Ribeiro *et al*., 2009).

One of the members of the macrolides group, tilmicosin, has been used successfully as a prophylaxis against infection in feedlot animals (Morck *et al*., 1993) and against undifferentiated bovine respiratory disease (Gorham *et al*., 1990). *Mannheimia haemolytica*-A1 is the most common bacterial pathogen found in these diseases (Thomson, 1980). *Mannheimia haemolytica* can also infect young calves as a secondary invader in the enzootic pneumonia complex (Morck *et al*., 1997).

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) have been used as a supplementary treatment alongside antimicrobial therapy to address acute respiratory disease because they possess analgesic, antipyretic, and anti-inflammatory properties (Fthenakis and Vasileiou, 2017; Politis *et al*., 2019). Meloxicam is an oxicam-class NSAID with powerful anti-inflammatory, analgesic, and antipyretic effects (Xu *et al*., 2014). It operates by inhibiting cyclooxygenase -2 enzymes, which lessens the production of tumor necrosis factor, an inflammatory cytokine that is produced during respiratory tract infection (Bednarek *et al*., 2003; Curry *et al*., 2005; Hirsch *et al*., 2003). In cattle, meloxicam has been clinically evaluated widley as an adjunctive therapy for the treatment of respiratory tract diseases (Salamon *et al*., 2000; Schmidt *et al*., 2000).

The effect of anti-inflammatory drugs on acute phase proteins in calves with respiratory diseases has been presented (El-Deeb *et al*., 2021), and in buffalo calves with pneumonic pasteurellosis (El-Deeb and Elmoslemany, 2016). However, to authors, there is little information about the effect of tilmicosin on clinical outcomes and acute phase proteins (APPs) in buffalo calves with acute respiratory disease. Therefore, the aim of the present study was to compare the therapeutic efficacy of tilmicosin and amoxicillin on the clinical findings, hematological parameters, and selected APPs in Buffalo calves with ARD.

Materials and methods

Animals and clinical examination

In this study, 18 buffalo calves with acute respiratory disease (ARD) were examined. Buffalo calves were randomly selected from different herds in Kafrelsheikh governorate. The age of the buffalo calves ranged from 2 to 5 months (Mean 4.8±0.6 months). The body weight of examined buffalo calves ranged from 46-70 kg (Mean 57.0±8.5 kg). Buffalo calves were raised at smallhoder farms and kept indoor. Buffalo calves were fed on green fooders, hay concentrates daily The animals were randomly allocated to two equally sized treatment groups, each containing 9 buffalo calves. The buffalo calves were diagnosed to have ARD based on compotent clinical examination ((Lacasta *et al*., 2019). Briefly, presence of cough, nasal discharge, and abnormal lung sound on auscultation are the

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major findings. In addition evidence of systemic signs were confirmatory. Systemic signs were fever (≥ 40°C), anorexia and depression. The present clinical trial was conducted according to the CONSORT guidelines. On the first examination and before treatment, clinical findings for each buffalo calves were identified, scored, and sum of such clinical index scores were recorded (Table 1).

Table 1. Scores and levels of clinical signs associated with acute respiratory disease in buffalo calves.

	Clinical variable	Level and description
1	Cough	Absent = 0 Dry cough = 1 Moist cough = 2
2	Nasal discharge	Absent = 0 Serous =1 Mucoid = 2 Mucopurulent = 3 Purulent = 4
3	Ocular discharge	Absent = 0 Serous = 1 Mucoid = 2 Purulent = 3
4	Heart rate (beat/min)	55-80 = 0 81-100 = 1 >100 = 2
5	Respiratory rate (cycle/min)	20-30: 0 > 30-40: 1 > 40-60: 2 > 60 : 3
6	Rectal temperature	< 40^{0}C: 0 > 40-41^{0}C: 1 > 41-42^{0}C : 2 > 42^{0}C : 3
7	Appetite	Inappetant= 1 Anorexia=2
8	Mental state	Bright= 0 Dull= 1 Depression= 2
9	Dyspnea	Absent= 0 Mild = 1 Severe = 2
10	Lung sounds	Vesicular= 0 Exaggerated= 1 Wheezes= 2 Crackles= 3
11	Conjunctivitis	Absent= 0 Mild to moderate= 1 Severe= 2

Treatment protocol

Calves were randomly allocated into two groups (9 each). Group 1 received treatment that involved subcutaneous administration of tilmicosin phosphate at a dosage of 10 mg/kg body weight, (Pneumotac® ADWIA co. S.A.D. 10th Ramadan city, Egypt) and intramuscular administration of meloxicam (METACAM, Boehringer Ingelheim Animal Health, USA Inc.) at a dosage of 1 mg/kg body weight for five consecutive days. The Group 2 received subcutaneous injection of Amoxicillin LA (Amoxypen LA, MSD Animal Health) at a dosage of 15 mg/kg body weight (El-Deeb *et al*., 2021), and intramuscular administration of meloxicam (El-Deeb and El-moslemany, 2016).

Clinical follow up

To assess the health of the buffalo calves, clinical examination and clinical index scores were recorded for each animal on the first day of the visit (T0), and on day 7 (T1) and day 14 (T2) post- treatment.

Blood samples

A jugular vein puncture was used to obtain two blood samples from each buffalo calves that were the subject of the experiment. No sedatives have been utilized during the sampling process. Sampling was done during the initial visit as well as on days seven and fourteen after therapy. One of the blood samples (5 ml) was drawn while taking an anticoagulant, 5 mg sodium ethylene diamine tetraacetic acid for the assessment of total and differential leukocytic counts. The second five milliliters of blood were drawn without the use of an anticoagulant in order to analyze the amounts of iron, zinc, copper, haptoglobin, albumin, total protein, and globulin, among other biochemical markers.

Hematological analysis

The red blood cell (RBCs, 10^{12}/L), hemoglobin (Hb, gm/dl), PCV%, total leukocytic, and differential leukocyte (WBCs10^9/µl) counts were determined using a hematology analyzer (MS9-5, Melet Schloesing Laboratories, France) according to Feldman *et al*. (2000).

Biochemical examination

Haptoglobin was measured by the nephlometric method using commercial test kits (Turbox, Orion diagnostica Oy, Finland). Nephelometry, was applied as simple, accurate and reliable technique for determination of haptaglobin (Van Lente *et al*., 1979). The haptaglobin was measure at a wavelength of 600 nm following the instruction of the manufacturer of used test kits. Albumin and total protein levels were measured colorimetrically using commercial test kits (Stanbio, Boerne).

Iron was measured colorimetrically using commercial test kits (Fortess Diagnostics Limited Co., United Kingdom). Zinc and copper levels were estimated colorimetrically using commercial test kits (Biodiagnostic Co., Egypt).

Statistical analysis

For statistical analysis, GraphPad version 9.0, a commercial software package from the USA, was utilized. First, the Kruskal–Walli test was used to check for homogeneity in each variable's results. After determining that the data was homogeneous, the variables' means and standard deviations were displayed. Analysis of variance (ANOVA) and Bonferroni multiple comparison test as post hoc were used to identify significant changes in the clinical index score. Using a general linear model with repeated measures ANOVA, the impact of anti-inflammatory medications on biochemical variables was assessed. Wilks' lambda test was employed as a sign of noteworthy alterations. Analysis of variance (ANOVA) and Tukey's comparison test as post hoc were conducted in cases where such a test was shown to be significant. For all data, the outcomes were considered significant when $p < 0.05$.

Results

When comparing buffalo calves treated with tilmicosin and meloxicam to those treated with amoxicillin and meloxicam, the clinical disease index score showed a substantial improvement. Fourteen days after therapy, this improvement was significant ($p < 0.05$). Additionally, the buffalo calves in the group that received amoxicillin showed a clinical index score of six on the fourteenth day after treatment, while the buffalo calves in the other group showed a complete recovery with a clinical index score of 0. Group 1 buffalo calves' heart and respiratory rates returned to normal more quickly than those in the other group.

The results of red blood cell count and hematological indices indicated that Hb concentration, RBC count, and MCHC% were significantly ($p < 0.01$) increased in buffalo calves of group1 compared to those of group

2 at 14 days post-treatment (Figure 1). But the total leukocyte count was significantly ($p < 0.01$) decreased in buffalo calves of group 1 compared to those of group 2 on the 14th days post-treatment. The neutrophil percentage was significantly ($p < 0.05$) decreased in buffalo calves of group1 compared to those of group 2 on 14 days post-treatment. In contrast, lymphocyte percentage was significantly ($p < 0.05$) increased in buffalo calves of group 1 compared to those of group and group 2 on 7 days days post-treatment (Figure 2).

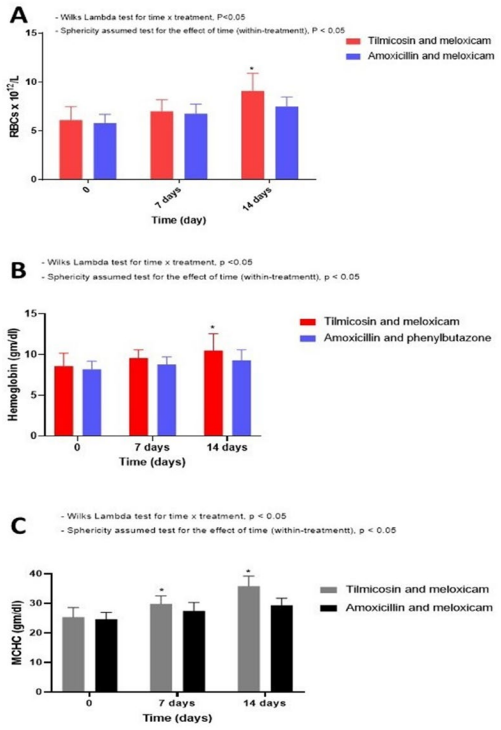

Figure 1. Hematological indices in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

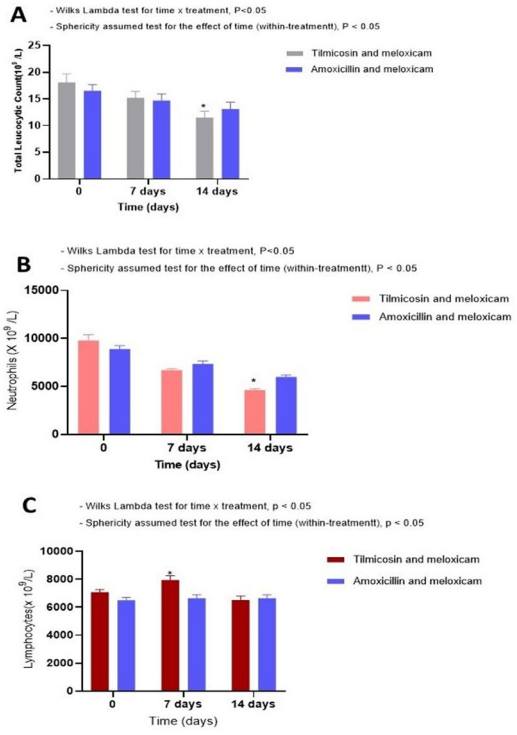

Figure 2. Mean values of total and differential leukocytic count in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

Serum haptoglobin showed non-significant ($p > 0.05$) decrease in buffalo calves (Figure 3). Serum globulin revealed a significant ($p < 0.05$) decrease in buffalo calves of group 1 compared to those of group 2 on the 14th days post-treatment. Both serum albumin and albumin/globulin (A/G) ratio indicated a significant ($p < 0.05$) increase in buffalo calves of group 1 compared with those of group 2 on 14 days post-treatment (Figure 4).

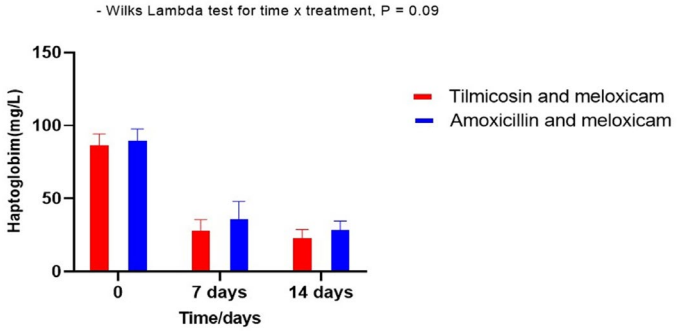

Figure 3. Haptaglobin in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

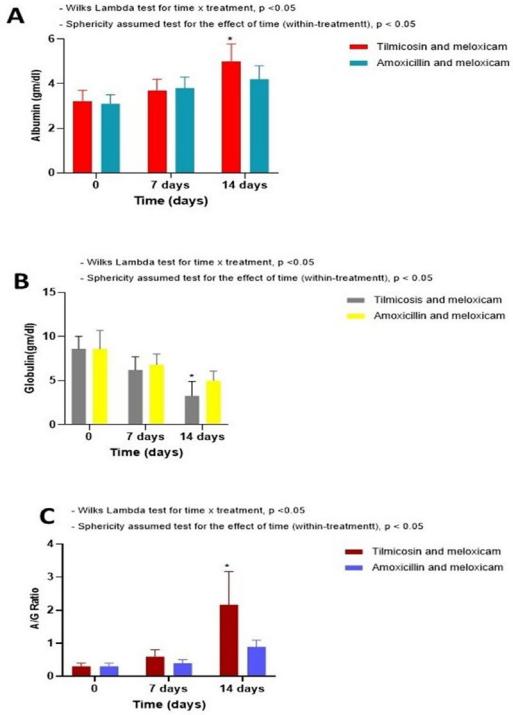

Figure 4. Mean values of serum protein in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

Serum iron levels were non-significantly ($p > 0.05$) increased in buffalo calves of group 1 compared with those of group 2 on 14 days post-treatment (Figure 5).

The serum copper levels in buffalo calves of group 1 demonstrated a significant ($p < 0.05$) decrease compared to those of group 2 on 7 days post-treatment, but on 14 days post-treatment, buffalo calves group 1 indicated a significant ($p < 0.05$) decrease in serum copper levels compared to those of group 2 (Figure 6). Serum zinc levels obtained were significantly ($p < 0.05$) increased in buffalo calves of group 1 compared to those of group 2 on 14 days post-treatment (Figure 7).

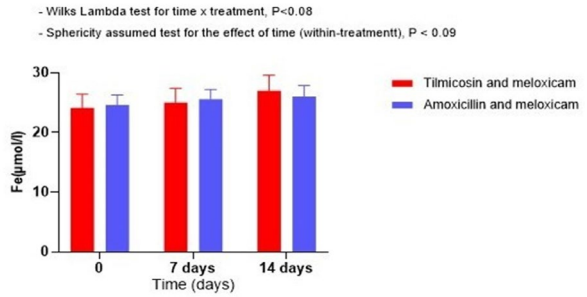

Figure 5. Mean values of serum iron in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

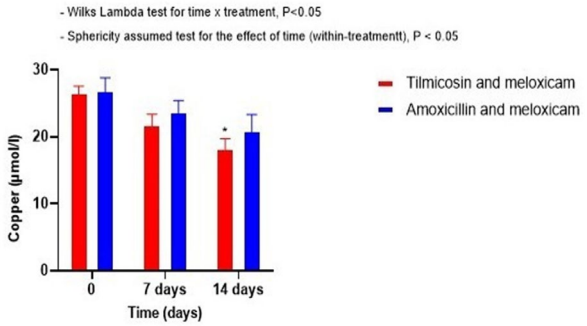

Figure 6. Mean values serum copper in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

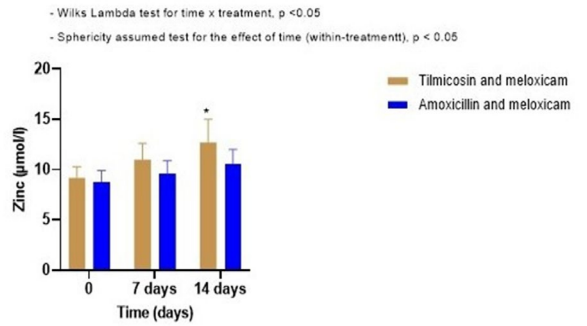

Figure 7. Mean values serum zinc in buffalo calves with acute respiratory disease before and after treatment with tilmicosin and amoxicillin LA. *: Means are significantly different at $p < 0.05$.

Discussion

In the present study, significant improvement in the clinical index score was recorded in calves treated with Tilmicosin compared to those treated with Amoxicillin. This findings are in accordance with that of previous reports (Aytekin *et al*., 2010; El-Adl, 2021; Frank *et al*., 2000). Additionally, the study of Bednarek *et al.* (2003) recorded high efficacy of tilmicosin in the treatment of acute respiratory disease in cattle calves.

According to Dudek *et al.* (Dudek *et al*., 2020) an increase in neutrophil levels is typically observed during the onset of pneumonia in calves. Neutrophils play a crucial role in defense mechanisms through phagocytosis and oxidative burst (Jimbo *et al*., 2017). Therefore, the significant decrease in neutrophils and increase in lymphocyte percentage observed in the group of calves treated with tilmicosin and meloxicam compared to the other treatment group may be due to combined effect of both tilmicosin and anti-inflammatory effect of meloxicam.

Concerning APPs, tilmicosin could induce a significant earlier decrease of serum haptoglobin and globulin but increase in serum albumin and albumin/globulin (A/G) ratio in comparison with moxicillin LA treated group. This finding suggests high efficacy and improvement in tilmicosin treated group than other one.

Haptoglobin is an acute-positive protein and is regarded as a clinically significant criterion for evaluating the frequency and intensity of inflammatory reactions, such as pneumonia in cattle (Eckersall, 2006). Therefore, the non-significant variation of haptaglobin between treated groups may be attributed to the combined effect of both antibiotic and anti-inflammatory effects. Haptaglobin is also an antioxidant, antibacterial, and anti-inflammatory scavenger protein (Gulhar *et al*., 2018).. Because haptoglobin can attach to the proteins CD11b/CD18 on neutrophils, it has an anti-inflammatory influence (El Ghmati *et al*., 1996). Albumin and globulin are other plasma proteins important in the process of inflammation that are usually measured to estimate the degree of malnutrition and severity of a disease (Laky *et al*., 2007).

It has been postulated that albumin is the major negative APP that occurs in all animal species (Cray *et al*., 2009). Albumin synthesis is depressed and amino acids are diverted to synthesize positive APPs during an inflammatory response (Aldred and Schreiber, 2020). The decrease in serum albumin in inflammation to an increase in the volume of dispersed albumin due to increased capillary permeability, which allowed serum albumin to leak out (Otal *et al*., 2022). Conversely, globulin elevation is associated with chronic inflammation and indicates prolonged exposure to several proinflammatory cytokines (Gopal *et al*., 2010). The extremely high globulin rise observed in calves with bovine respiratory disease might be due to the immune system's activation caused by pathogens (Abd El-Raof and Hassan, 1999). The A/G ratio, a biomarker combining albumin and globulin, reflects nutritional status and inflammation (Yang *et al*., 2022).. A number of respiratory disorders have been associated with A/G imbalances in patients with respiratory ailments (Chen *et al*., 2022; Qin *et al*., 2018).

In respect to copper, zinc, and iron, the calves receiving tilmicosin returned to their normal levels of these elements before the calves in the amoxicillin LA group. The strong action of tilmicosin could explain this result. Hypozincemia, hypoferremia, and hypercupremia usually occur in farm animals as a result of infection and toxemia (Constable *et al*., 2016). In addition, infection has been associated with the generation of oxidative stress in agricultural animals (Lykkesfeldt and Svendsen, 2007). An increased synthesis of the copper-binding protein ceruloplasmin could be a possible reason for the pre-therapy increased serum copper level. This protein acts as an antioxidant during infection and inflammation, scavenging free radicals (Fox *et al*., 1995). There as an association of the production of interleukin 1β and interleukin 6 with the decrease in zinc serum levels during infection in calves (Galarza *et al*., 2021). Cytokines associated with illness enhanced the absorption of zinc from the circulation in mice (Beker Aydemir *et al*., 2012; Liuzzi *et al*., 2005). The decreased hepatic production of transferrin, lactoferrin, and albumin - all transporters of iron and zinc - leads to decreased levels of both iron and zinc in the blood (Gruys *et al*., 2005).

In the present study, meloxicam as antiinflammatory induced its effects on both groups of calves. This finding may support the suggestion of variations in response to treatment is due to the antibiotic effect. Meloxicam, in one study, was able to reduce oxidative stress induced by unnecessary exercise by increasing superoxide dismutase activity (Gunes *et al*., 2011).On the other hand, a combined injectable trace elements and meloxicam did not influence the blood trace elements level or morbidity in fattening calves 45 days following the therapy (Hartschuh, 2015).

Conclusion

Tilmicosin treated calves had earlier clinical recovery and early normalization of blood parameters than those treated with amoxicillin LA. Further studies are needed to investigate the effect of tilmicosin on specific infections in calves with respiratoty signs.

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Conflict of interest

The authors have no conflict of interest to declare.

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