Original Article

Retrospective analysis of the incidence, aetiology and risk factors of sepsis based on post-mortem examination records in ruminants

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Abstract

Sepsis is an important disease in both humans and animals. In animals, it is usually caused by septicaemia after infection and has not been well-studied. This article describes a retrospective analysis of sepsis cases in small and large ruminants submitted to the Post-Mortem Laboratory, Faculty of Veterinary Medicine, Universiti Putra Malaysia between the years 2007 and 2017. The incidence of sepsis was found to be at 40.5% in small ruminants and 38.6% in large ruminants. In both small and large ruminants, sepsis was mainly caused by bacterial infection, which was significantly (p<0.05) higher compared to parasitic and viral infections. Most cases of sepsis occur due to infections originating from the gastrointestinal tract and this is followed by the respiratory tract. *Escherichia coli* has been found to be the most common bacterial pathogen of sepsis in ruminants; significantly (p<0.05) higher compared to other bacterial pathogens like *Klebsiella pneumoniae*, *Pasteurella* sp., and *Staphylococcus aureus*. Sepsis involving *E. coli* has often resulted in pure isolation of the pathogen, thus being suggestive of a single infection. Underlying or concurrent infection is the most important risk factor leading to sepsis in ruminants, with significant difference (p<0.05) compared to other risk factors such as stress or malnutrition. Associations between the gastrointestinal system as the point of entry and sepsis caused by either *E. coli* or *K. pneumoniae* have been noted. This study provides an insight into a basic understanding of sepsis in ruminants.

Keywords: sepsis, ruminants, *Escherichia coli*, *Klebsiella pneumoniae*, retrospective

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Introduction

Ruminants are herbivores that are important in the agricultural sector, especially for the production of meat, milk, wool, fertilizer, transport and draught power on agricultural land (Gowane *et al.*, 2017; Dumont *et al.*, 2018). In the developing regions of Southeast Asia and Africa, the production of ruminant-based products cannot meet local demand (Devendra, 2007). This has been attributed to multiple factors such as a lack of knowledge among farmers, a lack of capital for proper management and feeding of the animals and the occurrence of diseases (Salem and Smith, 2008; Etalema and Abera, 2018).

It has previously been reported that septicaemia and sepsis are among the most important health issues in ruminants, especially those caused by *Pasteurella multocida* B:2 and *Escherichia coli* (Zakaria *et al.*, 2019). Bacteria such as *Klebsiella pneumoniae* is also regarded as an important septicaemic agent in cat, dog and pigs (Maniam *et al.*, 2020; Bidewell et al., 2018). Previous studies have investigated the prevalence of these pathogens in animals but not the prevalence of the sepsis caused by them. It has been observed that prevalence of extended-spectrum beta-lactamase-producing *E. coli* isolated from cattle in Japan was 12.5% (Hiroi et al., 2011). Meanwhile, the prevalence of *E. coli* and *K. pneumoniae* was 19.1% and 6.7% respectively in dairy cattle in Korea (Nam *et al.*, 2009) and 17% for *P. multocida* in calves in Scotland (Hotchkiss *et al.*, 2010).

Septicaemia is the presence of bacteria and its toxin in the blood circulation. This triggers an acute and overwhelming systemic inflammatory response, termed as sepsis, and results in the death of animals (Brady and Otto, 2001; Annas *et al.*, 2015). Septicaemia and sepsis in animals have not been well-studied, largely due to the difficulty in their diagnosis. In human medicine, diagnosis and progression of sepsis is made based on clinical data and the sequential organ failure assessment (SOFA) score (Ioakeimidou *et al.*, 2017; Liu *et al.*, 2019). In farm animals including ruminants, this is extremely difficult to perform due to the limitations in diagnosing and monitoring the health status of animals in the field. Instead, septicaemia and sepsis are diagnosed based on the isolation and identification of the pathogens from tissue samples and histological observation including organ congestion, haemorrhage and acute cellular injury. It is important to understand the basics of septicaemia and sepsis in ruminants in order to design a preventative measure for the diseases.

A cost-efficient and reliable method for surveillance of animal health is by data collection and retrospective analysis of necropsy reports (Küker *et al.*, 2018). Similar approaches have been proven to be beneficial in providing information pertaining to common pathogens, incidence and important risk factors for septicaemia in small animals (Maniam *et al.*, 2019). This article describes the aetiological agents, risk factors and points of entry of sepsis in small and large ruminants.

Materials and Methods

Data Collection: Records of post-mortem examination of small ruminants (sheep, goats and deer) and large ruminants (cattle, buffalo and gaur) that were previously submitted to the Post-Mortem Laboratory, Faculty of Veterinary Medicine, Universiti Putra Malaysia (UPM) from 2007 until 2017 were collected and analysed in this study. Cases with inconclusive diagnosis, incomplete reports or missing reports were excluded from the study. Information pertaining to the clinical history, age and diagnostic laboratory results such as bacteriology, virology and parasitology were analysed. Cases with bacterial isolation from at least 3 organ samples detection with virus or parasite were tentatively diagnosed as sepsis. The histopathology reports by resident pathologists that suggested sepsis were used to arrive at a diagnosis of bacterial, viral or parasitic sepsis, respectively. This data was subsequently analysed to establish the association between species/genus of bacteria, points of entry and risk factors.

Determination of point of entry: The point of entry of pathogens was determined as previously described (Rathiymaler *et al.*, 2017) with slight modifications, and was based on those reported by resident pathologists. The points of entry were categorised according to body systems, namely, the gastrointestinal, respiratory, reproductive and integumentary systems. Body systems identified as point of entry in fewer than 5 cases were categorized as "Others".

Risk Factors: Following assessment of records, the risk factors were divided into underlying infection, stress, malnutrition, traumatic injury and others (e.g., post-surgical complications, poisoning, lightning strikes, idiopathic gastritis).

Data analysis: The data was analysed using Statistical Packages for the Social Sciences (SPSS) version 24. The data was categorical and non-continuous, thus a non-parametric test was used for data analysis. All tests were done at 95% confidence interval level. Subsequently, Pearson's chi-square test was used to determine the significant level of variables such as point of entry, risk factors and microorganisms isolated. The occurrence rate of the variables was analysed using Microsoft Excel 2010.

Results

Incidence: A total of 340 cases of small ruminants (goats, sheep and deer) and 111 cases of large ruminants (cattle, buffalo and gaur) were received by the Post-Mortem Laboratory, Faculty of Veterinary Medicine, Universiti Putra Malaysia between January 2007 and December 2017. From the 340 small ruminant cases, a total of 46 cases were excluded, thus the remaining 294 cases were used in this study. A total of 119 cases (40.47%) of sepsis was recorded in the small ruminants. For the large ruminants, 10 cases were excluded from the study. Thus, a total of 101 cases were analysed. A total of 39 cases (38.61%) were diagnosed as sepsis.

Aetiological agents: The aetiological agents of sepsis involved in small and large ruminants are bacteria, parasites and viruses. In both ruminants, bacterial sepsis contributed to a total of 138 cases, parasitic sepsis with 12 cases, and viral sepsis with 8 cases. Bacterial sepsis contributed to most of the sepsis cases with 105 cases (88.20%) in small ruminants and 33 cases (84.62%) in large ruminants. It was found that bacterial sepsis was significantly ($p<0.05$) higher compared to sepsis caused by parasites and viruses.

Points of Entry: In general, most sepsis in ruminants originated from the gastrointestinal tract with a total of 77 cases (48.73%). In small ruminants, sepsis with gastrointestinal origins recorded 56 cases (47.06%). This is significantly ($p<0.05$) higher compared to the 37 cases (31.09%) originating in the respiratory system, 14 cases (11.76%) originated from the reproductive system, 7 cases (5.88%) originated from the integumentary system and 5 cases (4.20%) originated from other systems. In the large ruminants, 21 sepsis cases (53.85%) originated from the gastrointestinal system which is significantly ($p<0.05$) higher compared to the respiratory system with 9 cases (23.08%), the integumentary system with 3 cases (7.69%) and other body systems with 6 cases (15.38%). Bacterial sepsis occurred mostly via the gastrointestinal system, involving 18 cases (54.55%), followed by the respiratory system with 9 cases (27.27%) (Table 1).

Table 1 Number, points of entry and aetiological agents of sepsis ruminants.

Ruminant type	Points of Entry	Aetiological agents			Total
		Bacteria	Virus	Parasite	
Small ruminant	Gastrointestinal	47	1	8	56
	Respiratory	35	1	1	37
	Reproductive	12	2	-	14
	Integumentary	6	1	-	7
	Others	5	-	-	5
	Total	105	5	9	119
Large ruminant	Gastrointestinal	18	2	1	21
	Respiratory	9	-	-	9
	Integumentary	1	1	1	3
	Others	5	-	1	6
	Total	33	3	3	39
Grand total		138	8	12	158

Bacterial Isolation: Based on the bacteriology reports from sepsis cases in small ruminants, pure bacterial cultures were isolated from 44 cases (36.97%). A total of 50 cases (42.01%) yielded 2 bacterial species, and 3 or more bacteria species were isolated from the remaining 46 cases (38.66%). *Escherichia coli* was found to be the most commonly isolated bacteria in sepsis cases among small ruminants with a total of 94 cases (78.99%). This was followed by *Klebsiella pneumoniae* with 31 cases (26.05%), *Pasteurella* sp. with 15 cases (12.6%), *Proteus mirabilis* with 10 cases (8.40%) and fewer than 10 cases caused by other bacteria. Statistical analysis suggested that isolation of *E. coli* from septicaemic small ruminants was significantly ($p<0.05$) higher compared to all other bacteria species including *Pasteurella* sp. and *K. pneumoniae*.

In the large ruminants, the three most commonly isolated bacteria were *E. coli*, *K. pneumoniae*, and *S. aureus*. Other bacterial pathogens with fewer than 5 cases were not included in the analysis. A total of 44 isolates of these three bacteria were cultured. It was noted that 20 cases (45.45%) yielded pure bacterial cultures, 9 cases (20.45%) resulted in isolation of 2 bacterial cultures and 15 cases (34.1%) resulted in the isolation of 3 or more bacterial cultures. *Escherichia coli* was found to be most common pathogen associated with sepsis with a total of 28 cases (56%). This was followed by *K. pneumoniae* with 22 cases (22%) and *S. aureus* with 5 cases (10%). Statistical analysis of these three bacteria showed that *E. coli* was significantly ($p<0.05$) higher compared to *K. pneumoniae* and *S. aureus*. No significant ($p>0.05$) difference was noted between *K. pneumoniae* and *S. aureus*. Most of the isolated *E. coli* were obtained from cases with pure bacterial infection, with 13 cases (29.5%), compared to 6 cases (13.6%) of *K. pneumoniae,* and 1 case (2.3%) of *S. aureus*.

The isolation of *E. coli* consistently showed significant ($p<0.05$) difference compared to the other bacteria whether it was isolated from cases with pure isolation, 2 isolation, or ≥ 3 isolation. Table 2 summarises the isolation and purity of bacterial isolation in ruminants with sepsis.

Table 2 Isolation and purity of isolation of bacteria from ruminants with sepsis.

Ruminant type	Bacteria	Isolation purity			Total
		Pure isolation	Isolation of 2 bacteria	Isolation of ≥ 3 bacteria	
Small ruminant	*E. coli*	39*	29*	26*	94*
	K. pneumoniae	2	13	16	31
	Pasteurella sp.	3	8	4	15
	Total	44	50	46	140
Large ruminant	*E. coli*	13*	7	8	28*
	K. pneumoniae	6	0	5	11
	S. aureus	1	2	2	5
	Total	20	9	15	44
Grand total		64	59	61	184

Risk Factors: The most common risk factor for sepsis in small ruminants was the presence of an underlying infection. This involved 68 cases (57.14%). Other risk factors for sepsis in small ruminants were stress, with 13 cases (10.92%), malnutrition, with 12 cases (10.08%), traumatic injury, with 3 cases (2.52%) and the remaining 23 cases (19.33%) involved other risk factors. The frequency of underlying infection as the risk factor for septicaemia was significantly ($p<0.05$) higher compared to all other risk factors. A further breakdown of the underlying infection risk factor found that the majority of the cases were due to underlying bacterial infection (57 cases, 83.82%), while the remaining cases involved underlying parasitic infection (8 cases, 11.76%) and underlying viral infection (3 cases, 4.41%).

Similar to the small ruminants, the most frequent risk factor causing sepsis in large ruminants was the presence of underlying infection which involved 24 cases (61.54%). The risk factor of having an underlying infection was significantly ($p<0.05$) higher compared to malnutrition, with 4 cases (10.26%), stress, with 3 cases (7.69%) and traumatic injury, with 3 cases (7.69%) and other risk factors, with 5 cases (12.8%). Underlying infection can be further classified into underlying bacterial, parasite or viral infection. There were 19 cases of underlying bacterial infection (79.17%), 3 cases (12.50%) of viral infection and 2 cases (8.33%) of underlying parasitic infection. The risk factors classified as 'others' included post-surgical complications, organ failure and management misconduct.

Association between points of entry and types of bacteria: As most cases of sepsis in ruminants were caused by bacteria, further analysis was done to evaluate the association between the points of entry and the three most commonly isolated species of bacteria.

In the small ruminant, the gastrointestinal system was found to be associated as the route of entry for sepsis caused by *E. coli* and *K. pneumoniae*. In cases of sepsis involving *E. coli*, the gastrointestinal system was the most common point of entry (52 cases, 55.32%), with significant ($p<0.05$) difference compared to all the other points of entry. A similar pattern was observed in cases involving *K. pneumoniae* where the gastrointestinal system was the most common point of entry associated with this pathogen. This was significantly ($p<0.05$) different compared to other points of entry. Statistical analysis suggested that *Pasteurella* sp. is associated with septicaemia originating from the respiratory system.

In large ruminants, analysis of the different points of entry against the three most commonly isolated bacteria showed that *E. coli* and *K. pneumoniae* were associated with sepsis originating from the gastrointestinal tract, with significant ($p<0.05$) difference compared to the other points of entry. In sepsis cases involving *K. pneumoniae,* both the gastrointestinal and respiratory tracts showed significantly ($p<0.05$) higher numbers of cases compared to the integumentary and other systems. Table 3 summarises the association between points of entry and the different bacteria isolated from ruminants with sepsis.

Table 3 Total number of cases of different bacteria and their associated points of entry among small ruminants.

Ruminant type	Points of Entry	*E. coli*	*K. pneumoniae*	*Pasteurella* sp.
Small ruminant	Gastrointestinal system	52 (55.3%)^{a}	16 (51.6%)^{a}	1 (6.7%)^{b}
	Respiratory system	20 (21.3%)^{b}	10 (32.3%)^{b}	14 (93.3%)^{a}
	Reproductive system	11 (11.7%)^{c}	2 (6.5%)^{c}	0
	Integumentary system	6 (6.4%)^{d}	2 (6.5%)^{c}	0
	Others	5 (5.3%)^{d}	1 (3.2%)^{c}	0
	Total	94 (100%)	31 (100%)	15 (100%)
	Points of Entry	***E. coli***	***K. pneumoniae***	***S. aureus***
Large ruminant	Gastrointestinal system	17 (60.7%)^{a}	5 (45.5%)^{a}	3 (60.00%)^{a}
	Respiratory system	5 (17.9%)^{b}	4 (30.4%)^{a}	2 (40.00%)^{b}
	Integumentary system	1 (3.6%)^{c}	1 (9.1%)^{b}	0
	Others	5 (17.9%)^{b}	1 (9.1%)^{b}	0
	Total	28 (100%)	11 (100%)	5 (100%)

Different superscript (^{a,b,c,d}) indicates statistical significance for each bacteria species for small or large ruminants.

Association between points of entry and risk factors: In the small ruminant, statistical analysis suggested significant ($p<0.05$) differences between point of entry and four risk factors which were the underlying infection, malnutrition, traumatic injury and other risk factors. The presence of underlying diseases was associated with sepsis originating from the respiratory system. This is significantly ($p<0.05$) different compared to the reproductive and integumentary systems. Malnutrition is associated with sepsis from the gastrointestinal system. In addition to that, traumatic injury was found to be associated with sepsis originating from the integumentary system. This is significantly ($p<0.05$) different compared to the rest of the system.

In the large ruminants, no significant difference ($p>0.05$) was noted between the points of entry and risk factors. Despite the statistical insignificance, large ruminants with underlying infection showed the highest amount of sepsis originating from gastrointestinal system with 11 cases. This was followed by the respiratory system, integumentary system and other systems with 5 cases, 2 cases and 4 cases respectively. Malnutrition involved only two possible points of entry of sepsis which were from the gastrointestinal system (3 cases) and from another point of entry (1 case).

Discussion

The gastrointestinal tract was found to be the most common point of entry for septicaemia and sepsis in ruminants. It is known to harbour opportunistic normal flora that do not cause infection in healthy animals but proliferate to cause infections in immune-compromised animals or in cases whereby there is an increase in the permeability or a damaged intestinal mucosal barrier (Berg, 1995). Hence, it was not surprising that in this particular study, underlying infection was an important risk factor for sepsis among ruminants. In fact, underlying infection is known to cause immunosuppression that allows the proliferation of opportunistic normal flora in the gut and eventually causes septicaemia (Whichard *et al.*, 2005). In general, the mucosal surface is a common location where pathogens can gain entry into the host. These mucosal surfaces include the gastrointestinal mucosa. Similarly, in other animals such as in poultry, aquatic creatures and other livestock, bacterial infection is known to commonly start from the mucosal surface (Quintana-Hayashi *et al.*, 2018). Most gastrointestinal bacterial pathogens are known to suppress gastrointestinal normal flora and enhance their own growth and adhesion to the host mucosa by inducing mucosal glycosylation.

Based on the findings of aetiological agents and points of entry, common microorganisms such as *E. coli* and *K. pneumoniae* can potentially be the opportunistic normal flora of the gastrointestinal tract. This association has been previously described in cases of septicaemia in dogs (Rathiymaler *et al.*, 2017) and in cats (Maniam *et al.*, 2019). Other than the gastrointestinal tract, *E. coli* is significantly associated with the respiratory tract suggesting an alternative point of entry for this particular bacterium. *Escherichia coli* is a common bacterial commensal of the intestine of diverse animals and humans. Despite that, some *E. coli* strains are pathogenic and can cause various diseases in humans and animals (Bélanger *et al.*, 2011). Pathogenic strains of *E. coli* of intestinal tracts of animals and humans have been characterised into multiple criteria such as the presence of specific serotypic markers, the presence of plasmid-mediated virulence factors, the capability of causing diarrhea, the capability of producing toxins and interaction with the mucosal epithelium of the intestine (Duhamel *et al.*, 1992).

On the other hand, *Pasteurella* sp. have been found to be associated with sepsis originating from the respiratory tract, gastrointestinal tract and reproductive tract of small ruminants. *Pasteurella* sp. are common commensal inhabitants of the upper respiratory tract of various domestic animals and are particularly important in small ruminants such as goats and sheep (Alemneh and Tewodros, 2016). They are known to reside in the nasopharynx and cause infection when the host body defence mechanism is weakened (Emikpe *et al.*, 2014) hence, explaining the respiratory tract as one of its point of entry in septicaemia caused by this organism. However, it should be noted that only certain species or serotypes of *Pasteurella* sp. are known to cause primary septicaemia in ruminants. This has been well-documented in large ruminants but not in small ruminants (De Alwis, 1999; Puspitasari *et al.*, 2020). For example, *P. multocida* B:2 and E:2 causes haemorrhagic septicaemia in buffalo and cattle. It would be intriguing to perform serotyping of *Pasteurella* sp. to determine the common species and serotype causing septicaemia in small ruminants. Although *Pasteurella* sp. has been found to mainly originate from the respiratory system, once septicaemia and sepsis has developed, it will eventually affect the gastrointestinal and reproductive systems (Annas *et al.*, 2014).

In both small and large ruminants, the presence of underlying disease was found to be the most important risk factor for sepsis. Similarly, in humans, underlying disease is known to be an important risk factor for sepsis where it has been noted that 55% of sepsis patients had underlying disorders (Angus *et al.*, 2001). This includes co-morbidity or chronic underlying disorders that intensify the condition or disease appointed as the principal diagnosis. In many chronic disorders, higher incidence and severity of infectious episodes indicates immunosuppression (Dhainaut, *et al.*, 2005). The presence of underlying diseases, especially infectious diseases, has been previously proven to increase the susceptibility of animals to bacterial infection that can lead to septicaemia and sepsis (Maniam *et al.*, 2019). This is especially true for Gram-negative opportunistic normal flora such as *E. coli* (Maniam *et al.*, 2019). The start and spread of infection only happens with the presence of a causative agent that causes the immune system to be distressed and facilitates infection to take place (Remick, 2007). It was previously observed that pneumonic mannheimiosis and pasteurellosis coupled with other stress factors has led to death due to severe colisepticaemia in deer. (Fitri *et al.*, 2017).

Through the study, it was observed that *S. aureus* also plays a significant role with regards to its points of entry which are the integumentary tract, gastrointestinal tract, respiratory tract and other tracts. *Staphylococcus aureus* is a Gram-negative bacterium that commonly colonizes diverse animal species. In animals, *S. aureus* infection affects dairy animals causing mastitis. The involvement of livestock–associated strains can be attributed to the imprudent use of antibiotics in farms (Lugsomya *et al.*, 2018). The other common pathogens of septicaemia including *E. coli* and *K. pneumoniae* were previously proven to be resistant towards commonly used antibiotics (Maniam *et al.*, 2020). One of the emerging classifications of *S. aureus* is the livestock-associated *S. aureus* despite its moderately causing infections in humans. However, studies in recent years suggest that bidirectional transmission of *S. aureus* strains is not a rare occurrence and not by chance (Weese and van Dujikeren, 2010). This suggests that, besides *E. coli* and *K. pneumoniae, S.*

aureus could potentially be an emerging pathogen of septicaemia in ruminants.

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