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Characteristics of bacterial sepsis among patients with visceral leishmaniasis

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PEER REVIEW

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Comments

This review is a valuable work in which authors have demonstrated that VL and VL-HIV co-infected patients which are affected by bacterial infections leading to sepsis, should be diagnosed and treated early. Optimal infection control measures should be timely taken in order to reduce nosocomial sepsis. Indwelling of central venous lines for immune-suppressed patients such as VL and VL-HIV co-infected should be reduced as much as possible.
Details on Page 874

ABSTRACT

Sepsis is one of the major causes and predictors of death in patients with visceral leishmaniasis (VL). Globally, incidence rate of sepsis ranged from 56-91 cases per 100 000 people, with a mortality rate of 30%. Incidence of sepsis has been raised due to aging of the population and the higher incidence of immunosuppressive conditions such as HIV, VL and others. The prevalence of sepsis was reported from 4.2% to 32.3% and 14.1% in VL and VL-HIV coinfected patients, respectively. The mortality rate of VL patients with sepsis is greater than 50%. Factors associated with sepsis in VL patients are immune suppression, pancytopenia, HIV co-infection, age <1 year old and >40 years old, indwelling of central venous lines and hospitalization. Although antimicrobial susceptibility patterns were not well reported, both Gram-positive and Gram-negative bacteria were isolated from patients with VL. So far, limited information is available on sepsis in VL, especially in VL-HIV coinfected patients. Therefore, further studies about sepsis prevalence, causative agents and their antibiotic patterns, and associated factors among VL and VL-HIV coinfected patients are necessary. This review provides information about bacterial sepsis in patients with VL.

KEYWORDS
Sepsis, Visceral leishmaniasis, VL-HIV, HIV/AIDS

1. Introduction

Sepsis is defined as the presence or presumed presence of an infection accompanied by evidence of a systemic response called the systemic inflammatory response syndrome[1]. Recently Vincent *et al.* defined as host's deleterious, non-resolving inflammatory response to infection that leads to organ dysfunction[2]. Although

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sepsis can be caused by viruses and fungi, most is due to bacterial infections[3]. Recent review by Jawad *et al.* revealed that the incidence rate of sepsis ranged from 56-91 cases per 100 000 people, with a reported mortality rate of 30%[4]. Incidence of sepsis is increasing due to nosocomial infection, aging of the population and the higher incidence of immunosuppressive conditions such as HIV/AIDS[5], visceral leishmaniasis (VL) and VL-HIV co-infection and others[6-8].

VL is one of the most neglected infectious diseases[9]. Over 90% of the estimated annual incidence in half a million VL cases worldwide occur in just six countries which are Bangladesh, India, Nepal, Sudan, Ethiopia and Brazil[10-12]. The highest prevalence of VL-HIV co-infection in the world was reported from Eastern African region reached up to 40%[10,13].

Patients with VL usually present with fever, weight loss, organomegaly and pancytopenia. *Leishmania donovani*, etiologic agent of VL, targets reticuloendothelial system, spleen, liver, bone marrow and lymph nodes[9]. *Leishmania* invade and replicate within host macrophages, evading innate and cell-mediated immune responses. Patients with VL show a continuum of immune responses from protective to non-protective[14]. Leucopenia, malnutrition and lack protective responses to *Leishmania* and other antigens including bacteria, predispose patients with VL to bacterial infections[15,16].

Studies conducted on the prevalence of sepsis ranged from 3% to 28% among VL patients[6-8,17-21]. Although sepsis has high prevalence and affects the outcome of patients with VL, the causative agents and their antimicrobial susceptibility patterns are poorly understood. Under knowing the current magnitude of sepsis in immuno-compromised individuals such as VL and VL-HIV coinfected patients, it is important to take rational management for them. This review, therefore aims to compile available information on the prevalence, associated risk factors and etiologic agents of bacterial sepsis in patients with VL and VL-HIV co-infection.

2. Methods

This review was developed after reviewing the pertinent information available about sepsis among patients with VL and VL-HIV co-infection from Hinari, Entrez-PubMed and Google Scholar web sites.

3. Sepsis

3.1. Prevalence of sepsis

The prevalence of sepsis in patients with VL and VL-HIV coinfected patients in the world is not clearly known. Recent studies showed sepsis was a main factor that affected the treatment outcome of patients with VL[22]. Bacterial infections and sepsis among VL and VL-HIV coinfected patients have been reported ranging from 15% to 84% and 3% to 28%, respectively (Table 1).

Table 1
Prevalence of bacterial infections and sepsis among patients with VL.

Country of study	Bacterial infections	Sepsis	Study group	Reference
Brazil	52.4%	NR	Admitted VL (*n*=63)	[24]
Brazil	60.0%	4.2%	Admitted VL (*n*=30)	[6]
Brazil	27.5%	9.1%	Paediatric VL (*n*=120)	[21]
Iran	41.0%	13.0%	Paediatric VL (*n*=54)	[7]
Albania	60.0%	NR	VL patients (*n*=50)	[25]
Albania	84.0%	3.0%	Admitted VL (*n*=1 210)	[20]
Iran	42.0%	28.0%	Paediatric VL (*n*=60)	[17]
Ethiopia	42.8%	5.0%	Non-HIV VL (*n*=247)	[8]
Ethiopia	23.1%	NR	Pediatric VL (*n*=77)	[26]
Ethiopia	15.0%	7.0%	All VL (*n*=81)	[18]
Ethiopia	16.0%+	10.0%+	Adult VL (*n*=241)	[19]
	40.0%++	14.0%++		

NR: Not reported, +: HIV negative, ++: HIV positive.

3.2. Associated risk factors

The increased susceptibility of VL patients to bacterial infections leads sepsis to be multi-factorial. Immuno-suppression, leucopenia and malnutrition are the most important factors associated with susceptibility to bacterial infections[8,17]. Extreme age (age <1 year old and >40 years old) and HIV are the factors associated with bacterial sepsis[8]. Malnutrition, pulmonary rales, severe anemia, severe absolute neutropenia and higher neutrophil count were also identified as risk factors related to bacterial infections that lead to death in patients with VL[15]. Neutropenia associated with bacteremia is common in immune-compromised patients including cancer patients[23].

Increased exposure to potentially resistant bacteria in nursing homes and utilization of insufficiently sterilized medical devices including indwelling catheters and central venous lines will also increase risks. Patients with VL treated in hospital had significantly higher rates of complications than those treated on outpatient basis (P<0.001)[8].

3.3. Sources for sepsis

The sources for sepsis are bacterial infections elsewhere in the body that include: lungs, wounds, soft tissues, central nervous system and urinary tract infections. Bacterial infections (such as pneumonia, otitis media, and gastrointestinal infections) cause sepsis, which are common in patients with VL ranging from 15% to 84%[6-8,17-21,24-26]. Patients with VL will stay in hospital for at least 30 d for the treatment of VL. In this period, they will be treated with the drugs (such as sodium stibogluconate, amphotericin b) intravenously. This intravenous dwelling may also contribute to the entrance of bacterial agents. A few studies in Ethiopia also reported bacterial infections ranging from 15% to 42.8% and 40% in patients with VL and VL-HIV co-infection, respectively[8,18,19,26].

3.4. Etiologic agents and their antimicrobial susceptibility patterns

Both Gram-positive and Gram-negative bacteria were isolated from patients with VL (Table 2). Among the Gram-positives, *Staphylococcus aureus* were the predominateing isolate. Unexpected Gram-negative bacteria such as *Shigella* was also reported from a VL case in Ethiopia[27]. Although some bacteria were isolated from patients with VL, their antimicrobial susceptibility patterns are not well studied (Table 2).

3.5. Mortality due to sepsis

Sepsis is a life-threatening disease that may lead to shock, multiple organ failure, and death, especially if not recognized early and treated promptly. Millions of people die of sepsis every year worldwide[28]. Bloodstream infections are usually serious infections typically causing a prolonged hospital stay, increased cost and risk of mortality, especially when it occurs with other co-infections like HIV[29]. Sepsis is the primary cause of death that contributes 34% to 75% of the total deaths in patients with VL[18,20-22,26]. Bacterial sepsis still remains the primary cause of death from infection in spite of advanced modern medicine, including vaccines, antibiotics and acute care.

Sepsis was one of the associated factors with poor treatment outcome (death) in patients with VL and VL- HIV coinfected. Patients with VL and sepsis have six times [odds ratio (OR)=6.44] more risk to die than with VL but not sepsis. In patients with VL-HIV coinfection and sepsis, this risk raises to nine times (OR=9.06)[19].

4. Conclusion

Sepsis is an important health problem causing death of VL and VL-HIV coinfected patients. Sepsis in VL patients is associated with immune suppression, pancytopenia, HIV coinfection, age <1 year old and >40 years old, indwelling of central venous lines and hospitalization. Bacterial infections such as pneumonia, otitis media, and gastrointestinal infections leading to sepsis were common among VL patients. Both Gram-positive and Gram-negative bacteria were isolated from blood cultures of sepsis suspected VL patients. VL and VL-HIV coinfected patients that are affected by bacterial infections (such as pneumonia, otitis media, gastrointestinal infections), which cause sepsis, should be diagnosed and treated early. Optimal infection control measures should be taken by concerned bodies in order to reduce nosocomial sepsis. Indwelling of central venous

Table 2

Bacterial agents isolated from blood culture of patients with VL and HIV co-infection.

Gram-reaction	Bacteria isolated	Case/total (%)	Susceptibility testing	Country	References
Gram-positives	*Staphylococcus aureus*	3/54 (5.6%)	DNR	Iran	[7]
		3/247 (1.2%)	ND	Ethiopia	[8]
	Streptococcus pneumonia	1*	ND	Spain	[30]
	Acinetobacter baumannii	1*	MDR	Greece	[31]
Gram-negatives	*Enterobacter* species	1/24 (4.2%)	ND	Brazil	[6]
		1/54 (1.9%)	DNR	Iran	[7]
	Escherichia coli	1*	ND	Spain	[30]
		1/247 (0.4%)	ND	Ethiopia	[8]
	Klebsiella pneumonia	2/54 (3.7%)	DNR	Iran	[7]
	Pseudomonas aeroginasa	1/54 (1.9%)	DNR	Iran	[7]
		1/247 (0.4%)	ND	Ethiopia	[8]
	Shigella species	1*	D	Ethiopia	[27]

*: Case report, ND: not done, DNR: done but not reported, MDR: multiple drug resistant, D: done (sensitive to all tested except ampicillin).

lines for immunosuppressed patients such as VL and VL-HIV coinfection should be reduced as much as possible. It is necessary to further study about sepsis causative agents, their antibiotic pattern and associated factor among VL and VL-HIV coinfected patients.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Sepsis is the presence of an infection accompanied by evidence of systemic inflammatory response syndrome. Incidence of sepsis is increasing due to nosocomial infection, aging of the population and the higher incidence of immunosuppressive conditions such as HIV/AIDS, VL and VL-HIV co-infection and others. VL is one of the neglected diseases in the world, affecting the poorest segment of rural populations. Studies have shown that the prevalence of sepsis ranged from 3% to 28% among VL patients. Therefore, knowing the current magnitude of sepsis in immuno-compromised individuals such as VL and VL-HIV co-infected patients is important for rational management of patients.

Research frontiers

As VL and VL-HIV co-infected patients are immunocompromized patients and studies showed that bacterial sepsis is becoming an important concern in this population segment. VL is one of the neglected diseases in developing countries where bacterial infection is equally important, hence addressing this problem may be important for increasing awareness of the community and give better attention for patient management.

Related reports

In recent reports sepsis was the main factor that affects the treatment outcome of patients with VL (Hussein *et al.*, 2001). Bacterial infections and sepsis among VL and VL-HIV co-infected patients have been reported ranging from 15% (Tadesse and Hurissa, 2009) to 84% (Petrela *et al.*, 2010) and 3% (Petrela *et al.*, 2010) to 28% (Barati *et al.*, 2008) respectively. Sepsis is the primary cause of death that contributes 34% to 75% of the total deaths in patients with VL (Rocha *et al.*, 2011).

Innovations and breakthroughs

As VL and VL-HIV co-infected patients are immunocompromized patients, in the present study authors have demonstrated the importance of bacterial sepsis in this population segments which become important public health concern.

Applications

It has been found that sepsis is the primary cause of death that contributes to a significant number of deaths in patients with VL. Addressing this issue may be important for increasing awareness of the community and give better attention for patient management.

Peer review

This review is a valuable work in which authors have demonstrated that VL and VL-HIV co-infected patients affected by bacterial infections leading to sepsis, should be diagnosed and treated early. Optimal infection control measures should be timely taken in order to reduce nosocomial sepsis. Indwelling of central venous lines for immune-suppressed patients such as VL and VL-HIV co-infected should be reduced as much as possible.

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