The effect of HIV infection on the host response to bacterial sepsis

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Bacterial sepsis is an important cause of morbidity and mortality in patients with HIV. HIV causes increased susceptibility to invasive infections and affects sepsis pathogenesis caused by pre-existing activation and exhaustion of the immune system. We review the effect of HIV on different components of immune responses implicated in bacterial sepsis, and possible mechanisms underlying the increased risk of invasive bacterial infections. We focus on pattern recognition receptors and innate cellular responses, cytokines, lymphocytes, coagulation, and the complement system. A combination of factors causes increased susceptibility to infection and can contribute to a disturbed immune response during a septic event in patients with HIV. HIV-induced perturbations of the immune system depend on stage of infection and are only in part restored by combination antiretroviral therapy. Immunomodulatory treatments currently under development for sepsis might be particularly beneficial to patients with HIV co-infection because many pathogenic mechanisms in HIV and sepsis overlap.

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Introduction

People infected with HIV are at increased risk of developing other infections. Reports from developed countries show that, with the introduction of combination antiretroviral therapy (cART), the incidence of opportunistic infections such as *Pneumocystis jirovecii* pneumonia has decreased substantially, and sepsis is now the principal cause of intensive care unit (ICU) admission and death in patients with HIV who are admitted to hospital.[1] Worldwide, patients with HIV are at increased risk of developing bacterial bloodstream infections, particularly with non-typhoidal salmonella (NTS) and *Streptococcus pneumoniae*,[2,3] even in those using effective cART.[4] In developing regions with high rates of HIV infection, the scale of the problem is immense. In African hospitals, 31–83% of patients presenting with fever are infected with HIV, and 10–32% of these patients have bacterial bloodstream infections, with mortality rates of 25–46% (table 1).[5-15] However, little is known about the particularities of the host response during bacterial sepsis in patients with HIV. The immune response during sepsis is thought to be an imbalance between proinflammatory and anti-inflammatory effects, which result in organ failure.[16,17] Likewise, HIV infection is characterised by a combination of immune suppression and chronic inflammation, which results in exhaustion of the immune system.[18] In this Review we describe how different components of the immune response might be affected by HIV during bacterial sepsis, and possible mechanisms for the increased risk of invasive bacterial infections. We also discuss parallels in immunomodulatory therapies proposed for sepsis and HIV, which represent an appealing area for future research.

First line defences

Overview

A sepsis event typically starts with a pathogen invading a normally sterile site. The first line of defence consists of epithelial cells of the skin, gut, and lungs. After breaching the epithelial barrier, pathogens are first detected by innate immune cells, including monocytes, macrophages, dendritic cells, and neutrophils.[19] These cells express pattern recognition receptors (PRRs) on their surface and in the cytosol to enable recognition of conserved motifs expressed by pathogens.[20,21] Four classes of PRRs have been identified: toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerisation domain leucine-rich-repeat containing receptors (NOD-LRRs), and retinoic acid-inducible gene I protein helicase receptors (RLRs).[20] In the context of sepsis pathogenesis, TLRs have been studied the most extensively. They are expressed on the cell surface (TLRs 1, 2, 4, 5, and 6) to enable recognition of bacterial outer membrane components, and in intracellular compartments (TLRs 3, 7, 8, and 9) for detection of nucleic acids derived from intracellular pathogens, mainly viruses.[20] For bacterial recognition, TLRs 2, 4, 5, and 9 are the most important. Additionally, TLR7 can sense bacterial RNA released within phagosomal vacuoles,[22] and TLR3 can function as an amplifier of host RNA-triggered inflammation during sepsis.[23] Ligand recognition by TLRs triggers a signalling cascade, which results in the production of cytokines.[20] Although essential for pathogen recognition and the innate immune response, uncontrolled stimulation causes excessive inflammation; hence TLR signalling is normally tightly regulated.

Innate immune cells have several specific functions in antibacterial immunity. Monocytes and macrophages have a crucial role in maintaining homoeostasis by phagocytosis of apoptotic cells and microorganisms.[19] As the main producers of proinflammatory cytokines, they are also thought to be key in sepsis pathogenesis.[19] Dendritic cells are the main antigen-presenting cells; maturation is induced after ingestion of antigen, followed by migration to lymphoid tissue. Mature dendritic cells express co-stimulatory molecules on their surface, which synergise with antigen to activate T cells.[24] Natural killer (NK) cells are implicated in

	Study location and timeframe	Primary inclusion criteria	Patients infected with HIV (% of patients tested)	CA bacterial BSI in patients with HIV (%)	Main isolates in patients with HIV (%)	Mortality in patients with HIV with CA bacterial BSI
Archibald, 1998[5]	Urban Tanzania, 1995	Febrile (≥37·5°C) admission	282 (55%)	51 (18%)	NTS (45%), *Escherichia coli* (14%), *Streptococcus pneumoniae* (12%)	Not reported
Archibald, 2000[6]	Urban Malawi, 1997	Febrile (≥37·5°C) admissions	173 (74%)	37 (21%)	*S pneumoniae* (57%), NTS (30%)	Not reported
Arthur, 2001[7]	Urban Kenya, 1988–97	Hospital admission	436 (32%)	87 (20%)	NTS (46%), *S pneumoniae* (33%), *E coli* (6%)	39%
Bell, 2001[8]	Urban Malawi, 1998	Febrile (37·5°C) admissions	173 (73%)	36 (21%)	NTS (62%), *E coli* (7%), *Salmonella* Typhi (7%)	Not reported
Crump, 2011[9]	Rural Tanzania, 2007–08	Febrile (≥38°C) admissions	161 (40%)	26 (16%)	*S pneumoniae* (54%), *E coli* (12%), NTS (8%), *S* Typhi (8%)	Not reported
Grant, 1997[10]	Ivory coast, 1995	Admission to the infectious disease unit	198 (79%)	39 (20%)	NTS (59%), *E coli* (15%), *S pneumoniae* (10%)	46%
Mayanja, 2010[11]	Rural Uganda, 1996–2007	Fever (≥38°C) with no detectable malaria parasites	488 (64%)	152 (31%)	*S pneumoniae* (43%), NTS (26%), *E coli* (6%)	Not reported
Meremo, 2012[12]	Urban Tanzania, 2011	Hospital admission with fever (>37·5°C)	156 (45%)	16 (10%)	NTS (75%)	35%
Nadjm, 2012[13]	Rural Tanzania, 2007	Fever and one severity criterion	69 (35%)	12 (17%)	NTS (25%), *S pneumoniae* (25%), *Streptococcus pyogenes* (17%)	25%
Peters, 2004[14]	Urban Malawi, 2000	Admission with fever (≥37·4°C) or history of fever in the past 4 days	291 (83%)	66 (23%)	NTS (67%), *S pneumoniae* (20%), *E coli* (6%)	Not reported
Ssali, 1998[15]	Uganda, 1997	Admission with fever (>38°C)	222 (76%)	33 (15%)	*Salmonella* spp (39%), *S pneumoniae* (33%)	Not reported

Data was derived from prospective observational studies, which were previously described by Huson and colleagues.[3] CA=community acquired. BSI=bloodstream infection. NTS=non-typhoidal salmonella.

Table 1: **Burden of community-acquired bacterial bloodstream infections in patients with HIV in African countries where HIV is highly prevalent**

antibacterial immune responses through the ability to directly lyse infected cells, provide early sources of proinflammatory cytokines, predominantly interferon-γ, induce dendritic cell maturation, and amplify the proinflammatory effects of myeloid cells.[25,26] Likewise, natural killer T cells (NK T cells), a subset that shares cell-surface proteins with conventional T cells and NK cells, have been implicated in sepsis pathogenesis because of their strong proinflammatory cytokine release.[27] Recruited neutrophils form an additional important first line of defence against invading pathogens. They kill microbes through phagocytosis, the release of lytic enzymes from their granules, the production of reactive oxygen intermediates, and the formation of neutrophil extracellular traps (NETs)—lattices of chromatin decorated with antimicrobial proteins with strong bactericidal capacity.[28]

The innate immune system is thought to be mostly responsible for the excessive release of proinflammatory cytokines early in sepsis pathogenesis.[29] The most extensively studied proinflammatory cytokines in sepsis are tumour necrosis factor α (TNFα) and interleukin 1β, both of which are capable of activating target cells and induce the production of more inflammatory mediators.[29] Additionally, host cells release damage-associated molecular patterns (DAMPs) in response to pathogens or injury, which are recognised by PRRs, thereby enhancing immune activation. The most investigated DAMP is HMGB1, which signals via TLR2, TLR4, and TLR9 to induce cytokine release, activation of coagulation, and neutrophil recruitment.[30] Proinflammatory cytokines and DAMPs seem to have a double role in sepsis pathogenesis; they are essential for an adequate innate defence during early stage infection, but also contribute to hyperinflammation during late phase uncontrolled infection.[20,21] In patients with severe sepsis and in murine sepsis models, high concentrations of interleukins 1, 6, 8, and 17, CCL2, CSF3, and HMGB1 are associated with mortality.[29]

HIV affects the first lines of defence in several ways. First, defects of epithelial barriers are common and have been particularly well described for the gut. In the gut, HIV causes barrier defects during acute infection, which are maintained during chronic infection, thereby enabling invasive infections by intestinal pathogens such as non-typhoidal salmonella.[31] Furthermore, microbial products that translocate into the circulation fuel chronic immune activation and exhaustion.[32]

Toll-like receptors

HIV infection and AIDS are associated with increased TLR2, TLR3, TLR4, TLR7, and TLR9 expression on various cells, including T lymphocytes, monocytes, macrophages, and dendritic cells,[33–38] although one study[34] reported lower peripheral blood mononuclear cell (PBMC) RNA expression levels of TLR3, TLR4, and TLR9 in patients with chronic HIV unresponsive to cART. Reports on the functional effect of differential TLR expression are inconsistent. Ex-vivo studies with PBMCs from patients with HIV noted a correlation between increased expression of TLRs and increased TNFα production after stimulation with lipopolysaccharide, a