The effect of stage of HIV disease as determined by CD4 count on clinical outcomes of surgical sepsis in South Africa

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ABSTRACT

INTRODUCTION This paper reviews the impact of the stage of human immunodeficiency virus (HIV) disease on the outcome of surgical sepsis.

METHODS All adult emergency general surgical patients (aged >15 years) who fulfilled the criteria for sepsis or septic shock, with a documented surgical source of infection, and who were HIV positive were reviewed.

RESULTS During the 5-year study period, a total of 675 patients with a documented surgical source of sepsis were managed by our service; 142 (21%) of these were HIV positive. Among the individuals who were HIV positive, the CD4 count was <200 cells/μl in 21 patients and ≥200 cells/μl in 121 patients. There was no difference between these two cohorts in terms of demography or spectrum of surgical conditions. The range of surgical procedures and complications was also similar in both groups. Nevertheless, patients with a CD count of <200 cells/μl had a significantly longer length of hospital stay than those in the cohort with ≥200 cells/μl. For HIV positive patients with a CD4 count of <200 cells/μl, the mortality rate was 66.7% (14/21) while the mortality rate for individuals with HIV and a CD4 count of ≥200 cells/μl was 2.5% (2/121). This difference was statistically significant ($p<0.001$).

CONCLUSIONS The clinical presentation and spectrum of surgical sepsis disease in cases with stage 1 and stage 2 HIV is not markedly different. However, in patients with a CD4 count of <200 cells/μl, the length of hospital stay and mortality is significantly higher. Stage of HIV disease must be considered when stratifying patients' risk for surgery.

KEYWORDS

HIV – Stage – CD4 count – Sepsis – Outcome

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The human immunodeficiency virus (HIV) epidemic has now existed for over three and a half decades. During this time, the prevalence in sub-Saharan Africa has remained one of the highest in the world, accounting for approximately 70% of the global burden of this disease.¹ KwaZulu-Natal province in South Africa has long been the epicentre of this pandemic.^{2–7} During the early days of the spread of the virus, the pathophysiology of the immunological impairment associated with HIV was poorly understood and there was no effective therapy available. It has also become increasingly recognised that patient outcomes differ according to the degree of immunosuppression they are experiencing.

One of the first studies to identify this was a controversial study from our parent institution, King Edward VIII Hospital in Durban, over 20 years ago.^{2,5} Heavily criticised at the time, it prospectively investigated the impact of HIV status on the outcome of critical illness. Contrary to what was expected, the findings suggested that being HIV positive actually conferred a slight survival advantage on critically ill patients. The authors felt that a limited degree of

immunosuppression may actually attenuate the septic response seen in critical illness. They drew the distinction between being HIV positive and immune competent, and the full blown immunological impairment that is seen in patients with acquired immunodeficiency syndrome (AIDS).

As a result of the tremendous amount of research on the disease over the last three decades, the actual pathophysiology is now better understood.^{8–11} Since that time, a massive coordinated effort has been put into combating HIV. It is now accepted that there is a major clinical difference between being HIV positive and having AIDS.^{2–7} Our study attempts to assess the impact of the stage of HIV disease on the outcome of patients with surgical sepsis.

Methods

This was a retrospective study undertaken at the Pietermaritzburg Metropolitan Surgical Service (PMSS) in South Africa. Our regional electronic registry¹² was reviewed over a five-year period (January 2010 – December 2014). Ethics

approval for this study and for the maintenance of the registry was provided by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Department of Health. KwaZulu-Natal is located on the east coast and has a population of over 11 million people. Fifty per cent of the population lives in the rural areas. The PMSS provides definitive surgical care to the city of Pietermaritzburg, the capital of KwaZulu-Natal province. It also serves as the referral centre for 19 other rural hospitals in the western part of the province, with a total catchment population of over 3 million people.

In April 2014 the US Centers for Disease Control (CDC) published the *Revised Surveillance Case Definition for HIV Infection*.¹⁰ According to the CDC staging system, a patient who is confirmed to be HIV positive is grouped into one of five infection stages (0, 1, 2, 3 or unknown).

Classification is usually based on CD4 count; adults with <200 cells/μl are deemed to have stage 3 HIV, those with 200–499 cells/μl are deemed to be stage 2 and those with ≥500 cells/μl are deemed to be stage 1.¹⁰ If an individual has tested negative for HIV at some point in the preceding six months and is now testing positive, he or she is classed as stage 0. This stage persists for six months following diagnosis. In addition, the stage is not based on CD4 count if the criteria for stage 0 are not met and the patient has an opportunistic infection; in this case, the individual is deemed to have stage 3 disease, regardless of the CD4 results.

All adult emergency general surgical patients (aged >15 years) admitted by the PMSS who fulfilled the criteria for sepsis or septic shock, with a documented surgical source of infection, were reviewed. Only those with laboratory documentation of positive HIV status were included in the study. Information obtained from the registry and patient medical records were all part of their routine clinical care. Data reviewed from the registry included basic demographic information, admission physiological parameters and

diagnosis. Clinical outcomes were described in terms of length of hospital stay, morbidity and mortality. Morbidities were grouped by organ systems (eg hospital acquired pneumonia was classified as a respiratory complication). Surgical pathologies were categorised as intra-abdominal sepsis, limb sepsis or soft tissues sepsis. All patients were staged according to their CD4 counts (<200 cells/μl indicating stage 2 and ≥200 cells/μl stage 3 disease).

Statistical analysis

Data were processed and analysed using Stata® version 13.0 (StataCorp, College Station, TX, US). Continuous variables were summarised using mean and standard deviation (SD). If there was evidence of skewing/asymmetrical outliers, then the median and interquartile range were used instead. Associations between CD4 groups and categorical explanatory variables were assessed using the Pearson chi-squared test (or Fisher's exact test if the expected cell count was <5). Differences in means/rank of continuous variables by CD4 group were assessed using Student's t-test and the Mann-Whitney U test respectively.

Results

During the 5-year study period, 675 patients with a documented surgical source of sepsis were reviewed; 142 (21%) were HIV positive. Among those with HIV, the CD4 count was <200 in 21 patients and ≥200 in 121 patients. Table 1 compares the two cohorts according to demography and baseline characteristics. The groups were similar in terms of age and sex distribution. Table 2 summarises the spectrum of surgical pathology in both cohorts. There were no major differences between the two groups. Table 3 lists the operative procedures undertaken. There was no difference between the cohorts with regard to the range of surgical procedures performed.

Table 1 Patient demographics and characteristics

	CD4 <200 cells/μl (n=21)	CD4 ≥200 cells/μl (n=121)	p-value
Median age in years	33 (IQR: 26–44)	36 (IQR: 29–43)	0.845
Male	14 (67%)	45 (37%)	0.145
Female	7 (33%)	76 (63%)	
Urban	7 (33%)	57 (47%)	0.516
Rural	14 (67%)	64 (53%)	
Smoker	4 (15%)	19 (16%)	0.638
Alcohol use	6 (22%)	20 (17%)	0.675
Antiretroviral therapy	14 (51%)	69 (57%)	0.925
Active tuberculosis	8 (30%)	28 (23%)	0.997
Median CD4 count in cells/μl	115 (IQR: 82–150)	504 (IQR: 339–600)	–
Mean CD4 count in cells/μl	112 (SD: 51)	500 (SD: 153)	–
IQR = interquartile range; SD = standard deviation			

Table 2 Surgical pathology			
	CD4 <200 cells/μl (n=21)	CD4 ≥200 cells/μl (n=121)	p-value
Appendicitis	3 (14.3%)	31 (25.6%)	0.103
Abdominal tuberculosis	5 (23.8%)	9 (7.4%)	
Biliary sepsis	2 (9.5%)	11 (9.1%)	
Diabetic foot sepsis	0 (0%)	6 (4.9%)	
Non-diabetic foot sepsis	1 (4.8%)	9 (7.4%)	
Perforated peptic ulcer	2 (9.5%)	9 (7.4%)	
Soft tissue necrotising fasciitis	2 (9.5%)	7 (5.8%)	
Pelvic inflammatory disease	0 (0%)	7 (5.8%)	
Head and neck abscess	0 (0%)	6 (4.9%)	
Intra-abdominal abscess	1 (4.8%)	5 (4.1%)	
Perianal abscess	1 (4.8%)	4 (3.3%)	
Trunk abscess	1 (4.8%)	2 (1.7%)	
Limb abscess	1 (4.8%)	3 (2.5%)	
Other intra-abdominal sepsis*	2 (9.5%)	12 (9.9%)	
*Includes traumatic and non-traumatic small and large bowel perforation with faecal contamination of the abdominal cavity at the time of presentation			

Table 3 Surgical procedures performed			
	CD4 <200 cells/μl (n=21)	CD4 ≥200 cells/μl (n=121)	p-value
Amputation	1 (4.7%)	13 (10.7%)	0.514
Soft tissue debridement	2 (9.5%)	5 (4.1%)	
Endoscopic retrograde cholangiopancreatography	1 (4.7%)	2 (1.7%)	
Incision and drainage	2 (9.5%)	15 (12.4%)	
Interventional radiology	0 (0%)	6 (5.0%)	
Laparoscopic cholecystectomy	0 (0%)	2 (1.7%)	
Laparotomy	14 (66.7%)	55 (45.4%)	
Open cholecystectomy	0 (0%)	1 (0.8%)	
Open appendectomy	0 (0%)	3 (2.5%)	
No surgical management	1 (4.7%)	19 (15.7%)	

Outcome by CD4 count

Table 4 summarises the complications, length of hospital stay and mortality in the study population. The spectrum of complications was similar in both cohorts. However, patients in the CD4 <200 cells/μl group had a significantly longer length of stay than those in the cohort with ≥200 cells/μl. Among patients who had a CD4 count of <200 cells/μl, mortality was 66.7% (14/21) while the mortality rate for those with a CD4 count of ≥200 cells/μl was 2.5% (3/121). This was highly statistically significant ($p<0.001$).

Discussion

The high prevalence of HIV disease in KwaZulu-Natal means that a significant number of patients who present with an acute surgical illness will have concomitant HIV coinfection.²⁻⁷ In addition, individuals who are HIV positive may present with a surgical complication of their chronic immunosuppressed state. Immunosuppression results in opportunistic infections such as tuberculosis and a number of viral infections as well as atypical malignancies (eg Kaposi's sarcoma). Treatment with highly active antiretroviral

Table 4 Complications, LOS and mortality

	CD4 <200 cells/ μ l (13/21 patients had complications*)	CD4 $\geq$ 200 cells/ μ l (35/121 patients had complications*)	p-value
Abdominal complications	2 (15.4%)	9 (25.7%)	1.000
Cardiac complications	1 (7.7%)	1 (2.9%)	0.314
Neurological complications	0 (0%)	0 (0%)	–
Renal complications	3 (23.1%)	8 (22.9%)	0.401
Respiratory complications	4 (30.8%)	12 (34.3%)	0.479
Urinary complications	0 (0%)	0 (0%)	–
Wound complications	2 (15.4%)	14 (40.0%)	1.000
Other complications	10 (76.9%)	4 (11.4%)	<0.001
Mean LOS in hospital	5 days (SD: 3 days)	9 days (SD: 8 days)	0.012
Median LOS in hospital	4 days (IQR: 3–6 days)	7 days (IQR: 4–13 days)	0.015
Mortality	14/21 (66.7%)	3/121 (2.5%)	<0.001

IQR = interquartile range; LOS = length of stay; SD = standard deviation
 *Some patients had complications involving more than one organ system.

therapy (HAART) decreases viral replication and increases CD4+ recovery, thereby reducing morbidity and mortality associated with HIV/AIDS. Although HAART leads to fewer opportunistic infections and decreased rates of hospitalisation, intensive care unit admission rates in the HAART era remain constant or have increased.¹⁵ However, in sub-Saharan Africa, most HIV infected patients present late for treatment, resulting in mortality rates that are higher than those in developing countries.¹⁴

It is believed that the main causes of the high mortality in African patients who are commenced on HAART are low CD4 counts and co-morbidities, especially tuberculosis.¹⁵ Only a small proportion of these deaths are attributed to toxicity of the antiretroviral drugs.^{14,15} Of note in our study, very few patients presented with specific surgical complications of their immunosuppressed state. The most common HIV associated cause of surgical sepsis in the PMSS is abdominal tuberculosis. This is consistent with the literature in that tuberculosis is by far the most widespread opportunistic infection associated with HIV disease in Africa.^{5–7} None of our cases had any complications of cytomegalovirus or atypical HIV associated malignancies. This is a somewhat unusual observation as it is not uncommon for patients in the PMSS to present with other specific HIV related diseases such as vasculopathy, nephropathy or cholangiopathy.^{4–7}

The CD4 lymphocyte is targeted directly by HIV and for that reason, the CD4 count can be used as a marker for the progressive immunological deterioration that eventually leads to the development of AIDS in HIV positive patients. The CDC staging system determines the severity of HIV disease based on CD4 cell counts and the presence of specific HIV related conditions. According to the CDC, the definition of AIDS includes all HIV infected individuals with CD4 counts of <200 cells/ μ l as well as those with so called disease defining conditions.¹⁰ The World Health Organization

staging system differs from the CDC system as it is predominantly based on the presence of clinical features of opportunistic infections and malignancies.¹¹ It was designed for use by staff with a heterogeneous degree of expertise and training in resource constrained settings.

The results of our study supports the use of the CDC classification in the PMSS. Apart from abdominal tuberculosis, AIDS defining opportunistic infections or malignancies were uncommon in our cohort. In addition, our data show clearly that worsening stage of HIV disease as determined by CD4 count correlates with deteriorating clinical outcomes. Patients with a low CD4 count had longer hospital stays and a significantly greater chance of death than those whose CD4 counts were $\geq$ 200 cells/ μ l.

The management of patients with a surgical disease and HIV coinfection remains contentious. Initially, there were concerns that HIV coinfection would place surgical patients at a prohibitively high risk of major morbidity.^{16–18} This may well have translated into a minimalistic (and ultimately fatalistic) approach to individuals with acute surgical emergencies.

This view was challenged by Bhagwanjee *et al.*^{2,3} In their controversial prospective trial, HIV coinfection actually appeared to offer a slight protective advantage to patients admitted to the surgical intensive care unit. It was postulated that the immunosuppression inherent in HIV infection dampened the septic response to critical illness. The authors felt that the stage of HIV disease may have an impact clinical outcome. In another study a decade later by Cacala *et al* at our sister institution, Prince Mshiyeni Memorial Hospital in Durban, it was concluded that HIV status does not affect the outcome of general surgical admissions and should therefore not influence management decisions.⁴ However, our study suggests that the clinical staging of HIV disease is important in assisting clinicians decide on management

strategies for acute surgical patients with HIV. Indeed, a more nuanced outlook has been adopted over the last three decades based on the CD4 count.^{16–25}

In general, CD4 count can be regarded as a good proxy marker for immune function. This is clinically significant as a significant difference in outcome was noted in our study between HIV patients with a CD4 count of <200 cells/μl and those with counts of ≥200 cells/μl. HIV infected individuals with surgical sepsis who have a CD4 count of <200 cells/μl are 36 times more likely to die than those who have a CD4 count of ≥200 cells/μl. This is very much in keeping with international reports over the last three decades.^{16–25} Our study shows that stage of HIV infection impacts significantly on the outcome of surgery for sepsis, and that the CDC system of staging HIV is accurate and useful in the assessment of patients requiring surgery.^{8,9}

Conclusions

The clinical presentation and spectrum of surgical sepsis disease in patients with stage 1 and stage 2 HIV is not markedly different. However, in individuals with a CD4 count of <200 cells/μl, which defines stage 3 disease, the length of hospital stay and mortality is significantly higher. Stage of HIV disease must be considered when stratifying patients' risk for surgery.

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