RETROSPECTIVE COMPARISON OF EMPYEMA THORACIS IN HIV INFECTED AND NON-INFECTED PATIENTS WITH REGARDS TO AETIOLOGY AND OUTCOMES

Dr Grace Helga Kaye-Eddie

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Masters of Medicine in the branch of Internal Medicine.

Johannesburg 2012

DECLARATION

I, Grace Helga Kaye-Eddie, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine in the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

_____

Grace Helga Kaye-Eddie

The _____ day of _____ , 2012

DEDICATION

Dedicated to my husband, Brandon, and my family, without whose love and support this research report would have seemed insurmountable.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Conference Oral Presentations

Kaye-Eddie GH. Retrospective Comparison of Empyema Thoracis in HIV infected and non-infected patients with regards to aetiology and outcomes.

Oral presentation at Copicon 3 CCSSA and SATS Congress held in August 2009 at Sun City, North West Province, South Africa. Abstract Number 12, South African Respiratory Journal: 2009; 15(3): 97.

Papers accepted for Publication

Kaye-Eddie GH, Black AD. Comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and outcome.

The above-mentioned manuscript has been accepted for publication by the South African Journal of Epidemiology and Infection.

ABSTRACT

Background

HIV is a risk factor for empyema. HIV-infected patients with empyema appear to have worse outcomes. This study assessed whether HIV infection affected aetiology or outcomes of patients with empyema.

Methods

A retrospective study of patients with empyema admitted to CHBAH from January 2006 to December 2009 was conducted. HIV-infected and non-infected patients were evaluated for differences in aetiology and outcomes. Sub-analysis according to CD4 counts and antiretroviral use in HIV-infected patients was performed.

Results

0f 172 patients, 125 (73%) were HIV-infected. HIV infected patients with lower CD4 counts were more often diagnosed with clinical tuberculosis ($p<0.05$). Aetiology of empyema was frequently not determined in HIV non-infected patients ($p<0.05$). More patients on antiretrovirals underwent thoracic surgery ($p<0.05$) and had shorter hospital stays than those not on antiretrovirals ($p<0.05$).

Conclusions

No differences in empyema aetiology among HIV-infected versus non-infected patients were found. Antiretroviral use was associated with improved outcomes.

ACKNOWLEDGEMENTS

Thank you to my supervisor, Dr Andrew Black, for your invaluable expertise and constant encouragement. You have been my mentor and my friend and I will always be grateful for all you have taught me.

Thank you to Dr Vivian Black for the many hours you set aside to edit my numerous manuscripts.

Thank you to Prof. Wong for allowing me access to the Respiratory unit's database.

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ABBREVIATIONS

HIV	Human Immunodeficiency Virus
CHBAH	Chris Hani Baragwanath Academic Hospital
TB	Tuberculosis
NTM	Non-tuberculous mycobacteria
AFB	Acid-Fast bacilli
MTB	*Mycobacterium tuberculosis*
ART	Antiretroviral therapy

INTRODUCTION

Empyema thoracis; the presence of pus in the pleural space,[1, 2, 3] remains a problem in developing countries,[4] its course is often prolonged and frequently requires surgical drainage. HIV infection is a risk factor for empyema[1] and complicates pneumonia more frequently in HIV infected patients.[5] Reported risk factors for the development of empyema include serum albumin <30 g/dl, intravenous drug use, ethanol abuse, younger age, male sex and current smoking. [6]

In our experience, the majority of patients with empyema are HIV infected and present with late stages of empyema. Despite expected low success rates of closed tube thoracostomy in the treatment of late empyema[7] it remains first-line therapy at our hospital as cardiothoracic services are limited and many patients are critically ill and unable to tolerate aggressive surgical procedures.

There is an impression that HIV infected patients do worse clinically. Limited literature exists to support this, some reports claim patients with CD4 counts <200 cells/mm^3 have higher complication rates and a poorer prognosis.[5]

This study compares microbiological aetiology, outcomes including; length of stay, whether surgical intervention was offered and local complications of tube thoracostomy, in patients with empyema according to HIV status. A secondary objective is to compare aetiology and outcomes in patients with HIV infection stratified according to CD4 cell count (≥200 cells/mm^3 or <200 cells/mm^3) and antiretroviral usage.

METHODS

CHBAH is a large academic hospital in Soweto Johannesburg, with 847 medical beds. It is the only in-patient facility for the greater Soweto area and serves as a referral centre for Southern Gauteng and the North West Province. The CHBAH Respiratory Unit database from January 2006 to December 2009 was reviewed. An Excel (Microsoft Corporation, Bellevue, WA) database was compiled from discharge summaries and case notes of patients referred to the Respiratory Unit. Permission to use the database was obtained from the database manager and permission to conduct this review was obtained by the Human Research Ethics committee of the University of the Witwatersrand.

Patients meeting at least one of the established criteria of empyema; a) aspiration of pus from the pleural space, b) pleural fluid pH <7.2 or pleural fluid glucose <3.4 mmol/l, or c) positive microbial stain and/or culture, [1, 2] were included.

Patients were divided into aetiological groups based upon initial pleural fluid results: [1] proven tuberculosis (TB), [2] clinical TB, [3] dual (TB and bacterial infection), [4] bacterial, [5] non-tuberculous mycobacteria (NTM) and [5] unknown. For proven TB either pleural fluid or sputum samples demonstrated Acid-Fast Bacilli (AFB) on microscopy and/or cultured *Mycobacterium tuberculosis*, or pleural biopsy demonstrated histological features of tuberculous infection. Patients with radiological features of TB, those in whom clinical suspicion of TB existed or responded to a trial of anti-tuberculous therapy were classified as clinical TB. Patients diagnosed with proven TB who also cultured a bacterial organism in their pleural fluid were classified as dual. Patients with bacterial infections were subdivided into Gram-positive, Gram-negative and polymicrobial infections. Patients in whom pleural

fluid analysis or histology failed to identify a microbiological aetiology were classified as unknown.

Outcomes were defined as: [1] resolution of empyema via closed tube thoracostomy in ≤14 days, [2] resolution of empyema via closed tube thoracostomy but requiring insertion of multiple tubes or prolonged drainage (>14 days), [3] long-term open tube thoracostomy, [4] cardiothoracic intervention and [5] death. Length of stay was compared among each group.

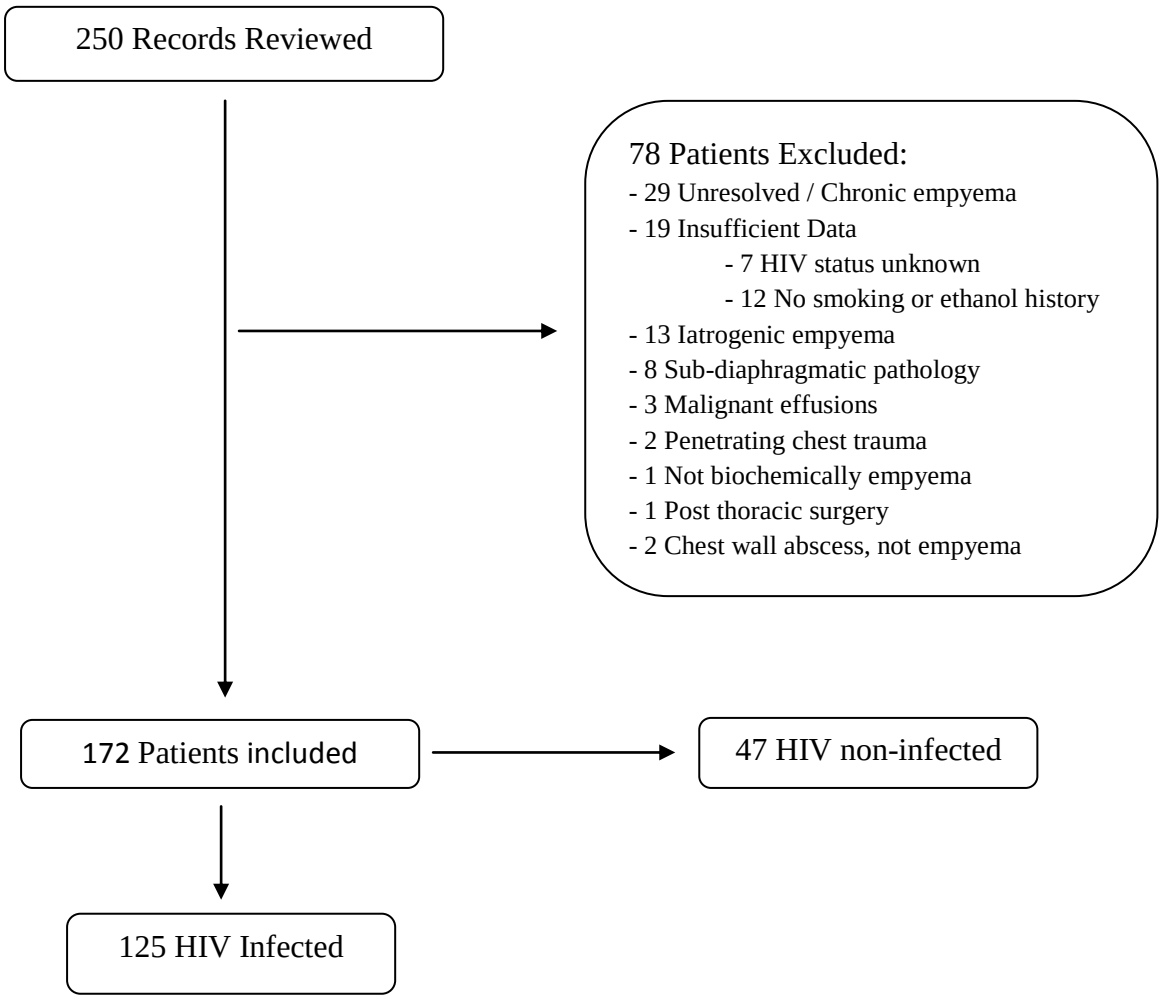
Complications were defined as: [1] wound sepsis at tube thoracostomy site and [2] secondary infection of the pleural space.

Statistical analysis was performed using STATA 10 software (StataCorp LP, College Station, Texas). Univariate analyses were performed in each of the groups against known risk factors for empyema; age, smoking, ethanol abuse and male sex. Association between categorical variables were tested using Fisher's exact test, odds ratios and 95% confidence intervals were calculated. Continuous variables with parametric distributions were tested with the student's t-test, those with nonparametric distributions with the Wilcoxon Rank Sum test. Where significance of risk factors was found between groups on univariate analysis, they were further analysed using multivariate regression. Significance was considered as a P value of <0.05.

RESULTS

Two hundred and fifty records were reviewed, 78 patients were excluded (fig 3.1). The 29 patients excluded for chronic/unresolved empyema were patients that had been previously admitted for primary empyema, prior to the start date of the study, and had returned with complications during the study period. We felt that inclusion of these patients would create bias.

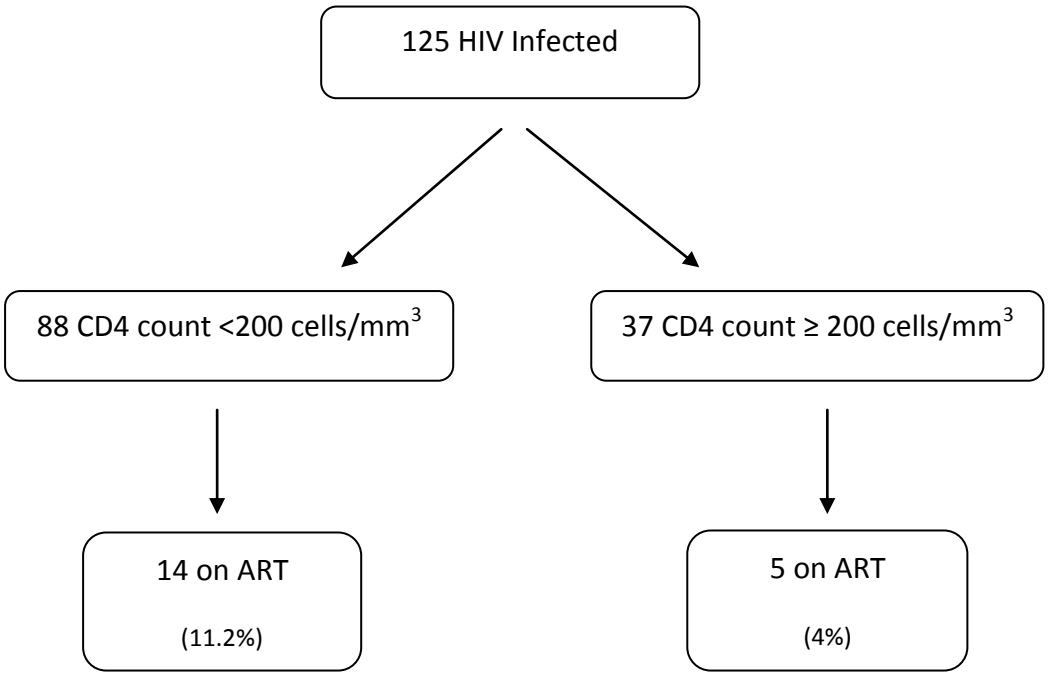
Figure 3.1



Flowchart summarising patient inclusion.

In total 172 patients were included, mean age was 39 (14-78). The study group comprised 110 (64%) males. Using all cause admissions to the medical wards during the study period, it was found that males were at greater risk of developing empyema ($p < 0.05$, OR 2.40, 95% CI 2.00-2.88). HIV infection was present in 125 (73%) patients with empyema. Amongst the HIV infected group, median CD4 count was 128 cells/mm^3 (1-885 cells/mm^3, IQR 62-219 cells/mm^3), 88 (70.4%) had a CD4 count <200 cells/mm^3 and 19 (15.2%) were on antiretroviral therapy (fig 3.2).

Figure 3.2



Flowchart summarising HIV infected patients' characteristics

With regards the reported risk factors for the development of empyema, statistical differences were found among the HIV infected and non-infected groups for age ($p < 0.05$), with

empyema occurring amongst younger patients with HIV, and sex ($p < 0.05$), with HIV infected males having a greater risk of developing empyema. In HIV infected patients stratified according to CD4 cell count, ethanol abuse was found to be a significant risk factor in the group with CD4 cell counts ≥ 200 cells/mm^3 ($p < 0.05$). No differences in risk factors were found in HIV infected patients stratified according to antiretroviral usage.

Microbiological aetiologies were as follows; 34 (19.8%) patients had proven TB, 34 (19.8%) had clinical TB, 8 (4.7%) had dual infections, 55 (32%) had bacterial infections, 1 (0.6%) had NTM infection, and in 40 (23.3%), no microbiological aetiology was identified. One patient cultured both *Streptococcus pneumoniae* and NTM and was classified as bacterial. We report 5 cases of Salmonella non-typhi empyema, all five patients were HIV infected; four had CD4 counts <100 cells/mm^3, the fifth was on antiretroviral therapy with a CD4 count of 118 cells/mm^3. Pleural fluid cultured *Salmonella* spp. in all five, in one *Salmonella* spp. was also cultured on sputum (Table 3.1).

With regards aetiology; HIV non-infected patients more often had no identifiable microbiological aetiology identified ($p < 0.05$, OR 0.18, CI 0.08-0.40) whereas HIV infected patients with lower CD4 cell counts had a significantly greater likelihood of being diagnosed with clinical TB ($p < 0.05$, OR 2.98, CI 1.22-7.3) and showed a trend towards having a greater incidence of infections caused by Gram-negative organisms (OR 10.6). Antiretroviral therapy did not alter the aetiology of empyema in this series (Table 3.2).

Table 3.1

Microbiological aetiologies by HIV Status

	HIV Positive (n=125)	HIV Negative (n=47)
* Proven Tuberculosis:	34 (27.2%)	8 (17%)
Pleural Fluid Microscopy AFB positive	7 (20.6%)	0
Pleural Fluid culture MTB positive	18 (53.0%)	1 (12.5%)
Sputum Microscopy AFB positive	12 (35.5%)	4 (50%)
Sputum Culture MTB positive	9 (26.5%)	2 (25%)
Blood Culture MTB positive	3 (8.8%)	0
Pleural Biopsy consistent with tuberculosis	2 (5.9%)	2 (25%)
Clinical Tuberculosis:	27 (21.6%)	7 (14.9%)
* Bacterial Infection:	53 (42.4%)	10 (21.3%)
S. pneumoniae	22 (41.5%)	3 (30%)
S. anginosus (formerly *S. milleri*)	5 (9.4%)	5 (50%)
K. pneumonia	5 (9.4%)	1 (10%)
Salmonella spp.	5 (9.4%)	0
S. aureus	3 (5.7%)	0
Peptostreptococcus spp.	3 (5.7%)	1 (10%)
E. coli	3 (5.7%)	0
Prevotella spp.	2 (3.8%)	3 (30%)
Nocardia spp.	2 (3.8%)	0
H. influenza	2 (3.8%)	0
P. mirabilis	2 (3.8%)	0
P. aeruginosa	2 (3.8%)	0
E. faecium	1 (1.9%)	0
E. faecalis	1 (1.9%)	0
S. viridans	1 (1.9%)	0
S. pyogenes	1 (1.9%)	0
A. baumannii	1 (1.9%)	0
Streptococcus Group F	1 (1.9%)	0
Streptococcus Group C	0	1 (10%)
Non-tuberculous mycobacteria:	1 (0.8%)	0
Mycobacterium avium-intracellulare complex	1 (0.8%)	0
Unknown:	18 (14.4%)	22 (46.8%)

MTB = *Mycobacterium tuberculosis*

* Includes those with dual infection.
Proof of MTB often obtained by more than one method.
Polymicrobial infection in 13 patients.

Table 3.2

Differences in aetiology of empyema

			P	OR (95% CI)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
Proven tuberculosis	8	34	>0.05	1.29 (0.52 – 3.2)
Clinical tuberculosis	7	27	>0.05	1.71 (0.65 – 4.45)
Dual Infection	0	8	*	*
Bacterial Infection	10	45	>0.05	2.10 (0.91 – 4.82)
- Gram-positive	5	31	>0.05	0.94 (0.21 – 4.30)
- Gram-negative	1	13	>0.05	10.60 (0.72 – 156.07)
- Polymicrobial	4	9	>0.05	0.25 (0.51 – 1.27)
Non-tuberculous mycobacteria	0	1	*	*
Unknown aetiology	22	18	<0.05	0.18 (0.08 – 0.40)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
Proven tuberculosis	26	8	>0.05	0.36 (0.11 – 1.37)
Clinical tuberculosis	14	13	<0.05	2.98 (1.22 – 7.30)
Dual Infection	4	4	>0.05	2.33 (0.54 – 10.07)
Bacterial Infection	36	9	>0.05	0.46 (0.19 – 1.09)
Non-tuberculous mycobacteria	1	0	*	*
Unknown aetiology	11	7	>0.05	1.75 (0.61 – 5.00)
¤ ART versus no ART:	ART (n=19)	No ART (n=106)		
Proven tuberculosis	6	28	>0.05	1.29 (0.36 – 4.06)
Clinical tuberculosis	7	20	>0.05	2.51 (0.73 – 7.94)
Dual Infection	0	8	*	*
Bacterial Infection	3	42	>0.05	0.29 (0.05 – 1.10)
Non-tuberculous mycobacteria	0	1	*	*
Unknown aetiology	3	15	>0.05	1.14 (0.19 – 4.72)

ART = Antiretroviral therapy

* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.

† Adjusted in logistic regression analysis for age and sex.

‡ Adjusted in logistic regression analysis for ethanol abuse.

¤ Univariate analysis using 2-tailed Fisher's exact test.

Tube thoracostomas were inserted in the general medical wards in all but 11 (6.4%) patients; 6 (3.5%) were transferred to cardiothoracic surgeons as their pleural collections were not amenable to tube thoracostomy, 3 (1.8%) had very small collections which were treated medically and 2 (1.2%) refused further hospital treatment.

Following closed tube thoracostomy; 16 (10%) patients had complete resolution of empyema within 14 days, 34 (20.4%) had resolution with prolonged drainage or multiple tubes. Following 14 days of closed tube thoracostomy, 47 (28.1%) were discharged home with an open tube thoracostoma; 14 (29.8%) of these following basal tube insertion by cardiothoracic surgeons. Thirty eight (22.8%) patients underwent cardiothoracic surgery; 35 had pleural toilette and basal tube insertion with subsequent resolution, 1 had a decortication, and 2 required surgical thoracostomy. Prior to resolution of empyema a further 12 (7%) patients refused further treatment and discharged themselves from hospital.

Of the patients converted to open tube thoracostomy; 6 (12.8%) were followed up by cardiothoracic services, 11 (23.4%) had resolution of empyema, 23 (48.9%) defaulted follow up, 5 (10.6%) were transferred to cardiothoracic surgeons for a procedure; toilette, decortication, thoracostomy or thoracoplasty and 2 (4.3%) demised due to ongoing pleural sepsis.

Overall length of stay was a median of 29 days (3-118 days). No differences were found with regards to length of stay between HIV infected and non-infected patients or between those stratified according to CD4 cell count. Patients on antiretroviral therapy had significantly shorter lengths of stay than those not on antiretroviral therapy.

Patients were evaluated for development of complications; 4 (2.4%) developed wound sepsis at tube thoracostomy site and 26 (15.6%) developed secondary infection of their pleural space. Mortality in this series was 12.8% (22/172), 20 patients died in the medical wards and 2 died post surgical intervention.

Regarding outcomes and complications; HIV infected patients on antiretrovirals are more likely to be offered cardiothoracic intervention ($p < 0.05$, OR3.43, CI 1.03-10.90). Length of stay was shorter ($p < 0.05$) and, though not statistically significant, there were no mortalities amongst patients on antiretroviral therapy. No other differences were found between the various groups (Table 3.3).

Table 3.3

Differences in outcomes and complications of empyema

			P	OR (95%)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
§ Length of stay	27 (4 – 94)	29 (3 – 118)	>0.05	
Resolution Simple	4	12	>0.05	0.83 (0.24 – 2.88)
Resolution Complicated	8	26	>0.05	1.38 (0.54 – 3.52)
Long term open tube thoracostomy	13	32	>0.05	0.90 (0.41 – 1.99)
Surgical intervention	12	26	>0.05	1.13 (0.31 – 1.62)
Death	6	16	>0.05	0.78 (0.40 – 3.40)
Wound sepsis at tube thoracostomy site	1	3	>0.05	1.21 (0.10 – 14.72)
Secondary infection of pleural space	5	21	>0.05	2.19 (0.71 – 6.71)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
§ Length of stay	29 (4 – 118)	31 (3 – 88)	>0.05	
Resolution Simple	8	4	>0.05	1.14 (0.32 – 4.09)
Resolution Complicated	18	8	>0.05	1.11 (0.43 – 2.90)
Long term open tube thoracostomy	23	9	>0.05	0.99 (0.40 – 2.45)
Surgical intervention	18	8	>0.05	1.07 (0.42 – 2.75)
Death	14	2	>0.05	0.27 (0.06 – 1.30)
Wound sepsis at tube thoracostomy site	3	0	*	*
Secondary infection of pleural space	15	6	>0.05	1.00 (0.99 – 1.00)
¤ ART versus no ART:	ART (n=19)	No ART (n=106)		
§ Length of stay	37 (19 – 71)	27 (3 – 118)	<0.05	
Resolution Simple	1	11	>0.05	0.47 (0.01 – 3.60)
Resolution Complicated	4	22	>0.05	0.98 (0.22 – 3.52)
Long term open tube thoracostomy	5	27	>0.05	1.01 (0.26 – 3.32)
Surgical intervention	8	18	<0.05	3.43 (1.03 – 10.90)
Death	0	16	*	*
Wound sepsis at tube thoracostomy site	1	2	>0.05	2.89 (0.05 – 57.56)
Secondary infection of pleural space	2	19	>0.05	0.54 (0.06 – 2.61)

ART = Antiretroviral therapy

‡ Adjusted in logistic regression analysis for ethanol abuse, CD4 cell count only done for HIV.

* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.

† Adjusted in logistic regression analysis for age and sex.

¤ Univariate analysis using 2-tailed Fisher's exact test

§ Length of stay adjusted in linear regression analysis.

DISCUSSION

Empyema thoracis remains an important problem in South Africa. The majority of empyemas (>50%) are as a result of direct extension of a pulmonary parenchymal infection into the pleural space.[1, 3] Empyema in HIV infected patients is uncommon in developed countries despite the increased risk HIV infection confers to the development of respiratory infections.[8, 9] In this series, at an ecological level there appears to be a strong association between HIV infection and the development of empyema with a disproportionate number of patients with empyema being HIV infected.

The microbiology of empyema is vast. Common pathogens include *S. pneumoniae, Staphylococcus aureus, Streptococcus anginosus, Streptococcus pyogenes, Prevotella* spp. and *M. tuberculosis.*[3] Since the availability of antibiotics the bacteriology has changed; *S. pneumonia* and *S. pyogenes* infections occur less, and *S. aureus* and enteric Gram-negative organisms occur more frequently.[10, 11] Infections caused by Gram-negative organisms occur more frequently in HIV infected patients[8] and a trend was found in our series. Infection with non-typhoidal salmonella is well described in patients with advanced HIV infection,[12] bacteraemia occurs frequently however pleuropulmonary complications are rare, with empyema usually occurring in the setting of CD4 counts <100 cells/mm^3.[13, 14] The incidence of non-typhoidal salmonella reported in our series suggests that non-typhoidal salmonella should be considered potential aetiological organisms in HIV infected patients with low CD4 cell counts. The identification of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as causes of empyema is worrying and may reflect the increased contact HIV infected patients have with health facilities. There appears to be a resurgence of important

pathogens from the pre-antibiotic era in the presence of the HIV pandemic with *S. pneumonia* being the most frequent identified bacterial agent in the HIV infected patients in this series.

Tuberculous empyema has been reported at frequencies of 3-6% in developed countries,[7, 8, 15] however in developing countries TB accounts for up to 35% of cases.[4] In Southern Africa, the majority of patients with tuberculous empyema are HIV infected.[16] Rates of tuberculous empyema are higher in our series than those stated in developed countries; when combining the patients with proven and clinical TB, 44.2% of empyemas were attributed to tuberculous infection. HIV infected patients tend to be given the diagnosis of clinical TB when no microbiological aetiology is found despite extensive investigation, we attribute this to clinician bias in a community where rates of HIV and TB co-infection are high. Dual infections were only found in patients with HIV infection and occurred over a range of CD4 counts (39-382 cells/mm^3).

Pleural involvement is unusual with NTM; pleural thickening adjacent to pulmonary parenchymal infection is described, pleural effusions if present are small.[17, 18] Empyema is rare with only one report of a clearly documented empyema due to NTM in a patient with advanced acquired immunodeficiency syndrome.[19] NTM were cultured in two patients (*Mycobacterium avium-intracellulare* in one, failed identification of species in the other due to contamination), both were HIV infected with advanced disease; CD4 counts of 7 and 25 cells/mm^3 and neither was on antiretroviral therapy.

Despite thorough investigation no identifiable microbiological aetiology for empyema was identified in 23.3%; patients may have been treated with antibiotics prior to admission or specimens for anaerobic cultures may not have been optimally processed thus underreporting anaerobic infections. Anaerobic bacteria remain important pathogens in adults.[20] Rapid

transfer in oxygen-free media to the laboratory and adequate anaerobic culture techniques are vital to increase diagnostic sensitivity.[10]

The treatment of empyema depends upon the pathophysiological stage in which the patient presents. Empyemas in the exudative stage, may be successfully drained via closed tube thoracostomy.[7, 21, 22] Empyemas in the fibrinopurulent stage often require more aggressive drainage procedures or video-assisted thoracoscopy.[21, 22, 23] There is contradictory evidence on the use of intrapleural fibrinolytics; they may be used as an adjunct to closed tube thoracostomy however do not reduce mortality or the need for surgery.[24, 25] Thoracoscopic drainage procedures are popular; with less post operative pain, lower costs, shorter hospital stays and better cosmetic results.[24, 26] Optimal timing is important as high failure rates have been reported in cases with advanced empyema.[27, 28] Empyema in the organisational stage is best managed via open surgery; decortication, thoracostomy or thoracoplasty to manage extensive pleural peel or control the underlying inflammatory process.[7, 21, 23] Decortication remains the modality of choice for treating advanced empyema, thoracoplasty and thoracostoma are reserved for debilitated patients who cannot tolerate aggressive surgery or those in whom decortication has failed.[21, 29] Our cardiothoracic surgeons offer a less aggressive option, with pleural toilette and the placement of a basal drain prior to considering the usual definitive procedures, described in the literature, for the management of complicated empyema. The success rate of closed tube thoracostomy for advanced or loculated empyema is low [7, 21] and the mortality of empyema treated by closed tube thoracostomy is high, 11-24%.[21, 29]

In our series 30.4% of patients were successfully treated via closed tube thoracostomy, however many required multiple tubes or prolonged drainage. Cardiothoracic intervention as a primary therapeutic measure was offered to only 6 (3.5%) patients, surgery was later offered to another 46 (26.7%). Development of local complications in 15 (28.9%) patients or

the necessity for multiple tube insertions in 15 (28.9%) appeared to be the criteria for surgery. Surgery was more readily offered to patients on antiretroviral therapy.

Long-term open tube thoracostomy via a tube thoracostomy cut short and the placement of a colostomy bag over the cut end of the tube is a technique (which we could not find described in the literature) used due to limited cardiothoracic resources available to us. The empyema space is allowed to drain freely and with regular withdrawal of the tube, the pleural space eventually obliterates. Of the 47 patients discharged with open tube thoracostomas, we were able to assess the outcomes in 38%. Of these, 11 (61%) patients had ultimate resolution, thus open tube thoracostomy may be a viable alternate treatment option in settings with limited cardiothoracic services. The high rate of patients lost to follow up doesn't allow for accurate assessment, however it is an intriguing alternative treatment and further prospective studies should be undertaken to assess this method further.

A significant proportion of patients refused hospital treatment; they had either required multiple tube insertion or waited for long periods of time for cardiothoracic intervention. Mortality in this series is in line with that of current literature, but may be underreported considering many patients refused hospital treatment or were lost to follow up.

Although this is a very large retrospective case series of empyema in HIV infected patients, this study is limited by the sample size of the subgroups and may not have had sufficient power to show statistical significance between the various groups. The fact that cardiothoracic surgery was offered largely only to patients on antiretroviral therapy is a further limitation as we were only able to assess whether patients underwent surgery as opposed to the need, as described in the literature, for cardiothoracic intervention. Only subjects referred to the respiratory unit were analysed and subjects with uncomplicated courses may have been excluded.

CONCLUSION

This is the largest series of empyema in HIV infected patients. It suggests that HIV infection is strongly associated with the development of empyema. We were unable to show that HIV alters the aetiology of empyema however a trend towards infection with enteric Gram-negative organisms in particular *Salmonella* spp. was found and a further case of NTM empyema is described. Clinical outcomes were similar in HIV infected and non-infected patients. Bias towards patients on antiretroviral therapy with regards to surgical intervention exists; and may translate to shorter length of stay or even reduced mortality.

Chris Hani Baragwanath Hospital ♦ Department of Medicine
P O Bertsham, 2013, South Africa ♦ Telephone: +27 11 933 2040 ♦ Fax: +27 11 938 1454

26 April 2010

Postgraduate Research Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Sir/Madam

AUTHORIZATION TO UTILIZE DATABASE FOR RESEARCH PURPOSES

This is to confirm that Dr Grace Kaye-Eddie has been granted permission by me to utilize the database comprising patients from the Division of Pulmonology at Chris Hani Baragwanath Hospital for the purposes of her MMed research report. In this retrospective study, the identity of patients will remain anonymous.

Yours sincerely

Prof M. Wong
Head: Division of Pulmonology, Chris Hani Baragwanath Hospital

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011)717-2075/6

Reference: Ms Tania van Leeve
E-mail: tania.vanleeve@.wits.ac.za
02 July 2010
Person No: 9701912N
PAG

Dr G Kaye-Eddie
P O Box 60010
Langlaagte
2102
South Africa

Dear Dr Kaye-Eddie

Master of Medicine (in the specialty of Internal Medicine): Approval of Title

We have pleasure in advising that your proposal entitled "*Retrospective comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and outcomes*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Grace H Kaye-Eddie

CLEARANCE CERTIFICATE	**M10521**
PROJECT	Retrospective Comparison of Empyema Thoracis in HIV INfected and Non-Infected Patients with Regards to Aetiology and Outcome
INVESTIGATORS	Grace H Kaye-Eddie.
DEPARTMENT	Department of Internal Medicine/Pulmonology
DATE CONSIDERED	28/05/2010

DECISION OF THE COMMITTEE*

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr A Black

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
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Comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and outcome.

Empyema thoracis in HIV infection.

ABSTRACT

Background: Empyema thoracis remains a problem in developing countries. Human Immunodeficiency Virus (HIV) is a risk factor for the development of empyema. There is a clinical impression that HIV infected patients with empyema have worse outcomes. This study was conducted to assess whether HIV infection affected aetiology or outcomes of patients with empyema.

Methods: A retrospective review was conducted of patients, meeting established criteria for the diagnosis of empyema, admitted to Chris Hani Baragwanath Hospital (CHBH) from January 2006 to December 2009. HIV infected and non-infected patients were evaluated for differences in aetiology and outcomes including; length of stay, need for surgical intervention and local complications of closed tube thoracostomy. A sub analysis of HIV infected patients stratified according to CD4 cell count and antiretroviral use was also performed.

Results: One hundred and seventy two patients were included, 125 (73%) were HIV infected and 47 (27%) were HIV non-infected. HIV infected patients with lower CD4 cell counts were more likely to be diagnosed with clinical tuberculosis. The aetiology of empyema was more commonly not determined in HIV non-infected patients. HIV infected patients on antiretrovirals were more likely to have definitive surgery and had shorter hospital stays than those not on antiretrovirals.

Conclusions: This study failed to demonstrate any significant differences in aetiology among HIV infected versus non-infected patients with empyema. There was a trend towards more Gram-negative infections in the HIV infected group. Antiretroviral use was associated with improved outcomes with regards to cardiothoracic intervention and length of stay.

INTRODUCTION

Empyema thoracis; the presence of pus in the pleural space,[1, 2, 3] remains a problem in developing countries,[4] its course is often prolonged and frequently requires surgical drainage. HIV infection is a risk factor for empyema[1] and complicates pneumonia more frequently in HIV infected patients.[5] Reported risk factors for the development of empyema include serum albumin <30 g/dl, intravenous drug use, ethanol abuse, younger age, male sex and current smoking. [6]

At CHBH, an academic hospital with 847 medicine beds in Soweto, South Africa, majority of patients with empyema are HIV infected and present with late stages of empyema. Despite expected low success rates of closed tube thoracostomy in the treatment of late empyema[7] it remains first-line therapy at our hospital as cardiothoracic services are limited and many patients are critically ill and unable to tolerate aggressive surgical procedures.

There is an impression that HIV infected patients do worse clinically. Limited literature exists to support this, some reports claim patients with CD4 counts <200 cells/mm^3 have higher complication rates and a poorer prognosis.[5]

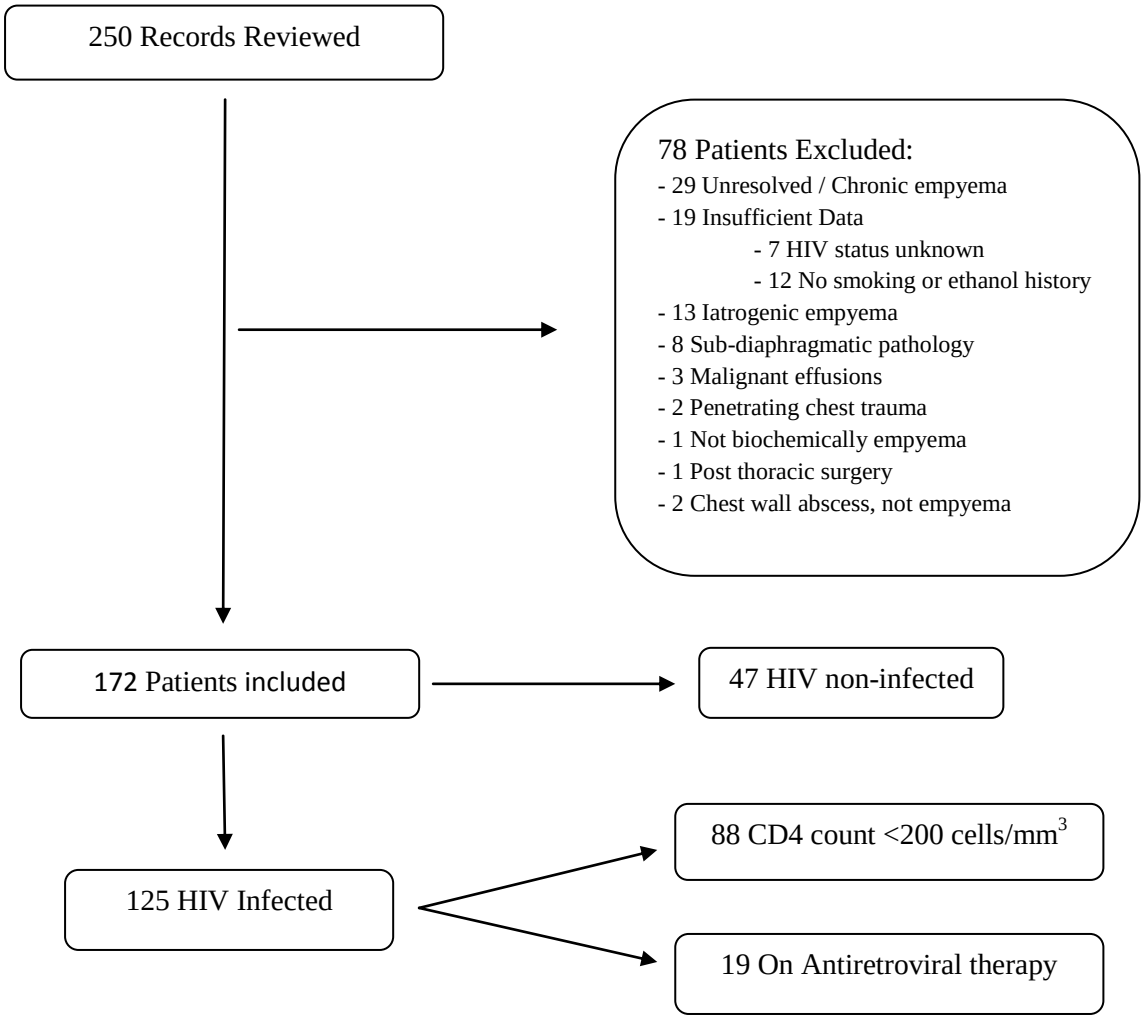
This study compares microbiological aetiology, outcomes including; length of stay, need for surgical intervention and local complications of tube thoracostomy, in patients with empyema according to HIV status. A secondary objective is to compare aetiology and outcomes in patients with HIV infection stratified according to CD4 cell count (≥200 cells/mm^3 or <200 cells/mm^3) and antiretroviral usage.

METHODS

The CHBH Respiratory Unit database from January 2006 to December 2009 was reviewed. This Excel (Microsoft Corporation, Bellevue, WA) database is compiled from discharge summaries and case notes of patients referred to the Respiratory Unit. Permission to use the database was obtained from the database manager and permission to conduct this review was obtained by the Human Research Ethics committee of the University of the Witwatersrand.

Patients meeting established criteria of empyema; aspiration of pus from the pleural space, pleural fluid pH <7.2, pleural fluid glucose <3.4 mmol/l (60 mg/dl) or positive microbial stain and/or culture, [1, 2] were included. Of the 250 records reviewed, 78 patients were excluded (fig 1).

Figure 1



Flowchart summarising patient inclusion.

Patients were divided into aetiological groups based upon initial pleural fluid results: [1] proven tuberculosis (TB), [2] clinical TB, [3] dual, [4] bacterial, [5] non-tuberculous mycobacteria (NTM) and [5] unknown. For proven TB either pleural fluid or sputum samples demonstrated Acid-Fast Bacilli (AFB) on microscopy and/or cultured *Mycobacterium tuberculosis* or pleural biopsy demonstrated histological features of tuberculous infection. Patients with radiological features of TB, those in whom clinical suspicion of TB existed or responded to a trial of anti-tuberculous therapy were classified as clinical TB. Patients diagnosed with proven TB who also cultured a bacterial organism were classified as dual. Patients with bacterial infections were subdivided into Gram-positive, Gram-negative and polymicrobial infections. Patients in whom pleural fluid analysis or histology failed to identify a microbiological aetiology were classified as unknown.

Outcomes were defined as: [1] resolution of empyema via closed tube thoracostomy in ≤14 days, [2] resolution of empyema via closed tube thoracostomy but requiring insertion of multiple tubes or prolonged drainage (>14 days), [3] long-term open tube thoracostomy, [4] definitive cardiothoracic intervention and [5] death. Length of stay was compared among each group.

Complications were defined as: [1] wound sepsis at tube thoracostomy site and [2] secondary infection of the pleural space.

Statistical analysis was performed using STATA 10 software (StataCorp LP, College Station, Texas). Univariate analyses were performed in each of the groups against known risk factors for empyema; age, smoking, ethanol abuse and male sex. Association between categorical variables were tested using Fisher's exact test, odds ratios and 95% confidence intervals were calculated. Continuous variables with parametric distributions were tested with the student's t-test, those with nonparametric distributions with the Wilcoxin Rank Sum test. Where significant risk factors were identified between groups, they were analysed using multivariate regression analyses. Significance was considered as a P value of <0.05.

RESULTS

In total 172 patients were included, mean age was 39 (14-78). The study group comprised 110 (64%) males. Using all cause admissions to the medical wards during the study period, it was found that males were at greater risk of developing empyema (p <0.0001, OR 2.40, 95% CI 2.00-2.88). HIV infection was present in 125 (73%) patients. Using a HIV prevalence in Gauteng of 12.5%, [8] HIV infection was confirmed as a risk factor for the development of empyema (p <0.0001, OR 18.55, 95% CI 14.60-23.60). Amongst the HIV infected group, median CD4 count was 128cells/mm^3 (1-885 cells/mm^3, IQR 62-219 cells/mm^3), 88 (70.4%) had a CD4 count <200 cells/mm^3 and 19 (15.2%) were on antiretroviral therapy.

With regards the reported risk factors for the development of empyema, statistical differences were found among the HIV infected and non-infected groups for age (p = 0.0003) and sex (p = 0.05). In HIV infected patients stratified according to CD4 cell count, ethanol abuse was found to be significant (p = 0.04). No differences in risk factors were found in HIV infected patients stratified according to antiretroviral usage.

Microbiological aetiologies were as follows; 34 (19.8%) patients had proven TB, 34 (19.8%) had clinical TB, 8 (4.7%) had dual infections, 55 (32%) had bacterial infections, 1 (0.6%) had NTM infection, and in 40 (23.3%), no microbiological aetiology was identified. One patient cultured both *Streptococcus pneumoniae* and NTM and was classified as bacterial. We report 5 cases of Salmonella non-typhi empyema, all five patients were HIV infected; four had CD4 counts <100 cells/mm^3, the fifth was on antiretroviral therapy with a CD4 count of 118 cells/mm^3. Pleural fluid cultured *Salmonella* spp. in all five, in one *Salmonella* spp. was also cultured on sputum (Table 1).

Table 1
Microbiological aetiologies by HIV Status

	HIV Positive (n=125)	HIV Negative (n=47)
* Proven Tuberculosis:	34 (27.2%)	8 (17%)
Pleural Fluid Microscopy AFB positive	7 (20.6%)	0
Pleural Fluid culture MTB positive	18 (53.0%)	1 (12.5%)
Sputum Microscopy AFB positive	12 (35.5%)	4 (50%)
Sputum Culture MTB positive	9 (26.5%)	2 (25%)
Blood Culture MTB positive	3 (8.8%)	0
Pleural Biopsy consistent with tuberculosis	2 (5.9%)	2 (25%)
Clinical Tuberculosis:	27 (21.6%)	7 (14.9%)
* Bacterial Infection:	53 (42.4%)	10 (21.3%)
S. pneumoniae	22 (41.5%)	3 (30%)
S. anginosus (formerly *S. milleri*)	5 (9.4%)	5 (50%)
K. pneumonia	5 (9.4%)	1 (10%)
Salmonella spp.	5 (9.4%)	0
S. aureus	3 (5.7%)	0
Peptostreptococcus spp.	3 (5.7%)	1 (10%)
E. coli	3 (5.7%)	0
Prevotella spp.	2 (3.8%)	3 (30%)
Nocardia spp.	2 (3.8%)	0
H. influenza	2 (3.8%)	0
P. mirabilis	2 (3.8%)	0
P. aeruginosa	2 (3.8%)	0
E. faecium	1 (1.9%)	0
E. faecalis	1 (1.9%)	0
S. viridans	1 (1.9%)	0
S. pyogenes	1 (1.9%)	0
A. baumannii	1 (1.9%)	0
Streptococcus Group F	1 (1.9%)	0
Streptococcus Group C	0	1 (10%)
Non-tuberculous mycobacteria:	1 (0.8%)	0
Mycobacterium avium-intracellulare complex	1 (0.8%)	0
Unknown:	18 (14.4%)	22 (46.8%)

MTB = *Mycobacterium tuberculosis*

* Includes those with dual infection.
Proof of MTB often obtained by more than one method.
Polymicrobial infection in 13 patients.

With regards aetiology; HIV non-infected patients more often had no identifiable microbiological aetiology identified whereas HIV infected patients with lower CD4 cell counts had a significantly greater likelihood of being diagnosed with clinical TB and showed a trend towards having a greater incidence of infections caused by Gram-negative organisms (OR 10.6). Antiretroviral therapy did not alter the aetiology of empyema (Table 2).

Table 2
Differences in aetiology of empyema

			P	OR (95% CI)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
Proven tuberculosis	8	34	0.58	1.29 (0.52 – 3.2)
Clinical tuberculosis	7	27	0.27	1.71 (0.65 – 4.45)
Dual Infection	0	8	*	*
Bacterial Infection	10	45	0.08	2.10 (0.91 – 4.82)
- Gram-positive	5	31	0.94	0.94 (0.21 – 4.30)
- Gram-negative	1	13	0.09	10.60 (0.72 – 156.07)
- Polymicrobial	4	9	0.10	0.25 (0.51 – 1.27)
Non-tuberculous mycobacteria	0	1	*	*
Unknown aetiology	22	18	<0.005	0.18 (0.08 – 0.40)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
Proven tuberculosis	26	8	0.08	0.36 (0.11 – 1.37)
Clinical tuberculosis	14	13	0.02	2.98 (1.22 – 7.30)
Dual Infection	4	4	0.26	2.33 (0.54 – 10.07)
Bacterial Infection	36	9	0.08	0.46 (0.19 – 1.09)
Non-tuberculous mycobacteria	1	0	*	*
Unknown aetiology	11	7	0.30	1.75 (0.61 – 5.00)
¤ ART versus no ART:	ART (n=19)	ART (n=106)		
Proven tuberculosis	6	28	0.78	1.29 (0.36 – 4.06)
Clinical tuberculosis	7	20	0.13	2.51 (0.73 – 7.94)
Dual Infection	0	8	*	*
Bacterial Infection	3	42	0.07	0.29 (0.05 – 1.10)
Non-tuberculous mycobacteria	0	1	*	*
Unknown aetiology	3	15	0.74	1.14 (0.19 – 4.72)

ART = Antiretroviral therapy
* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.
† Adjusted in logistic regression analysis for age and sex.
‡ Adjusted in logistic regression analysis for ethanol abuse.
¤ Univariate analysis using 2-tailed Fisher's exact test.

Tube thoracostomas were inserted in the general medical wards in all but 11 (6.4%) patients; 6 (3.5%) were transferred to cardiothoracic surgeons as their pleural collections were not amenable to tube thoracostomy, 3 (1.8%) had very small collections which were treated medically and 2 (1.2%) refused further hospital treatment.

Following closed tube thoracostomy; 16 (10%) patients had complete resolution of empyema within 14 days, 34 (20.4%) had resolution with prolonged drainage or multiple tubes. Following 14 days of closed tube thoracostomy, 47 (28.1%) were discharged home with an open tube thoracostoma; 14 (29.8%) of these following basal tube insertion by cardiothoracic surgeons. Definitive cardiothoracic intervention was required in 38 (22.8%); 35 had pleural toilette and basal tube insertion with subsequent resolution, 1 had a decortication, and 2 required thoracostomy. Prior to resolution of empyema, 14 (8.3%) patients refused further treatment and discharged themselves from hospital.

Of the patients converted to open tube thoracostomy; 6 (12.8%) were followed up by cardiothoracic services, 11 (23.4%) had resolution of empyema, 23 (48.9%) defaulted follow up, 5 (10.6%) were transferred to cardiothoracic surgeons for a definitive procedure; toilette, decortication, thoracostomy or thoracoplasty and 2 (4.3%) demised due to ongoing pleural sepsis.

Overall length of stay was a median of 29 days (3-118 days). No differences were found with regards to length of stay between HIV infected and non-infected patients or between those stratified according to CD4 cell count. Patients on antiretroviral therapy had significantly shorter lengths of stay.

Patients were evaluated for development of complications; 4 (2.4%) developed wound sepsis at tube thoracostomy site and 26 (15.6%) developed secondary infection of their pleural space. Mortality in this series was 12.8% (22/172).

Regarding outcomes and complications; HIV infected patients on antiretrovirals are more likely to be offered definitive cardiothoracic intervention. Length of stay was shorter and, though not statistically significant, there were no mortalities amongst patients on antiretroviral therapy. No other differences were found between the various groups (Table 3).

Table 3
Differences in outcomes and complications of empyema

			P	OR (95%)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
§ Length of stay	27 (4 – 94)	29 (3 – 118)	0.65	
Resolution Simple	4	12	0.78	0.83 (0.24 – 2.88)
Resolution Complicated	8	26	0.50	1.38 (0.54 – 3.52)
Long term open tube thoracostomy	13	32	0.80	0.90 (0.41 – 1.99)
Definitive surgical intervention	12	26	0.42	1.13 (0.31 – 1.62)
Death	6	16	0.80	0.78 (0.40 – 3.40)
Wound sepsis at tube thoracostomy site	1	3	0.88	1.21 (0.10 – 14.72)
Secondary infection of pleural space	5	21	0.17	2.19 (0.71 – 6.71)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
§ Length of stay	29 (4 – 118)	31 (3 – 88)	0.73	
Resolution Simple	8	4	0.84	1.14 (0.32 – 4.09)
Resolution Complicated	18	8	0.82	1.11 (0.43 – 2.90)
Long term open tube thoracostomy	23	9	0.98	0.99 (0.40 – 2.45)
Definitive surgical intervention	18	8	0.89	1.07 (0.42 – 2.75)
Death	14	2	0.10	0.27 (0.06 – 1.30)
Wound sepsis at tube thoracostomy site	3	0	*	*
Secondary infection of pleural space	15	6	0.82	1.00 (0.99 – 1.00)
¤ ART versus no ART:	ART (n=19)	ART (n=106)		
§ Length of stay	37 (19 – 71)	27 (3 – 118)	0.05	
Resolution Simple	1	11	0.69	0.47 (0.01 – 3.60)
Resolution Complicated	4	22	1.00	0.98 (0.22 – 3.52)
Long term open tube thoracostomy	5	27	1.00	1.01 (0.26 – 3.32)
Definitive surgical intervention	8	18	0.03	3.43 (1.03 – 10.90)
Death	0	16	*	*
Wound sepsis at tube thoracostomy site	1	2	0.39	2.89 (0.05 – 57.56)
Secondary infection of pleural space	2	19	0.74	0.54 (0.06 – 2.61)

ART = Antiretroviral therapy
* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.
† Adjusted in logistic regression analysis for age and sex.
‡ Adjusted in logistic regression analysis for ethanol abuse.
¤ Univariate analysis using 2-tailed Fisher's exact test.
§ Length of stay adjusted in linear regression analysis.

DISCUSSION

Empyema thoracis remains an important problem in South Africa. Majority of empyemas (>50%) are as a result of direct extension of a pulmonary parenchymal infection into the pleural space.[1, 3] Empyema in HIV infected patients is uncommon in developed countries despite the increased risk HIV infection confers to the development of respiratory infections.[9, 10]

The microbiology of empyema is vast. Common pathogens include *S. pneumoniae, Staphylococcus aureus, Streptococcus anginosus, Streptococcus pyogenes, Prevotella* spp. and *M. tuberculosis.*[3] Since the availability of antibiotics the bacteriology has changed; *S. pneumonia* and *S. pyogenes* infections occur less, and *S. aureus* and enteric Gram-negative organisms occur more frequently.[11, 12] Infections caused by Gram-negative organisms occur more frequently in HIV infected patients[9] and a trend which was found in our series. Infection with non-typhoidal salmonella is well described in patients with advanced HIV infection,[13] bacteraemia occurs frequently however pleuropulmonary complications are rare, with empyema usually occurring in the setting of CD4 counts <100 cells/mm^3.[3, 14, 15] The incidence of non-typhoidal salmonella reported in our series suggests that non-typhoidal salmonella should be considered potential aetiological organisms in HIV infected patients with low CD4 cell counts. The identification of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as causes of empyema is worrying and may reflect the increased contact HIV infected patients have with health facilities. There appears to be a resurgence of important pathogens from the pre-antibiotic era in the presence of the HIV pandemic.

Tuberculous empyema has been reported at frequencies of 3-6% in developed countries,[7, 9, 16] however in developing countries TB accounts for up to 35% of cases.[4] In Southern Africa, majority of patients with tuberculous empyema are HIV infected.[17] Rates of tuberculous empyema are higher in our series than those stated in developed countries; when combining the patients with proven and clinical TB, 44.2% of empyemas were attributed to tuberculous infection. HIV infected patients tend to be given the diagnosis of clinical TB when no microbiological aetiology is found despite extensive investigation, we attribute this to clinician bias in a community where rates of HIV and TB co-infection are high. Dual infections were only found in patients with HIV infection and occurred over a range of CD4 counts (39-382 cells/mm^3).

Pleural involvement is unusual with NTM; pleural thickening adjacent to pulmonary parenchymal infection is described, pleural effusions if present are very small.[18, 19] Empyema is rare with only one report of a clearly documented empyema due to NTM in a patient with advanced acquired immunodeficiency syndrome.[20] NTM were cultured in two patients (*Mycobacterium avium-intracellulare* in one, failed identification of species in the other due to contamination), both were HIV infected with advanced disease; CD4 counts of 7 and 25 cells/mm^3 and neither was on antiretroviral therapy.

Despite thorough investigation no identifiable microbiological aetiology for empyema was identified in 23.3%; patients may have been treated with antibiotics prior to admission or specimens for anaerobic cultures may not have been optimally processed thus underreporting anaerobic infections. Anaerobic bacteria remain important pathogens in adults.[21] Rapid transfer in oxygen-free media to the laboratory and adequate anaerobic culture techniques are vital to increase diagnostic sensitivity.[11]

The treatment of empyema depends upon the pathophysiological stage in which the patient presents. Empyemas in the exudative stage, may be successfully drained via closed tube

thoracostomy.[7, 22, 23] Empyemas in the fibrinopurulent stage often require more aggressive drainage procedures or video-assisted thoracoscopy.[22, 23, 24] There is contradictory evidence on the use of intrapleural fibrinolytics; they may be used as an adjunct to closed tube thoracostomy however do not reduce mortality or the need for surgery.[25, 26] Thoracoscopic drainage procedures are popular; less post operative pain, lower costs, shorter hospital stays and better cosmetic results.[25, 27] Optimal timing is important as high failure rates have been reported in cases with advanced empyema.[28, 29] Empyema in the organisational stage is best managed via open surgery; decortication, thoracostomy or thoracoplasty to manage extensive pleural peel or control the underlying inflammatory process.[7, 22, 24] Decortication remains the modality of choice for treating advanced empyema, thoracoplasty and thoracostoma are reserved for debilitated patients who cannot tolerate aggressive surgery or those in whom decortication has failed.[22, 30] The success rate of closed tube thoracostomy for advanced or loculated empyema is low [7, 22] and the mortality of empyema treated by closed tube thoracostomy is high, 11-24%.[22, 30]

In our series 30.4% of patients were successfully treated via closed tube thoracostomy, however many required multiple tubes or prolonged drainage. Cardiothoracic intervention as a primary therapeutic measure was offered to only 6 (3.5%) patients, surgery was required in another 46 (26.7%). Of the 52 patients requiring surgery, 38 (22.1%) had definitive surgery, 14 (8.1%) were discharged home with open tube thoracostomas and 2 (3.9%) demised. Development of local complications in 15 (28.9%) patients or the necessity for multiple tube insertions in 15 (28.9%) appeared to be the criteria for surgery. Surgery was more readily offered to patients on antiretroviral therapy.

Long-term open tube thoracostomy via a tube thoracostomy cut short and the placement of a colostomy bag over the cut end of the tube is a technique (which we could not find described in the literature) used due to limited cardiothoracic resources available to us. The empyema space is allowed to drain freely and with regular withdrawal of the tube, the pleural space eventually obliterates. Of the 47 patients discharged with open tube thoracostomas, we were able to assess the outcomes in 38%. Of these, 11 (61%) patients had ultimate resolution, thus open tube thoracostomy may be a viable alternate treatment option in settings with limited cardiothoracic services. The high rate of patients lost to follow up doesn't allow for accurate assessment, however it is an intriguing alternative treatment and further prospective studies should be undertaken to assess this method further.

A significant proportion of patients refused hospital treatment; they had either required multiple tube insertion or waited for long periods of time for cardiothoracic intervention. Mortality in this series is in line with that of current literature, but may be underreported considering many patients refused hospital treatment or were lost to follow up.

CONCLUSION

This is the largest series of empyema in HIV infected patients. It confirms that HIV infection is a risk factor for the development of empyema. We were unable to show that HIV alters the aetiology of empyema however a trend towards infection with enteric Gram-negative organisms in particular *Salmonella* spp. was found and a further case of NTM empyema is described. Clinical outcomes were similar in HIV infected and non-infected patients. Bias towards patients on antiretroviral therapy with regards to surgical intervention exists; and may translate to shorter length of stay or even reduced mortality.

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5. Click on "NOTIFY THE EDITOR" after that and send me a short message to that effect.

We would like to receive your revised manuscript within 1 week of today's date, i.e. 25 January 2012.

I look forward to receiving the revised draft of your manuscript.

Yours sincerely
Prof H Koornhof
Editor: SAJEI

Email: toc@sajei.co.za

Reviewer B:
This large retrospective case series of empyema provides interesting local data on aetiology by HIV status and outcomes. The discussion needas a paragraph on study limitations - notably th fact that surgery seems to largely only have been offered to HIV+ patients on ART & that need for surgery cannot be assessed in a retrospective study like this.

Specific comments:
Abstract will need amending after analyses have been revised (see below) Line 45 - this sentence should be moved to methods with more detail on the nature of the hospital, only the practice at CHBH should be included Line 53 need for surgery cannot be assessed in this study - only whether surgery was done can be recorded Line 61 reword: "An Excel (Microsoft Corporation, Bellevue, WA) database iwas compiled..."
Line 67 were pH & glucose required or "or"? Delete non-SI glucose units Line 69 Unclear why 29 Unresolved / Chronic empyema were excluded given that one outcome isf long-term open tube thoracostomy.
Line 98 specily that dual means TB & bacterial.
Line 104 I assume culture was from pleural specimen - specify Line 120 Wilcoxon is mis-spelled
Results: a table of patient characteristics by HIV status should be included & much of the text in the 1st 2 paragraphs then becomes superfluous Line 129 Inappropriate to statistically analyse HIV prevalence in community & patients - delete (point can be made in discussion) Table 2 I do not see the value of

this table as detailed aetiology is given in table 1 & feel that providing ORs & P for every line is uninformative.
The table should be revised to show only pooled analyses of aetiology (eg all TB, all bacterial, unknown) - by the way under ART the 2nd column heading should be "No ART" (same error in table 3) - also specify that CD4 was only done in HIV+.
Results after table 2 (line numbering disappears at this point, which is irritating - tables & figures should be at the end of manuscripts):
Page 7 paragraph 2 sentence 3 should read "Definitive cardiothoracic intervention was required done in...:Definitive cardiothoracic intervention was required done in..."; last paragraph 1st sentence should read "...HIV infected patients on antiretrovirals weare more likely to be offeredundergo definitive cardiothoracic intervention"

Reviewer C:
When seeing the title, I was immediately interested inreading further. The content did not disappoint!
Very interesting article, well written, concise.

The article illustrates the fact that over the course of the HIV epidemic, we've accumulated a wealth of clinical experience and case series. Unfortunately the time is seldom found to write it up and share that experience with other clinicians. The authors should be commended for taking the time to collect the data (albeit retrospectively), do the analysis and write it up. It is much appreciated!

Comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and outcome.

Empyema thoracis in HIV infection.

ABSTRACT

Background: Empyema thoracis remains a problem in developing countries. Human Immunodeficiency Virus (HIV) is a risk factor for the development of empyema. There is a clinical impression that HIV infected patients with empyema have worse outcomes. This study was conducted to assess whether HIV infection affected aetiology or outcomes of patients with empyema.

Methods: A retrospective review was conducted of patients, meeting established criteria for the diagnosis of empyema, admitted to Chris Hani Baragwanath Hospital (CHBH) from January 2006 to December 2009. HIV infected and non-infected patients were evaluated for differences in aetiology and outcomes including; length of stay, surgical intervention and local complications of closed tube thoracostomy. A sub analysis of HIV infected patients stratified according to CD4 cell count and antiretroviral use was also performed.

Results: One hundred and seventy two patients were included, 125 (73%) were HIV infected and 47 (27%) were HIV non-infected. HIV infected patients with lower CD4 cell counts were more likely to be diagnosed with clinical tuberculosis. The aetiology of empyema was more commonly not determined in HIV non-infected patients. HIV infected patients on antiretrovirals were more likely to have thoracic surgery and had shorter hospital stays than those not on antiretrovirals.

Conclusions: This study failed to demonstrate any significant differences in aetiology among HIV infected versus non-infected patients with empyema. There was a trend towards more Gram-negative infections in the HIV infected group. Antiretroviral use was associated with improved outcomes with regards to cardiothoracic intervention and length of stay.

INTRODUCTION

Empyema thoracis; the presence of pus in the pleural space,[1, 2, 3] remains a problem in developing countries,[4] its course is often prolonged and frequently requires surgical drainage. HIV infection is a risk factor for empyema[1] and complicates pneumonia more frequently in HIV infected patients.[5] Reported risk factors for the development of empyema include serum albumin <30 g/dl, intravenous drug use, ethanol abuse, younger age, male sex and current smoking. [6]

In our experience, majority of patients with empyema are HIV infected and present with late stages of empyema. Despite expected low success rates of closed tube thoracostomy in the treatment of late empyema[7] it remains first-line therapy at our hospital as cardiothoracic services are limited and many patients are critically ill and unable to tolerate aggressive surgical procedures.

There is an impression that HIV infected patients do worse clinically. Limited literature exists to support this, some reports claim patients with CD4 counts <200 cells/mm^3 have higher complication rates and a poorer prognosis.[5]

This study compares microbiological aetiology, outcomes including; length of stay, whether surgical intervention was offered and local complications of tube thoracostomy, in patients with empyema according to HIV status. A secondary objective is to compare aetiology and outcomes in patients with HIV infection stratified according to CD4 cell count (≥200 cells/mm^3 or <200 cells/mm^3) and antiretroviral usage.

METHODS

CHBH is a large academic hospital in Soweto Johannesburg, with 847 medical beds. It is the only in-patient facility for the greater Soweto area and serves as a referral centre for Southern Gauteng and the North West Province. The CHBH Respiratory Unit database from January 2006 to December 2009 was reviewed. An Excel (Microsoft Corporation, Bellevue, WA) database was compiled from discharge summaries and case notes of patients referred to the Respiratory Unit. Permission to use the database was obtained from the database manager and permission to conduct this review was obtained by the Human Research Ethics committee of the University of the Witwatersrand.

Patients meeting at least one of the established criteria of empyema; a) aspiration of pus from the pleural space, b) pleural fluid pH <7.2 or pleural fluid glucose <3.4 mmol/l or c) positive microbial stain and/or culture, [1, 2] were included. Of the 250 records reviewed, 78 patients were excluded (fig 1). The 29 patients excluded for chronic/unresolved empyema were patients that had been previously admitted for primary empyema, prior to the start date of the study, and had returned with complications during the study period. We felt that inclusion of these patients would create bias.

Patients were divided into aetiological groups based upon initial pleural fluid results: [1] proven tuberculosis (TB), [2] clinical TB, [3] dual (tuberculosis and bacterial infection), [4] bacterial, [5] non-tuberculous mycobacteria (NTM) and [5] unknown. For proven TB either pleural fluid or sputum samples demonstrated Acid-Fast Bacilli (AFB) on microscopy and/or cultured *Mycobacterium tuberculosis* or pleural biopsy demonstrated histological features of tuberculous infection. Patients with radiological features of TB, those in whom clinical suspicion of TB existed or responded to a trial of anti-tuberculous therapy were classified as

clinical TB. Patients diagnosed with proven TB who also cultured a bacterial organism in their pleural fluid were classified as dual. Patients with bacterial infections were subdivided into Gram-positive, Gram-negative and polymicrobial infections. Patients in whom pleural fluid analysis or histology failed to identify a microbiological aetiology were classified as unknown.

Outcomes were defined as: [1] resolution of empyema via closed tube thoracostomy in ≤14 days, [2] resolution of empyema via closed tube thoracostomy but requiring insertion of multiple tubes or prolonged drainage (>14 days), [3] long-term open tube thoracostomy, [4] cardiothoracic intervention and [5] death. Length of stay was compared among each group.

Complications were defined as: [1] wound sepsis at tube thoracostomy site and [2] secondary infection of the pleural space.

Statistical analysis was performed using STATA 10 software (StataCorp LP, College Station, Texas). Univariate analyses were performed in each of the groups against known risk factors for empyema; age, smoking, ethanol abuse and male sex. Association between categorical variables were tested using Fisher's exact test, odds ratios and 95% confidence intervals were calculated. Continuous variables with parametric distributions were tested with the student's t-test, those with nonparametric distributions with the Wilcoxon Rank Sum test. Where significant risk factors were identified between groups, they were analysed using multivariate regression analyses. Significance was considered as a P value of <0.05.

RESULTS

In total 172 patients were included, mean age was 39 (14-78). The study group comprised 110 (64%) males. Using all cause admissions to the medical wards during the study period, it was found that males were at greater risk of developing empyema ($p < 0.0001$, OR 2.40, 95% CI 2.00-2.88). HIV infection was present in 125 (73%) patients. (fig 2.)

With regards the reported risk factors for the development of empyema, statistical differences were found among the HIV infected and non-infected groups for age ($p = 0.0003$) and sex ($p = 0.05$). In HIV infected patients stratified according to CD4 cell count, ethanol abuse was found to be significant ($p = 0.04$). No differences in risk factors were found in HIV infected patients stratified according to antiretroviral usage.

Microbiological aetiologies were as follows; 34 (19.8%) patients had proven TB, 34 (19.8%) had clinical TB, 8 (4.7%) had dual infections, 55 (32%) had bacterial infections, 1 (0.6%) had NTM infection, and in 40 (23.3%), no microbiological aetiology was identified. One patient cultured both *Streptococcus pneumoniae* and NTM and was classified as bacterial. We report 5 cases of Salmonella non-typhi empyema, all five patients were HIV infected; four had CD4 counts <100 cells/mm^3, the fifth was on antiretroviral therapy with a CD4 count of 118 cells/mm^3. Pleural fluid cultured *Salmonella* spp. in all five, in one *Salmonella* spp. was also cultured on sputum (Table 1).

With regards aetiology; HIV non-infected patients more often had no identifiable microbiological aetiology identified ($p < 0.005$, OR 0.18, CI 0.08-0.40) whereas HIV infected patients with lower CD4 cell counts had a significantly greater likelihood of being diagnosed with clinical TB ($p = 0.02$, OR 2.98, CI 1.22-7.3) and showed a trend towards having a greater incidence of infections caused by Gram-negative organisms (OR 10.6). Antiretroviral therapy did not alter the aetiology of empyema.

Tube thoracostomas were inserted in the general medical wards in all but 11 (6.4%) patients; 6 (3.5%) were transferred to cardiothoracic surgeons as their pleural collections were not amenable to tube thoracostomy, 3 (1.8%) had very small collections which were treated medically and 2 (1.2%) refused further hospital treatment.

Following closed tube thoracostomy; 16 (10%) patients had complete resolution of empyema within 14 days, 34 (20.4%) had resolution with prolonged drainage or multiple tubes. Following 14 days of closed tube thoracostomy, 47 (28.1%) were discharged home with an open tube thoracostoma; 14 (29.8%) of these following basal tube insertion by cardiothoracic surgeons. Thirty eight (22.8%) patients underwent definitive cardiothoracic surgery; 35 had pleural toilette and basal tube insertion with subsequent resolution, 1 had a decortication, and 2 required thoracostomy. Prior to resolution of empyema, 14 (8.3%) patients refused further treatment and discharged themselves from hospital.

Of the patients converted to open tube thoracostomy; 6 (12.8%) were followed up by cardiothoracic services, 11 (23.4%) had resolution of empyema, 23 (48.9%) defaulted follow up, 5 (10.6%) were transferred to cardiothoracic surgeons for a definitive procedure; toilette, decortication, thoracostomy or thoracoplasty and 2 (4.3%) demised due to ongoing pleural sepsis.

Overall length of stay was a median of 29 days (3-118 days). No differences were found with regards to length of stay between HIV infected and non-infected patients or between those stratified according to CD4 cell count. Patients on antiretroviral therapy had significantly shorter lengths of stay.

Patients were evaluated for development of complications; 4 (2.4%) developed wound sepsis at tube thoracostomy site and 26 (15.6%) developed secondary infection of their pleural space. Mortality in this series was 12.8% (22/172).

Regarding outcomes and complications; HIV infected patients on antiretrovirals are more likely to be offered definitive cardiothoracic intervention. Length of stay was shorter and, though not statistically significant, there were no mortalities amongst patients on antiretroviral therapy. No other differences were found between the various groups (Table 2).

DISCUSSION

Empyema thoracis remains an important problem in South Africa. Majority of empyemas (>50%) are as a result of direct extension of a pulmonary parenchymal infection into the pleural space.[1, 3] Empyema in HIV infected patients is uncommon in developed countries despite the increased risk HIV infection confers to the development of respiratory infections.[8, 9] In this series, at an ecological level there appears to be a strong association between HIV infection and the development of empyema with a disproportionate number of patients with empyema being HIV infected.

The microbiology of empyema is vast. Common pathogens include *S. pneumoniae, Staphylococcus aureus, Streptococcus anginosus, Streptococcus pyogenes, Prevotella* spp. and *M. tuberculosis.*[3] Since the availability of antibiotics the bacteriology has changed; *S. pneumonia* and *S. pyogenes* infections occur less, and *S. aureus* and enteric Gram-negative organisms occur more frequently.[10, 11] Infections caused by Gram-negative organisms occur more frequently in HIV infected patients[8] and a trend which was found in our series.

Infection with non-typhoidal salmonella is well described in patients with advanced HIV infection,[12] bacteraemia occurs frequently however pleuropulmonary complications are rare, with empyema usually occurring in the setting of CD4 counts <100 cells/mm^3.[13, 14] The incidence of non-typhoidal salmonella reported in our series suggests that non-typhoidal salmonella should be considered potential aetiological organisms in HIV infected patients with low CD4 cell counts. The identification of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as causes of empyema is worrying and may reflect the increased contact HIV infected patients have with health facilities. There appears to be a resurgence of important pathogens from the pre-antibiotic era in the presence of the HIV pandemic.

Tuberculous empyema has been reported at frequencies of 3-6% in developed countries,[7, 8, 15] however in developing countries TB accounts for up to 35% of cases.[4] In Southern Africa, majority of patients with tuberculous empyema are HIV infected.[16] Rates of tuberculous empyema are higher in our series than those stated in developed countries; when combining the patients with proven and clinical TB, 44.2% of empyemas were attributed to tuberculous infection. HIV infected patients tend to be given the diagnosis of clinical TB when no microbiological aetiology is found despite extensive investigation, we attribute this to clinician bias in a community where rates of HIV and TB co-infection are high. Dual infections were only found in patients with HIV infection and occurred over a range of CD4 counts (39-382 cells/mm^3).

Pleural involvement is unusual with NTM; pleural thickening adjacent to pulmonary parenchymal infection is described, pleural effusions if present are very small.[17, 18] Empyema is rare with only one report of a clearly documented empyema due to NTM in a patient with advanced acquired immunodeficiency syndrome.[19] NTM were cultured in two patients (*Mycobacterium avium-intracellulare* in one, failed identification of species in the other due to contamination), both were HIV infected with advanced disease; CD4 counts of 7 and 25 cells/mm^3 and neither was on antiretroviral therapy.

Despite thorough investigation no identifiable microbiological aetiology for empyema was identified in 23.3%; patients may have been treated with antibiotics prior to admission or specimens for anaerobic cultures may not have been optimally processed thus underreporting anaerobic infections. Anaerobic bacteria remain important pathogens in adults.[20] Rapid transfer in oxygen-free media to the laboratory and adequate anaerobic culture techniques are vital to increase diagnostic sensitivity.[10]

The treatment of empyema depends upon the pathophysiological stage in which the patient presents. Empyemas in the exudative stage, may be successfully drained via closed tube thoracostomy.[7, 21, 22] Empyemas in the fibrinopurulent stage often require more aggressive drainage procedures or video-assisted thoracoscopy.[21, 22, 23] There is contradictory evidence on the use of intrapleural fibrinolytics; they may be used as an adjunct to closed tube thoracostomy however do not reduce mortality or the need for surgery.[24, 25] Thoracoscopic drainage procedures are popular; less post operative pain, lower costs, shorter hospital stays and better cosmetic results.[24, 26] Optimal timing is important as high failure rates have been reported in cases with advanced empyema.[27, 28] Empyema in the organisational stage is best managed via open surgery; decortication, thoracostomy or thoracoplasty to manage extensive pleural peel or control the underlying inflammatory process.[7, 21, 23] Decortication remains the modality of choice for treating advanced empyema, thoracoplasty and thoracostoma are reserved for debilitated patients who cannot tolerate aggressive surgery or those in whom decortication has failed.[21, 29] The success rate of closed tube thoracostomy for advanced or

loculated empyema is low [7, 21] and the mortality of empyema treated by closed tube thoracostomy is high, 11-24%.[21, 29]

In our series 30.4% of patients were successfully treated via closed tube thoracostomy, however many required multiple tubes or prolonged drainage. Cardiothoracic intervention as a primary therapeutic measure was offered to only 6 (3.5%) patients, surgery was offered to another 46 (26.7%). Of the 52 patients who underwent surgery, 38 (22.1%) had definitive surgery, 14 (8.1%) were discharged home with open tube thoracostomas and 2 (3.9%) demised. Development of local complications in 15 (28.9%) patients or the necessity for multiple tube insertions in 15 (28.9%) appeared to be the criteria for surgery. Surgery was more readily offered to patients on antiretroviral therapy.

Long-term open tube thoracostomy via a tube thoracostomy cut short and the placement of a colostomy bag over the cut end of the tube is a technique (which we could not find described in the literature) used due to limited cardiothoracic resources available to us. The empyema space is allowed to drain freely and with regular withdrawal of the tube, the pleural space eventually obliterates. Of the 47 patients discharged with open tube thoracostomas, we were able to assess the outcomes in 38%. Of these, 11 (61%) patients had ultimate resolution, thus open tube thoracostomy may be a viable alternate treatment option in settings with limited cardiothoracic services. The high rate of patients lost to follow up doesn't allow for accurate assessment, however it is an intriguing alternative treatment and further prospective studies should be undertaken to assess this method further.

A significant proportion of patients refused hospital treatment; they had either required multiple tube insertion or waited for long periods of time for cardiothoracic intervention. Mortality in this series is in line with that of current literature, but may be underreported considering many patients refused hospital treatment or were lost to follow up.

Although this is a very large retrospective case series of empyema in HIV infected patients, this study is limited by the sample size of the subgroups and may not have had sufficient power to show statistical significance between the various groups. The fact that cardiothoracic surgery was offered largely only to patients on antiretroviral therapy is a further limitation as we were only able to assess whether patients underwent surgery as opposed to the need for cardiothoracic intervention. Only subjects referred to the respiratory unit were analysed and subjects with uncomplicated courses may have been excluded.

CONCLUSION

This is the largest series of empyema in HIV infected patients. It suggests that HIV infection is strongly associated with the development of empyema. We were unable to show that HIV alters the aetiology of empyema however a trend towards infection with enteric Gram-negative organisms in particular *Salmonella* spp. was found and a further case of NTM empyema is described. Clinical outcomes were similar in HIV infected and non-infected patients. Bias towards patients on antiretroviral therapy with regards to surgical intervention exists; and may translate to shorter length of stay or even reduced mortality.

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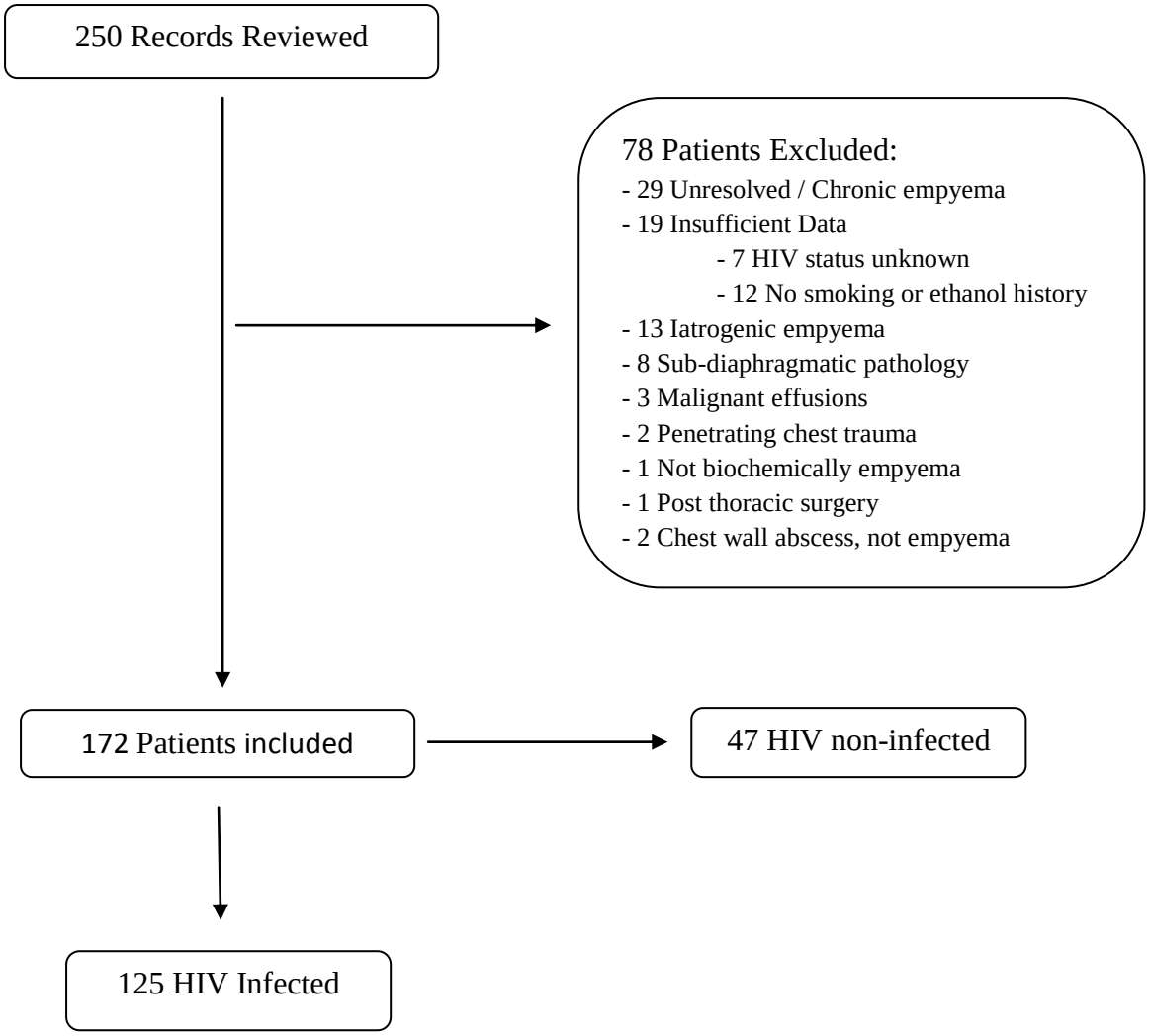
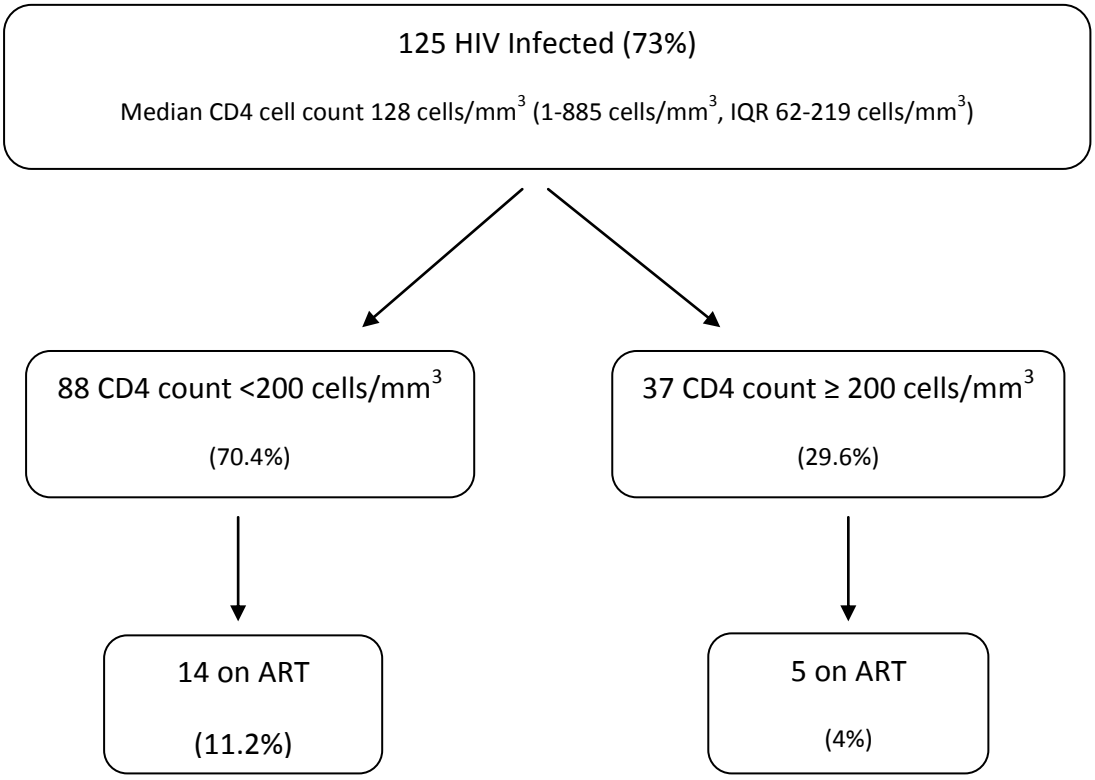
Figure 1



Flowchart summarising patient inclusion.

Figure 2



Flowchart summarising HIV infected patients' characteristics

Table 1
Microbiological aetiologies by HIV Status

	HIV Positive (n=125)	HIV Negative (n=47)
* Proven Tuberculosis:	34 (27.2%)	8 (17%)
Pleural Fluid Microscopy AFB positive	7 (20.6%)	0
Pleural Fluid culture MTB positive	18 (53.0%)	1 (12.5%)
Sputum Microscopy AFB positive	12 (35.5%)	4 (50%)
Sputum Culture MTB positive	9 (26.5%)	2 (25%)
Blood Culture MTB positive	3 (8.8%)	0
Pleural Biopsy consistent with tuberculosis	2 (5.9%)	2 (25%)
Clinical Tuberculosis:	27 (21.6%)	7 (14.9%)
* Bacterial Infection:	53 (42.4%)	10 (21.3%)
S. pneumoniae	22 (41.5%)	3 (30%)
S. anginosus (formerly *S. milleri*)	5 (9.4%)	5 (50%)
K. pneumonia	5 (9.4%)	1 (10%)
Salmonella spp.	5 (9.4%)	0
S. aureus	3 (5.7%)	0
Peptostreptococcus spp.	3 (5.7%)	1 (10%)
E. coli	3 (5.7%)	0
Prevotella spp.	2 (3.8%)	3 (30%)
Nocardia spp.	2 (3.8%)	0
H. influenza	2 (3.8%)	0
P. mirabilis	2 (3.8%)	0
P. aeruginosa	2 (3.8%)	0
E. faecium	1 (1.9%)	0
E. faecalis	1 (1.9%)	0
S. viridans	1 (1.9%)	0
S. pyogenes	1 (1.9%)	0
A. baumannii	1 (1.9%)	0
Streptococcus Group F	1 (1.9%)	0
Streptococcus Group C	0	1 (10%)
Non-tuberculous mycobacteria:	1 (0.8%)	0
Mycobacterium avium-intracellulare complex	1 (0.8%)	0
Unknown:	18 (14.4%)	22 (46.8%)

MTB = *Mycobacterium tuberculosis*

* Includes those with dual infection.
Proof of MTB often obtained by more than one method.
Polymicrobial infection in 13 patients.

Table 2
Differences in outcomes and complications of empyema

			P	OR (95%)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
§ Length of stay	27 (4 – 94)	29 (3 – 118)	0.65	
Resolution Simple	4	12	0.78	0.83 (0.24 – 2.88)
Resolution Complicated	8	26	0.50	1.38 (0.54 – 3.52)
Long term open tube thoracostomy	13	32	0.80	0.90 (0.41 – 1.99)
Definitive surgical intervention	12	26	0.42	1.13 (0.31 – 1.62)
Death	6	16	0.80	0.78 (0.40 – 3.40)
Wound sepsis at tube thoracostomy site	1	3	0.88	1.21 (0.10 – 14.72)
Secondary infection of pleural space	5	21	0.17	2.19 (0.71 – 6.71)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
§ Length of stay	29 (4 – 118)	31 (3 – 88)	0.73	
Resolution Simple	8	4	0.84	1.14 (0.32 – 4.09)
Resolution Complicated	18	8	0.82	1.11 (0.43 – 2.90)
Long term open tube thoracostomy	23	9	0.98	0.99 (0.40 – 2.45)
Definitive surgical intervention	18	8	0.89	1.07 (0.42 – 2.75)
Death	14	2	0.10	0.27 (0.06 – 1.30)
Wound sepsis at tube thoracostomy site	3	0	*	*
Secondary infection of pleural space	15	6	0.82	1.00 (0.99 – 1.00)
¤ ART versus no ART:	ART (n=19)	No ART (n=106)		
§ Length of stay	37 (19 – 71)	27 (3 – 118)	0.05	
Resolution Simple	1	11	0.69	0.47 (0.01 – 3.60)
Resolution Complicated	4	22	1.00	0.98 (0.22 – 3.52)
Long term open tube thoracostomy	5	27	1.00	1.01 (0.26 – 3.32)
Definitive surgical intervention	8	18	0.03	3.43 (1.03 – 10.90)
Death	0	16	*	*
Wound sepsis at tube thoracostomy site	1	2	0.39	2.89 (0.05 – 57.56)
Secondary infection of pleural space	2	19	0.74	0.54 (0.06 – 2.61)

ART = Antiretroviral therapy
‡ Adjusted in logistic regression analysis for ethanol abuse, CD4 cell count only done for HIV.
* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.
† Adjusted in logistic regression analysis for age and sex.
¤ Univariate analysis using 2-tailed Fisher's exact test
§ Length of stay adjusted in linear regression analysis.

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Yours sincerely
Prof H Koornhof
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Comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and outcome.

Empyema thoracis in HIV infection.

ABSTRACT

Background: Empyema thoracis remains a problem in developing countries. Human Immunodeficiency Virus (HIV) is a risk factor for the development of empyema. There is a clinical impression that HIV infected patients with empyema have worse outcomes. This study was conducted to assess whether HIV infection affected aetiology or outcomes of patients with empyema.

Methods: A retrospective review was conducted of patients, meeting established criteria for the diagnosis of empyema, admitted to Chris Hani Baragwanath Hospital (CHBH) from January 2006 to December 2009. HIV infected and non-infected patients were evaluated for differences in aetiology and outcomes including; length of stay, surgical intervention and local complications of closed tube thoracostomy. A sub analysis of HIV infected patients stratified according to CD4 cell count and antiretroviral use was also performed.

Results: One hundred and seventy two patients were included, 125 (73%) were HIV infected and 47 (27%) were HIV non-infected. HIV infected patients with lower CD4 cell counts were more likely to be diagnosed with clinical tuberculosis. The aetiology of empyema was more commonly not determined in HIV non-infected patients. HIV infected patients on antiretrovirals were more likely to have thoracic surgery and had shorter hospital stays than those not on antiretrovirals.

Conclusions: This study failed to demonstrate any significant differences in aetiology among HIV infected versus non-infected patients with empyema. There was a trend towards more Gram-negative infections in the HIV infected group. Antiretroviral use was associated with improved outcomes with regards to cardiothoracic intervention and length of stay.

INTRODUCTION

Empyema thoracis; the presence of pus in the pleural space,[1, 2, 3] remains a problem in developing countries,[4] its course is often prolonged and frequently requires surgical drainage. HIV infection is a risk factor for empyema[1] and complicates pneumonia more frequently in HIV infected patients.[5] Reported risk factors for the development of empyema include serum albumin <30 g/dl, intravenous drug use, ethanol abuse, younger age, male sex and current smoking. [6]

In our experience, majority of patients with empyema are HIV infected and present with late stages of empyema. Despite expected low success rates of closed tube thoracostomy in the treatment of late empyema[7] it remains first-line therapy at our hospital as cardiothoracic services are limited and many patients are critically ill and unable to tolerate aggressive surgical procedures.

There is an impression that HIV infected patients do worse clinically. Limited literature exists to support this, some reports claim patients with CD4 counts <200 cells/mm^3 have higher complication rates and a poorer prognosis.[5]

This study compares microbiological aetiology, outcomes including; length of stay, whether surgical intervention was offered and local complications of tube thoracostomy, in patients with empyema according to HIV status. A secondary objective is to compare aetiology and outcomes in patients with HIV infection stratified according to CD4 cell count (≥200 cells/mm^3 or <200 cells/mm^3) and antiretroviral usage.

METHODS

CHBH is a large academic hospital in Soweto Johannesburg, with 847 medical beds. It is the only in-patient facility for the greater Soweto area and serves as a referral centre for Southern Gauteng and the North West Province. The CHBH Respiratory Unit database from January 2006 to December 2009 was reviewed. An Excel (Microsoft Corporation, Bellevue, WA) database was compiled from discharge summaries and case notes of patients referred to the Respiratory Unit. Permission to use the database was obtained from the database manager and permission to conduct this review was obtained by the Human Research Ethics committee of the University of the Witwatersrand.

Patients meeting at least one of the established criteria of empyema; a) aspiration of pus from the pleural space, b) pleural fluid pH <7.2 or pleural fluid glucose <3.4 mmol/l, or c) positive microbial stain and/or culture, [1, 2] were included.

Patients were divided into aetiological groups based upon initial pleural fluid results: [1] proven tuberculosis (TB), [2] clinical TB, [3] dual (tuberculosis and bacterial infection), [4] bacterial, [5] non-tuberculous mycobacteria (NTM) and [5] unknown. For proven TB either pleural fluid or sputum samples demonstrated Acid-Fast Bacilli (AFB) on microscopy and/or cultured *Mycobacterium tuberculosis*, or pleural biopsy demonstrated histological features of tuberculous infection. Patients with radiological features of TB, those in whom clinical suspicion of TB existed or responded to a trial of anti-tuberculous therapy were classified as clinical TB. Patients diagnosed with proven TB who also cultured a bacterial organism in their pleural fluid were classified as dual. Patients with bacterial infections were subdivided into Gram-positive, Gram-negative and polymicrobial infections. Patients in whom pleural

fluid analysis or histology failed to identify a microbiological aetiology were classified as unknown.

Outcomes were defined as: [1] resolution of empyema via closed tube thoracostomy in ≤14 days, [2] resolution of empyema via closed tube thoracostomy but requiring insertion of multiple tubes or prolonged drainage (>14 days), [3] long-term open tube thoracostomy, [4] cardiothoracic intervention and [5] death. Length of stay was compared among each group.

Complications were defined as: [1] wound sepsis at tube thoracostomy site and [2] secondary infection of the pleural space.

Statistical analysis was performed using STATA 10 software (StataCorp LP, College Station, Texas). Univariate analyses were performed in each of the groups against known risk factors for empyema; age, smoking, ethanol abuse and male sex. Association between categorical variables were tested using Fisher's exact test, odds ratios and 95% confidence intervals were calculated. Continuous variables with parametric distributions were tested with the student's t-test, those with nonparametric distributions with the Wilcoxon Rank Sum test. Where significant risk factors were identified between groups, they were analysed using multivariate regression analyses. Significance was considered as a P value of <0.05.

RESULTS

Two hundred and fifty records were reviewed, 78 patients were excluded (fig 1). The 29 patients excluded for chronic/unresolved empyema were patients that had been previously admitted for primary empyema, prior to the start date of the study, and had returned with complications during the study period. We felt that inclusion of these patients would create bias.

In total 172 patients were included, mean age was 39 (14-78). The study group comprised 110 (64%) males. Using all cause admissions to the medical wards during the study period, it was found that males were at greater risk of developing empyema (p <0.0001, OR 2.40, 95% CI 2.00-2.88). HIV infection was present in 125 (73%) patients (fig 2).

With regards the reported risk factors for the development of empyema, statistical differences were found among the HIV infected and non-infected groups for age (p = 0.0003) and sex (p = 0.05). In HIV infected patients stratified according to CD4 cell count, ethanol abuse was found to be significant (p = 0.04). No differences in risk factors were found in HIV infected patients stratified according to antiretroviral usage.

Microbiological aetiologies were as follows; 34 (19.8%) patients had proven TB, 34 (19.8%) had clinical TB, 8 (4.7%) had dual infections, 55 (32%) had bacterial infections, 1 (0.6%) had NTM infection, and in 40 (23.3%), no microbiological aetiology was identified. One patient cultured both *Streptococcus pneumoniae* and NTM and was classified as bacterial. We report 5 cases of Salmonella non-typhi empyema, all five patients were HIV infected; four had CD4 counts <100 cells/mm^3, the fifth was on antiretroviral therapy with a CD4 count of 118 cells/mm^3. Pleural fluid cultured *Salmonella* spp. in all five, in one *Salmonella* spp. was also cultured on sputum (Table 1).

With regards aetiology; HIV non-infected patients more often had no identifiable microbiological aetiology identified (p < 0.005, OR 0.18, CI 0.08-0.40) whereas HIV infected patients with lower CD4 cell counts had a significantly greater likelihood of being

diagnosed with clinical TB (p = 0.02, OR 2.98, CI 1.22-7.3) and showed a trend towards having a greater incidence of infections caused by Gram-negative organisms (OR 10.6). Antiretroviral therapy did not alter the aetiology of empyema.

Tube thoracostomas were inserted in the general medical wards in all but 11 (6.4%) patients; 6 (3.5%) were transferred to cardiothoracic surgeons as their pleural collections were not amenable to tube thoracostomy, 3 (1.8%) had very small collections which were treated medically and 2 (1.2%) refused further hospital treatment.

Following closed tube thoracostomy; 16 (10%) patients had complete resolution of empyema within 14 days, 34 (20.4%) had resolution with prolonged drainage or multiple tubes. Following 14 days of closed tube thoracostomy, 47 (28.1%) were discharged home with an open tube thoracostoma; 14 (29.8%) of these following basal tube insertion by cardiothoracic surgeons. Thirty eight (22.8%) patients underwent cardiothoracic surgery; 35 had pleural toilette and basal tube insertion with subsequent resolution, 1 had a decortication, and 2 required thoracostomy. Prior to resolution of empyema, a further 12 (7%) patients refused further treatment and discharged themselves from hospital.

Of the patients converted to open tube thoracostomy; 6 (12.8%) were followed up by cardiothoracic services, 11 (23.4%) had resolution of empyema, 23 (48.9%) defaulted follow up, 5 (10.6%) were transferred to cardiothoracic surgeons for a definitive procedure; toilette, decortication, thoracostomy or thoracoplasty and 2 (4.3%) demised due to ongoing pleural sepsis.

Overall length of stay was a median of 29 days (3-118 days). No differences were found with regards to length of stay between HIV infected and non-infected patients or between those stratified according to CD4 cell count. Patients on antiretroviral therapy had significantly shorter lengths of stay.

Patients were evaluated for development of complications; 4 (2.4%) developed wound sepsis at tube thoracostomy site and 26 (15.6%) developed secondary infection of their pleural space. Mortality in this series was 12.8% (22/172), 20 patients died in the medical wards and 2 died post surgical intervention.

Regarding outcomes and complications; HIV infected patients on antiretrovirals are more likely to be offered definitive cardiothoracic intervention. Length of stay was shorter and, though not statistically significant, there were no mortalities amongst patients on antiretroviral therapy. No other differences were found between the various groups (Table 2).

DISCUSSION

Empyema thoracis remains an important problem in South Africa. Majority of empyemas (>50%) are as a result of direct extension of a pulmonary parenchymal infection into the pleural space.[1, 3] Empyema in HIV infected patients is uncommon in developed countries despite the increased risk HIV infection confers to the development of respiratory infections.[8, 9] In this series, at an ecological level there appears to be a strong association between HIV infection and the development of empyema with a disproportionate number of patients with empyema being HIV infected.

The microbiology of empyema is vast. Common pathogens include *S. pneumoniae, Staphylococcus aureus, Streptococcus anginosus, Streptococcus pyogenes, Prevotella* spp. and *M. tuberculosis.*[3] Since the availability of antibiotics the bacteriology has changed; *S. pneumonia* and *S. pyogenes* infections occur less, and *S. aureus* and enteric Gram-negative organisms occur more frequently.[10, 11] Infections caused by Gram-negative organisms occur more frequently in HIV infected patients[8] and a trend which was found in our series. Infection with non-typhoidal salmonella is well described in patients with advanced HIV infection,[12] bacteraemia occurs frequently however pleuropulmonary complications are rare, with empyema usually occurring in the setting of CD4 counts <100 cells/mm^3.[3, 13, 14] The incidence of non-typhoidal salmonella reported in our series suggests that non-typhoidal salmonella should be considered potential aetiological organisms in HIV infected patients with low CD4 cell counts. The identification of *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as causes of empyema is worrying and may reflect the increased contact HIV infected patients have with health facilities. There appears to be a resurgence of important pathogens from the pre-antibiotic era in the presence of the HIV pandemic.

Tuberculous empyema has been reported at frequencies of 3-6% in developed countries,[7, 8, 15] however in developing countries TB accounts for up to 35% of cases.[4] In Southern Africa, majority of patients with tuberculous empyema are HIV infected.[16] Rates of tuberculous empyema are higher in our series than those stated in developed countries; when combining the patients with proven and clinical TB, 44.2% of empyemas were attributed to tuberculous infection. HIV infected patients tend to be given the diagnosis of clinical TB when no microbiological aetiology is found despite extensive investigation, we attribute this to clinician bias in a community where rates of HIV and TB co-infection are high. Dual infections were only found in patients with HIV infection and occurred over a range of CD4 counts (39-382 cells/mm^3).

Pleural involvement is unusual with NTM; pleural thickening adjacent to pulmonary parenchymal infection is described, pleural effusions if present are very small.[17, 18] Empyema is rare with only one report of a clearly documented empyema due to NTM in a patient with advanced acquired immunodeficiency syndrome.[19] NTM were cultured in two patients (*Mycobacterium avium-intracellulare* in one, failed identification of species in the other due to contamination), both were HIV infected with advanced disease; CD4 counts of 7 and 25 cells/mm^3 and neither was on antiretroviral therapy.

Despite thorough investigation no identifiable microbiological aetiology for empyema was identified in 23.3%; patients may have been treated with antibiotics prior to admission or specimens for anaerobic cultures may not have been optimally processed thus underreporting anaerobic infections. Anaerobic bacteria remain important pathogens in adults.[20] Rapid transfer in oxygen-free media to the laboratory and adequate anaerobic culture techniques are vital to increase diagnostic sensitivity.[10]

The treatment of empyema depends upon the pathophysiological stage in which the patient presents. Empyemas in the exudative stage, may be successfully drained via closed tube thoracostomy.[7, 21, 22] Empyemas in the fibrinopurulent stage often require more aggressive drainage procedures or video-assisted thoracoscopy.[21, 22, 23] There is contradictory evidence on the use of intrapleural fibrinolytics; they may be used as an adjunct to closed tube thoracostomy however do not reduce mortality or the need for surgery.[24, 25] Thoracoscopic drainage procedures are popular; less post operative pain, lower costs, shorter hospital stays and better cosmetic results.[24, 26] Optimal timing is important as high failure rates have been reported in cases with advanced empyema.[27, 28] Empyema in the organisational stage is best

managed via open surgery; decortication, thoracostomy or thoracoplasty to manage extensive pleural peel or control the underlying inflammatory process.[7, 21, 23] Decortication remains the modality of choice for treating advanced empyema, thoracoplasty and thoracostoma are reserved for debilitated patients who cannot tolerate aggressive surgery or those in whom decortication has failed.[21, 29] The success rate of closed tube thoracostomy for advanced or loculated empyema is low [7, 21] and the mortality of empyema treated by closed tube thoracostomy is high, 11-24%.[21, 29]

In our series 30.4% of patients were successfully treated via closed tube thoracostomy, however many required multiple tubes or prolonged drainage. Cardiothoracic intervention as a primary therapeutic measure was offered to only 6 (3.5%) patients, surgery was offered to another 46 (26.7%). Development of local complications in 15 (28.9%) patients or the necessity for multiple tube insertions in 15 (28.9%) appeared to be the criteria for surgery. Surgery was more readily offered to patients on antiretroviral therapy.

Long-term open tube thoracostomy via a tube thoracostomy cut short and the placement of a colostomy bag over the cut end of the tube is a technique (which we could not find described in the literature) used due to limited cardiothoracic resources available to us. The empyema space is allowed to drain freely and with regular withdrawal of the tube, the pleural space eventually obliterates. Of the 47 patients discharged with open tube thoracostomas, we were able to assess the outcomes in 38%. Of these, 11 (61%) patients had ultimate resolution, thus open tube thoracostomy may be a viable alternate treatment option in settings with limited cardiothoracic services. The high rate of patients lost to follow up doesn't allow for accurate assessment, however it is an intriguing alternative treatment and further prospective studies should be undertaken to assess this method further.

A significant proportion of patients refused hospital treatment; they had either required multiple tube insertion or waited for long periods of time for cardiothoracic intervention. Mortality in this series is in line with that of current literature, but may be underreported considering many patients refused hospital treatment or were lost to follow up.

Although this is a very large retrospective case series of empyema in HIV infected patients, this study is limited by the sample size of the subgroups and may not have had sufficient power to show statistical significance between the various groups. The fact that cardiothoracic surgery was offered largely only to patients on antiretroviral therapy is a further limitation as we were only able to assess whether patients underwent surgery as opposed to the need, as described in the literature, for cardiothoracic intervention. Only subjects referred to the respiratory unit were analysed and subjects with uncomplicated courses may have been excluded.

CONCLUSION

This is the largest series of empyema in HIV infected patients. It suggests that HIV infection is strongly associated with the development of empyema. We were unable to show that HIV alters the aetiology of empyema however a trend towards infection with enteric Gram-negative organisms in particular *Salmonella* spp. was found and a further case of NTM empyema is described. Clinical outcomes were similar in HIV infected and non-infected patients. Bias towards patients on antiretroviral therapy with regards to surgical intervention exists; and may translate to shorter length of stay or even reduced mortality.

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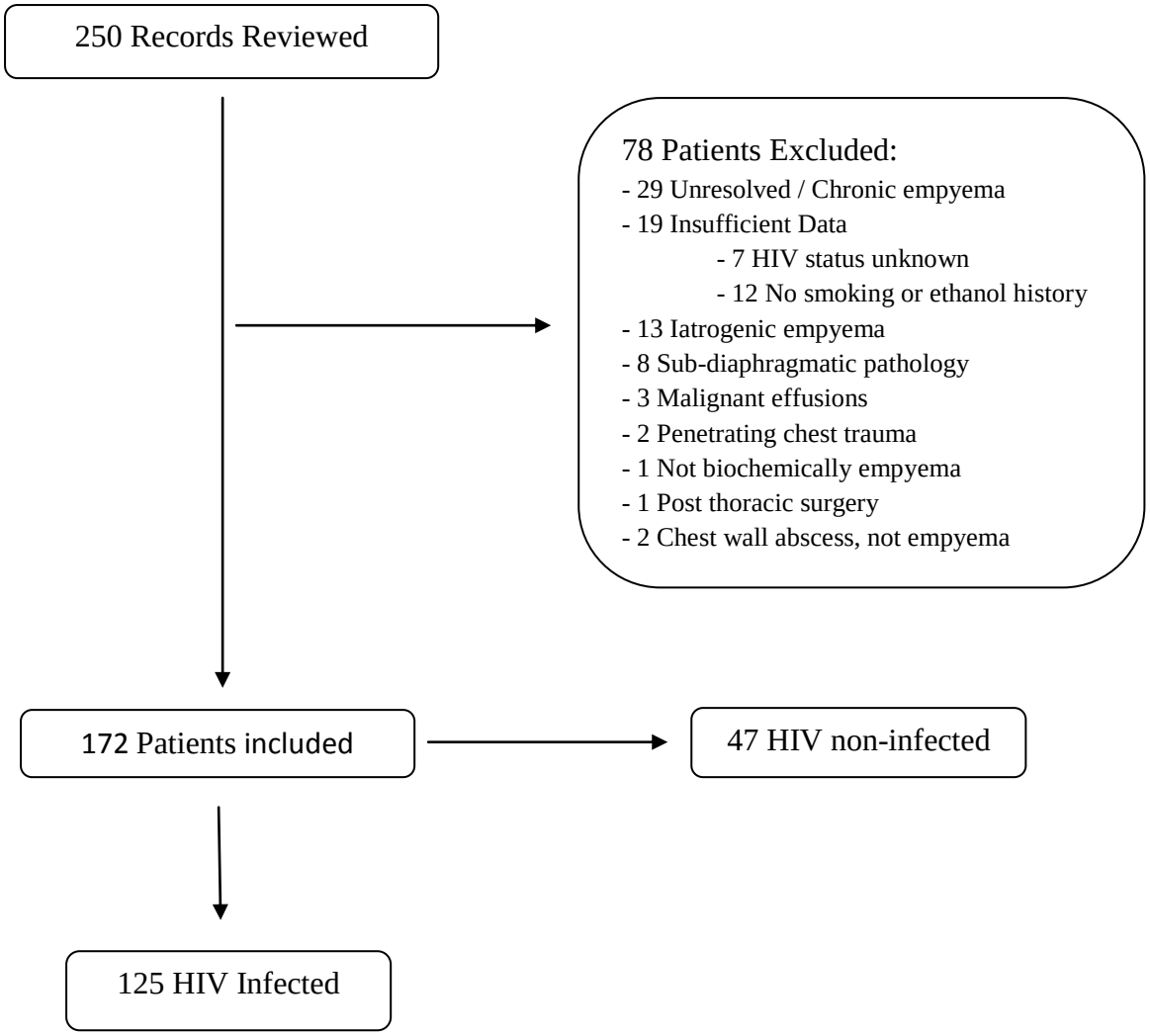
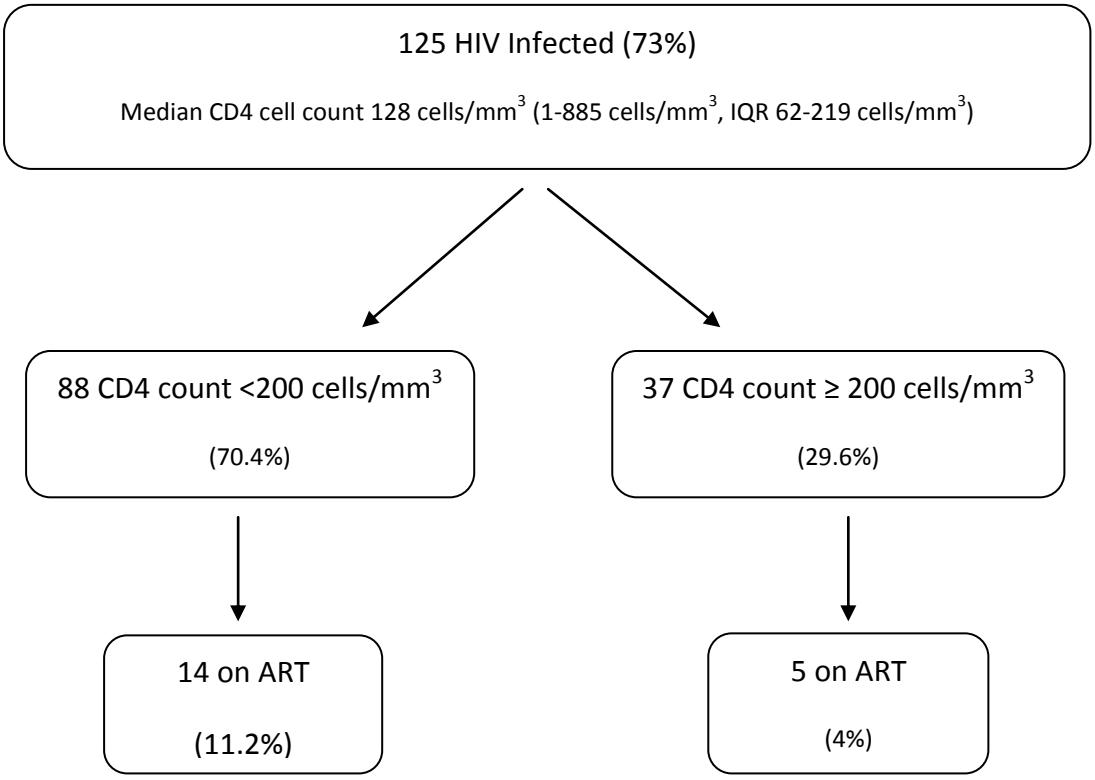
Figure 1



Flowchart summarising patient inclusion.

Figure 2



Flowchart summarising HIV infected patients' characteristics

Table 1
Microbiological aetiologies by HIV Status

	HIV Positive (n=125)	HIV Negative (n=47)
* Proven Tuberculosis:	34 (27.2%)	8 (17%)
Pleural Fluid Microscopy AFB positive	7 (20.6%)	0
Pleural Fluid culture MTB positive	18 (53.0%)	1 (12.5%)
Sputum Microscopy AFB positive	12 (35.5%)	4 (50%)
Sputum Culture MTB positive	9 (26.5%)	2 (25%)
Blood Culture MTB positive	3 (8.8%)	0
Pleural Biopsy consistent with tuberculosis	2 (5.9%)	2 (25%)
Clinical Tuberculosis:	27 (21.6%)	7 (14.9%)
* Bacterial Infection:	53 (42.4%)	10 (21.3%)
S. pneumoniae	22 (41.5%)	3 (30%)
S. anginosus (formerly *S. milleri*)	5 (9.4%)	5 (50%)
K. pneumonia	5 (9.4%)	1 (10%)
Salmonella spp.	5 (9.4%)	0
S. aureus	3 (5.7%)	0
Peptostreptococcus spp.	3 (5.7%)	1 (10%)
E. coli	3 (5.7%)	0
Prevotella spp.	2 (3.8%)	3 (30%)
Nocardia spp.	2 (3.8%)	0
H. influenza	2 (3.8%)	0
P. mirabilis	2 (3.8%)	0
P. aeruginosa	2 (3.8%)	0
E. faecium	1 (1.9%)	0
E. faecalis	1 (1.9%)	0
S. viridans	1 (1.9%)	0
S. pyogenes	1 (1.9%)	0
A. baumannii	1 (1.9%)	0
Streptococcus Group F	1 (1.9%)	0
Streptococcus Group C	0	1 (10%)
Non-tuberculous mycobacteria:	1 (0.8%)	0
Mycobacterium avium-intracellulare complex	1 (0.8%)	0
Unknown:	18 (14.4%)	22 (46.8%)

MTB = *Mycobacterium tuberculosis*

* Includes those with dual infection.
Proof of MTB often obtained by more than one method.
Polymicrobial infection in 13 patients.

Table 2
Differences in outcomes and complications of empyema

			P	OR (95%)
† HIV infected versus non infected patients:	HIV Negative (n=47)	HIV Positive (n=125)		
§ Length of stay	27 (4 – 94)	29 (3 – 118)	0.65	
Resolution Simple	4	12	0.78	0.83 (0.24 – 2.88)
Resolution Complicated	8	26	0.50	1.38 (0.54 – 3.52)
Long term open tube thoracostomy	13	32	0.80	0.90 (0.41 – 1.99)
Definitive surgical intervention	12	26	0.42	1.13 (0.31 – 1.62)
Death	6	16	0.80	0.78 (0.40 – 3.40)
Wound sepsis at tube thoracostomy site	1	3	0.88	1.21 (0.10 – 14.72)
Secondary infection of pleural space	5	21	0.17	2.19 (0.71 – 6.71)
‡ CD4 <200 versus ≥200 cells/mm^3:	CD4 < 200 (n=88)	CD4 ≥ 200 (n=37)		
§ Length of stay	29 (4 – 118)	31 (3 – 88)	0.73	
Resolution Simple	8	4	0.84	1.14 (0.32 – 4.09)
Resolution Complicated	18	8	0.82	1.11 (0.43 – 2.90)
Long term open tube thoracostomy	23	9	0.98	0.99 (0.40 – 2.45)
Definitive surgical intervention	18	8	0.89	1.07 (0.42 – 2.75)
Death	14	2	0.10	0.27 (0.06 – 1.30)
Wound sepsis at tube thoracostomy site	3	0	*	*
Secondary infection of pleural space	15	6	0.82	1.00 (0.99 – 1.00)
¤ ART versus no ART:	ART (n=19)	No ART (n=106)		
§ Length of stay	37 (19 – 71)	27 (3 – 118)	0.05	
Resolution Simple	1	11	0.69	0.47 (0.01 – 3.60)
Resolution Complicated	4	22	1.00	0.98 (0.22 – 3.52)
Long term open tube thoracostomy	5	27	1.00	1.01 (0.26 – 3.32)
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Death	0	16	*	*
Wound sepsis at tube thoracostomy site	1	2	0.39	2.89 (0.05 – 57.56)
Secondary infection of pleural space	2	19	0.74	0.54 (0.06 – 2.61)

ART = Antiretroviral therapy
‡ Adjusted in logistic regression analysis for ethanol abuse, CD4 cell count only done for HIV.
* P value, odds ratios and 95% confidence intervals were not calculated in groups which included a zero.
† Adjusted in logistic regression analysis for age and sex.
¤ Univariate analysis using 2-tailed Fisher's exact test
§ Length of stay adjusted in linear regression analysis.

W|R|H|I
The Wits Reproductive Health & HIV Institute

4 February 2012

Re: Comparison of empyema thoracis in HIV infected and non-infected patients with regards to aetiology and out comes. SAJEI *in press*

Dr G Kaye-Eddie was the principle investigator and author for the above paper and fulfilled the requirements for first authorship. I have no reservations nor objection to her submitting this work as partial requirement for the degree Masters of Medicine in the branch of Internal Medicine.

Yours sincerely

AD Black

WRHI Johannesburg National Office:
University of the Witwatersrand,
Hillbrow Health Precinct, Hugh Solomon Building,
Esselen Street (Cnr Klein St), Hillbrow,
Johannesburg 2001

Postal Address: P O 18512, Hillbrow, 2038,
Johannesburg, South Africa
Tel: +27 (0)11 358 5300 Fax: +27 (0)11 358 5400

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