MANAGEMENT AND OUTCOMES OF PATIENTS ADMITTED TO CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL WITH GRADE THREE AND FOUR PELVIC INFLAMMATORY DISEASE

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Declaration:

I Najwa Juma Aldagdag declare that this thesis is my own unaided work. It is being submitted for the degree of Master of Medicine at University of Witwatersrand, Johannesburg and has not been submitted before for any degree or examination at any other university.

19/04/2020

Dedication:

I dedicate this research report to my parents, my husband and my kids; thank you for your sacrifices.

Acknowledgement:

I would like to gratefully acknowledge my supervisor Dr Coceka Nandipha Mnyani, for her invaluable support, patience and guidance. I thank her for her valuable time that was given to me. I would also like to thank the nursing staff at the Gynaecology Department at Charlotte Maxeke Johannesburg Academic Hospital for their help.

Abstract:

Pelvic inflammatory disease (PID) is inflammation of the female upper genital tract and if not treated appropriately can result in serious complications such as chronic pelvic pain, infertility, and ectopic pregnancies. There are multiple risk factors for PID and the most common are young age at sexual intercourse, multiple sexual partners, vaginal douching, and instrumentation of the female genital tract. There have been reports of a higher prevalence of HIV infection in women diagnosed with PID. There is limited literature from South Africa on the diagnosis and management of grade three and four PID.

A retrospective study of cases of grade three and four PID, diagnosed in the period from January 2015 to December 2016, was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). A total of 98 patients were identified, 80 diagnosed with grade three PID and 18 with grade four PID. The proportion of both grade three and four PID was more in HIV-positive patients. The majority of the cases were diagnosed clinically, with ultrasound the most useful, frequently used radiological diagnostic tool. In terms of laboratory investigations, C-reactive protein was a good predictor for the diagnosis of PID. Endogenous gastrointestinal bacteria flora were the most commonly identified causative organisms.

Medical management of grade three PID had a high success rate of 72.4%, and the most antibiotics used were a combination of Ampicillin, Metronidazole and Gentamicin. The majority of patients who required surgical intervention had grade four PID, and most of the time fertility-sparing procedures were done. The requirement for second line antibiotics, surgical intervention, relook surgery, and intensive care unit admission was more in HIV-positive patients. A total of two patients died, both HIV-positive and diagnosed with grade four PID, with multidrug resistant bacteria isolated in one of them.

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List of abbreviations:

ART: antiretroviral therapy

CDC: Centre for Disease Control and prevention

CI: confidence interval

CRP: C- reactive protein

E COLI: Escherichia coli

ESR: erythrocyte sedimentation rate

HIV: human immunodeficiency virus

ICU: intensive care unit

IM: intramuscular

IQR: interquartile range

IUCD: intrauterine contraceptive device

IV: intravenous

MRI: magnetic resonance imaging

NHLS: national health laboratory services

NSFG: National Survey of Family Growth

PEACH: PID Evaluation and Clinical Health

PID: pelvic inflammatory disease

POPI: Prevention of Pelvic Inflammatory Disease

Red Cap: Research Electronic Data Capture

SD: standard deviation

STI: sexually transmitted infection

TB: Tuberculous Bacteria

TOA: tubo-ovarian abscess

US: ultrasound

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Pelvic inflammatory disease:

CHAPTER ONE:

1.1 Background and literature review:

Pelvic inflammatory disease (PID) is inflammation of the female upper genital tract, including the endometrium, fallopian tubes, ovaries and pelvic peritoneum.[1] It can be clinical (acute or chronic) or subclinical. Acute PID presents with symptoms and signs for a period of less than 30 days, while chronic PID presents with symptoms and signs for a period of more than 60 days and does not include recurrent PID. PID, especially grade three and four, can result in serious complications such as chronic pelvic pain, infertility, and ectopic pregnancies.[2] There have been suggestions that PID is associated with an increased risk of ovarian carcinoma. In a cohort study, done in western Australia, of 44 1382 women who had ever been admitted to hospital, 454 of them were diagnosed with high grade serous cell carcinoma.[3] It was found that there was a significant association between PID and the development of ovarian carcinoma with hazard ratio of 1.47 and 95% confidence interval (CI) of 1.04-2.07.[3] A life-threating complication of PID is the rupture of the tubo-ovarian abscess and is considered a surgical emergency with a mortality rate of 2%.[4] Cases of PID have also been reported during pregnancy.[5]

1.2 Prevalence of PID:

The Centre for Disease Control and prevention (CDC) has estimated that the prevalence of PID is more than one million cases annually in the United States of America (USA).[6] A National Survey of Family Growth (NSFG), which was done from 2006 to 2010 in the USA, reported that 0.5% of women had received treatment for PID in their life.[6] The prevalence has however decreased since 1985 owing to the introduction of screening for Chlamydia trachomatis, with the aim to treat cervicitis before progression to PID.[7] Data from England, from 2017, showed that 33.6% of

women in the age group between 35- 44 years had experienced at least one episode of PID.[8] A total of 10.7% had salpingitis only and no other episodes of PID, 3.7% had one episode of salpingitis and further one episode of PID, and 1.7% had salpingitis with further two recurrent episodes of PID.[8] A study from three hospitals in Australia, for the period 2009-2014, showed that the prevalence of grade three and four PID was 63.3 per 100 000 women (95% CI: 60.8-65.9), in the age group 15-44 years.[9] Regarding developing countries, a retrospective cross-sectional study done in Cameron from October 2013 to March 2014 showed that the prevalence of PID ranged between 0.3-1.7% in the 29±7.7 years age group.[10] Another study done in Abuja, Nigeria, the group of women most affected by PID had a mean age of 30.5 years, and the group least affected had a mean age of 40.5 years, and represented only 5% of those affected.[11] Regarding data from South Africa, results of a study done in Kalafong hospital, in Pretoria, where they studied the incidence of PID and other sexually transmitted infections (STIs) in relation to the HIV prevalence over five years from 2004 to 2008, showed that the incidence of PID with tubo-ovarian abscess (TOA) was 3% in 2004 and 4.6% in 2008. This was less than expected in comparison to the HIV prevalence which was 33.1% in 2004 and 29.8 % in 2008, and the explanation was that it might be because of the syndromic management of lower genital tract infections and condom use. Also, the investigators reported a reduction in the need for surgical interventions, from 19.5% in 2004 to 2.5% in 2008.[12]

1.3 Aetiology of PID:

The most common causative organisms of grade three and four PID are Neisseria gonorrhoea and Chlamydia trachomatis, but their incidence has decreased. Results of a retrospective study that was done in Sweden, through 25 years from1970 to 1994, where records of 2 499 patients were reviewed, showed that the incidence of Neisseria gonorrhoea has decreased from 42% in 1970 to 0% in 1994.[13] In the same study, they found that the incidence of Chlamydia trachomatis has decrease from 28.4% in 1985 to 7.7% in 1994.[13] Regarding complications, Chlamydia trachomatis tends to cause more

complications in comparison to Neisseria gonorrhoea. In a retrospective cross-sectional study done in Canada over 10 years, from 2004 to 2014, with 8 387 patients, they found that among 100 patients who were identified with complications, in 81% of them the PID was caused by Chlamydia trachomatis,12% by Neisseria gonorrhoea, and 7% caused by both organisms.[1] Streptococcus, Staphylococcus species and Escherichia coli (E. coli) are also considered as causative organisms for PID.[11] In the study done in Abuja, Nigeria, they found that the culture was pure of one organism in 43%, mixed culture in 2% and there was no bacterial growth in 55%.[11]The bacteria that were grown were Staphylococcus aureus in 16%, E. coli in 10%, Streptococcus faecalis in 8%, Pseudomonas aeruginosa in 4%, Streptococcus pyogenus in 3%, Klebsiella pneumonia in 3% and Proteus mirabilis in 1%.[11] Atopobium vaginae, which causes bacterial vaginosis, has also been noted to have role in PID. In a study done in Nairobi, Kenya, in 2014, to detect uncultivable causative organism of PID using polymerase chain reaction, they confirmed the presence of Atopobium vaginae in three out of 11 patients who were diagnosed laparoscopically with PID.[14] Polymicrobial infections were identified in cases of persistent TOA.[15] In another Kenyan study involving patients who had failed antibiotics for treatment of PID and surgical intervention was warranted, seven of them cultured polymicrobes, with a combination of aerobic and anaerobic gram negative bacilli, including Prevotella species, porphyromonas species, Bacteroides, E. Coli, Streptococcus viridans and Streptococcus agalactiae. Neisseria gonorrhoea and Chlamydia trachomatis were not isolated in any specimen, and the conclusion from the study was that the bacterial species which cause persistent TOA are similar to the bacterial flora of the gastrointestinal tract.[15]

Rare cases have been described where PID is a complication of systemic infection. A case report published in 2017 describes a patient with a tubo-ovarian complex found to be caused by Salmonella enterica typhi A.[16] The diagnosis was made from a laparotomy specimen and this case was considered a rare complication of enteric fever.[16] Tuberculum bacteria (TB), as a causative organism for PID, has also been reported in a case report.[17] The patient presented with a history of lower abdominal pain and fever, and had had a caesarean section two months before the presentation. She

did not respond to antibiotics and needed surgery. Histology of the laparotomy specimen showed TB and the patient had a past history of pulmonary TB.[17] Another rare causative organism of PID published as a case report is Bunkholdenia Psnomallei the causative organism of melioidosis.[18] Melioidosis is a systemic infectious disease which is endemic in North-eastern parts of Thailand, south East Asia, and Northern Australia, and requires prolonged courses of antibiotics.[18]

1.4 Risk factors for PID:

There are multiple risk factors for grade three and four PID and the most common are young age at sexual intercourse, multiple sexual partners, vaginal douching, and instrumentation of the female genital tract such as evacuation of the uterus.[19] Delay in seeking medical advice and the co-infection with HIV can contribute to progress of PID from grade one and two, to grade three and four PID.[12] A study was done to compare the effects of demographics, historical and behavioural factors among women who had PID as result of sexually transmitted and non-sexually transmitted organisms.[20] The study found that the risk factors for PID varied according to the causative organism. For sexually transmitted organisms, race, multiple sexual partners and history of previous PID were the most important risk factors identified. In cases due to non-sexually transmitted organisms, the risk is more with intrauterine contraceptive device (IUCD) users, and with history of uterine instrumentation and pelvic surgery.[20]

1.5 Effect of human immunodeficiency virus (HIV) on PID:

Some studies report a higher prevalence of HIV infection in women diagnosed with grade three and four PID.[22] A study done in Nairobi, Kenya, by Cohen et al, to study the effect of HIV-1 virus on acute salpingitis, found that 52% of the patients who were diagnosed with PID had HIV infection.[21] A case-control study was done in Abidjan, Ivory Coast, to study the impact of HIV infection on PID.[22] The study involved 170 patients

who were diagnosed with PID, 113 were HIV-negative, and 57 were HIV-positive. They found no difference between HIV-positive and HIV-negative patients in term of causative organisms and the response to treatment.[22]

1.6 Diagnosis of PID:

1.6.1 Clinical:

Diagnosis of grade three and four PID depends more on the clinical picture. Sexually active women with the following symptoms and signs must be considered as having PID until proven otherwise, and the clinician must always keep a low threshold for a PID diagnosis because of the risk of complications in cases that are not treated properly. The symptoms and signs include: abdominal pain, abnormal vaginal discharge, intermenstrual bleeding, post-coital bleeding, lower back pain, abdominal tenderness, pelvic mass, cervical excitation tenderness, and fever.[23] The 2015 CDC guidelines recommend that a diagnosis of PID should be considered if a sexually active woman presents with unexplained lower abdominal pain with at least one of the following signs on examination: cervical motion tenderness, uterine tenderness and adnexal tenderness.[6]

1.6.2 Laboratory tests:

An increase in the white blood cell count only happens in 60% of patients with PID, and an increase in the erythrocyte sedimentation rate (ESR) in 75%.[23] C-reactive protein (CRP) is considered a good parameter to determine the effectiveness of treatment; it has a sensitivity of 93% and specificity of 83%.[24] The ESR and CRP are also considered good predictive parameters to predict presence of a TOA, and to predict the severity of disease. In a study done by Omar et al, they found that CRP of more than 11.5 and ESR of more than 19.5 were good predictors for the presence of a TOA.[25]

They also found that the higher the values, the more severe the disease and the longer the period of hospital stay.[25] The measurement of CA 125 is beneficial in prediction of peritoneal involvement.[26] The predictive value of a raised CA 125 to predict salpingitis is 97%, but the predictive value of a normal CA 125 to indicate normal observation at laparoscopy is only 47%.[26] In a study done in Finland by Paavonen and Miettinen, where the CA 125 was measured in 31 patients, they found that there was an association between the size of the tubo-ovarian complex and the level of CA 125.[27] They also concluded that CA 125 is a good parameter to follow up the response to treatment. Another study done in Spain looked at the significance of tumour markers – carcinoembryonic antigen, CA 19-9 and insulin-like growth factor – to screen for acute PID.[28] Tumour markers were measured in three groups of patients, one group with confirmed PID, either laparoscopically or at laparotomy, one group who had PID excluded, and the third group (the control group) who had bilateral tubal ligation. The study found no difference in the level of carcinoembryonic antigen, CA 19-9, and insulin-like growth factor between the three groups.[28] However, CA125 was significantly higher in patients diagnosed with PID, with a mean of 78.8 U/mmol in the PID group, 23.1 U/mmol in the control group, and 24.1 U/mmol in the PID negative group, $p<0.001$.[28] The study concluded that measurement of CA125 is only recommended to justify the invasive procedure for those undergoing laparoscopy for pelvic pain.[28]

1.6.3 Endometrial biopsy:

The presence of inflammatory cells like neutrophils and plasma cells in endometrial biopsy samples helps in the diagnosis of upper genital tract infection. A study done by Kiviate et al concluded that the presence of five or more neutrophils, with the use of 400 times magnification microscopic field, as well as one or more plasma cells, with the use of 120 times magnification microscopic field, is considered the best predictor of upper genital tract infection, with a sensitivity of 92% and a specificity of 87%.[29] There is however no recommendation to use endometrial biopsy routinely as it is not cost effective.[23]

1.6.4 Imaging techniques:

Transvaginal sonography is considered the first recommended imaging diagnostic tool for the diagnosis of PID.[30] The next diagnostic tool is magnetic resonance imaging (MRI) which is more sensitive and specific than sonography, but is expensive. A study done in Finland by Tukeva et al. found that MRI was able to detect PID in 95% of patients who had laparoscopically proven PID, with a sensitivity of 95%, specificity of 89% and accuracy of 93%, compared to transvaginal sonography which has a sensitivity of 81%, specificity of 78% and accuracy of 80%.[30]

1.7 Clinical stages of PID:[31]

The Gainesville staging of PID is used for clinical assessment and there are 4 grades:

- Grade one: presents only with salpingitis with no peritonitis,
- Grade two: presents with salpingitis associated with peritonitis,
- Grade three: there is formation of a tubo-ovarian abscess as result of occlusion of the fallopian tube,
- Grade four: when the tubo-ovarian abscess ruptures resulting in generalized peritonitis [31]

1.8 Management of PID:

Once the diagnosis of PID has been made, antibiotics to cover the most common causative organisms such as Chlamydia trachomatis, Neisseria gonorrhoea and anaerobes should be started, bearing in mind that antibiotics can vary according to the

severity of the disease.[32] In-patient treatment is necessary in the following cases: failure of outpatient treatment, grade three or four PID, patients who are unable to tolerate oral treatment and pregnant patients diagnosed with PID.[32] For those suitable for outpatient management, the University of the Witwatersrand Obstetrics and Gynaecology protocol[33] and the South African guidelines for the treatment of sexually transmitted diseases recommend the use of Ceftriaxone 250mg intramuscular injection (IM) stat dose and Azithromycin 1g stat dose orally, followed by Metronidazole 400mg orally twice a day for 7 days.[34]

European guidelines recommend to start with Ceftriaxone 500mg IM as a single dose, Doxycycline 100 mg twice daily orally and Metronidazole 400mg orally for 14 days (evidence level 1a, A).[32] Alternative treatment is Ofloxacine 400mg twice daily and Metronidazole 400mg twice daily for 14 days (evidence level 1b, A), or Moxifloxacine 400mg once daily for 14 days (evidence level1a, A).[32] Outpatient treatment recommended by the PID evaluation and clinical health (PEACH) study is the use of Cefoxitin with Probencide, followed by 14 days treatment with oral Doxycycline 100mg twice a day.[35] This antibiotic regimen has a cure rate of 98% in comparison to multiple parenteral Cefoxitin[34] and there is no difference between the two regimens in terms of short- and long-term complications such as infertility and chronic pelvic pain.[36]

For patients who need in-patient management, the University of the Witwatersrand Obstetrics and Gynaecology protocol recommends this regimen: ceftriaxone 500 mg imi one dose then penicillin G 6 million ivi 6 hourly or ampicillin 1 G stat dose then 500mg 6 hourly and gentamicin 240 mg daily, metronidazole 1 G rectally twice a day or 500 mg ivi 12 hourly ,[33] the European guidelines recommend to start with Ceftriaxone 1g intravenous injection (IV) or IM, Doxycycline 100mg IV twice a day and Metronidazole 500 mg IV three times a day for 14 days (evidence level 1a, A).[32] If this regimen is not available, the alternative regimen is to start with Ofloxacine 400 mg IV twice a day and Metronidazole 500mg IV three times a day for 14 days (evidence level 1b, A), or IM Ceftriaxone 500mg and oral Azithromycin 1g, and another dose of Azithromycin after one week (evidence level 1b, A).[32]

Reed et al did a study comparing the use of broad-spectrum beta lactam antibiotics to a Clindamycin-containing regimen in the treatment of a TOA and found no significant difference between the two antibiotic regimens; the total response to medical treatment was 75%.[37] Patients who do not respond to antibiotic treatment after 72 hours will require surgical intervention, either in the form of laparoscopy, laparotomy, or imaging-guided percutaneous drainage. Failure to respond to treatment is more common in patients who have large TOAs.[35] A study done by Goharkhay et al compared the cure rate of using parenteral IV antibiotics with either primary or secondary Computed tomography (CT) or ultrasound (US) guided drainage.[38] They found that the cure rate of TOA treated with antibiotics was only 58%, while the cure rate in the group who had primary drainage and IV antibiotics was 100%. Those who failed IV antibiotics and underwent secondary drainage had a cure rate of 94%. They concluded that primary drainage of TOA decreases the period of hospital stay without an increase in the risk of complications associated with the drainage procedure,[38] but according to Chappell and Wiesenfeld in their article, the need for relook surgery might reach 20% in the group of patients who undergo fertility-sparing surgical interventions.[39]

1.9 Prevention of PID:

Primary prevention includes education about safe sex and use of condoms as this decreases the risk of primary infection and prevents reinfection after treatment.[40] According to the POPI (Prevention of Pelvic Inflammatory disease) trial, screening and treatment of asymptomatic Chlamydial cervicitis is considered an effective tool in decreasing the risk of development of PID as it decreases the risk by 80%.[41] This was a randomized control trial done in England between 2004 and 2007. A total of 2 529 women were enrolled and randomly allocated to two groups, a screening group and a control group. Vaginal swabs were collected from all participants and were examined for those in the screening group and treatment was given for Chlamydia positive women. Swabs from the control group were kept for one year with no examination. The trial found that the incidence of PID was decreased by 35% in the screening group and

concluded that screening and early treatment of Chlamydia trachomatis decreases the incidence of PID. Also, that treatment of the partner has role in decreasing the recurrence of PID.[41]

A review of epidemiological studies suggests that immunity to reinfection develops after infection with Chlamydia. A prospective study done in Birmingham, England, of 200 women who had cervical Chlamydia infection and where treatment was delayed for one month revealed that those who cleared the infection spontaneously were less likely to have re-infection due to natural immunity.[42] Another study, a cohort study which was done in Nairobi, Kenya, enrolled 200 sex workers who had Chlamydia infection at the time of enrolment.[43] The women were followed up and assessed for re-infection and the finding was that the incidence of re-infection correlates inversely with age and duration of treatment. These findings suggest that more immunity against Chlamydia develops with repeated exposure.[43] Taking these studies into consideration, which show the development of immunity against Chlamydia, make development of a vaccine against Chlamydia feasible. Development of the vaccine is still in the preclinical phase, and will be considered for females in the adolescent age group and most likely for males as well.[44]

1.10 Problem statement:

PID is a common problem in women of reproductive age, with serious complications and sequelae which can lead to death if the appropriate diagnosis is not made and treatment started on time. Most of the literature on diagnosis and management of grade three and four PID comes from the developed world, with specifically limited literature from South Africa. Given that PID is a common condition with associated morbidity and mortality, it is important to standardise diagnosis and management, and to determine the effectiveness of the different treatment options used.

CHAPTER TWO:

2.1. Aim of the study

The aim of this study was to evaluate the diagnosis, management and outcomes of women with grade three and grade four PID admitted to Charlotte Maxeke Johannesburg Academic Hospital from 01 January 2015 to 31 December 2016.

2.2 Objectives:

The objectives of the study are:

1. To describe the diagnosis of grade three and grade four PID, specifically to assess which clinical and radiological parameters were used in the diagnosis.
2. To describe the choice of antibiotics used in management of the patients.
3. To determine the microbiological causes of PID, based on laboratory specimens.
4. To describe surgical interventions used in the management of grade three and four PID.
5. To evaluate the outcomes of patients diagnosed with grade three and grade four PID.

CHAPTER THREE:

Methods

3.1 Study setting:

This study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a tertiary hospital and referral center for many other hospitals and clinics in Johannesburg. The gynaecology department at CMJAH provides care for acute and chronic cases, and there is also an oncology department. Approximately 130 acute cases are seen in the department every month, and of these, 3% are cases of PID.

3.2 Study design:

This was a retrospective record review of patients admitted at CMJAH with grade three and four PID, from 01 January 2015 to 31 December 2016. Patients were identified from registers in the gynaecology wards and also from registers in theatre and ICU.

3.3 Study population:

The study population included all patients diagnosed with grade three and four PID. Broad criteria were used for possible inclusion in the study and these were: a recorded diagnosis of PID; all patients admitted with lower abdominal pain and/or vaginal discharge; pelvic mass or suspected torsion of an ovarian cyst. Also, patients who were recorded as having had surgery for PID or exploratory laparotomy for an uncertain diagnosis.

3.4 Inclusion criteria:

All patients with a confirmed diagnosis of grade three or four PID. Diagnosis was made based on clinical symptoms and signs the patients presented with, as well as laboratory investigations and imaging techniques. Some patients had surgical interventions where the diagnosis was confirmed.

3.5 Exclusion criteria:

All patients who were initially admitted with a diagnosis of PID, but later diagnosed with other conditions.

3.6 Data collection and data analysis:

Patients' files were retrieved from the records' room at CMJAH. Information was extracted from patients' files using a standardised questionnaire (Appendix 1). The following information was collected: demographics (age, gravidity, parity, and HIV status); presenting complaint (abdominal pain, nausea, vomiting, and vaginal discharge); findings on general examination and abdominal examination; blood and other special investigations. Details on medical and surgical management were also collected, and also information on need for ICU admission. Results of investigations done, but not recorded in the patients' files were looked up in the National Health Laboratory Services (NHLS) database. Data were then captured on Research Electronic Data Capture (REDCAP),[45] and then exported onto Microsoft Excel. Data analysis was done using IBM SPSS Statistics 25 software. Continuous data were analysed using means and standard deviations, and medians and interquartile ranges as appropriate. Categorical data were analysed using frequencies and percentages.

3.7 Ethics:

Ethical approval was obtained from the human research ethics committee at the University of the Witwatersrand, clearance number M171135 (Appendix 2). No names or any other form of identification were entered onto the data sheets. Study numbers were assigned to patients, and names and hospital numbers were kept separately and used if there was a need to follow up any further information needed.

CHAPTER FOUR:
RESULTS

4.1 Demographics

In this retrospective record review, a total of 98 patients were admitted to CMJAH with a diagnosis of grade three and four PID between 1 January 2015 and 31 December 2016. The demographics of the patients are presented in Table 1. The mean age of the patients was 30.2 years, standard deviation (SD) ± 6.8. The median gravidity was 1, interquartile range (IQR) 1,2, and the median parity was 1, IQR 0,2. With regards to HIV status, 61/98 (62.2%) were HIV-positive and 28/61 (45.0%) were on antiretroviral therapy (ART). A total of 19/28 (67.0%) patients that were on ART were on an efavirenz-based fixed dose combination; 1/28 (3.6%) was on a combination of Aluvia, Zidovudine and Lamivudine, and 1/28 (3.6%) on a combination of Abacavir, Efavirenz and Lamivudine. The ART regimens of 7/28 (25.0%) were unknown. The duration of treatment was known for 21 patients with a median of 36 months, IQR 15,48.

4.2 Presenting complaints and findings on examination

The commonest presenting complaint was abdominal pain, present in 95/98 (96.9%) of the patients. The other common presenting complaints were vaginal discharge and bleeding, dyspareunia, and nausea and vomiting – Figure 1. The general condition of the patient on examination was documented in 57/98 (58.1%) and 30/98 (30.6%) were well, while 27/98 (27.6%) were documented as ill-looking. The blood pressure was more than 120/80 mmHg in 38/98 (38.8%) and was less than 120/80 mmHg in 60/98 (61.2) The mean pulse rate was 106 beats per minute (SD ±18.8) and the mean temperature was 37 degree Celsius, SD± 0.9.

Table 1: Demographics of patients admitted with grade three and four PID, n=98

Demographics	**n (%)**
Age, years: • Mean, SD: • <25 • 25-35 • >35	 30.2 (6.8) 22 (22.5) 58 (59.2) 18 (18.3)
Gravidity: • Median (IQR): • 0 • 1-2 • 3-4 • >4	 1 (1,2) 23 (23.5) 51 (52.1) 19 (19.3) 5 (5.1)
Parity: • Median (IQR) • 0 • 1-2 • 3-4 • >4	 1 (0,2) 33 (33.6) 50 (51.1) 14 (14.3) 1 (1.0)
HIV status • HIV-positive • CD4 count, median (IQR) **On ART:** • Yes • No • Unknown	 61 (62.0) 324 cells/mm^3 (133,604) 28/61 (45.9) 32/61 (52.5) 1/61 (1.6)

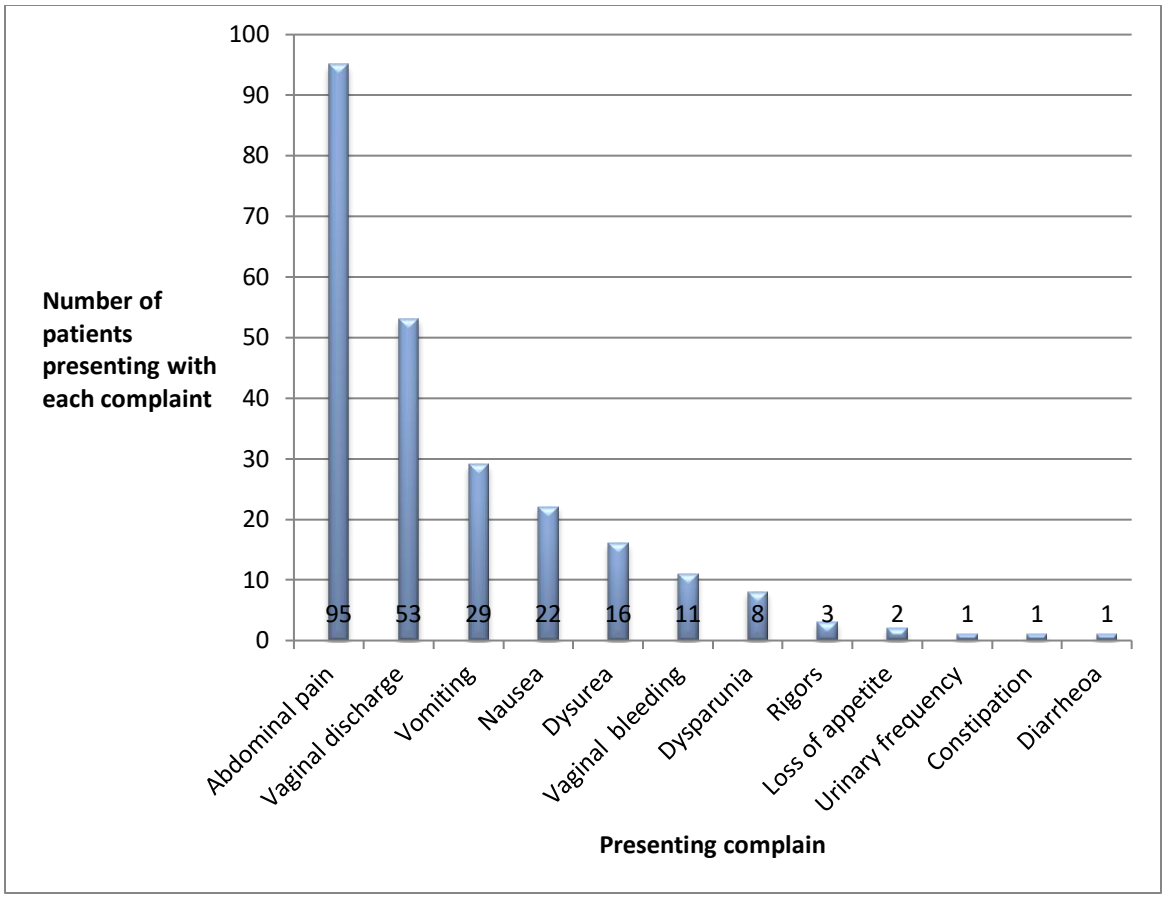

Figure 1: Presenting complaints

Overall, 96/98 (98.0%) of the patients had a tender abdomen; 79/98 (80.6%) had cervical excitation tenderness, 48/98 (49%) had signs of peritonitis, and 13/98 (13.3%) had a distended abdomen. An abdominal mass was palpable in 10/98 (10.2%) of the patients – Figure 2.

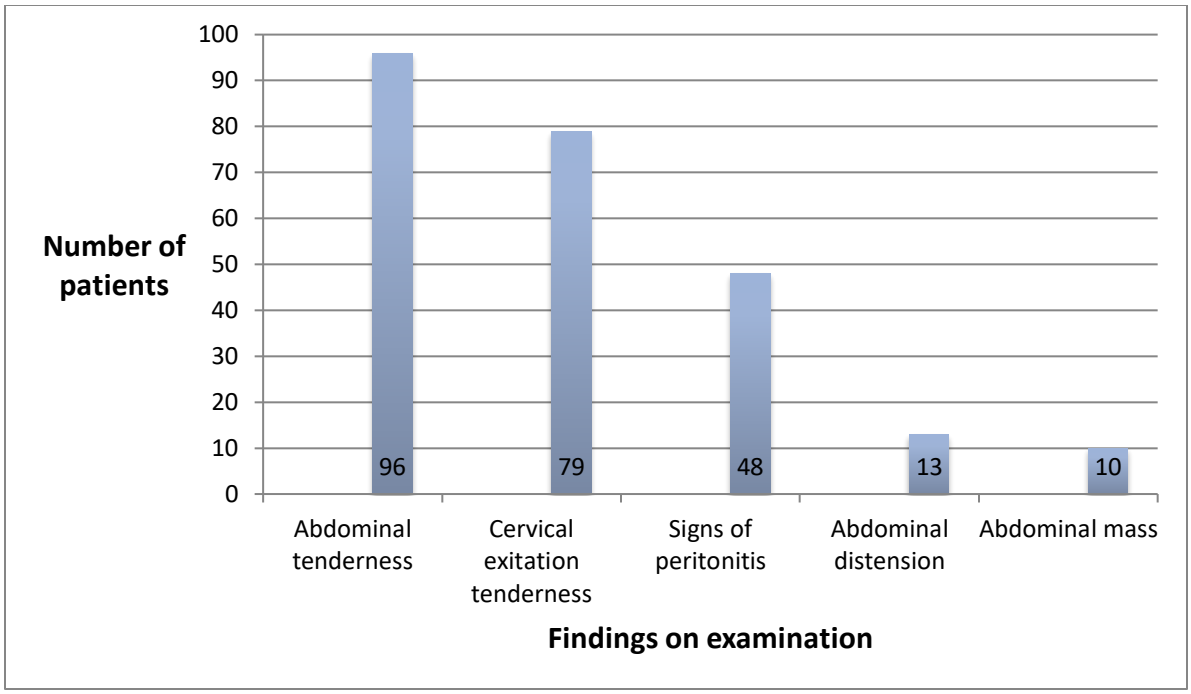

Figure 2: Finding on abdominal examination

4.3 Special investigations:

4.3.1 Blood investigations

Of the special investigations done at the time of presentation, a blood gas was done in 16/98 (16.3%) patients. The pH was normal in 12/16 (75.0%), in the acidotic range in 3/16 (18.8%) and in the alkalotic range in 1/16 (6.2%). PCO_2 was normal in 8/16 (50%) and it was higher than normal in 8/16 (50%). The lactate was abnormal in 4/16 (25%) and was normal in 12/16 (75%). A full blood count was done in 96/98 (96.9%) patients. The white cell count was within the normal range in 48/95 (50.5%) and was higher than the upper limit of normal in 47/95 (49.5%). The platelet count was normal in 80/96 (83.3%); 2/96 (2.1.0%) had thrombocytopaenia and 14/96 (14.6%) had thrombocytosis. A C-reactive protein was done in 82/98 (83.6%) patients with a mean of 160.41, SD±3.06. Renal function test was done in 97/98 (98.9%) with a mean for urea of 4.40 mmol/l (SD±3.06) and a mean for creatinine of 74 mmol/l (SD± 45.8). A blood culture

was done in 31/98 (31.6%) patients and there was bacterial growth in 9/38 (29.0%) of the specimens – results are shown in Table 2.

Table 2: Bacterial growth on blood cultures, n=9

Type of bacterial growth and antibiotic sensitivity	Number
Streptococcus viridians sensitive to Penicillin	1
Streptococcus pyogenes sensitive to Ampicillin and Clindamycin	1
Klebsiella pneumonia sensitive to Ertapenem	1
E. Coli sensitive to Augmentin	1
Corynebactrium species sensitivity not recorded	1
Coagulase negative staph, sensitivity not recorded	1
Proteus mirabilis sensitive to Augmentin	1
Bacteroid ovatus sensitive to Augmentin	1
Bacterial fragilis sensitive to Augmentin	1

4.3.2 Radiological investigations

An ultrasound was done in 93/98 (92.8%) of the patients, with 65/93 (69.9%) done by a gynaecology registrar and 4/93 (4.3%) reviewed by a consultant; 4/93(4.3) were done by a consultant. A total of 23/93 (24.7%) ultrasounds were done by a radiologist and 1/93 (1.1%) by a general surgery registrar. Five patients had a CT scan done and the findings supported the ultrasound diagnosis of PID in three patients. A pelvic mass found in 91/98 (95.7%), and were unilateral in 78/91 (85.7%) and bilateral in 13/91 (14.3.%). The size of the pelvic mass was recorded for 61 patients, with a mean length of the mass of 5.65 cm (SD± 2.57) and mean width of 4.04 cm (SD± 1.82). Free fluid in the abdomen was found in 29/98 (29.6%) of the patients.

4.4 Management

Of the 98 patients, 80 were diagnosed as having grade three PID, and 18 grade four PID. A total of 71/98 (72.4%) patients were treated medically and 27/98 (27.5%) had surgical interventions.

4.4.1 Medical management

Of the antibiotics used as first line treatment, the majority of patients received a combination of Ampicillin, Metronidazole and Gentamicin. The median duration of treatment with first line antibiotics was 6 days. Overall, 25/98 (26%) of patients required second line antibiotics which consisted of Ceftriaxone and Clindamycin, or Augmentin alone, or Tazosin alone. The reasons for changing to second line antibiotics were: in 17/25 (68.0%) due to no response to first line antibiotics; 3/25 (12%) changed after surgery; 2/25 (8%) changed due to allergic reaction to first line antibiotics; 3/25 (12%) changed according to antibiotic sensitivity results from blood cultures and in 1/25 (4.0%) the reason was unknown. The median duration of second line antibiotics was 4 days. A total 3/25 (12.0%) patients required third line antibiotics which were Tazosin for two patients and Augmentin for one patient. The reasons for changing to third line antibiotics in the three patients were: one was according to blood culture and sensitivity results; one was changed after surgery and for one patient no reason was recorded. In terms of HIV status for the patients who required second line antibiotics, the majority, 20/27 (74.1%), were HIV-positive, 5/27 (18.5%) were HIV-negative and 2/27 (7.4%) had an unknown status. The median duration of ART was 10 months (IQR1.8,48) in the group that did not require second line antibiotics and 24 months (IQR 9.5,72) for those who required second line antibiotics. The median CD4 count was 342 cells/mm^3 (IQR 216,586) for those who required second line antibiotics and 577 cells/mm^3 (IQR 300,695) in those who did not.

4.4.2 Surgical management

A total of 27 patients had a surgical intervention and the reasons for surgery were documented as: an acute abdomen for 13 patients (48.0%), no improvement on first line antibiotics for 4 (15.0%), no improvement on second line antibiotics for 3 (11.1%), suspected ovarian torsion in 1 (3.7%), suspected appendicitis in 1 (3.7%), PID Grade 4 in 1 (3.7%), previous multiple admissions for PID in 1 (3.7%), and for an acute abdomen and renal dysfunction in 1 (3.7%). The reason was not documented for 2/27 (7.4%) patients. For those patients who required a surgical intervention, 21 (77.7%) were HIV-positive and 6 (22.2%) were HIV-negative. Details of the surgical interventions are presented in Figure 3.

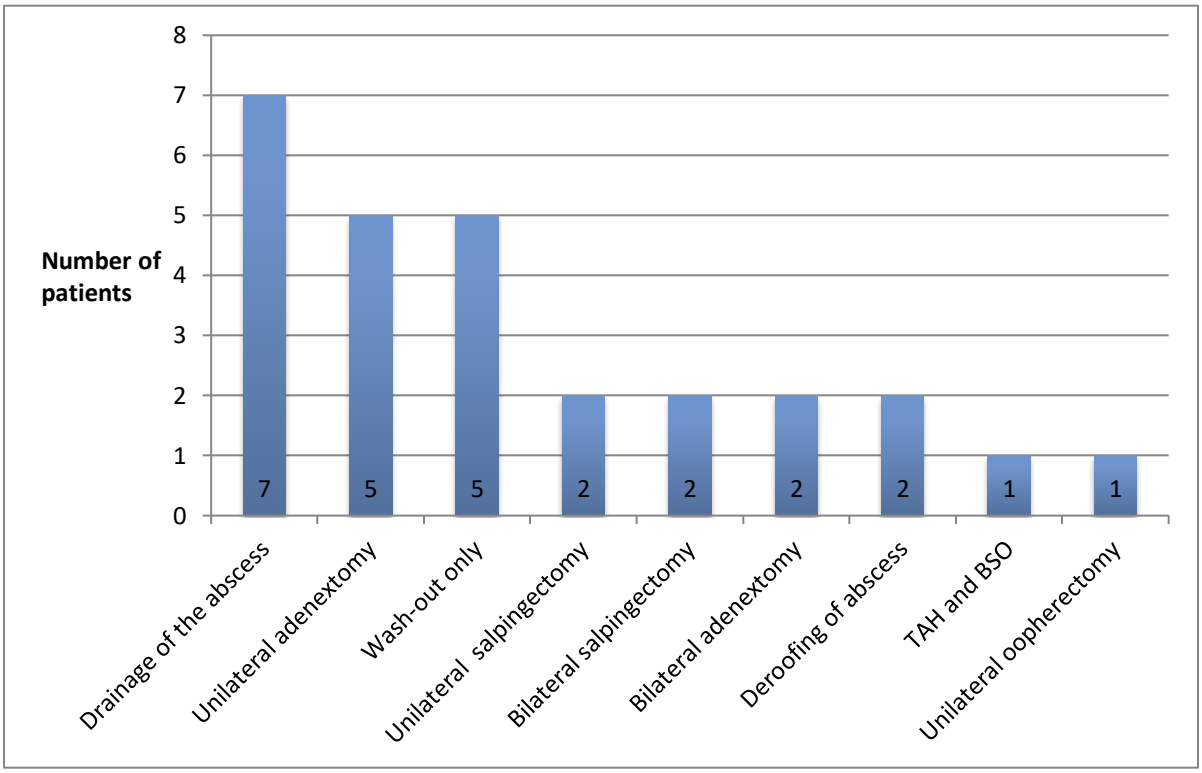

Figure 3: Details of surgical management, n=2

Sepsis was found to be generalised involving all four abdominal quadrants in 8/27 (29.6%), localized in 7/27 (25.9%), and no sepsis was found in 1/27 (3.7%). The extent of the sepsis was not documented in 11/27 (40.7%). A surgical specimen was sent for microscopy, culture and sensitivity for 21/27 (77.8%) patients. Organisms most commonly cultured were Enterococcus faecium, Pseudomonas aeruginosa, Proteus hauseri, Klebsiella pneumonia, E. Coli, Proteus mirabilis, Streptococcus salivarius Streptococcus anginosus and Alcaligenes fecalis. Histology results are presented in Table 3.

Table 3: Histology results of the patients who had a surgical intervention, n=14

Histology result	**n (%)**
• Acute osuppurative salpingitis • Sever suppurative salpingitis and peritonitis. • Ectopic pregnancy with paratubal pyogenic abscess. • Sever peritonitis	5 (35.7) 4 (28.5% 1 (7.2) 4 (28.6)

4.5 Outcomes

A total of five patients required a relook laparotomy and the reasons were: 3/5 patients were still pyrexial five days after surgery and five days on second line antibiotics; 1/5

patients was still pyrexial with tachycardia after 48 hours on Tazosin; and 1/5 was confirmed to still have intraabdominal collections on CT scan. Of the five patients who required a relook laparotomy, 4 (8.0%) were HIV-positive and 1 (20.0%) was HIV-negative. Out of the 27 patients who had surgery, seven required admission to the intensive care unit (ICU); 6 (85.7%) were HIV-positive and 1 (14.2%) was HIV-negative. The mean duration of stay in ICU was 3.3 days, SD± 1. The reasons for ICU admission were a need for ventilatory support and inotropes secondary to septic shock.

Of the 98 patients, 96 (97.9%) resolved and were discharged. The median of total days spent in the hospital was 5 days with (IQR 3,7). However, of the discharged patients, four required readmission, two of them due to recurrence of PID, one due to intraabdominal sepsis and enteroatmospheric fistula, and one due to chronic pelvic pain. A total of 2 patients out of the 98 admissions died, and both were HIV-positive.

4.6 Details of the deaths:

First patient: This was a 44-year-old patient who was HIV positive and was on ART for seven years, with a CD4 count of 302 cells/mm^3. Her first presentation was for lower abdominal pain, vaginal discharge, nausea and vomiting, and night sweats. A pelvic mass was found on ultrasound and the patient was discharged after tumour markers were pulled. She presented again four days later and was ill-looking, pyrexial and had raised septic markers. She was admitted and started on Keflex. After four days of antibiotics with no improvement, she went into septic shock. An exploratory laparotomy was done and the patient was found to have generalized abdominal sepsis. A bilateral adenexectomy and wash out were done, and the patient required ICU admission due to septic shock. She required inotropes and ventilatory support, and was converted to Augmentin and Etarpenem, but did not respond to treatment and died of multiple organ failure, her intraoperative specimen showed sever salpingitis and peritonitis, but did not grow any organisms.

Second patient: This was a 26-year-old patient who was HIV-positive and not on treatment, and her CD4 count was unknown. She was referred from another hospital where an exploratory laparotomy and left adenexectomy were done for Garde four PID.

She was referred for lower abdominal pain and a septic wound. The patient was found to still have signs of sepsis and her blood culture grew gram negative bacilli, Klebsillla pneumonia, sensitive to Ertapenem. An abdominal ultrasound showed collections in the Pouch of Douglas. The patient was managed on intravenous antibiotics and a relook laparotomy was done on day seven of admission where a frozen pelvis was found. The wash-out specimen was sent for microscopy, culture and sensitivity, and grew multiple organisms – Alcaligenes Faecalis, E. coli Enterococcus faecium and Klebsilla pneumoniae. She went into septic shock and required admission to ICU for ventilatory support and inotropes. She died on day three in ICU, due to septic shock and multiorgan failure.

CHAPTER FIVE:

DISCUSSION

In our study, PID occurred in women 35 years and younger, and the majority were HIV-positive. Clinical findings were used for provisional diagnosis, and ultrasound played an important role in supporting the clinical findings. CRP was a good predictor in the diagnosis of PID. The most common causative microorganisms were endogenous gastrointestinal bacteria flora, and medical management was effective in management of grade three PID. Surgical intervention was required in all patients diagnosed with grade four PID, and some with grade three PID. The response to treatment, the need for surgical interventions and ICU admission were influenced by HIV status.

5.1 Relationship between demographics and PID:

In this study, we found the most affected age group were young patients, with more than half between the ages of 25 and 35 years. This finding is in keeping with results from the study by Spencer et al[11], where they found the mean age of patients most affected by PID was 30.5 years. This can be explained by the fact that PID is a sexually transmitted disease and it is likely to affect the most sexually active age group. The proportion of cases of PID was more in HIV-positive patients in our study, and this is consistent with results from a study by Cohen et al[21], where they found that 52% of their patients who were diagnosed with PID were HIV-positive. This can be explained by the fact that individuals who are HIV-positive are more susceptible to sexually transmitted diseases, predisposing to PID. The difference between their study and our study is that their patients who were HIV-positive were immunologically suppressed. In our study, most of the patients did not have severe immune suppression and the median CD4 count was 324 cells/mm^3.

5.2 Diagnosis of PID:

In the majority of cases, the diagnosis of PID was made clinically. A high suspicion of PID was raised when patients presented with abdominal pain, vaginal discharge, nausea and vomiting. The signs commonly found were tachycardia, mild pyrexia, abdominal tenderness and cervical excitation tenderness. These symptoms and signs are consistent with those in the CDC guidelines for the diagnosis of PID.[6] Investigations were used to support the diagnosis of PID and these included blood tests and radiological diagnostic tools. Full blood count, kidney function and C-reactive protein were done for most of the patients. The white cell count was not markedly deranged from the normal, but the C –reactive protein was high in most of the patients and was a good predictor for the diagnosis of PID, findings similar from a study by Omar et al.[25]

In terms of radiological investigations, ultrasound was the most frequently used diagnostic tool. In patients who had surgery and PID proven histologically, the initial diagnosis was made on ultrasound. This finding is similar to that in the study by Tukeva et al[30], where they found that ultrasound was the most reliable diagnostic radiological tool. It is also cost-effective in comparison to doing a CT scan which had a minor role in the diagnosis of PID in our study.

5.3 Aetiology of PID:

We found that although mixed cultures were detected in some histology specimens, grade three and grade four PID tended to be due to infection with one type of microorganism. This finding is different to that reported by Cohen et al[15] where they found that TOAs were caused by multiple organisms. Our study findings did agree though with their results in terms of the type of the microorganism identified where we noted that Neisseria gonorrhoea and Chlamydia trachomatis were not the causative organisms of TOAs in those patients who had culture results. Most of the organisms identified are endogenous gastrointestinal bacterial flora and included Escherichia Coli, Enterococcus faecium, Klebsiella pneumonia, and Alcaligenes Faecalis. All specimens

that were sent for histology did show acute inflammation, or acute-on-chronic inflammation. Ectopic tubal pregnancy complicated by an abscess was also confirmed on histology in one patient and that may indicate that PID can coexist with early pregnancy as was reported by Blanch AC, et al.[5]

5.4 Management of PID:

5.4.1 Medical management and most effective antibiotics:

The majority of patients were successfully treated medically (72.4%) and most of them received Ampicillin, Metronidazole and Gentamicin as first line antibiotics. The success rate of this combination was noted to be 78.0%, although when we look at the culture and sensitivity results these antibiotics were not noted as the most effective, but clinically they were effective. Second line antibiotics were required more in HIV-positive patients than in HIV-negative patients. The second line antibiotics most commonly used were a combination of Clindamycin and Ceftriaxone, and the improvement rate was noted to be 85%, which appears to be more effective than the combination of Ampicillin, Metronidazole, and Gentamicin. The number of patients who received second line antibiotics was small so might not be comparable to the group who received first line antibiotics, but looking at the culture and sensitivity results it was regularly noted that the microorganisms were sensitive to a Cephalosporin.

The other antibiotic that was most used was Augmentin and patients' condition improved in 71.4% of cases when it was used alone, and in 87.5% of cases when it was used as a combination with another antibiotics. Looking at the culture and sensitivity results, Augmentin was the most frequent antibiotic which microorganisms were sensitive to. Another effective combination was Penicillin, Gentamicin and Metronidazole, but this combination is similar to the standard first line antibiotic regimen. Penicillin and Ampicillin are both beta lactam inhibitors, so it appears that the use of a beta lactam inhibitor in combination with other antibiotics is fairly effective as concluded

by Reed et al about the efficacy of broad-spectrum antibiotics in treatment of grade three PID.[36]

5.4.2 Surgical management:

Looking at the number of patients who needed surgery (27), most of them had an acute abdomen and 18/27 were proven as grade four PID. This shows that the diagnosis and surgical management were appropriate. The majority of patients who had surgery had fertility-sparing procedures where evacuation of the abscess was done, either by drainage or deroofing. The second most common procedure done was unilateral adenextomy. A relook laparotomy was done for 5/27 (18.5%) patients who had satisfactory primary surgery but had no clinical improvement after the surgery. The necessity for relook surgery was not correlated to the degree of intrabdominal sepsis at the first surgery. It was noted that the group of patients who had localised intraabdominal sepsis at the initial surgery were more likely to need a relook laparotomy than those who had generalized intraabdominal sepsis. It is likely that the fact that the majority of the primary surgery were fertility-sparing procedures contributed to the need for relook laparotomy. This is in keeping with what was reported by Chappel and Wiesenfeld in their review article[38] where they reported that the need for repeat surgery with conservative surgery reach 20%. Also, HIV status might have played a role as most of the patients in our study who required relook surgery where HIV-positive.

In general, the success rate of surgical interventions was high and the need for ICU admission was more in HIV-positive patients. Overall, HIV infection affected the response to treatment, the necessity for surgical interventions and the need for ICU admission. This finding is in agreement with what was reported by Kamenga et al[22] where they found that HIV-positive patients were more likely to require surgical intervention than HIV negative patients, with odds ratio of 6.5, CI of 1.1 to 67.5.

5.5 Overall outcomes:

In general, the management of grade three PID was appropriate as there were no deaths reported among patients in this category, whether they were managed medically or in combination with surgical interventions. The death rate among patients with grade four PID was high (18%) in comparison to that in a study by Wiesenfeld and Sweet,[4] where they reported a death rate of 2% in patients with grade four PID. Two patients died as result of sepsis complicated by septic shock and multiple organ dysfunction. One patient was not treated appropriately where she should have had second line antibiotics when she did not show any improvement to first line antibiotics, and that could make this death avoidable. Regarding the other patient, there was a delay in her relook laparotomy, but also the culture of her intraoperative specimen showed growth of Alcaligenes Faecalis with multidrug resistance, and this might have made her death unavoidable.

5.6 Strengths and limitations:

The strength of this study is that broad criteria were used to identify patients with grade 3 and 4 PID, so it is unlikely that patients who fitted the inclusion criteria were missed. Also, detailed information on each patient was collected. The major limitation of this study is that it is a retrospective study with a small sample size. In addition, some investigations were not done for all the patients.

5.7 Recommendation:

Owing to the acute and chronic complications of grade three and four PID, clinicians should have a low threshold for the diagnosis of PID, especially for sexually active young women, where early treatment decreases the morbidity and mortality.

5.8 Conclusion:

In conclusion, diagnosis of PID depends on clinical findings with ultrasound considered the most appropriate, supportive diagnostic tool. Most causative organisms are endogenous gastrointestinal flora. The use of a combination of broad-spectrum antibiotics has a high success rate in the management of grade three PID, with the need for surgical intervention mandatory in some cases. For grade four PID, surgical interventions are the main form of management.

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Appendices

APPENDEX 1: Data collection tool

Study number:

Date of data collection:

1. Demographics

Age _____ Parity _____ Gravidity _____

HIV status: positive/negative/unknown

If HIV positive, on ART: yes/no/unknown CD4 count: _____

If on ART, date started _____ or how long on treatment _____

What ART: _____

2. Presenting complaint

Abdominal pain: yes/no/unknown

Vaginal discharge: yes/no/unknown

Nausea: yes/no/unknown Vomiting: yes/no/unknown

Other, specify:

_____

Findings on admission

3. General examination findings

Well/ill-looking/unknown

BP value:

Pulse rate:

Temperature:

4. Abdominal examination findings

Distended: yes/no/unknown

Tender: yes/no/unknown

Signs of peritonitis: yes/no/unknown

Abdominal mass palpable: yes/no/unknown

Cervical excitation tenderness: yes/no/unknown

5. Special investigations

Blood gas: done/ not done/ unknown

Metabolic status on blood gas: acidotic (respiratory or metabolic)/alkalotic (respiratory or metabolic) **Blood gas parameters:**

Ph

PO2

PCO2

Lactate

Bicarbonate

Base excess

White cell count:

Platelets:

C-reactive protein:

Urea:

Creatinine:

Blood culture results: no growth/bacterial growth/unknown

If bacterial growth, organism grown:

_____

Not Hospital acquired/ hospital acquired.

Sensitivity results:

_____

Were the antibiotics changed according to the sensitivity: yes/no /unknown.

Other blood results:

_____

Abdominal ultrasound findings:

Pelvic mass: yes/no/unknown If yes, size of the mass:

_____

Free fluid in the pelvis/abdomen: yes/no/unknown

Other ultrasound findings, specify:

_____

Who did the ultrasound: O&G registrar/ O&G consultant/ radiologist

Other, specify: _____

Other radiological investigations, specify:

_____

6. Management

First line antibiotics used:

_____

Duration of treatment with first line antibiotics: _____ days

Requirement for second line antibiotics: yes/no/unknown

If yes, reason:

_____

Duration of treatment with second line antibiotics: _____ days

Requirement for surgery: yes/no/unknown

If yes, reason for surgery:

_____

Surgery performed:

_____

If hysterectomy done: total /subtotal/unknown.

Intraabdominal sepsis: localized / generalized/ unknown

Washout: yes/no/ unknown.

Specimen from surgery sent for:

Histology: yes/no/unknown

If yes, histology results:

Microscopy, culture and sensitivity (MCS): yes/no/unknown

If yes, MCS results:

_____

Requirement for relook laparotomy: yes/no/unknown

If yes, reason for relook laparotomy:

_____

_____

_____

Requirement for ICU: yes/no/unknown

If yes, reason for ICU admission:

_____

_____

_____

Period of ICU admission:

What were the antibiotics used during ICU admission?

What were the antibiotics the patient was discharged on?

Requirement for readmission to hospital: yes/no/unknown

If yes, reason for readmission:

_____

Outcome: PID resolved and discharged/ died

Total number of days in hospital: _____ days

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R14/49 Dr Najwa Aldagdag

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M171135

NAME: (Principal Investigator)	Dr Najwa Aldagdag
DEPARTMENT:	Obstetrics and Gynaecology Charlotte Maxeke Johanesburg Academic Hospital
PROJECT TITLE:	Management and Outcomes of Patients Admitted to Charlotte Maxeke Johannesburg Academic Hospital with Grade Three and Four Pelvic Inflammatory Disease
DATE CONSIDERED:	24/11/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Coceka Nandipha Mnyani
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/02/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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by Najwa Aldagdag

Submission date: 27-Apr-2019 07:00PM (UTC+0200)
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ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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