Post-Cesarean Section Peritonitis at a Referral Hospital in Rwanda: Factors Associated with Maternal Morbidity and Mortality

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background: Post-cesarean section peritonitis is the leading cause of maternal morbidity and mortality at the main referral hospital in Rwanda. Published data on the management of post-cesarean section peritonitis is limited. This study examined predictors of maternal morbidity and mortality for post-cesarean peritonitis.

Methods: We performed a prospective observational cohort study at the University Teaching Hospital Kigali (CHUK) from January 1 until December 31 2015, followed by a retrospective chart review of all subjects with post-cesarean section peritonitis admitted to CHUK from January 1 until December 31, 2014. All patients admitted with the diagnosis of post-cesarean section peritonitis undergoing exploratory laparotomy at CHUK were enrolled. Patients were followed to either discharge or death. Study variables included baseline demographic/clinical characteristics, admission physical exam, intraoperative findings, and management. Data were analyzed using STATA version 14.

Results: Of the 167 patients enrolled, 81 survived without requiring hysterectomy (49%), 49 survived requiring hysterectomy (29%), and 36 died (22%). In the multivariate analysis, severe sepsis was the most significant predictor of mortality (RR=4.0 [2.2-7.7]) and uterine necrosis was the most significant predictor of hysterectomy (RR=6.3 [1.6-25.2]). There were high rates of antimicrobial resistance (AMR) among the bacterial isolates cultured from intra-abdominal pus, with 52% of bacteria resistant to third-generation cephalosporins.

Conclusions: Post-cesarean section peritonitis carries a high mortality rate in Rwanda. It is also associated with a high rate of hysterectomy. Understanding the disease process and identifying factors associated with outcomes can help guide management during admission.

Dedication

I dedicate this thesis to the women of Rwanda, to my patients on Wards 4 and 5, to those who survived post-cesarean section peritonitis and especially to those who did not. I dedicate this thesis to the Rwandan nurses, doctors, social workers, and care takers who continue to address this disease.

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Acknowledgements

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1. Introduction

The cesarean section (CS) is the most common major surgical procedure performed worldwide, with at least 18.5 million cesarean sections performed each year.[1] There has been a global increase in the rates of CS over the past decade, with no evidence of abating.[2] In resource-limited countries, cesarean section rates are a marker for access to emergency obstetric care, with corresponding reductions in maternal mortality.[3] Several studies have shown an inverse relationship between nationwide CS rates and maternal mortality rates over the last decade,[1,4,5] with rates of CS above 5% associated with the greatest reductions.[1] However, rates of CS greater than 10% at a population level were not associated with reductions in maternal mortality rates.[3] This is because cesarean sections are still major surgical procedures with risks of surgical site infections, injury to other organ sites, and other severe morbidities.[6,7]

1.1 Post-cesarean section surgical site infections

Cesarean sections are associated with a 5-fold to 20-fold increased risk of infection when compared to vaginal delivery.[6] Post-cesarean surgical site infection rates vary globally, ranging from 3-8% in the United States to 3-24% in sub-Saharan Africa.[8-13] This is consistent with other data on all hospital-acquired infections (HAIs) in sub-Saharan Africa, showing a significantly higher average rate of HAI compared to Europe (10.1% versus 7.1%). Surgical site infection (SSI) is most commonly defined as an infection at the surgical site within thirty days of the operative procedure, further

divided into superficial incisional (involving the skin of the incision), deep incisional (involving the muscle or fascia beneath the skin incision), and organ/space (involving any part of the anatomy other than the incision that was opened or manipulated during the operation).[14] The majority of SSIs are superficial (70-90%).[9,15-18] SSIs can be considered a proxy indicator of surgical quality, with higher rates of SSI suggesting lower overall surgical quality (poor tissue handling, longer operative times, greater blood loss, improper antiseptic skin preparation, etc.).[15]

Risk factors for surgical site infection after cesarean section are multifactorial. Timing of prophylactic antibiotics, chlorhexidine skin preparation, surgical techniques, and operating room safety checklists and maintenance are some factors associated with reduced surgical site infections.[9,11,15-22] Increased length of surgery, maternal comorbidities and immune status, obesity, premature rupture of membranes (PROM), and increased vaginal exams have been associated with increased surgical site infection risk after cesarean section.[15] In resource-limited countries, tracking maternal morbidity and mortality due to post-cesarean section infections is difficult. First, as indicated by the paucity of data on surgical site infections in sub-Saharan Africa, these data are not systematically recorded. Second, there is heterogeneity in the reported literature on the definition of surgical site infection.[20] Third, there is likely underreporting of maternal mortality due to infectious etiologies.[23] It is estimated that 10% of all maternal deaths worldwide are associated with bacterial infections surrounding childbirth, but there is

no estimate regarding the global impact of bacterial infections arising after cesarean section.[23]

1.2 Peritonitis and abdominal sepsis

Information on post-cesarean section peritonitis, a sub-category of organ/space surgical site infection, is lacking. Peritonitis is a rare but severe infectious complication of cesarean section. It is a significant and prolonged peritoneal inflammatory response, usually due to bacteria introduction at the time of surgery.[24] There are few reported cases of peritonitis after cesarean section in the literature, [25-27] with the majority of knowledge on pathophysiology and treatment arising from the general surgery literature after perforated appendices or colorectal anastomotic leakages.[24] Peritonitis involves cytokine cascades and toxic-mediated endothelial damage, resulting in increased capillary leakage and the onset of abdominal sepsis. The most common bacterial etiologies are polymicrobial, a combination of common gut flora, such as Escherichia coli, Klebsiella pneumoniae, Streptococcus spp. and Bacteroides fragilis, with other gram-negative, gram-positive, and anaerobic bacteria.[24]

As peritonitis leads to abdominal sepsis, it carries significant morbidity and mortality. With each additional systemic inflammatory response syndrome (SIRS) criteria, mortality increases, with average mortality from severe sepsis around 30%.[28,29] But if patients are young (<44 years old) with no other comorbidities, mortality from severe sepsis can be as low as 5%.[30] Management of severe sepsis and septic shock in

abdominal sepsis involves early, appropriate broad-spectrum antibiotic use plus early, aggressive source control of necrotic tissue.[24,31] Choosing appropriate antibiotics in resource-limited countries, however, can be difficult due to availability of supplies, availability of microbiology laboratory diagnosis and antibiograms, and the emergence of antimicrobial resistance.[32]

1.3 Antimicrobial resistance in sub-Saharan Africa

Antimicrobial resistance (AMR) is an underappreciated threat to health in low-resource settings.[33] The unregulated and injudicious use of antibiotics in the community and in health-care settings, coupled with poor infection control practices, are some of the principal factors contributing to this problem.[34]

In sub-Saharan Africa, the emergence and rising prevalence of extended-spectrum β-lactamase (ESBL)-producing organisms is being documented and is quite concerning.[32,34,35] For example, in Uganda, AMR rates among bacterial isolates obtained from infected surgical wound showed that more than 75% of the Enterobacteriaceae isolates were ESBL-producers.[36] Similarly, a surveillance study on bacterial flora associated with surgical site infections in Tanzania, showed that 79.3% of Enterobacteriaceae isolates were ESBL-producers.[37] In Rwanda, a study conducted on the medical wards of a tertiary referral hospital, found high rates of AMR as well, with 31.4% of *Escherichia coli* and 58.7% of *Klebsiella* isolates being resistant to third-generation cephalosporins.[32] These resistance patterns are alarming, especially with the limited

access to and affordability of broad spectrum antibiotics, including those with activity against ESBL-producing pathogens, in many sub-Saharan African countries.

AMR plays a particularly important role in management of abdominal sepsis from post-cesarean section peritonitis. Because patients with abdominal sepsis from post-cesarean section peritonitis present with severe sepsis and have high rates of morbidity and mortality,[38] initial selection of appropriate antibiotics is critically important.[24,39] As discussed above, abdominal sepsis from peritonitis is commonly mediated by gut flora such as Enterobacteriaceae isolates. If trends in antimicrobial resistance among bacterial isolates causing post-cesarean section peritonitis follow those documented in Uganda, Tanzania, and the medical wards of Rwanda, patients may not be receiving appropriate antibiotic coverage and may suffer worse morbidity and mortality.

1.4 Post-cesarean section peritonitis in Rwanda

Over the past 15 years, Rwanda has been the poster child of Millennium Development Goal (MDG) 5, leading the LMIC countries in an 8% annual decline of its maternal mortality ratio from 1990 to 2010.[40] It has achieved this goal through governmental stewardship of health, investment in infrastructure, and upscaling of emergency obstetric care throughout the country. According to 2013 statistics, Rwanda's nationwide cesarean section rate was 14.8%, performing approximately 44,321 cesarean sections in district hospitals (59% of all surgical procedure performed in the country that

year). In 2010, the nationwide cesarean section rate was 10.9%. The number of maternal deaths in 2013 recorded from audits and reporting from the districts was 267, with 9% due to infectious etiology.[41] But at the University Teaching Hospital of Kigali (CHUK), the main tertiary referral hospital for 29 of Rwanda's 42 districts, maternal sepsis is the leading cause of morbidity and mortality. In 2012, peritonitis accounted for 30% of all maternal deaths and 30.2% of all maternal morbidity.[38] The majority of these cases were post-cesarean section peritonitis and over 96% were transferred to CHUK from outside district hospitals.

Since post-cesarean section peritonitis is a form of abdominal sepsis, source control and appropriate broad-spectrum antibiotics must play a role in its management. But no previous published study has investigated patient factors associated with need for hysterectomy (morbidity) or with mortality, and no previous study has investigated the antibiogram of bacterial isolates from intra-abdominal pus cultures. This study aims to investigate demographic, clinical, operative, and microbiological factors associated with hysterectomy and death among post-partum patients presenting to CHUK with the diagnosis of peritonitis after cesarean section. Understanding the clinical course of this emerging disease and the resistance patterns of bacterial isolates within this specific high-risk population could lead to better protocols for management and improved outcomes.

2. Methods

This was a two-part study. The first part was a prospective observational cohort study conducted from January 1, 2015 until December 31, 2015 at the University Teaching Hospital of Kigali (CHUK), in Kigali, Rwanda. The second part was a retrospective chart review of all patients admitted to CHUK from January 1, 2014 until December 31, 2014 for post-cesarean section peritonitis.

2.1 Setting

The University Teaching Hospital of Kigali (CHUK) is one of five referral hospitals in Rwanda with a catchment of 29 district hospitals. It is the main referral hospital, located in the urban capital, Kigali. CHUK has 429 beds, 15 clinical departments with 8 residency training programs, including an OBGYN residency training program. There is an intensive care unit (ICU) with at least six ventilators. The Maternity Ward has 4 patient wards with a total of 43 beds, 1 labor room with 6 beds, 1 preeclampsia/monitoring room with 3 beds, 1 recovery room with 3 beds, and two operating theaters.

2.2 Participants

The study population was composed of all post-partum patients admitted to the CHUK Obstetrics and Gynecology (OBGYN) department with the diagnosis of post-cesarean section peritonitis who underwent at least one laparotomy at CHUK. Peritonitis was diagnosed initially by clinical exam findings at time of admission and

then confirmed by exploratory laparotomy findings (see Appendix 1). Patients were excluded if delivery mode was not a cesarean section, if the procedure occurred more than 8 weeks prior to the index admission, if a previously unrecognized bowel injury was determined to be the cause of peritonitis, or if the patient did not undergo an exploratory laparotomy at CHUK. Variables recorded included baseline demographic information, admission vital signs, complete blood count results and clinical examination findings. In addition, we captured the following data: operative findings at time of initial laparotomy; surgical procedures performed including hysterectomy; medical management including antibiotic use and intensive care unit (ICU) admission; length of hospitalization; and death. Sepsis and severe sepsis were defined according to the 2012 Surviving Sepsis Campaign guidelines.[31,42]

2.3 Procedures

2.3.1 Demographic, clinical, and operative variable collection

In the prospective arm of the study, patients meeting inclusion criteria for the study were followed in-house until discharge or death. Patients were identified at morning report and on daily ward rounds in the OBGYN department. Each patient was assigned a unique study identification code by the researcher and linked to her name and medical record on a secure server through Duke University. Data were extracted from charts on a daily basis using the study questionnaire (Appendix B) under the study identification code. Questionnaires were kept in a locked cabinet in the CHUK

Department of Research office. Data were entered into a password-protected, Microsoft Excel database stored on a secure server through Duke University. Passwords to the database were only available to the researcher, the research assistant, and the Principal Investigator of the study. Quality assurance was performed once a month on 10% of the charts to ensure accurate reporting of data points. A Waiver or Alteration of Consent and HIPAA Authorization was granted for this study as all data collected were standard of care variables.

In the retrospective arm of the study, patients meeting the inclusion criteria were identified from Maternity ward admission books, operating records, and maternal death reports from January 1, 2014 until December 31, 2014. The medical record number was recorded and brought to the CHUK medical records. A chart review of those records utilizing the study questionnaire was conducted. Quality assurance was performed on 10% of the charts to ensure accurate reporting of data points.

2.3.2 Intra-abdominal pus sample collection and processing

It is standard of care to obtain pus samples from patients undergoing laparotomy for complicated intra-abdominal infections in the CHUK OBGYN operating theatre and to process them for antimicrobial sensitivities in the CHUK microbiology laboratory. Pus from the intra-abdominal cavity was obtained using a sterile syringe and transferred to a sterile container. Samples were sent to the CHUK microbiology laboratory for processing within 24 hours of collection.

The morphology of bacteria on gram stain of samples determined the selection of appropriate media for culture, which were then incubated at 37 °C for 24 hours. Identification of bacterial genus and/or species was done using morphology of colonies, growth characteristics on selective media, and confirmatory biochemical tests.

Antibiotic susceptibility testing was performed by the Kirby Bauer disk diffusion method. The following antibiotic disks were used: ampicillin, 10 μg; ceftazidime, 30 μg; cefotaxime, 30 μg; ceftriaxone, 30 μg; cefuroxime, 30 μg; ciprofloxacin, 5 μg; amikacin, 30 μg; amoxicillin/ clavulanic acid (amox/clav), 20/10 μg; gentamicin, 10 μg; imipenem, 10 μg; co-trimoxazole 1.25/23.75 μg, and chloramphenicol 30 μg.

A suspension from growth on a solid media plate was prepared by adding bacterial colonies into sterile distilled water until it approximated the same turbidity as the MacFarland turbidity standard 0.5. The resulting suspension was inoculated on Muller Hinton agar by using a sterile cotton swab. After this procedure, the antibiotic disks were added to the plate with at least 20 mm between each disk and subsequently incubated at 35°C for 16–18 hours; thereafter, interpretation of the diameter of inhibition was done according to 2012 Clinical and Laboratory Standards Institute (CLSI) guidelines.

For patients with persistently positive cultures, data were collected only on bacterial isolates from the first positive specimen.

Laboratory materials including sterile containers, antibiotic disks, and culture media, were manufactured by Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA.

2.3.3 De-identification and ethical considerations

In the prospective arm, patient data underwent complete de-identification after 2 weeks of discharge or death. Identifying patient information linked to the unique study identification code was deleted from the secure server, and the corresponding study questionnaire was shredded.

In the retrospective arm, data were immediately de-identified after completion of the study questionnaire. Once data from the questionnaire were entered into the secure Microsoft Excel database, the questionnaires were shredded.

The study was reviewed and approved by the ethics committee of CHUK (EC/CHUK/11/25) and exempted from Institutional Review Board review at Duke University (Pro00060165).

2.4 Measures

The key outcome variables of interest were hysterectomy and death. Secondary outcome variables of interest was intensive care unit (ICU) admission.

The key independent variables of interest were post-operative day (POD) on admission, number of days at district hospital (DH) prior to admission (both reported as medians and interquartile ranges); bacterial isolates from intra-abdominal pus samples

at time of laparotomy, operative findings at time of initial laparotomy (uterine dehiscence, uterine necrosis, fascial necrosis, fascial dehiscence); vital signs on admission and laboratory findings on admission (reported as means with standard deviations). Sepsis and severe sepsis were also key variables of interest and were defined according to the 2012 Surviving Sepsis Campaign guidelines.[31,42] Due to resource limitations in this study, sepsis was defined as two or more systemic inflammatory response (SIRS) criteria using vital signs (heart rate, respiration rate, temperature) and complete blood count results (white blood count). Severe sepsis was defined as sepsis plus evidence of hypoperfusion or coagulopathy (decreased Glasgow coma scale, systolic blood pressure less than 90 mmHg, or platelet count less than 100,000 microL-1).

Uterine necrosis was further divided into three categories: full lower-segment necrosis, necrosis between 1 and 3 centimeters from the uterine incision, and necrosis 1 centimeter or less from the uterine incision. We divided it into these categories to assess the role of necrosis in need for hysterectomy. Given the importance of source control in cases of abdominal sepsis after peritonitis, hysterectomy is often performed when necrosis is noted.[26] However, maintaining fertility in primiparous women is also a high priority. Understanding the level of necrosis and need for hysterectomy would be of great importance to fertility preservation in this population.

2.5 Analysis

Data were collected into a Microsoft Excel database as described above. Data from the two arms of the study were combined for data analysis.

Demographic, clinical, and operative variables were reported as frequencies and percentages of total samples. Pearson chi-square, fisher's exact, Mann-Whitney and student's t-tests were used to assess the statistical relationship between key independent variables and key outcome measures (hysterectomy and death). Missing variables were not reported.

Outcomes were further divided into all alive patients who did not undergo a hysterectomy (A: Alive – no hysterectomy), all alive patients who did undergo a hysterectomy (B: Alive – hysterectomy), and all patients who died (All Death). This was done to assess the hypothesis that post-cesarean section peritonitis can be placed on a spectrum -- mild, moderate, or severe disease.

Only microbiology data from 2015 was analyzed. The frequency of individual bacterial species isolated was reported as a percentage or a fraction of total samples. The frequency of microbes resistant to antibiotics was reported as a simple percentage of the total number of same-species microbes against which the antibiotic was tested for susceptibility. Fisher's exact tests were used to assess the impact of ESBL-producing organisms on markers of morbidity and mortality.

Factors with a p-value of 0.05 or smaller on univariate analysis were included in the multivariate model. A backwards selection algorithm was used to confirm goodness of fit. All tests and confidence intervals were considered to be significant at a p-value less than or equal to 0.05. All analyses were performed using STATA version 14 (StataCorp. 2014. Stata: Release 14. Statistical Software. College Station, TX: StataCorp LP).

3. Results

3.1 Study subject characteristics

There were 92 cases of post-cesarean section peritonitis admitted to CHUK Maternity ward in 2015, up from 75 cases in 2014. A total of 167 patients were included in the analysis. Table 1 lists the demographic, clinical, and operative factors for all subjects. The median age was 26 years with interquartile range of 23-33 years and a range of 19-41 years. Fifty-nine percent of the patients were primiparous. Overall, the top three indications for cesarean section in this population were fetal distress (N=43, 26%), prolonged labor (N=41, 24%), and history of previous cesarean section (N=29; 18%). Eleven patients (6.6%) had human immunodeficiency virus (HIV) infection, which was the main co-morbidity noted in this study. One patient had diabetes, one patient had pre-eclampsia, and two patients had malaria. No other co-morbidities were reported by subjects or noted in the charts.

The median post-operative day (POD) of admission was 7 (IQR 5-11). Subjects first noticed symptoms a median of 4 days post-cesarean section (IQR 3-7). The most common symptoms reported were abdominal pain/distention (N=125; 75%) and wound discharge (n=113; 68%). Based on data available, 43% of patients had been discharged from the DH prior to readmission and 94% were transferred to CHUK from an outside DH.

Sixteen percent of subjects presented with severe sepsis on admission to CHUK. The mean heart rate was 121 beats per minute (bpm; +/-22), and mean respiration rate was 26 cycles per minute (+/- 7). Sixteen subjects (10%) presented with a Glasgow coma scale (GCS) of less than 15, and sixteen subjects (10%) presented with a platelet count less than 100,000 microL-1.

The most common operative findings were intra-abdominal pus (N=154; 92%), uterine necrosis (N=117; 71%), and uterine hysterotomy dehiscence (N=114; 68%). There were also high rates of fascial dehiscence (N=78; 47%) and fascial necrosis (N=94; 57%). The subjects underwent a median of 2 surgeries (IQR 1-3) and had a median length of stay of 27 days (IQR 17-38).

Thirty-one patients (18%) required intensive care unit (ICU) admission. Seventy-five (45%) hysterectomies were performed, 66 initial hysterectomies (88%) and 9 delayed hysterectomies (12%). There were a total of 36 deaths from post-cesarean section peritonitis over the two-year period, giving an overall case fatality rate of 22% at CHUK.

3.2 Trends in demographic, clinical, operative variables and morbidity outcomes from 2014 to 2015

Table 1 also shows trends in demographic, clinical, and operative factors, as well as outcomes, from 2014 to 2015. Significantly more subjects were multiparous in 2015 compared to 2014 (49% versus 27%, p=0.01), and significantly more subjects had a history of a previous cesarean section in 2015 compared to 2014 (28% versus 9%, p=0.006). There were also significant differences in the frequencies of fascial necrosis and

uterine necrosis at time of initial laparotomy reported in 2015 compared to 2014 (67% versus 44%, p=0.004; 78% versus 61%, p=0.025). Lastly, the rate of hysterectomy was also significantly higher in 2015 compared to 2014 (54% versus 36%, p=0.037).

3.3 Factors associated with morbidity

Table 2 shows key demographic, clinical, and operative variables of subjects by the main morbidity (hysterectomy) and mortality outcome.

Of the 167 subjects, 130 (78%) survived until discharge from CHUK. Of the 130 surviving patients, 81 (62%) never required hysterectomy (group A) and 49 (38%) underwent hysterectomy (group B). With regards to demographic factors, there was a significant difference in parity between the two groups (68% primiparous in A compared to 51% primiparous in B, p=0.047), history of previous cesarean section (12% in A compared to 27% in B, p=0.035), and median POD on admission (10 IQR 6-14.5 in A compared to 7 IQR 5-10 in B, p=0.025). With regards to vital signs and laboratory values, there was a significant difference in mean heart rate (113 +/- 20 bpm in A compared to 123 +/- 19 bpm in B, p=0.004) and platelet count below 100,000 microL-1 (0% in A compared to 8% in B, p=0.009, RR=2.8 [2.2-3.6]). Among operative findings, group B had significantly higher rates of uterine necrosis (94% compared to 49%, p<0.001, RR=7.8 [2.6-23.8]) and higher rates of more than 1000 cubic centimeters (cc) of inflammatory fluid at time of initial laparotomy (39% compared to 25%, p=0.013, RR=2.1 [1.1-4.0]). In

the multivariate analysis, uterine necrosis was the most predictive of need for hysterectomy.

3.4 Factors associated with mortality

Comparing all those who survived to those who did not (Table 2), there was a statistically significant difference in median POD on admission (8 IQR 5.5-13 versus 6 IQR 4.5-8, p=0.015) and days at DH (5 IQR 2-8 versus 3 IQR 1-6, p=0.017). Subjects who died had significantly different vital signs on admission, with higher heart rates (134 +/- 22 bpm versus mean 117 +/- 20 bpm, p<0.001), higher respiration rates (mean 31 +/- 7 cycles per minute versus mean 25 +/- 7 cycles per minute, p<0.001), and lower oxygen saturation percentages (93 +/-5 versus 96 +/-4, p=0.009). They were more likely to have a systolic blood pressure less than 90 mmHg (11% versus 2%, p=0.041), have a GCS less than 15 (36% versus 2%, p<0.001, RR=5.3 [3.4-8.3]), have a lower white blood cell count (mean 8.9 +/- 5.4 versus 13 +/- 5.8, p<0.001) and platelet count below 100,000 microL-1 (33% versus 3%, p<0.001, RR=4.9 [3.0-7.9]).

Presence of fascial dehiscence was protective against mortality (RR=0.49 [0.26-0.93]), however uterine necrosis, more than 1000cc inflammatory fluid, and hysterectomy were higher in subjects who died compared to those who survived (86% versus 66%, p=0.023; 53% versus 30%, p<0.001; 72% versus 38%, p<0.001).

Severe sepsis and greater than 1000cc inflammatory fluid on admission were most predictive of mortality in the multivariate analysis (RR=4.1 [2.2-7.7]; RR=10.5 [1.4-76.6]).

Dividing those who survived by hysterectomy, there were also statistically significant differences between those subjects who underwent hysterectomy and survived (group B) and those who died. Looking specifically at factors that were significantly different between those who survived without need for hysterectomy (group A) and those who survived who underwent hysterectomy (group B), those who died had lower median days at DH compared to group B (3 IQR 1-6 versus 6 IQR 3-8, p=0.008). Subjects who died had significantly higher heart rates (134 +/- 22 bpm versus mean 123 +/- 19 bpm, p=0.018), were more likely to have a platelet count below 100,000 microL-1 (33% versus 8%, p=0.004, RR=2.2 [1.4-3.5]), and were more likely to have more than 1000cc inflammatory fluid at time of initial laparotomy (53% versus 39%, p=0.017).

3.5 Uterine conservation

Of the 117 subjects with uterine necrosis at time of initial laparotomy, 41 (35%) did not undergo hysterectomy and survived compared to 46 (53%) who underwent hysterectomy and survived (Table 3). Uterine necrosis less than 1 cm from the hysterotomy site was most predictive of uterine conservation among these subjects compared to subjects who underwent hysterectomy (95% versus 9%, p<0.001, RR=10.3 [4.0-26.2]).

3.6 Bacterial isolates and AMR

Table 4 shows descriptive statistics for antibiotic use prior to CHUK admission and during admission by year and by intra-abdominal pus culture result. There were no statistically significant differences in antibiotic use prior to CHUK admission between 2014 and 2015. In 2015, 71% of patients had data available on antibiotic use prior admission to CHUK, 88% of whom received intravenous (IV) antibiotics at the transferring district hospital. An initial regimen of ampicillin, gentamicin, and metronidazole was the most frequently prescribed (44%). In 2015, we see a change in inpatient antibiotic prescribing patterns with more use of third-generation cephalosporins (100% versus 59%) and less use of ampicillin and gentamicin regimens (0-1% versus 48-49%) compared to 2014.

In 2015, all patients received IV metronidazole 500mg dosed 12-hourly on admission and either IV cefotaxime or ceftriaxone 1gram dosed 8-hourly, and 6 (23%) patients received additional oral ciprofloxacin 500mg dosed 12-hourly (table 4).

Of the 37 samples obtained in 2015, 27 (73%) had culture and sensitivity results available. All 27 samples yielded gram-negative isolates (Table 5), with *E.coli* and *Klebsiella* spp. being the most common organisms (29.7% and 35.1% respectively).

E. coli was found to have low resistance rates to cefotaxime (13%), ceftriaxone (20%), and ciprofloxacin (20%). It was the most resistant to amoxicillin-clavulanate (89%) and ampicillin (73%). The organism had high rates of resistance to gentamicin (43%), co-

trimoxazole (50%), and ceftazidime (50%), as well (Table 6).

Klebsiella isolates were found to be least resistant to cefuroxime (33%), but had high resistance to co-trimoxazole (100%), amoxicillin-clavulanate (83%), ampicillin (88%), chloramphenicol (80%), gentamicin (71%), ceftriaxone (71%), and cefotaxime (71%). *Klebsiella* spp. also had high resistance to ceftazidime (66%) and amikacin (63%; Table 6).

There were only single isolates of *Proteus, Enterobacter*, and *Acinetobacter*. When taken together with the *Klebsiella* and *Ecoli isolates,* overall resistance rates were 82% to ampicillin; 89% to amoxicillin-clavulanate; 73% to co-trimoxazole; 57% to chloramphenicol; 75%, 54%, and 44% to the third-generation cephalosporins (ceftazidime, ceftriaxone, and cefotaxime, respectively); 60% to gentamicin, 50% to amikacin, and 32% to ciprofloxacin.

Comparing subjects with positive culture results to those with negative results (Table 7), 8 (30%) had severe sepsis on admission (compared to 1), 6 (24%) were admitted to ICU (compared to 1), and 7 (26%) died (compared to 1). There was a significant association with hysterectomy and positive pus culture result (n=20, 74% compared to n=3, 30%; p=0.018).

Of the 27 positive culture results, 23 had information on resistance to third-generation cephalosporins, a marker of ESBL-producing organisms (Table 7). Of the 7 patients who died and had resistance profiles available, 6 were resistant to third

generation cephalosporins (cefotaxime or ceftriaxone). Among the 8 patients admitted with severe sepsis for whom resistance profiles are available, 6 had isolates that were resistant to third generation cephalosporins. There was a significant difference in ICU admission between patients with cultures resistant to third-generation cephalosporins and those with cultures not resistant (*n*=6, 46% versus 0%, p=0.046).

Table 1: Demographic, clinical, operative variables and outcomes of patients presenting to CHUK with post-cesarean section peritonitis in 2014, 2015, and combined

Variable	2015 (N=92)	2014 (N=75)	*P-value*	Combined 2014-2015 (N=167)
	Mean (standard deviation)			
Median Age (IQR)	25 (21-32)	24 (20-28)		25 (21-30)
Parity				
Primiparous (1)	46 (51%)	52 (69%)	0.010	98 (59%)
Multiparous (>1)	45 (49%)	20 (27%)		65 (40%)
HIV- positive	5 (5.5%)	6 (8%)		11 (6.6%)
Stillborn at delivery	15 (15%)	14 (19%)		29 (17%)
Cesarean Section (CS) Reason				
Malpresentation	6 (7%)	6 (8%)		12 (7%)
Arrest of Descent	4 (4%)	3 (4%)		7 (4%)
Prolonged Labor	26 (29%)	15 (20%)		41 (24%)
Fetal Distress	15 (16%)	28 (37%)		43 (26%)
Previous CS	21 (24%)	8 (11%)		29 (18%)
History of Previous CS	25 (28%)	7 (9%)	0.006	32 (19%)
Median POD on Admission to CHUK	7 (5-10)	8 (5-13)		7 (5-11)
Median days at District Hospital (DH) prior to transfer	4 (3-7)	4 (1-6)		4 (2-7)
Median POD of first symptoms	4.5 (3-7)	4 (3-6)		4 (3-7)
Symptoms				
Wound discharge	59 (65%)	55 (73%)		114 (68%)
Nausea/Vomiting	61 (66%)	4 (5%)	<0.001	65 (39%)
Fever	36 (40%)	20 (27%)	<0.001	56 (34%)

Abdominal pain and/or distention	72 (79%)	53 (71%)		125 (75%)
Wound separation	37 (41%)	19 (25%)	0.039	56 (34%)
Fascial dehiscence	21 (23%)	9 (12%)		30 (18%)
Discharged from DH prior to transfer	40 (43%)	31 (41%)		71 (43%)
Missing	5 (5%)	33 (44%)		
Cases transferred from DH	87 (95%)	70 (93%)		157 (94%)
Sepsis on Admission	79 (86%)	61 (83%)		140 (84%)
Severe Sepsis on Admission*	19 (21%)	8 (11%)	0.067	27 (16%)
Admission Vitals				
Heart Rate (bpm)	121 (22)	121 (22)		121 (22)
Respiratory Rate	25 (6)	26 (8)		26 (7)
Oxygen saturation (%)	95 (5)	95 (5)		95 (4)
Temperature (*C)	37.7 (1)	37.7 (1.0)		37.7 (1.0)
Systolic Blood Pressure (mmHg)	111 (13)	118 (16)	0.004	114 (15)
Glasgow Coma Scale (GCS) <15	10 (11%)	6 (8%)		16 (10%)
Admission Labs				
White Blood Cell Count (10^3 microL^{-1})	12 (6)	12.4 (6.0)		12.2 (6.0)
Hemoglobin (10^3 microL^{-1})	10.5 (2.5)	9.9 (1.9)		10.2 (2.2)
Platelet Count (10^3 microL^{-1})	306 (193)	344 (219)		325 (208)
<100,000 microL-1	10 (11%)	6 (9%)		16 (10%)
Operative Room Findings				
Fascial Dehiscence	43 (47%)	35 (47%)		78 (47%)
Abdominal Pus	85 (93%)	69 (92%)		154 (92%)
Fascial Necrosis	61 (67%)	33 (44%)	0.004	94 (57%)

Uterine Dehiscence	67 (74%)	47 (63%)		114 (68%)
Uterine Necrosis	71 (78%)	46 (61%)	0.025	117 (71%)
Inflammatory Fluid				
<=1000cc	29 (48%)	15 (34%)		44 (42%)
>1000cc	31 (52%)	29 (66%)		60 (58%)
Median laparotomies at CHUK	2 (1-4)	1 (1-3)		2 (1-3)
Median length of CHUK hospitalization (days)	28.5 (17-37.5)	26 (19-38)		27 (17-38)
ICU Admission	20 (22%)	11 (16%)		31 (18%)
Hysterectomy	49 (54%)	26 (36%)	0.037	75 (45%)
Initial	43 (47%)	23 (32%)		66 (40%)
Delayed	6 (7%)	3 (4%)		9 (6%)
Death	22 (25%)	14 (19%)		36 (22%)

Table 2: Key demographic, clinical, and operative variables of patients presenting to CHUK with post-cesarean section peritonitis from 2014-2015, by outcome

Variable	All Alive* (N=130; 78%)	A: Alive – No Hysterectomy (N=81; 31%)	B: Alive – Hysterectomy** (N=49; 38%)	*P-value* *(Comparison of A with B)*	All Death (N=36; 22%)	*P-value* *Comparison of All Death with All Alive **Comparison of All Death with B: Alive – Hysterectomy
Parity						
Primiparous (1)	80 (63%)	55 (70%)	25 (52%)	0.047	18 (50%)	
Multiparous (>1)	47 (37%)	24 (30%)	23 (48%)		18 (50%)	
History of previous CS	23 (18%)	10 (13%)	13 (28%)	0.035	8 (26%)	
Median POD on admission to CHUK (IQR)	8 (5.5-13)	10 (6-14.5)	7 (5-10)	0.025	6 (4.5-8)	*0.001
Median days at District Hospital (DH)	5 (2-8)	5 (2-8)	6 (3-8)		3 (1-6)	*0.017 **0.008
Sepsis on Admission	106 (83%)	64 (80%)	42 (90%)		34 (94%)	
Severe Sepsis on Admission*	7 (5%)	2 (2%)	5 (11%)	0.098	20 (55%)	*<0.001; RR=7.6 [4.3-13.3] **<0.001; RR=3.3 [2.0-5.5]
Admission Vitals						
Heart Rate (bpm)	117 (20)	113 (20)	123 (19)	0.004	134 (22)	*<0.001 **0.018
Respiratory Rate	25 (7)	24 (5)	26 (8)	0.139	31 (7)	*<0.001 **0.006

Oxygen saturation (%)	96 (4)	96 (4)	95 (3)		93 (5)	*0.009 **0.037
Systolic Blood Pressure (mmHg)	115 (14)	115 (15)	114 (14)		113 (16)	
<90 mmHg	3 (2.5%)	2 (2.4%)	1 (2.1%)		4 (11%)	*0.041
Glasgow Coma Scale (GCS) <15	3 (2%)	0	3 (6%)	0.052	13 (34%)	*<0.001; RR=5.3 [3.4-8.3] **<0.001; RR=2.4 [1.6-3.7]
Admission Labs						
White Blood Cell Count (10^3 microL^{-1})	13 (5.8)	13.4 (5.7)	12.3 (6.0)		8.9 (5.4)	*<0.001 **0.016
Hemoglobin (10^3 microL^{-} 1)	9.9 (2.2)	9.9 (2.1)	9.9 (2.2)		11.1 (2.3)	*0.006 **0.020
Platelet Count (10^3 microL^{-} 1)	368 (200)	401 (204)	312 (183)	0.017	170 (149)	*<0.001 **<0.001
<100,000 microL-1	4 (3%)	0	4 (8%)	0.009; RR=2.8 [2.2-3.6]	12 (33%)	*<0.001; RR=4.9 [3.0-7.9]; **0.004; RR=2.2 [1.4-3.5]
Operative Room Findings						
Fascial Dehiscence	67 (52%)	41 (51%)	26 (53%)		11 (31%)	*0.023 **0.039
Uterine Dehiscence	91 (70%)	56 (69%)	35 (71%)		23 (64%)	
Uterine Necrosis	86 (66%)	40 (49%)	46 (94%)	<0.001; RR=7.8 [2.6-23.8]	31 (86%)	*0.023; RR=2.6 [1.1-6.3]

Inflammatory Fluid				0.013; RR=2.1 [1.1-4.0]		*<0.001; RR=2.0 [1.6-2.6] **0.017
<1000cc	43 (53%)	33 (63%)	10 (34%)		1 (5%)	
>1000cc	40 (47%)	21 (37%)	19 (66%)		20 (95%)	
Median laparotomies at CHUK	2 (1-4)	1 (1-2)	3 (2-6)	<0.001	1 (1-3)	
Median length of CHUK hospitalization (Days)	30.5 (23-41)	28 (21-35)	38 (29-53)	<0.001	3 (1.5-14)	
ICU Admission	6 (5%)	2 (2%)	4 (8%)	0.198	25 (69%)	*<0.001; RR=9.9 [5.5-17.9] **<0.001; RR=4.4 [2.5-7.6]
Hysterectomy	49 (38%)				26 (72%)	*<0.001; RR=3.2 [1.6-6.1]

Table 3: Uterine conservation among patients presenting to CHUK with post-cesarean peritonitis

	All Alive (N=130; 78%)	A: Alive – No Hysterectomy (N=81; 31%)	B: Alive – Hysterectomy (N=49; 38%)	*P-value (Comparison of A with B)*	All Death (N=36; 22%)
Uterine necrosis	86 (66%)	40 (49%)	46 (94%)		31 (86%)
<1 cm	43 (50%)	39 (98%)	4 (8%)	<0.001	6 (19%)
1-3cm	3 (3%)	1 (2%)	2 (4%)		0
Lower uterine segment	40 (47%)	0	40 (82%)		25 (81%)

Table 4: Antibiotic use prior to admission to CHUK and during admission to CHUK, by year and intra-abdominal pus culture result

	All subjects (N=167)	2014 (N=75)	2015 (N=92)	Subjects with negative pus culture 2015 (N=10)	Subjects with positive pus culture 2015 (N=27)
	(N=113; 68%)	(N=48; 64%)	(N=65, 71%)		
Antibiotic use prior to CHUK	102 (90%)	45 (94%)	57 (88%)		
Ampicillin	54 (53%)	28 (62%)	26 (46%)	5 (50%)	11 (41%)
Gentamicin	55 (54%)	30 (67%)	25 (44%)	4 (40%)	11 (41%)
Ceftriaxone	35 (34%)	14 (31%)	21 (37%)	2 (20%)	6 (22%)
Cefotaxime	11 (11%)	2 (4%)	9 (16%)	1 (10%)	1 (4%)
Metronidazole	84 (82%)	45 (100%)	39 (68%)	6 (60%)	17 (63%)
Antibiotic use during CHUK admission					
Ampicillin		48 (64%)	1 (1%)	0	0
Gentamicin		49 (65%)	0	0	0
Ceftriaxone		24 (32%)	13 (14%)	3 (30%)	5 (19%)
Cefotaxime		20 (27%)	81 (88%)	7 (70%)	23 (85%)
Metronidazole		72 (96%)	92 (100%)	10 (100%)	27 (100%)
Ciprofloxacin		5 (7%)	12 (13%)	1 (10%)	6 (22%)
Imipenem		1 (1%)	1 (1%)	0	1 (4%)

Table 5: Distribution of bacterial isolates among post-cesarean section peritonitis patients in 2015 with pus culture results available

Organism	***Total (N=37)***	***% Total***
Escherichia coli	11	29.7
Klebsiella spp.	13	35.1
Proteus spp.	1	2.7
Acinetobacter spp.	1	2.7
Enterobacter spp.	1	2.7
Negative	10	27

Table 6: Antimicrobial resistance rate (%) of principal bacterial isolates among post-cesarean section peritonitis patients in 2015

	Escherichia coli (N=11)			*Klebsiella* spp. *(N=13)*		
Antimicrobial Drug	Number of isolates tested	Number of isolates resistant	Resistance Rate %	Number of isolates tested	Number of isolates resistant	Resistance Rate %
Ampicillin	4	3	75	6	5	83
Amox-Clav	9	8	89	8	7	88
Gentamicin	7	3	43	7	5	71
Chloramphenicol	7	2	29	5	4	80
Co-trimoxazole	4	2	50	5	5	100
Cefuroxime	3	1	33	3	1	33
Ceftazidime	4	2	50	3	2	66
Cefotaxime	8	1	13	7	5	71
Ceftriaxone	5	1	20	7	5	71
Ciprofloxacin	10	2	20	12	5	42
Amikacin	3	1	33	8	5	63
Imipenem	2	0	0	7	0	0

Table 7: Association of bacterial isolates versus negative cultures and ESBL versus non-ESBL organisms with key clinical variables and morbidity and mortality outcomes

Outcomes	Gram-negative bacterial isolate (N=27; 73%)	Negative culture (N=10; 27%)	*P-value*	Culture with non-ESBL*-producing organism (N=9; 33%)	Culture with ESBL*-producing organism (N=14; 52%)	*P-value*
Severe Sepsis	8 (30%)	1 (10%)	0.225	2 (25%)	6 (43%)	0.649
Hysterectomy	20 (74%)	3 (30%)	**0.018; RR=2.6 [1.0-6.8]**	6 (67%)	11 (79%)	0.643
ICU Admission	6 (22%)	1 (10%)	0.645	0	6 (46%)	**0.046**
Death	7 (26%)	1 (10%)	0.391	1 (11%)	6 (46%)	0.165

*ESBL=Extended spectrum beta-lactamase

4. Discussion

Post-cesarean peritonitis in Rwanda is a serious disease with a 22% case fatality rate. This is the first study to systematically describe the disease process in post-cesarean patients. In our study population, symptoms of peritonitis would start a median of 4 days after cesarean section and usually consist of abdominal pain and/or distention. This is consistent with the pathophysiology of abdominal sepsis from peritonitis, with cytokine release causing a prolonged inflammatory response within the peritoneal cavity.[24] Our analysis suggests that peritonitis post-cesarean section can be placed on a spectrum, with "mild" disease defined as patients who survived without needing a hysterectomy, "moderate" disease defined as patients who survived and underwent a hysterectomy, and "severe" disease defined as patients who died. This is supported by results in Table 2. Comparing patients who survived without needing hysterectomy (group A) to those who survived and underwent hysterectomy (group B), there were significant differences in median POD of admission (lower in group B), mean heart rate on admission (higher in group B), and platelet count below 100,000 microL-1, an indicator of worsening sepsis (8% in group B versus 0% in group A). Operative factors between the two groups also support this theory, with more cases of uterine necrosis and inflammatory fluid greater than 1000cc in group B compared to group A. Finally, hysterectomy was more likely if bacteria were isolated from intra-abdominal pus cultures (Table 7), suggesting a possible role of antimicrobial resistance or

undertreated bacteria in mediating the transition between "mild" and "moderate" disease.

Comparing group B to patients who died, the above factors are still significantly different, with lower median days at DH for patients who died, higher heart rate on admission, more cases of patients with platelet counts below 100,000 microL-1, and more cases of patients with greater than 1000cc of inflammatory fluid at time of laparotomy compared to group B (Table 2). In addition, hysterectomy was also significantly associated with mortality when comparing all subjects who survived to all subjects who died ($p<0.001$, RR=3.2 [1.6-6.1]. This suggests a progression from "mild" to "moderate" to "severe" disease in key factors. Though there was no significant difference in severe sepsis on admission between group A ("mild") and group B ("moderate"), there was a significant difference in severe sepsis on admission between group B and patients who died (10% versus 55%, $p<0.001$), suggesting severe sepsis may mediate the transition between "moderate" and "severe" disease. This is further supported by the multivariate analysis, where severe sepsis was the main predictor of mortality. Overall, it appears that patients with "severe" disease become sicker faster, as indicated by the significantly lower median POD of admission and days at DH prior to admission between subjects who did not survive and patients who did (Table 2).

The protective effect of fascial dehiscence (Table 2) in our study is consistent with the pathophysiology of peritonitis and abdominal sepsis. The substantial, intra-

abdominal inflammatory response can lead to high volumes of inflammatory fluid, which can lead to abdominal compartment syndrome.[24,43] Fascial dehiscence alleviates this increased abdominal pressure, which may reduce the risk of end organ damage and severe sepsis. It also suggests that the intra-abdominal infection may not be introduced from the skin incision. The high rate of uterine dehiscence (68%) and uterine necrosis (71%) in this population suggest that the source of the infection may be the uterus. However, this study cannot determine if uterine dehiscence lead to the introduction of bacteria into the peritoneal cavity and subsequent abdominal sepsis and necrosis, or if bacteria-induced uterine necrosis lead to uterine dehiscence and a subsequent pronounced inflammatory intra-abdominal response. In the limited literature on post-cesarean peritonitis, one previous study did link uterine dehiscence to development of peritonitis, supporting a possible relationship.[27] However, more research would be needed to tease apart the role of uterine dehiscence.

Our study was also the first to document a series of successful uterine conservations in the presence of necrosis and peritonitis. Forty patients with uterine necrosis underwent successful tissue debridement and did not require a hysterectomy (Table 3). Previous studies had recommended hysterectomy in cases of post-cesarean peritonitis, especially if there was evidence of necrotic tissue.[25,26,44] Literature from necrotizing fasciitis case series also had few descriptions of uterine conservation. In both necrotizing fasciitis and peritonitis, source control of necrotic tissue is a pillar of

treatment, with early aggressive debridement highly recommended.[45-52] We showed that tissue debridement is possible in select cases of peritonitis with uterine necrosis, with less than one centimeter of necrotic tissue along the hysterotomy site significantly associated with successful uterine conservation (Table 3, $p<0.001$).

The most significant finding of this study was the high rate of antimicrobial resistance among gram-negative bacterial isolates from cultures obtained from post-cesarean section women admitted with abdominal sepsis. The observed AMR rates are similar to previous data published at this institution for internal medicine patients and corroborate the concerns for emergence of antibiotic resistance in Rwanda [32].

The high rate of resistance to third generation cephalosporins (ceftazidime, ceftriaxone, cefotaxime), suspicious for ESBL-producers, was seen in both *E.coli* (28%) and *Klebsiella* (69%). The prevalence of third-generation cephalosporin resistance among *E.coli* is similar to previously published rates from the internal medicine patient population of CHUK (28% vs 31.4%) but higher for *Klebsiella* spp. (69% vs 58.7%). [32] Though this rate is much lower than those described in post-surgical populations in Uganda (92.3%) and Tanzania (92.3%), it still suggests a role for ESBL-producing *Klebsiella* as a pathogen that is frequently a cause of nosocomial infection in East Africa.[36,37]

As *Klebsiella* was the most frequently isolated organism (35.1% of samples), its extremely high rate of resistance to all antibiotics tested (except imipenem) is

particularly concerning (Table 6). This resistance profile severely limits antibiotic treatment options for septic patients infected with this organism. As the rate of severe sepsis in our population was 16% with the highest risk ratio for mortality (Table 2, RR=7.6 [4.3-13.3]), it is possible that the poor outcomes were associated with multidrug resistant pathogen infections that were inappropriately treated. Studies have indeed shown that delayed or inappropriate use of antibiotics, including those with inadequate spectrum of activity, is associated with increased mortality. [53]

It should be noted, however, that 8 patients with ESBL-producing bacteria on culture never received the appropriate antibiotics (either ciprofloxacin or imipenem) to which their isolates were susceptible survived (Table 7, data not shown). It is possible that these patients with multi-drug resistant organisms were effectively treated with adequate source control at initial laparotomy. This observation lends support to the role of source control in the management of abdominal sepsis. It is widely accepted that the appropriate management of abdominal sepsis should include both appropriate antibiotics and adequate source control in order to achieve improved clinical outcomes.[24,52,54]

Abdominal sepsis is more frequently caused by polymicrobial flora including gram-negative, gram-positive, and anaerobic bacteria. [24] The finding of predominantly monomicrobial cultures in our study was unusual but likely reflects selection pressure from antibiotics received from prior hospitalizations (Table 4). Due to laboratory

constraints, culture of anaerobic bacteria, fungi and mycobacteria are not routinely performed such that their role in peritonitis among our patient population remains unknown. However, it is plausible that post-cesarean section peritonitis is predominately caused by Enterobacteriaceae.

In this study, there were no statistically significant differences in morbidity or mortality outcomes between patients with ESBL-producing and non-ESBL producing organisms. The only significant result was a higher rate of ICU admission among subjects with cultures positive for ESBL-producing organisms compared to those with non-ESBL producing organisms (4 6% versus 0%, p=0.046). This may have been due to small sample size. The lack of observed mortality differences may also be due to successful source control with recurrent surgical debridement procedures, including hysterectomy occurring in many cases and disproportionately for those with ESBL infections.

It is important to note that this is an otherwise healthy population with a prevalence of HIV of 6.6% (comparable to rates of HIV in Kigali).[41] In our analysis, HIV was not a significant predictor of morbidity or mortality, though this could be due to low numbers of HIV-infected patients. It is important to note that the patient with diabetes and the patient with pre-eclampsia died from post-cesarean peritonitis, accounting for 6% of all deaths from peritonitis in this study (data not shown). This suggests that co-morbidities increase one's risk of mortality from peritonitis, likely

because the immune system is already compromised at baseline in these conditions. Adding the patients with diabetes, pre-eclampsia, and HIV-infection together and comparing to patients without comorbidities, there is a significant association between having one of these three comorbidities and death (19% versus 6%; p=0.014, RR=2.42 [1.29-4.57]).

When comparing demographic factors of patients in 2014 to 2015, there was a significant difference in patients reporting a history of cesarean section between the two years (28% in 2015 versus 9% in 2014, p=0.006). Though data from 2014 was collected from chart review, there was minimal missing data on obstetric history for the 75 patients (only 2 records), and thus missing data are unlikely to have impacted this finding. The increased number of patients reporting a history of cesarean section is reflective of Rwanda's increasing cesarean section rate, which was officially reported as 14.8% in 2013.[41] This begs the question, are too many cesarean sections being performed in Rwanda? This is a difficult question to ask, as many countries in sub-Saharan Africa struggle to meet the 5% CS rate recommended by the WHO.[1] Over the past 24 years, sub-Saharan Africa has only increased its regional CS rate from 2.3% to 3.5%, the lowest of any region in the world.[5] But in Rwanda, the nationwide CS rate has been steadily increasing over the past 4 years (10.9% in 2010, 14% in 2011, 11.9% in 2012, and 14.8% in 2013), and, during that time, post-cesarean section peritonitis has emerged as a major cause of maternal morbidity and mortality.[38,41] The addition of high rates of AMR among

the bacterial isolates further compounds the severity of the disease. It is possible that OB-GYN patients are colonized with AMR bacteria from frequent contact with health care providers and centers during their pregnancy. If that is the case, routine antibiotic prophylaxis (if it is indeed given) at the time of cesarean section will have little effect, increasing the possibility of introducing skin bacteria into the peritoneal cavity and subsequent infection. It is possible that the emergence of AMR in a resource-limited country that is increasing the number of cesarean sections performed each year has lead to the emergence of peritonitis on the scale documented in this study. It is also possible that Rwanda is the first case example of this effect of AMR and high CS rates in resource-limited settings.

Another contributing factor to the emergence of peritonitis may be the surgical skill used when performing the cesarean section. Though uterine dehiscence was not a significant predictor of morbidity or mortality in this study, the high rate of uterine dehiscence (68%) may reflect low surgical quality at the referring district hospital. This is consistent with literature on risk factors for surgical site infection, which state that improper tissue handling and poor surgical technique increase the risk for SSI.[11,13,15,55]

The high rate of AMR may also be contributing to the high rate of mortality in this study. As noted above, our study population was young and otherwise healthy. In previous studies from New Zealand and Australia on sepsis in this type of patient population, mortality from severe sepsis was 5%.[28] In our study, 74% of patients

presenting with severe sepsis died (table 2). Whether it is due to delayed recognition of disease severity, delayed broad-spectrum antibiotic administration, antimicrobial resistance leading to inappropriate first line antibiotic treatment, or inadequate source control, sepsis is a serious disease that requires more aggressive guidelines for management and treatment in this population.

4.1 Implications for policy and practice

Our findings on AMR strongly support more renewed efforts to streamline injudicious prescribing, expand the antibiotic formulary and revise treatment guidelines. The AMR pattern observed in our study closely reflects antibiotic usage among OBGYN patients at the district hospitals. Amoxicillin/clavulanate, co-trimoxazole and chloramphenicol are frequently prescribed in the outpatient population. In the hospital setting, ampicillin, gentamicin, and ceftriaxone are the most common antibiotics used prior to transfer (Table 4). With average rates of resistance greater than 70% for ampicillin and gentamicin in our study population, first-line treatment with that regimen is not recommended; however, as seen in Table 4, more than 40% of the subjects received this regimen as first-line treatment of sepsis.[31]

Unfortunately, in spite of its indication for use in patients with multidrug resistant pathogen infections, imipenem was not given routinely in this cohort due to the lack of availability and its high cost. Our data suggests that imipenem should be used for patients with severe sepsis, at least empirically, until full organism sensitivities are

available. This is supported by the 2010 guidelines from the Surgical Infection Society and the Infectious Diseases Society of America on the management of intra-abdominal infections, which recommend the use of single-agent imipenem as first line treatment for high-risk, community-acquired intra-abdominal infections, as well as hospital-acquired intra-abdominal infections [52].

The emergence of AMR organisms in patients with post-cesarean peritonitis limits antibiotic treatment options in this population and contributes to an already high risk of morbidity and mortality. The high prevalence of likely ESBL-producing organisms (54-63%) is alarming and suggests the need for carbapenems as standard first line treatment, especially in patients presenting with severe sepsis. The high prevalence of AMR underscores the need for antibiotic stewardship and infection control within obstetric healthcare facilities in Rwanda.

Taking a step back, this study also raises the question regarding the possible overuse of cesarean sections in this population and the need to address the surgical skills of those performing the cesarean sections. Increasing transparency on surgical site infection rates at the hospital level has been shown to reduce SSI rates, but in Rwanda, currently there is no standardized reporting of SSI. [11,15]

4.2 Implications for further research

Further research is needed to identify methods to prevent post-cesarean section peritonitis at the district hospital, specifically to identify indications for cesarean section

at these district hospitals, rates of surgical site infections, and antibiotic prescribing patterns. Further research is also needed to determine rates of AMR colonization among patients presenting to CHUK from the districts to help promote antibiotic stewardship programs nationwide. Lastly, little is known regarding subsequent fertility in patients with uterine conservation after post-cesarean section peritonitis, and further follow-up with these patients would be useful from both a research and a clinical perspective.

4.3 Study strengths and limitations

We note several limitations. First, we were unable to obtain much data from the transferring district hospitals, including labor variables, cesarean section operating notes, and antibiotic administration. Second, the methodology used for the study (a prospective and retrospective approach) is not as strong as a two-year prospective study. Given time constraints, the retrospective arm was necessary to increase the sample size for better power. Data from the retrospective arm may have been less reliable with fewer data points recorded. This is suggested by the statistically significant differences between 2014 and 2015 regarding presenting peritonitis symptoms (Table 1). Lack of data from 2014 on pus culture results reduced data points, limiting any meaningful associations between bacterial isolates and morbidity and mortality outcomes. More data would strengthen the findings.

Third, regarding our results on AMR, this study was performed in a tertiary referral hospital, which likely has higher rates of AMR than lower tier hospitals. Fourth,

the CHUK microbiology lab is resource-limited and may not perform standard quality control as frequently as in the developed world. Thus, the microbiologic yield of cultures may have been suboptimal. The lab also does not have the ability to do confirmatory testing or genotyping for ESBL isolates. Fifth, the majority of patients received antibiotics prior to admission to CHUK, which probably contributed to the negative cultures. Sixth, the length of time between sample collection in the operating theater and sample culture in the microbiology lab were not recorded, and delayed transporting of specimens to the lab could have resulted in the negative pus culture results. Seventh, neither fungal nor acid-fast bacilli (AFB) cultures, which may contribute to post-cesarean section peritonitis, were done.

Lastly, our study is unable to comment on overall rates of post-cesaraean peritonitis, as data on number of cesarean sections performed per district hospital were unavailable. We also cannot comment on rates of sepsis from post-cesarean surgical site infections that improved at district hospitals with routine use of antibiotics.

Despite the limitations, this study offers unique insight into the pathophysiology and microbial pathogenesis of post-cesarean section peritonitis, a condition that occurs with disturbing frequency in Rwanda. Understanding the role of AMR in this disease process can significantly contribute to developing the best initial treatment modalities for these patients, especially in resource-limited countries.

5. Conclusion

Post-cesarean section peritonitis carries a high rate of hysterectomy and high mortality rate in Rwanda. Understanding the disease process and identifying factors associated with outcomes can help guide management during admission and hopefully identify meaningful strategies to prevent this disease in the future.

Appendix A

Diagnostic criteria for post-cesarean section peritonitis

Labor History	Underwent cesarean section within 8 weeks of admission to CHUK
Symptoms (any of the following)	Abdominal distention or pain
	Wound discharge
	Wound separation
	Fever >38*C
	Stool or gas arrest
	Nausea/vomiting
Vital signs on admission (any single vital sign abnormality or combination)	Fever >38*C
	Tachypnea (respiration rate >90 beats/minute)
	Tachycardia (heart rate >20 breaths/minute)
	Hypotension (Systolic blood pressure <90 mmHg)
Physical exam findings on admission (any of the following PLUS vital sign abnormality)	Free fluid on bedside sonogram
	Wound separation
	Fascia dehiscence
Findings at time of laparotomy (any of the following)	Abdominal pus
	Subcutaneous tissue necrosis
	Fascia necrosis
	Rectus muscle necrosis
	Uterine hysterotomy dehiscence
	Uterine necrosis
	Tubo-ovarian abscess

Appendix B

Study Questionnaire

A ID#: _____
B Date of admission: _____
C Time of admission: _____

J Insurance:

None	0
Mutuelle	1
RAMA	2
Other	3

K Comorbidities

None	**0**
PEC/HTN	**1**
DM	**2**
Malaria	**3**
Jehovah's Witness	**4**
PPROM	**5**
Cardiac Disease	**6**
Other	**7**

L Referral Hospital: _____
M HIV

No	0
Yes	1
Unknown	99

N Age

O Gravitdity
P Parity

Q Term	_____
R Preterm	_____
S Abortion	_____
T Living	_____

U Gestational Age

Term	0
Preterm	1
Unknown	99

V Live Infant

No	0
Yes	1

W Date of CS_____

Z Reason for CS

Malpresentation (breech, transverse)	1
Arrest of Descent	2
Obstructed Labor	3
Uterine Rupture	4
Maternal Risk NOS	5
Fetal distress	6
Maternal Complication	7
Previous CS	8
Maternal HIV	9
PEC/Eclampsia	10
Cord Prolapse	11
Abruption	12
IUFD	13
Other	14
Unknown	99

AA Previous CS

No	0
Yes	1

AB Type of incision

Pfannensteil	1
Vertical	2
T-incision	3

AC Chorio in labor

No	0
Yes	1
Unknown	99

AD Discharge from DH

No	0
Yes	1
Unknown	99

AE Date of Discharge from DH _____
AF Date of Readmission DH _____
AG Date of Transfer CHUK _____
AH Date symptoms began _____
AI #Days at District Hospital _____

AJ Weight (kg) _____
AK Height (m) _____

AM CHUK Pulse/HR _____
AN CHUK RR _____
AO CHUK SBP _____
AP CHUK DBP _____
AQ CHUK O2 sat _____

AR CHUK Temp _____
AS GCS _____

Reason for Admission to DH

AT Wound discharge
No 0
Yes 1

AU N/V
No 0
Yes 1

AV Abd distention/pain
No 0
Yes 1

AW Fever
No 0
Yes 1

AX
Other_____
___

Findings at DH

Wound separation 0
Yes 1

AZ Wound pus 0
Yes 1

BA Fascial Dehiscence
Yes 1

BQ Fascial Dehiscence
No

BX Transfusion CHUK
No

Antibiotics Given at DH 0
Yes 1
Unknown 99

CB
BD Ampicillin No
No 0
Yes 1 CC
Unknown 99 No
0

BE Gentamicin
No 0
Yes 1
Unknown 99

BF Ceftriaxone
No 0
Yes 1
Unknown 99

BG Cefotaxime
No 0
Yes 1
Unknown 99

BH Flagyl
No 0
Yes 1
Unknown 99
BI Other _____

BJ Transfusion at DH
No 0
Yes 1
BK DH Pulse/HR _____
BL DH RR _____
BM DH SBP _____
BN DH DBP _____
BO DH O2 _____
BP DH Temp _____

Findings at CHUK

BV CHUK Hgb _____
BW CHUK PLT _____

0
Yes 1

BY Date of Initial Surgery _____

Findings in OR:

Wound Dehiscence 0
Yes 1

Abdominal Pus

Yes 1

CD SQ tissue necrosis
No 0
Yes 1

Uterine necrosis
No 0
Yes 1

CF Rectus muscle necrosis
0
Yes 1

G Uterine dehiscence
0
Yes 1

CH Uterine necrosis
0
Yes 1
If Yes
<1 cm along hysterotomy 0
1-3cm along hysterotomy
Lower uterine segment necrosis 2

Bowel Necrosis
0
Yes 1

CJ Abscesses
0
Yes 1

CK Tissue Debridement
0
Yes 1

colostomy
0
Yes 1

Uterine debridement
0
Yes 1

Bogota Bag 0
Yes 1

CO Initial Procedure Complication
None 0
Bladder Injury and Repair 1
Bowel Injury and Repair 2
PPH after CS 3
Foreign Body Removed 4
Other _____

CQ Initial Hysterectomy
No

CT Sono done1durin
NoNon

CS Subsequent Procedure
NoNon

DA
No

CP Inflammatory Fluid/Pus _____

0
Yes 1

CR Type of Incision
Pfannensteil 1
Vertical 2
T-incision 3

None 0
Delayed Hysterectomy 1
Washout Only 2

CW Total Number of surgeries_____

Date	Findings/Procedure

CZ Days with Bogota Bag _____

Antibiotics at CHUK
0
Yes 1

DB Ampicillin
No 0
Yes 1

DC Gentamicin
No 0

Yes 1

DE Ceftriaxone
No 0
Yes 1

DF Cefotaxime/Zimat
No 0
Yes 1

DG Flagyl
No 0
Yes 1

DH Cipro
No 0
Yes 1

DI Imipenem
No 0
Yes 1

DJ Erythromycin
No 0
Yes 1

DK Days of Antibiotics _____

DL Pus culture
No 0
Yes 1

DM Organism
Ecoli 1
Klebsiella 2
Proteus 3
Enterobacter 4
Gram + 5
No growth 6
Other:_____

Antibiogram

DN Cefotaxime Sensitive
No 0
Yes 1

DO Ceftazidime Sensitive
No 0
Yes 1

DP Ceftriaxone Sensitive
No 0
Yes 1

DQ Ampicillin Sensitive
No 0
Yes 1

DR Gentamicin Sensitive
No 0
Yes 1

DS Ciprofloxacin Sensitive
No 0
Yes 1

DU ICU Admission
No 0
Yes 1

DV Complication

None 0
PE 1
PNA 2
Septic Shock 3
Abscess requiring general surgery 4
Colostomy/Ileostomy 5
Anoxic brain injury 6
Urologic procedure 7
Other 98

DW Condition at Discharge
Alive 0
Dead 1

DX Cause of Death
_____

Date of discharge from CHUK:

I Length of Hospitalization (Days)
_____

Sepsis on Admission
0

DY
DZ Severe Sepsis on Admission
No 1

List of Abbreviations

AFB – acid-fast bacilli

Amox/Clav - amoxicillin-clavulanate

AMR – antimicrobial resistance

CHUK - University Teaching Hospital, Kigali

CS – cesarean section

DH – district hospital

ESBL – extended-spectrum β-lactamase

HIV – human immunodeficiency virus

ICU - intensive care unit

IUFD – intrauterine fetal demise

IV – intravenous

OBGYN – obstetrics and gynecology

POD – post-operative day

SD – standard deviation

SSI – surgical site infection

WHO – World Health Organization

References

1. Gibbons L, Belizan JM, Lauer JA, Betran AP, Merialdi M, Althabe F. Inequities in the use of cesarean section deliveries in the world. *Am J Obstet Gynecol.* 2012;206(4):331.e331-319.

2. Betran AP, Torloni MR, Zhang JJ, Gulmezoglu AM. WHO Statement on caesarean section rates. *BJOG : an international journal of obstetrics and gynaecology.* 2015.

3. WHO Statement on caesarean section rates. *Geneva: World Health Organization.* 2015:WHO/RHR/15.02.

4. Ye J, Zhang J, Mikolajczyk R, Torloni MR, Gulmezoglu AM, Betran AP. Association between rates of caesarean section and maternal and neonatal mortality in the 21st century: a worldwide population-based ecological study with longitudinal data. *BJOG : an international journal of obstetrics and gynaecology.* 2015.

5. Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. *PloS one.* 2016;11(2):e0148343.

6. Brubaker SG, Friedman AM, Cleary KL, et al. Patterns of use and predictors of receipt of antibiotics in women undergoing cesarean delivery. *Obstetrics and gynecology.* 2014;124(2 Pt 1):338-344.

7. Dahlke JD, Mendez-Figueroa H, Rouse DJ, Berghella V, Baxter JK, Chauhan SP. Evidence-based surgery for cesarean delivery: an updated systematic review. *American journal of obstetrics and gynecology.* 2013;209(4):294-306.

8. Chu K, Cortier H, Maldonado F, Mashant T, Ford N, Trelles M. Cesarean section rates and indications in sub-Saharan Africa: a multi-country study from Medecins sans Frontieres. *PloS one.* 2012;7(9):e44484.

9. Amenu D, Belachew T, Araya F. Surgical site infection rate and risk factors among obstetric cases of jimma university specialized hospital, southwest ethiopia. *Ethiopian journal of health sciences.* 2011;21(2):91-100.

10. Anderson DJ, Kaye KS, Classen D, et al. Strategies to prevent surgical site infections in acute care hospitals. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America.* 2008;29 Suppl 1:S51-61.

11. Caban R, Cohn I, Hsu CD. Evidence-based approach to reduce surgical site infections after cesarean delivery. *Obstetrics and gynecology.* 2014;123 Suppl 1:42s.

12. Lee I, Agarwal RK, Lee BY, Fishman NO, Umscheid CA. Systematic review and cost analysis comparing use of chlorhexidine with use of iodine for preoperative skin antisepsis to prevent surgical site infection. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America.* 2010;31(12):1219-1229.

13. Fitzwater JL, Tita AT. Prevention and management of cesarean wound infection. *Obstetrics and gynecology clinics of North America.* 2014;41(4):671-689.

14. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America.* 1992;13(10):606-608.

15. Chu K, Maine R, Trelles M. Cesarean section surgical site infections in sub-saharan Africa: a multi-country study from medecins sans frontieres. *World journal of surgery.* 2015;39(2):350-355.

16. Mawalla B, Mshana SE, Chalya PL, Imirzalioglu C, Mahalu W. Predictors of surgical site infections among patients undergoing major surgery at Bugando Medical Centre in Northwestern Tanzania. *BMC surgery.* 2011;11:21.

17. Mpogoro FJ, Mshana SE, Mirambo MM, Kidenya BR, Gumodoka B, Imirzalioglu C. Incidence and predictors of surgical site infections following caesarean sections at Bugando Medical Centre, Mwanza, Tanzania. *Antimicrobial resistance and infection control.* 2014;3:25.

18. Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA, Fraser VJ. Risk factors for surgical site infection after low transverse cesarean section. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America.* 2008;29(6):477-484; discussion 485-476.

19. Hadiati DR, Hakimi M, Nurdiati DS. Skin preparation for preventing infection following caesarean section. *The Cochrane database of systematic reviews.* 2012;9:Cd007462.

20. Aiken AM, Karuri DM, Wanyoro AK, Macleod J. Interventional studies for preventing surgical site infections in sub-Saharan Africa - A systematic review. *International journal of surgery (London, England).* 2012;10(5):242-249.

21. Costantine MM, Rahman M, Ghulmiyah L, et al. Timing of perioperative antibiotics for cesarean delivery: a metaanalysis. *American journal of obstetrics and gynecology.* 2008;199(3):301.e301-306.

22. Mackeen AD, Packard RE, Ota E, Berghella V, Baxter JK. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. *The Cochrane database of systematic reviews.* 2014;12:Cd009516.

23. WHO Guidelines Approved by the Guidelines Review Committee. *WHO Recommendations for Prevention and Treatment of Maternal Peripartum Infections*. Geneva: World Health Organization. Copyright (c) World Health Organization 2015.; 2015.

24. Sartelli M, Catena F, Di Saverio S, et al. Current concept of abdominal sepsis: WSES position paper. *World journal of emergency surgery : WJES.* 2014;9(1):22.

25. Rivlin ME, Carroll CS, Morrison JC. Conservative surgery for uterine incisional necrosis complicating cesarean delivery. *Obstet Gynecol.* 2004;103(5 Pt 2):1105-1108.

26. Rivlin ME, Carroll CS, Sr., Morrison JC. Infectious necrosis with dehiscence of the uterine repair complicating cesarean delivery: a review. *Obstet Gynecol Surv.* 2004;59(12):833-837.

27. Bharatam KK, Sivaraja PK, Abineshwar NJ, et al. The tip of the iceberg: Post caesarean wound dehiscence presenting as abdominal wound sepsis. *Int J Surg Case Rep.* 2015;9:69-71.

28. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *The New England journal of medicine.* 2015;372(17):1629-1638.

29. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis*. *Critical care medicine.* 2014;42(3):625-631.

30. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *Jama.* 2014;311(13):1308-1316.

31. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive care medicine.* 2013;39(2):165-228.

32. Ntirenganya C, Manzi O, Muvunyi CM, Ogbuagu O. High prevalence of antimicrobial resistance among common bacterial isolates in a tertiary healthcare facility in Rwanda. *Am J Trop Med Hyg.* 2015;92(4):865-870.

33. Antibiotic Resistance Threats in the United States, 2013. Atlanta, GA: Centers for Disease Control and Prevention; 2013.

34. WHO. *Antimicrobial resistance in the African Region: Issues, challenges and actions proposed.* March 2013.

35. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev.* 2012;25(4):682-707.

36. Seni J, Najjuka CF, Kateete DP, et al. Antimicrobial resistance in hospitalized surgical patients: a silently emerging public health concern in Uganda. *BMC Res Notes.* 2013;6:298.

37. Manyahi J, Matee MI, Majigo M, Moyo S, Mshana SE, Lyamuya EF. Predominance of multi-drug resistant bacterial pathogens causing surgical site infections in Muhimbili National Hospital, Tanzania. *BMC Res Notes.* 2014;7:500.

38. Rulisa S, Umuziranenge I, Small M, van Roosmalen J. Maternal near miss and mortality in a tertiary care hospital in Rwanda. *BMC Pregnancy Childbirth.* 2015;15(1):203.

39. Tellor B, Skrupky LP, Symons W, High E, Micek ST, Mazuski JE. Inadequate Source Control and Inappropriate Antibiotics are Key Determinants of Mortality

in Patients with Intra-Abdominal Sepsis and Associated Bacteremia. *Surg Infect (Larchmt).* 2015;16(6):785-793.

40. Bhutta ZA, Chopra M, Axelson H, et al. Countdown to 2015 decade report (2000-10): taking stock of maternal, newborn, and child survival. *Lancet (London, England).* 2010;375(9730):2032-2044.

41. Annual Health Statistics Booklet. *Rwanda Ministry of Health* 2013.

42. Levy MM FM, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, . 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. 2003.

43. Diaz JJ, Jr., Cullinane DC, Dutton WD, et al. The management of the open abdomen in trauma and emergency general surgery: part 1-damage control. *The Journal of trauma.* 2010;68(6):1425-1438.

44. Rivlin ME, Hunt JA, Rubin A. Continual postoperative antibiotic peritoneal lavage in diffuse peritonitis complicating cesarean section. *J Reprod Med.* 1984;29(3):173-178.

45. Bilton BD, Zibari GB, McMillan RW, Aultman DF, Dunn G, McDonald JC. Aggressive surgical management of necrotizing fasciitis serves to decrease mortality: a retrospective study. *The American surgeon.* 1998;64(5):397-400; discussion 400-391.

46. Childs L, Moores KL, Dhingra S. Uterine preservation in necrotising fasciitis following caesarean section. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2012;32(2):190-191.

47. Durai R, Ng PC, Uzkalnis A. Necrotising fasciitis following a caesarean section. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2012;32(1):96-98.

48. Gallup DG, Freedman MA, Meguiar RV, Freedman SN, Nolan TE. Necrotizing fasciitis in gynecologic and obstetric patients: a surgical emergency. *American journal of obstetrics and gynecology.* 2002;187(2):305-310; idscussion 310-301.

49. Goepfert AR, Guinn DA, Andrews WW, Hauth JC. Necrotizing fasciitis after cesarean delivery. *Obstetrics and gynecology.* 1997;89(3):409-412.

50. Gonzalez Castro A, Rodriguez-Borregan JC, Obeso T, Castellanos A, Perez-Ceballos A, Sesmero JR. Necrotizing fasciitis after cesarean section. *Archives of gynecology and obstetrics.* 2008;277(6):579-581.

51. Haldar MK, Shabarwal SD, Moore PJ. Necrotising fasciitis following a caesarean section. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 2004;24(1):87-88.

52. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt).* 2010;11(1):79-109.

53. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med.* 2014;42(8):1749-1755.

54. Turza KC, Campbell CA, Rosenberger LH, et al. Options for closure of the infected abdomen. *Surg Infect (Larchmt).* 2012;13(6):343-351.

55. Tran TS, Jamulitrat S, Chongsuvivatwong V, Geater A. Risk factors for postcesarean surgical site infection. *Obstetrics and gynecology.* 2000;95(3):367-371.