JAC-Antimicrobial Resistance

Occurrence and significance of fluoroquinolone-resistant and ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* complex of the rectal flora in Ghanaian patients undergoing prostate biopsy

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Background: Reports suggest that fluoroquinolone (FQ)-resistant and ESBL-producing rectal flora are associated with infectious complications in men undergoing transrectal ultrasound-guided prostate needle biopsy (TRUS-B)

Objectives: We investigated the relationship between carriage of FQ-resistant and ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* complex of the rectal flora, and the 30 day incidence rate of post-TRUS-B infectious complications.

Methods: From 1 January 2018 to 30 April 2019, rectal swabs of 361 patients were cultured pre-TRUS-B for FQ-resistant and ESBL-producing flora. Patients were followed up for 30 days for infectious complications post-biopsy. Multivariable logistic regression analyses were used to identify risk factors.

Results: Overall, 86.4% ($n = 312/361$) and 62.6% ($n = 226/361$) of patients carried FQ-resistant and ESBL-producing *E. coli* and *K. pneumoniae* complex, respectively. Approximately 60% ($n = 289/483$) of the FQ-resistant and 66.0% ($n = 202/306$) of the ESBL-positive isolates exhibited *in vitro* resistance to the pre-biopsy prophylactic antibiotic regimen of levofloxacin and gentamicin. Amikacin and meropenem were the most effective antibiotics against the MDR rectal *E. coli* and *K. pneumoniae* complex (78.7% and 84.3%, respectively). The 30 day incidence rate for post-biopsy infections was 3.1% ($n = 11/361$), with an overall high probability (96.9%) of staying free of infections within the 30 day period post-TRUS-B. Antibiotic use in the previous 3 months was a risk factor for rectal carriage of FQ-resistant and ESBL-positive isolates. Rectal colonization by ESBL-positive *E. coli* and *K. pneumoniae* complex comprised an independent risk factor for post-biopsy infectious complications.

Conclusions: The findings suggest that a change in prophylactic antibiotics to a more targeted regimen may be warranted in our institution.

Introduction

Prostate cancer is the most common non-skin cancer in men.[1,2] Transrectal ultrasound-guided prostate needle biopsy (TRUS-B) is the standard of care to confirm the diagnosis of prostate cancer with elevated prostate-specific antigen.[3–5] This procedure is endorsed by several bodies including the American Urological Association (AUA), International Society of Geriatric Oncology (SIOG) and the European Association of Urology (EAU) guidelines on screening, diagnosis and local treatment of prostate cancer.[3–8] Although a relatively simple procedure, TRUS-B may be associated with significant infectious complications.[6] The spectrum of bacteria involved in the infectious complications represent faecal colonizing bacteria and are characterized mainly by

Enterobacterales, predominantly *Escherichia coli* and *Klebsiella pneumoniae* complex.[3,9–12] These pathogens are transferred from the rectum into the prostate and bloodstream by the biopsy needle. The impact of TRUS-B-related infections prompted the AUA, EAU, SIOG, the European Society of Urogenital Radiology and several other agencies to recommend prophylactic use of antibiotics based on local antibiograms of infection and colonization bacteria.[3–8,13] In a meta-analysis of 22 randomized controlled trials that included 3846 patients, Yang *et al.*[14] showed that prophylactic antibiotics, single-dose or short-course oral administration of any type of antibiotic could be beneficial for the reduction of infective complications after TRUS-B.

Evidence shows that antimicrobial resistance (AMR) in Ghana is on the increase, with high levels of MDR to routinely used antibiotics observed mainly in Gram-negative organisms.[15,16] Previous prospective studies have shown high levels of ESBL-producing Enterobacterales in both carriage and clinical isolates.[17–19] The ESBL-positive bacteria, particularly the CTX-M producers, are resistant to most β-lactam antibiotics and are usually associated with co-resistance to aminoglycosides, fluoroquinolones, sulphonamides and tetracyclines.[20–22] Such high levels of AMR have the potential to hamper antibiotic prophylactic strategies and increase the rate of TRUS-B-related infectious complications in Ghana.[15,17,23] At our clinic in Ghana, patients undergoing TRUS-B are administered an aminoglycoside (240 mg gentamicin IV stat dose) before biopsy and a 5 day FQ course of 500 mg oral levofloxacin once daily. Systematic reviews and meta-analysis of retrospective and prospective study types highlight the prophylactic ability of FQs and aminoglycosides to reduce post-biopsy infectious complications due to their broad spectrum and ability to concentrate in the prostate.[14,24–27] However, we have no evidence base in Ghana to describe the threat of FQ resistance or ESBL-producing rectal flora to the utility of our antibiotic prophylactic regimens for patients undergoing TRUS-B. There are currently no studies to characterize the antibiogram of the rectal flora of patients undergoing TRUS-B, and it is unknown if the FQ-resistant and ESBL-producing rectal flora contribute to the development of infectious complications post-TRUS-B. In this study, we report on the rectal carriage of FQ-resistant and ESBL-producing Enterobacterales, the occurrence of post-TRUS-B infections, and the utility of our current antibiotic prophylactic strategy.

Methods

Study setting

The study was conducted at the genitourinary clinic of the surgical department of Korle-Bu Teaching Hospital (KBTH). KBTH is the leading referral healthcare facility in Ghana, with a 2000 bed capacity.[28] The clinic averages about 10 600 outpatient attendants annually, with about 5.6% (*n*=600) of outpatient cases yearly referred for TRUS-B. We aimed to enrol ≥380 patients taking into account 5% loss to follow-up. Thus, a minimum of 360 patients undergoing TRUS-B were needed to achieve 80% power with a type 1 alpha of 5%,[29] using 6% as the maximum 30 day incidence of infectious complications.[14,25,26]

Study design and participants

We conducted a prospective cohort study involving patients presenting for TRUS-B either because of an increased age-corrected prostate-specific antigen (PSA) level and/or abnormal digital rectal examination findings—including a nodule, induration or asymmetry—that might indicate prostate cancer.[30–32] Our primary aim was to report on the rectal carriage of FQ-resistant and ESBL-producing enterobacteria, the occurrence of post-TRUS-B infections, and the current antibiotic prophylactic strategy. The secondary aims were risk factors for rectal carriage and factors that may contribute to the predisposition of the patients to post-biopsy infection. Sampling was conducted from 2 January 2018 through to 31 April 2019. The study was approved by the Ethical and Protocol Review Committee of KBTH (CHS-Tt/M.9C/2016-017) and written consent was obtained from all participants.

Specimen collection and laboratory processing

At the clinic, rectal swabs in Cary–Blair transport medium (Oxoid, UK) were collected by the attending urologist immediately before placement of the rectal ultrasound probe for TRUS-B. Each swab was streaked onto MacConkey agar plates with a 5 μg ciprofloxacin disc and a 30 μg cefotaxime disc placed on them and incubated overnight at 37°C in ambient air. Representative colonies of each distinct enterobacterial morphotype with reduced susceptibility (≤30 mm zone of inhibition) to ciprofloxacin or cefotaxime were respectively considered as presumptive FQ-resistant or ESBL-producers and were selected for identification with the Bruker MALDI-TOF Biotyper. For the purposes of this study, only isolates identified as *E. coli* or *K. pneumoniae* complex were selected for further studies. Interpretation of isolate susceptibility to different antimicrobial agents was based on CLSI guidelines.[33] FQ resistance was defined as inhibition zone size ≤21 mm to ciprofloxacin and ≤19 mm to levofloxacin. ESBL producers were isolates positive for CLSI confirmatory tests using cefotaxime (30 μg) and ceftazidime (30 μg), with and without clavulanic acid(10 μg).[33]

Clinical outcomes

To determine clinical outcomes post-TRUS-B, patients were contacted weekly by telephone over 30 days for signs of infections. A post-biopsy questionnaire was administered to screen for infectious complications including fever (temperature ≥38.5°C), symptoms of urinary tract infections and presentation to hospital or physician for any reason. Patients with suspicion of infections were asked to come back to the ward for examination by a doctor. For all suspected infections, appropriate specimens were obtained for bacterial culture to isolate the causative organism. Post-TRUS-B-related infection was based on the incidence of clinical symptoms diagnosed by clinical or laboratory examination and for which antibiotics were administered. Infectious complications were defined as urinary tract infection symptoms accompanied by body temperature ≥38.5°C (fever) or sepsis within 30 days after the biopsy, according to the eleventh revision of the International Classification of Diseases.[34] Urinary tract infection symptoms were defined as the presence of chilliness, frequency, urgency and dysuria. Febrile urinary tract infections included fever (≥38.3°C), leucocytes in urine sediment, or tenderness of the prostate during digital rectal examination. Sepsis was defined as the presence of clinically or microbiologically documented infection in conjunction with systemic inflammatory response (SIR) syndrome.[35] At the time of sampling, many healthcare facilities were using the previous SIR sepsis definition and implementation of the new recommendations was not fully evolved.[36] Although the SIR criteria have been excluded from the current definition of sepsis,[36] they are still effective for identifying infections and can be used to screen potential individuals who are at risk for sepsis. In the analysis, non-infectious complications such as haematuria, rectal bleeding and perineal pain were noted and differentiated from infections complications. In this study, we collected basic demographic and clinical data that were subsequently analysed for potential risk factors for the development of infective complications and possible predictors of rectal carriage of FQ-resistant and

ESBL-producing isolates. The data collection form (Supplementary file 1) was developed after review of the literature and discussion with consultant physicians in TRUS-B. The form was administered by a member of nursing staff supervised by the lead investigator who performed the biopsies. The 40 item form collected information under three cluster headings. The first included demographics and general information data (including age, gender, occupation). The second cluster comprised clinical history (including comorbidities and peri-procedural data such as the number of biopsy cores). The last cluster incorporated questions on risk factors for infectious complications as well as FQ-resistant and ESBL-positve faecal carriage (including antibiotic use in the past 3 months, history of catheterization, and patient characteristics post-TRUS-B).

Statistics

We expressed univariate continuous variables as mean (with SD) or median (with IQR) where appropriate.[37] Antibiotic resistance data were expressed as categorical variables and analysed as absolute numbers with percentages of the total. The 99 level greyscale method was used to construct a heat map of pairwise MDR analysis. MDR was defined as resistance to at least one antibiotic in three or more antimicrobial categories. The Kaplan–Meier survival curve was used to estimate the cumulative probability incidence of post-TRUS-B-related infections.[29] Bivariate comparisons between patients with and without rectal carriage by FQ-resistant or ESBL-producing isolates, and between patients with and without post-TRUS-B infections were computed using the Kruskal–Wallis test for continuous variables and the χ^2 or Fisher's exact tests for categorical variables.[37] The Mood's median was used as a non-parametric test to compare the medians of two independent samples.[37] All univariate variables that had a P value of <0.2 were entered into multivariate logistic regression, with results expressed as ORs with 95% CIs.[29,37,38] All tests were two-sided and P value <0.05 was statistically significant.

Results

During the study period, 602 patients were referred to the clinic for TRUS-B. Of these, 381 provided informed consent and were willing to fully participate in the study. Twenty recruited patients (5.3%) were unable to provide rectal swabs or were lost to follow-up and were excluded from the study. Rectal swabs were recovered from 361 of 381 TRUS-B patients (94.7%) and none were lost to follow-up. The mean age of all 361 participants was 69.1 ± 8.9 years, the median serum PSA was 22.4 ng/mL (IQR, 10.2–65.5 ng/mL) and the mean prostate volume was 63.1 ± 47.1 mL.

Numbers of FQ-resistant and ESBL-producing rectal cultures

Overall, 86.4% (n = 312/361) of the patients rectally carried at least one FQ-resistant E. coli and/or K. pneumoniae complex (Table 1). About 46% (n = 142/312) and 47% (n = 170/361) of the patients carried >1 morphologically distinct colony type of FQ-resistant E. coli or K. pneumoniae complex, respectively. An ESBL-producing E. coli and/or K. pneumoniae complex was detected in 62.6% (n = 226/361) of the TRUS-B patients. Seventy-four (32.7%, n = 74/361) patients carried >1 morphologically distinct colony type of an ESBL-producing isolate. All patients with ESBL carriage also carried FQ-resistant isolates. Forty-nine (13.6%, n = 49/361) patients had no faecal carriage of FQ-resistant or ESBL-producing isolates. Eighty-six (23.8%,

n = 86/361) patients had faecal carriage by FQ-resistant flora but carried no ESBL producers. In total, there were 483 FQ-resistant and 306 ESBL-producing rectal E. coli and K. pneumoniae complex flora recovered from TRUS-B patients (Table 1). Gentamicin-resistant E. coli and/or K. pneumoniae complex were recovered from 77.8% (n = 281/361) of TRUS-B patients.

Antibiogram of rectal cultures

Figure 1 shows the antibiogram for all 483 FQ-resistant and 306 ESBL-producing rectal isolates recovered from TRUS-B patients. All the ESBL producers were FQ resistant. Most isolates were susceptible to meropenem [84.3% (n = 407/483) for FQ-resistant isolates; 85.9% (n = 263/306) for ESBL producers] and amikacin [78.7% (n = 380/483) for FQ-resistant isolates; 74.9% (n = 229/306) for ESBL producers]. Conversely, 59.8% (n = 289/483) of FQ-resistant isolates and 66.0% (n = 202/306) of ESBL producers were resistant to gentamicin. An MDR phenotype was observed in 71.0% (n = 343/483) of FQ-resistant isolates and all ESBL producers. Figure 2 shows a multidrug antibiotic co-resistance map for total FQ-resistant and ESBL-producing rectal cultures. Meropenem showed the lowest level of co-resistance, ranging from 8.1% (n = 39/483) to amoxicillin plus clavulanic acid up to 14.3% (n = 69/483) to tigecycline. Amikacin also maintained a wide coverage over the majority of the MDR rectal flora, with the lowest co-resistance to meropenem (4.8%; n = 23/483), sulfamethoxazole/trimethoprim (18.8%; n = 91/483), cefotaxime (19.7%; n = 95/483) and tigecycline (19.9%; n = 96/483).

Infection rates

Figure 3 shows the incidence of infectious complications during the study period. Of the 361 patients who underwent TRUS-B, 11 developed post-biopsy infections, representing a 30 day incidence rate of 3.1%. All 11 patients acquired urinary tract infections; 6 of them consequently developed sepsis, another 4 had fever without sepsis and 1 had epididymo-orchitis. Blood and urine cultures were performed for all 11 patients. One blood culture yielded a pathogen (FQ-resistant non-ESBL-producing E. coli susceptible to cephalosporins, amikacin and meropenem) from a patient with sepsis. The patient recovered on meropenem 500 mg three times daily for 2 days followed by cefuroxime 500 mg for 5 days. Pathogens were not detected from any of the urine cultures. It is noteworthy that all 11 patients with post-TRUS-B infections had pre-biopsy rectal cultures positive for FQ-resistant and ESBL-producing E. coli. Seven of the patients also carried gentamicin-resistant rectal cultures pre-biopsy. Eight of the post-biopsy infections occurred after the cessation of prophylaxis. The number of days (mean ± SD) from TRUS-B to the onset of infections was 16.91 ± 11.48 days (IQR, 6–19 days). The proportion of infections among patients who carried FQ-resistant isolates (3.5%; n = 11/312) was not statistically different (Z-score P = 0.124) from the proportion of infections among patients who carried FQ-susceptible isolates (0%; n = 0/49). Similarly, the proportion of infections among patients who colonized by ESBL producers (3.5%; n = 11/226) was not statistically different (Z-score P = 0.479) from the proportion of infections among patients with no ESBL colonization (0%; n = 0/135). As illustrated in Figure 4(a), we encountered 56 weeks between the first post-TRUS-B infection (Week 8, Day 56) and the last (Week 65,

Table 1. Prevalence of FQ-resistant and ESBL-producing *E. coli* and/or *K. pneumoniae* complex in rectal swabs of TRUS-B patients

Characteristics	Patients with FQ-resistant rectal carriage (%)					Patients with GEN-resistant rectal carriage (%)				Patients with rectal carriage of ESBL producers (%)			
		Number of morphologically distinct colonies with unique resistant phenotype					Number of morphologically distinct colonies with unique resistant phenotype				Number of morphologically distinct colonies with unique resistant phenotype		
	Total	1	2	3	4	Total	1	2	3	Total	1	2	3
TRUS-B patients (n=361)	312 (86.4)	170 (47.1)	116 (32.1)	24 (6.6)	2 (0.6)	281 (77.8)	160 (44.3)	120 (33.2)	1 (0.3)	226 (62.6)	152 (42.1)	68 (18.8)	6 (1.7)
Patients who developed post-TRUS-B infections (n=11)	11					7				11			
Type of rectal colonization													
Only *E. coli*	295	163 (55.1)	107 (36.1)	23 (7.8)	2 (0.7)	214	145 (40.2)	120 (33.2)	0	212	143 (48.3)	63 (21.3)	6 (2.0)
E. coli+KP	3	1 (33.3)	2 (66.7)	0	0	4	2 (0.6)	0	0	2	0	2 (0.6)	0
2 *E. coli*+1 KP	1	0	0	1 (100)	0	0	—	—	—	0	—	—	—
Only KP	13	6 (46.2)	7 (53.8)	0	0	6	13 (3.6)	0	1 (0.3)	12	9 (69.2)	3 (23.1)	0
Total isolates	483 FQ-resistant strains recovered from 312 patients					306 GEN-resistant strains recovered from 281 patients				306 ESBL strains recovered from 152 patients			

GEN, gentamicin; KP, *K. pneumoniae* complex. Total number isolates is calculated by adding up all the different strains with distinct morphology and resistant phenotype for each type of patient rectal colonization (i.e. *E. coli*, *E. coli*+KP, 2 *E. coli*+1 KP, only KP).

Day 455), and when an infection occurred it was often the only case in the several TRUS-B performed for the batch of patients in that week. The Kaplan–Meier curve [Figure 4(b)] showed an overall high probability (96.9%) of staying free of infections within the 30 day period post-TRUS-B. The data showed that the probability of remaining free of infections reduced with each passing day, and ranged from 99.5% (95% CI, 96.7%–99.8%) on Day 2 to 96.5% (95% CI, 92.9%–98.1%) by Day 24.

Risk factor analysis

Table 2 illustrates the results of multivariable analysis for independent risk factors associated with rectal carriage of FQ-resistant and ESBL-producing isolates as well as infectious complications post-TRUS-B. Increasing patient age (aOR, 1.03; 95% CI, 1.01–1.08; $P=0.004$) and antibiotic use in the past 3 months (aOR, 4.11; 95% CI, 2.71–9.62; $P=0.001$) were independent risk factors for rectal carriage of FQ-resistant rectal flora. The most significant risk factor associated with rectal carriage of FQ-resistant isolates was rectal carriage of an ESBL-producing organism (aOR, 11.34; 95% CI, 7.23–19.78; $P=0.001$). Similarly, antibiotic use in past 3 months (aOR, 3.63; 95% CI, 2.11–6.43; $P=0.001$) and rectal culture of FQ-resistant isolates (aOR, 8.76; 95% CI, 86.98–17.54; $P=0.001$) were predictive for carriage of ESBL-positive rectal flora. The top five antibiotics used by TRUS-B patients in the last 3 months prior to sampling were amoxicillin/clavulanic acid, cefuroxime, metronidazole, ceftriaxone and azithromycin. However, none of the antibiotics by type or category constituted a risk factor for intestinal carriage by FQ-resistant or ESBL-producing *E. coli* and *K. pneumoniae* or a risk factor for the occurrence of post-TRUS-B infections. Overall, patients with rectal carriage of an ESBL-producing organism had a 13-fold increased risk of developing an infectious complication post-TRUS-B (aOR, 13.12; 95% CI, 7.11–9.11; $P=0.001$).

Discussion

This is the largest prospective study in Western Africa regarding the occurrence and significance of FQ-resistant and ESBL-producing rectal flora in patients undergoing TRUS-B. Our report describes a high co-prevalence of FQ-resistant (86.4%) and ESBL-producing (62.4%) rectal flora in patients undergoing TRUS-B. We observed a 3.1% post-biopsy 30 day infection rate. Rectal carriage of ESBL-positive flora and diagnosis of prostate cancer were definite clinical factors associated with infectious complications post-TRUS-B. Overall, the findings suggest that a change in empirical prophylactic guidelines for patients undergoing TRUS-B is needed. Four major observations merit attention.

First, the frequent isolation of FQ-resistant bacteria and the ubiquitous presence of ESBL-producing organisms suggest that quinolones do not have an optimal susceptibility profile against rectal isolates in our setting and may not be suitable for use as a prophylactic antibiotic in patients undergoing TRUS-B.[26,39–45] Recent studies that used FQ-based prophylaxis, depending on the study design and the partner antibiotics, have demonstrated varying rates of infections post-TRUS-B ranging from 2% to 55%. The 3.1% infection rate observed in this study is equivalent to post-intervention hospitalization rates reported in the placebo control arms of similar studies.[14] There are no published benchmarks for
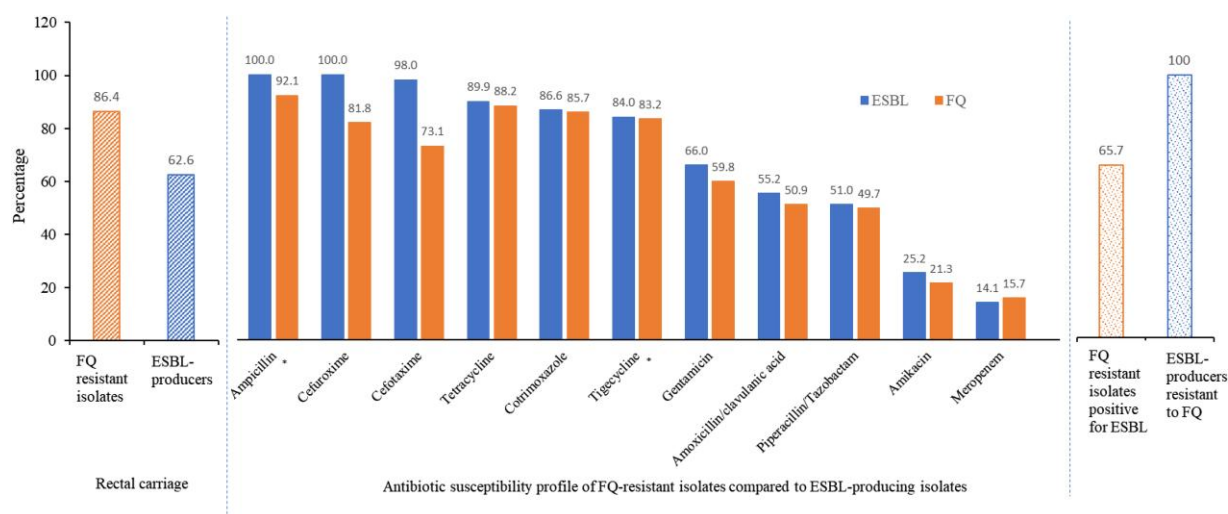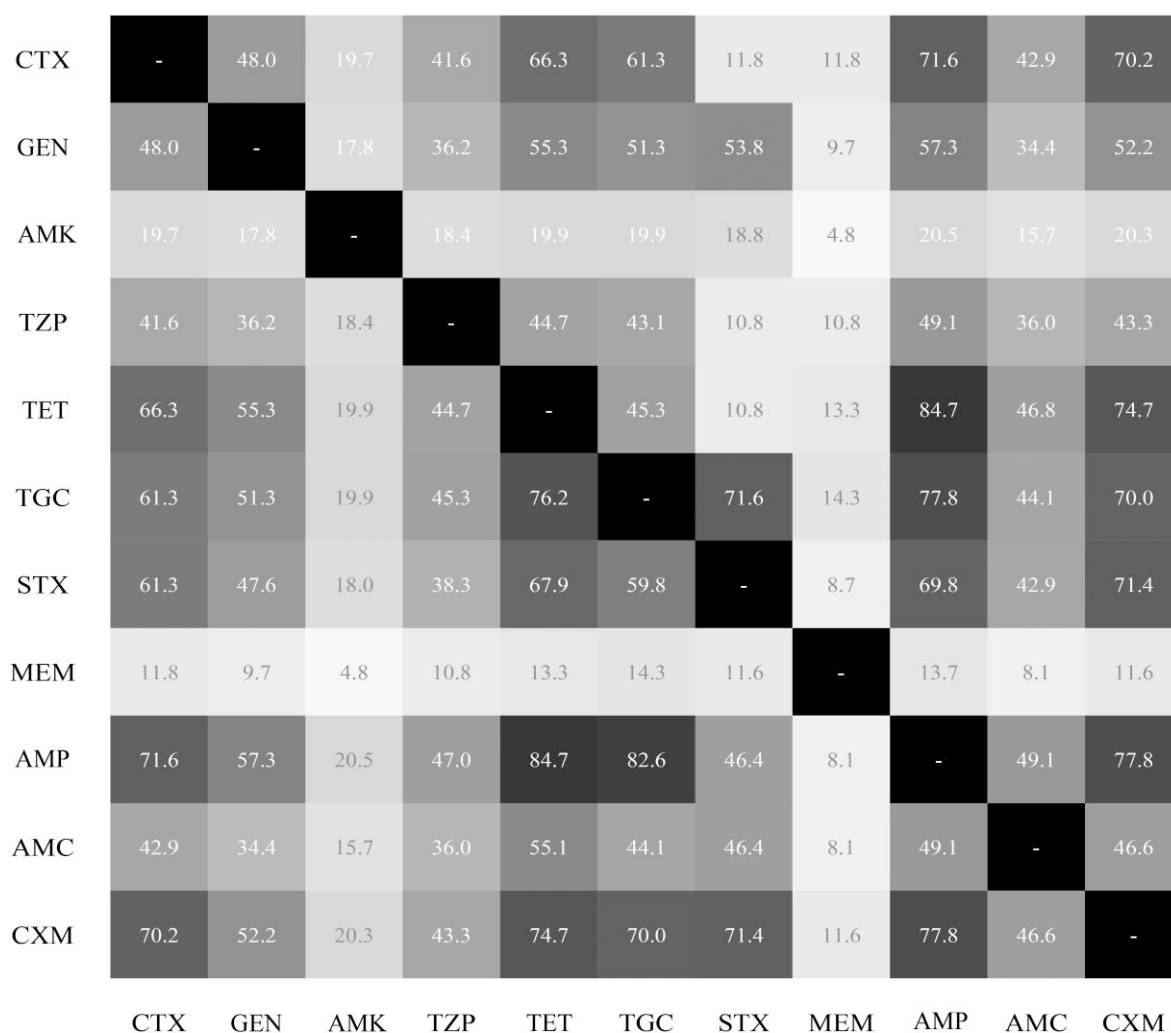
Figure 1. Prevalence of rectal carriage, post-TRUS-B infections, and antibiotic susceptibility profile of FQ-resistant and ESBL-producing isolates. *Ampicillin not reported for *K. pneumoniae* complex due to intrinsic resistance; tigecycline tested for only *E. coli*.

an acceptable rate of infections post-TRUS-B. Suffice it to say that any single case of infection post-TRUS-B poses a serious threat for the patient's health and represents elevated costs, therefore prophylactic regimens must be selected based on adequate proof of safety and effectiveness. Our results also showed poor susceptibility to gentamicin of rectal flora. The findings bring forth the debate that the 3.1% incidence of infections observed over the 16 month study period, coupled with the high probability of remaining free of infections many days post-biopsy, may suggest that a change in prophylactic strategy is not warranted despite the high resistance exhibited by the rectal flora. However, there is clear evidence that there is no role for empirical quinolone-plus-gentamicin regimens. While almost 87% of patients carried an FQ-resistant isolate, about 60% of all the FQ-resistant isolates were non-susceptible to both levofloxacin and gentamicin. The results show that the probability of encountering an FQ-susceptible isolate pre-TRUS-B in our setting is likely to be low and there is no justification for continuing levofloxacin therapy. Even in patients without colonization by resistant isolates, the high background FQ resistance and ESBL prevalence suggest that the use of the FQ regimen post-operatively is not advised because of poor outcomes from the selection of resistant strains.

Second, meropenem and amikacin were effective against most rectal *E. coli* and *K. pneumoniae* complex isolates, and they showed low-level co-resistance to other antibiotics. Changing the TRUS-B prophylactic regimen from FQ-based to other alternatives with high susceptibility against rectal flora is well discussed in the literature.[9,11,24,40,46–49] Yet, there are unresolved controversies across countries and regional regulatory bodies regarding the preferred prophylactic regimen for TRUS-B. Several studies using prophylactic antibiotics to reduce post-biopsy infectious complications have reported success, mostly with amikacin and meropenem.[41,48,50–53] However, several studies also do not recommend their routine use for prophylaxis because of the selection and spread of antibiotic resistance.[42,52,54,55] Given that 3.1% of TRUS-B patients developed post-biopsy complications, the option for no antibiotic

prophylaxis pre-TRUS-B has also been proposed for our setting in the attempt to reduce the selective burden of FQ-resistant and ESBL-positive pathogens. The proponents suggest that rather, when patients develop post-TRUS-B infections, antibiotics like amikacin and meropenem—which showed wide coverage against the resistant pathogens in our study— may be used for treatment based on local antibiograms. The argument is premised on the observation that the 3.1% incidence rate coupled with a high level of faecal drug resistance probably reflects the contribution of other factors such as lack of virulence factors among the colonizing pathogens or low infective dose of inoculated bacteria by the biopsy needle, or patient characteristics that predispose them to infectious complications. A meta-analysis by Yang *et al.*[14] seems to indicate substantial benefit of the no-prophylaxis strategy, albeit in settings with low prevalence of rectal carriage by MDR bacteria. The general reservations with a no-prophylaxis regimen for our setting is the potential increase in infectious complications post-TRUS-B due to high carriage rates of MDR rectal flora. It is worth mentioning that the only isolate recovered from blood cultures of patients who developed post-biopsy infections was susceptible to amikacin and meropenem but resistant to ciprofloxacin and gentamicin. Amikacin and meropenem have been on the Ghanaian market for a relatively short period. They are parenteral, and more expensive in the case of meropenem, thus its use and abuse are not widespread in Ghanaian hospitals.[56,57] Carbapenem resistance was 15.7% among FQ-resistant isolates and 14.1% in the ESBL producers. Although we are unable to confirm what proportion of these isolates express carbapenemase enzymes, because that is the focus of an ongoing study elsewhere, the level of carbapenem resistance in this study agrees well with the reported prevalence of carbapenemase production in member species of the Enterobacterales in Ghana.

Third, there appears to be an appreciable probability of infective complications in the FQ-resistant group. However, based on the small number of patients colonized by FQ-susceptible isolates and the lack of infectious complications within this cohort, the

	CTX	GEN	AMK	TZP	TET	TGC	STX	MEM	AMP	AMC	CXM
CTX	-	48.0	19.7	41.6	66.3	61.3	11.8	11.8	71.6	42.9	70.2
GEN	48.0	-	17.8	36.2	55.3	51.3	53.8	9.7	57.3	34.4	52.2
AMK	19.7	17.8	-	18.4	19.9	19.9	18.8	4.8	20.5	15.7	20.3
TZP	41.6	36.2	18.4	-	44.7	43.1	10.8	10.8	49.1	36.0	43.3
TET	66.3	55.3	19.9	44.7	-	45.3	10.8	13.3	84.7	46.8	74.7
TGC	61.3	51.3	19.9	45.3	76.2	-	71.6	14.3	77.8	44.1	70.0
STX	61.3	47.6	18.0	38.3	67.9	59.8	-	8.7	69.8	42.9	71.4
MEM	11.8	9.7	4.8	10.8	13.3	14.3	11.6	-	13.7	8.1	11.6
AMP	71.6	57.3	20.5	47.0	84.7	82.6	46.4	8.1	-	49.1	77.8
AMC	42.9	34.4	15.7	36.0	55.1	44.1	46.4	8.1	49.1	-	46.6
CXM	70.2	52.2	20.3	43.3	74.7	70.0	71.4	11.6	77.8	46.6	-

Figure 2. Antibiotic co-resistance heatmap of all FQ-resistant and ESBL-producing rectal flora. Colour gradient (from light to dark) indicates increasing co-resistance. Figures within cells denote the percentage co-resistance between two overlapping antibiotics. Meropenem and amikacin exhibited the least co-resistance patterns and showed the widest coverage over MDR rectal flora. FOX, cefoxitin; CTX, cefotaxime; GEN, gentamicin; AMK, amikacin; TZP, piperacillin/tazobactam; TET, tetracycline; TGC, tigecycline; STX, co-trimoxazole, MEM, meropenem; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; CXM, cefuroxime.

study may not be sufficiently powered to detect an association between FQ resistance and incidence of infections. We found that the risk of 30 day post-biopsy infections was not significantly higher in patients who carried FQ-resistant organisms before TRUS-B compared with those who carried FQ-susceptible organisms. Recent meta-analyses demonstrate, with wide statistical heterogeneity, that FQ-resistant rectal flora is a significant predictor of post-biopsy infections.[26,39,40,44] Our result is to the contrary but does not dismiss such reports. We attribute the discrepancy to the endemicity of FQ-resistant rectal flora (>86%) in our study cohort and the 3.1% incidence of post-biopsy infections. For instance, although all 11 patients with post-biopsy infections were colonized with FQ-resistant isolates, a significant proportion (86%) of the infection-free cohort also harboured FQ-resistant rectal flora. Only a few patients harboured FQ-susceptible rectal flora. It is noteworthy that over 72% of

patients with FQ-resistant rectal flora also harboured ESBL-producing organisms. In this study, the presence of FQ-resistant rectal flora was predictive for ESBL rectal carriage, whereas rectal carriage with ESBL-producing organisms constituted an independent risk factor for the occurrence of post-TRUS-B infection. It is well recognized that gut colonization with ESBL-positive organisms is a risk factor for infections.[22,58] Our observations subscribe to recent reports that quinolone resistance data should be considered together with ESBLs when planning antibiotic prophylaxis.[21,59] Also, the high carriage of ESBL-positive organisms means that the utility of cephalosporins as agents for managing biopsy-related infections is limited.

Last, our findings imply the need for urologists to be aware of the local prevalence of AMR in intestinal flora of patients undergoing TRUS-B. This begs the question of whether antibiogram-directed prophylaxis based on pre-biopsy culture
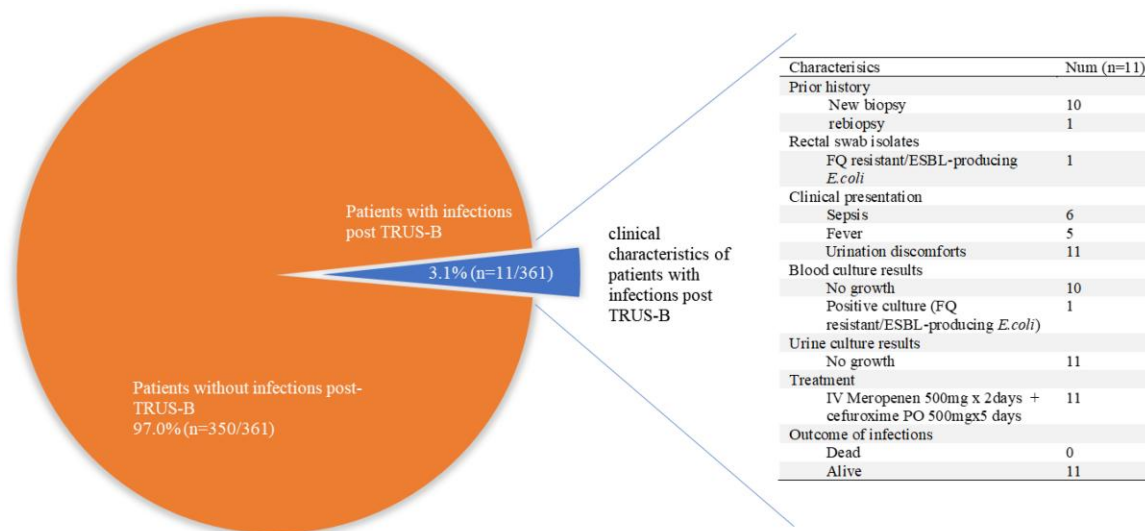
Characterisics	Num (n=11)
Prior history	
New biopsy	10
rebiopsy	1
Rectal swab isolates	
FQ resistant/ESBL-producing E.coli	1
Clinical presentation	
Sepsis	6
Fever	5
Urination discomforts	11
Blood culture results	
No growth	10
Positive culture (FQ resistant/ESBL-producing E.coli)	1
Urine culture results	
No growth	11
Treatment	
IV Meropenen 500mg x 2days + cefuroxime PO 500mgx5 days	11
Outcome of infections	
Dead	0
Alive	11

Figure 3. Occurrence and clinical characteristics of infection post-TRUS-B.
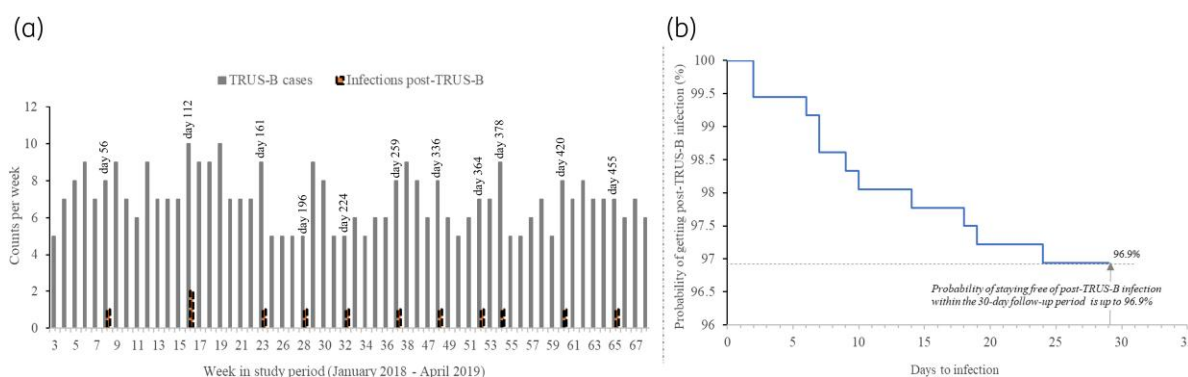

Figure 4. Distribution of (a) TRUS-B cases and infections by week; and (b) Kaplan–Meier curve for the cumulative probability of infections within 30 days post-TRUS-B. The probability of getting post-TRUS-B infection reduces from 100% to 96.9% from Day 0 to Day 28. The probability of staying free of infection is high at 96.9%.

and susceptibility testing for resistant pathogens is a strategy to consider in settings where post-biopsy infections are a concern. In a meta-analysis from 15 studies representing 12 320 participants, the incidence of infectious complications was 3.4% in TRUS-B patients who received empirical antibiotic prophylaxis and 0.8% in those who had targeted prophylaxis based on pre-biopsy rectal culture screening for resistant pathogens.[25] Pre-biopsy rectal cultures are associated with extra logistics and cost. The challenge of routinely detecting resistant pathogens in rectal swabs will be formidable in low-income countries where microbiological services are accessible only in a few hospitals. Whereas many laboratories may not be fully aware of the importance of routinely detecting resistant pathogens, others may lack the ability to correctly report these organisms. Rather, in low-income settings, a tailored assessment of TRUS-B patients using a risk-based approach will better inform urologists of patients at higher risk of post-biopsy infection. Our results show that antibiotic use history may predict the rectal carriage of FQ-resistant and ESBL-positive organisms. As widely reported, a common risk factor of rectal carriage of antibiotic-resistant organisms is previous antibiotic exposure.[14,26,39,43] A predicted rectal carriage of antibiotic-resistant pathogens plus evidence of patient-related risk factors such as cancer diagnosis may suggest infectious complications post-biopsy. There is also the potential role of changing how the prostate biopsy is performed in our settings. Considering the growing interest in transperineal biopsies, and the supporting evidence to demonstrate lower infective complications, switching from transrectal to transperineal would be an effective intervention for reducing infection rates in populations with a very high burden of resistance.[4] Compared with TRUS-B, transperineal biopsy poses a significantly lower risk of infection because the needle passes through the perineum, rather than the rectum. The rate of sepsis post-transperineal biopsy is reportedly negligible and significantly several-fold less than those currently reported for transrectal biopsy.[60] However, universal adoption of transperineal biopsy is constrained by the inconsistencies in outcomes and lack of level 1 evidence.

Table 2. Multivariable analysis for risk factors of rectal carriage with FQ-resistant and/or ESBL-producing isolates, and subsequent infectious complications post-TRUS-B

| | Rectal carriage | | | | | | Post-TRUS-B infections | | |
| | FQ resistant | | | ESBL producing | | | | | |
Factors	Change in factor	aOR (95% CI)	P value	Change in factor	aOR (95% CI)	P value	Change in factor	aOR (95% CI)	P value
Mean age	1.03 per year	1.03 (1.01–1.08)	0.004	—	—		—	1.06 (0.60–1.09)	0.212
Median PSA (ng/mL)	—	1.82 (0.71–4.14)	0.087	—	—		—	1.09 (0.05–2.33)	0.481
Mean prostate volume (mL)	—	2.32 (0.41–6.24)	0.107	—	—		—	—	
Previous TRUS-B	Yes/No	1.89 (0.16–8.45)	0.261	Yes/No	1.04 (0.51–4.66)	0.105	Yes/No	2.22 (0.91–3.81)	0.313
Antibiotic use the in past 3 months	Yes/No	4.11 (2.71–9.62)	0.001	Yes/No	3.63 (2.11–6.43)	0.001	—	—	
Had diabetes	—	—		Yes/No	2.87 (0.33–11.1)	0.371			
History of catheterization	—	—		—	—		Yes/No	3.02 (0.83–8.52)	0.086
FQ-resistant rectal culture	—	—		Yes/No	8.76 (6.98–17.54)	0.001	—	—	
FQ-resistant rectal culture >1	—	—		—	—		Yes/No	3.12 (0.23–17.1)	0.311
ESBL rectal culture	Yes/No	11.34 (7.23–19.78)	0.001	—	—		Yes/No	13.12 (7.11–9.11)	0.001
ESBL rectal culture >1	—	—		—	—		Yes/No	2.66 (0.45–28.45)	0.166

Only factors with significant associations (*P* value < 0.2) in bivariate comparisons are shown and were included as variables in multivariate logistic regression models. aOR, adjusted OR. The top five antibiotics used by TRUS-B patients in the last 3 months prior to sampling were amoxicillin/clavulanic acid, cefuroxime, metronidazole, ceftriaxone and azithromycin. None of the individual antibiotics at Anatomical Therapeutic Chemical (ATC) level 4 or 5 constituted a predisposing factor for intestinal carriage of FQ-resistant or ESBL-producing isolates or for the occurrence of post-TRUS-B infections.

This study has some limitations. The study sample size was relatively small and drawn from a single institution. Thus, the observations might not be wholly representative of Ghanaian patients undergoing TRUS-B. Information on antibiotic use was obtained verbally from patients and subject to recall bias. We could not draw a direct link between carriage isolate and pathogens responsible for infectious complications. Such data would be helpful to directly relate bacterial source and post-biopsy infection. This report does not include molecular data on resistance mechanisms. Such information would help to better delineate the genotypic basis of the findings.

Conclusions

We observed a high prevalence of FQ resistance in rectal flora, with a concomitant incidence of infectious complications despite using an FQ-based prophylaxis regimen. The question we had to consider is what constitutes an appropriate prophylaxis regimen or whether no antibacterial prophylaxis is advised rather than adding a further selective burden on FQ-resistant and ESBL-positive pathogens by giving an FQ-based regimen? Given the cost and cumbersomeness, a pre-TRUS biopsy stool culture-based regimen may not be justifiable in low-income settings. Based on conservative costing and avoiding admissions from infectious complication post-TRUS-B, the strategy we recommend from our study findings is amikacin-based prophylaxis based on patient stratification by risk factors such as prior antimicrobial use. Transperineal biopsy may be considered as a strategy in the near future to reduce the risk of developing infections caused by MDR organisms. Meropenem should be reserved for the management of infectious complications to reduce the spread of antibiotic resistance.

Transparency declarations

None to declare.

Author contributions

A.K.L., N.O.N., J.E.M. conceptualized the study, participated in its design and acquisition of data; N.T.K.D.D., A.F., M.M.O., B.M.A., B.E. helped to draft the manuscript and revise it critically for important intellectual content. A.K.L., N.O.N., J.E.M. performed the statistical analysis. All authors have approved the final article.

Data availability

The data are available from the corresponding author upon request.

Supplementary data

Supplementary File 1 is available as Supplementary data at *JAC* Online.

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