Infections

Evaluating the Safety of Performing Flexible Cystoscopy When Urinalysis Suggests Presence of “Infection”: Results of a Prospective Clinical Study in 2350 patients

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\textbf{Abstract}

\textbf{Background:} There is significant underutilisation of allocated health service resources when a scheduled flexible cystoscopy (FC) is cancelled because a pre-cystoscopy urinalysis (PCU) suggests “infection”, despite patients being asymptomatic for urinary tract infection (UTI).

\textbf{Objective:} To evaluate the risk of UTI or urinary sepsis when FC is performed in asymptomatic patients with a PCU positive for leucocyte esterase and/or nitrites.

\textbf{Design, setting, and participants:} A prospective cohort study was conducted in a high-volume UK centre recruiting all patients undergoing outpatient FC.

\textbf{Intervention:} A protocol was developed to guide response to PCU performed prior to FC, which was performed regardless of the result, unless patients were symptomatic for UTI. All patients completed a questionnaire to identify risk factors and were followed up via a telephone survey and a review of electronic clinical records.

\textbf{Outcome measurements and statistical analysis:} Post-FC UTI was defined as hospital admission with UTI/urinary sepsis or if patients were symptomatic for UTI with receipt of antibiotics or with positive urine culture and sensitivity. An analysis of the association was performed.

\textbf{Results and limitations:} An initial pilot study confirmed the safety and feasibility of our protocol. Of 1996 patients, 136 (6.8\%) developed a UTI by our definition, with 51 (2.6\%) having a culture-proven infection. The risk was higher in patients with a positive PCU (odds ratio [OR] 1.61, 95\% confidence interval [CI] = 1.07–2.40, \(p = 0.02\)), history of UTI (OR 1.72, 95\% CI = 1.09–2.73, \(p = 0.02\)), or a bladder tumour on FC (OR 2.22, 95\% CI = 1.27–3.90, \(p = 0.005\)). No patient with a positive PCU developed urinary sepsis. The main limitation of this study was the lack of pre-protocol control.

\textbf{Conclusions:} We observed a clinically low and acceptable risk of UTI, with no incidence of sepsis, when FC was performed in asymptomatic patients with a PCU

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suggesting “infection”. Routine cancellation of these patients is unnecessary and may worsen the burden on health service resources.

**Patient summary:** We evaluated the safety of performing flexible cystoscopy when the urine dipstick on the day suggested presence of an “infection” but the patient had no symptoms of urinary tract infection (UTI). Our study in over 2000 patients demonstrated a low incidence of UTI, and none of these patients developed sepsis. We therefore recommend that flexible cystoscopy should not be cancelled automatically on the basis of the dipstick result alone, as it might delay a time-sensitive crucial diagnosis.

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1. **Introduction**

Amid unprecedented healthcare demand and rising financial burden worldwide, optimisation of existing services is of utmost importance. One sector in which there is potential to enhance efficiency is outpatient diagnostic investigations, where high cancellation rates result in underutilisation of valuable resources [1].

Flexible cystoscopy (FC), the most frequently performed urological procedure, was introduced in 1984 [2] and permits visualisation of the lower urinary tract for a variety of indications. These include investigation of visible haematuria (VH), lower urinary tract symptoms, and urinary tract infection (UTI) in addition to bladder cancer (BC) surveillance. The procedure is generally well tolerated by patients; however, adverse effects include dysuria, VH, and UTI, with the latter carrying a risk of sepsis [3,4]. Existing literature reports that the post-FC UTI risk is between 1% and 10% [3–11]; however, both the European Association of Urology (EAU) [12] and the American Urological Association (AUA) [13] do not recommend routine antibiotic prophylaxis (AP).

At our high-volume centre, we observed frequent automatic cancellation of outpatient FC appointments, with significant service implications, when a pre-cystoscopy urinalysis (PCU) suggested the presence of “infection” (leucocyte esterase and/or nitrites), even when patients were asymptomatic for UTI. The lack of a robust local policy provided an opportunity to streamline clinical practice and enhance service efficiency by introducing a new protocol for processing elective FC patients.

Therefore, the aim of this study was to evaluate the risk of UTI and urinary sepsis within 2 wk of FC following the introduction of a pragmatic protocol allowing the procedure to be performed in asymptomatic patients with a PCU positive for “infection”.

2. **Patients and methods**

2.1. **Development of protocol**

A literature review revealed a wide range of UTI risks following FC [3–11] including a risk of 9.1% in the placebo arm of one randomised controlled trial (RCT) [8]. To address inefficiencies in our service consequent to automatic cancellation of FC when a PCU was positive, our department decided to evaluate the risk of UTI and sepsis when FC was carried out in asymptomatic patients with a PCU positive for leucocyte esterase or nitrites. Thus, in October 2015, senior authors (P.M., R.D., and P.K.) developed a protocol (Fig. 1) that specified “high-risk” patients determined by consensus (based on features that would normally result in our clinicians using AP), the low incidence of UTI with the absence of sepsis in the pilot study and encouragement received at the British Association of Urological Surgeons (BAUS) annual meeting in 2017 [14] gave clinicians confidence in utilising the protocol. Based on institutional antibiogram and existing data [15], expert microbiologists (P.K. and team) recommended AP with single-dose gentamicin when appropriate.

A PCU detecting “trace” leucocyte esterase/nitrites was considered negative, and because FC was performed for various indications, findings of blood or protein in the PCU were not considered relevant for this study. Following review and acceptance of the protocol within the Department of Urology, patient information documents were modified and clinical evaluation was performed in two phases—phase 1: a pilot study to ascertain the feasibility of and compliance with the protocol, and phase 2: a cohort study to assess the association between a PCU and a post-FC UTI (Fig. 2).

We have used the following definitions throughout the article:

1. Positive PCU: pre-FC urinalysis positive for leucocyte esterase and/or nitrites; we utilised the Siemens multistix® (Siemens Helhineers, Erlangen, Germany) with automated reading using the Bayer Clinitek Status® Urine Analyzer
2. Pre-FC culture and sensitivity: urine specimen sent for culture and sensitivity (C&S) just before FC
3. Post-FC bacteriuria: positive urine C&S within 2 wk of FC

2.2. **Phase 1—pilot study**

From May to June 2016, all patients undergoing elective FC were subject to the protocol following a robust consent process. A midstream urine sample was analysed (PCU) on attendance, and, as per the protocol, patients with symptomatic UTI and a positive PCU were treated with antibiotics and rescheduled, whilst all other patients underwent FC. Patients with a positive PCU who underwent FC were recommended to have a specimen sent for pre-FC C&S, and when this was positive, general practitioners (GPs) were contacted to evaluate patients and treat as appropriate. By contacting GPs and utilising our electronic patient record system (TrakCare [16]) and online pharmacy record (Emergency Care Summary [ECS]) used by all primary and secondary care centres, we recorded patient presentation to their GP or hospital with symptoms of UTI/sepsis within 2 wk of FC. An analysis of association was carried out.
between PCU results, pre-FC C&S, risk factors, and subsequent development of UTI. Outcomes from the pilot study demonstrated safety in performing FC in asymptomatic patients with a positive PCU and protocol feasibility. Support and feedback from the presentation of the results at the BAUS annual meeting [14] allowed for minor modifications to the methodology and, following departmental consensus, encouraged continuation with the protocol in a larger prospective cohort study.

2.3. Phase 2—cohort study

In this phase, the applicable protocol (Fig. 1) largely remained constant, except for modification to the “high-risk” criteria and introduction of follow-up telephone survey. All consecutive patients attending elective FC between November 2017 and August 2018 were included, completed a questionnaire to identify specific risk factors for UTI, and had a PCU. Those with a positive PCU who were considered to be at a “high risk” for UTI (Fig. 1) were counselled appropriately and considered for AP at the discretion of the cystoscopist.

With consent, all patients were contacted by telephone to record development of new symptoms (dysuria, frequency, urgency, suprapubic discomfort, and pyrexia) and receipt of antibiotics. Intending pragmatism, post-FC UTI was defined as one or more of the following occurring within 2 wk:

1. Hospital admission with UTI or urosepsis
2. Symptomatic UTI with receipt of antibiotics
3. Culture-proven symptomatic UTI
4. In patients uncontactable by telephone, record of receipt of post-FC antibiotics or record of post-FC bacteriuria

Additional validation was made utilising TrakCare [16], to identify hospital presentations and post-FC bacteriuria, and ECS, to record antibiotic prescription. Patients uncontactable by telephone were followed up via their GP and electronic records. Following the advice of microbiology colleagues, only cultures that harboured a single organism present in $\geq 10^5$ colony forming units per millilitre were considered positive and described as “bacteriuria” in this article. We were advised that cultures reporting “mixed growth” frequently reflected contamination and so were considered negative.

2.4. Statistical modelling

The pragmatic nature of the study utilised the assumption that all patients were managed as per the department protocol—an analysis reflected this. To determine the factors associated with post-FC UTI, we used a univariate logistic regression considering the following variables: (1) demographics: gender and patient age; (2) risk factors: history of UTI, diabetes, urethelial cancer, ureteric stent or catheter, and immunosuppression; (3) positive PCU; and (4) reported cystoscopic findings: bladder tumour, bladder outlet obstruction (BOO), bladder stone, urethelial red patch, and opaque urine/bladder sediment. Variables statistically significant at 5% level were included in a multivariable logistic regression, and using forward selection, a final model was determined. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows (IBM Corp, Armonk, NY, USA).

3. Results

The study schema is described in Figure 2.

3.1. Pilot study

Of 381 patients who attended for FC during the pilot study period, 27 (7.1%) were cancelled due to symptomatic UTI with a positive PCU, and thus 354 patients underwent FC, of whom 81 (22.9%) had a positive PCU and would have been cancelled if not for the protocol. In all, 40 patients (11.3%) developed “UTI”, as per our definition, within 2 wk of FC, of whom 15 (37.5%) had a positive PCU. There were no hospital admissions with urinary sepsis. From this small cohort, the risk of “UTI” when the PCU was “positive” was twofold higher than that in those with a negative PCU (odds ratio 2.25, 95% confidence interval = 1.13–4.52, p = 0.02).

3.2. Cohort study

In all, 2062 consecutive patients attended for FC between November 2017 and August 2018. After excluding 66 patients (3.2%), as described in Figure 2, we had
1996 patients who underwent PCU and FC. Table 1 describes patient demographics, indications for cystoscopy, prevalence of risk factors, and reported cystoscopic findings. In all, 373 patients (18.7%) had a positive PCU. Of 562 patients who underwent FC for BC surveillance, 99 (17.6%) had a positive PCU and may otherwise have been automatically cancelled. Six (6.1%) had intravesical recurrence.

3.2.1. Association between PCU, pre-FC C&S, and post-FC UTI
In all, 1755 patients (87.9%) were contacted via phone-call follow-up, with the remainder followed up via their GP and electronic records. Table 2 describes the relationship between PCU, pre-FC C&S, and post-FC UTI. Overall, 136 patients (6.8%) fulfilled our defined criteria for a post-FC UTI. A positive PCU and positive pre-FC C&S increased the odds of this by almost two fold (Table 2).

Comparing those with a positive and those with a negative PCU, for every 26 patients who underwent FC with a positive PCU there was one additional UTI.

3.2.2. Hospital admissions
Six patients (0.3%) were admitted to hospital 3–14 d (mean 7.7 d) after FC (Table 2). Four had post-FC bacteriuria (treated as UTI), whilst two had bacteraemia (treated as urosepsis)—both had a negative PCU. Of the two hospitalised patients who had a positive PCU, one was admitted 3 d after FC and had a primary diagnosis of influenza with incidental bacteriuria during their inpatient stay and the other (who underwent FC for ureteric stent removal, and had type 1 diabetes and candiduria identified at FC) was admitted 14 d after FC for inpatient antifungal treatment.
Table 1 – Demographics and characteristics of patients included in the analysis (n = 2062)

| Category                                           | Value |
|----------------------------------------------------|-------|
| Total patients who attended for FC (n)             | 1996  |
| Patients excluded, n (% of total)                  | 1996  |
| Total patients who underwent FC, n (% of total)    | 1996  |
| Patient age (yr), median (range)                   | 67 (16–100) |
| Gender, n (% of total)                             | 1190 (59.6) |
| Female                                             | 806 (40.4) |
| Indication for FC, n (% of total)                  |       |
| Visible haematuria                                  | 614 (30.8) |
| Nonvisible haematuria                               | 344 (17.2) |
| Check (previous urothelial cancer)                 | 562 (28.2) |
| Recurrent/persistent UTI                           | 256 (12.8) |
| LUTS                                               | 150 (7.5) |
| Removal of ureteric stent                          | 44 (2.2) |
| Botulinum toxin injection                          | 7 (0.4) |
| Suspicion of ureteric stricture                    | 3 (0.2) |
| Other                                              | 70 (3.5) |
| Risk factors, n (% of total)                       |       |
| Recurrent/persistent UTI                           | 256 (12.8) |
| Diabetes                                           | 281 (141) |
| Urothelial cancer                                   | 596 (29.9) |
| Indwelling ureteric stent                          | 44 (2.2) |
| Indwelling catheter (urethral/SP)                  | 70 (3.5) |
| Immunosuppression                                   | 85 (4.3) |
| FC findings, n (% of total)                        |       |
| No pathology                                       | 1321 (65.2) |
| Bladder tumour                                     | 135 (6.8) |
| Bladder stone                                      | 19 (1.0) |
| Ureteral stricture                                  | 80 (4.0) |
| Opaque urine/Bladder sediment                      | 44 (2.2) |
| Bladder outlet obstruction                         | 363 (17.2) |
| Urothelial red patch                               | 100 (5.0) |
| Other                                              | 22 (1.1) |

FC = flexible cystoscopy; LUTS = lower urinary tract symptoms; SP = suprapubic; UTI = urinary tract infection.

3.2.3. Association between risk factors, cystoscopic findings, PCU, and post-FC UTI

Table 3 describes the association between risk factors, cystoscopic findings, and post-FC UTI when stratified according to PCU results. Patients with bladder tumour detected had a higher risk of post-FC UTI when PCU positive.

3.2.4. Predictive factors

Of the factors included in the model (Table 4), PCU positive for “infection”, history of recurrent or persistent UTI, and bladder tumour on FC were independent predictors of UTI.

4. Discussion

Our study, reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17], is the largest prospective, observational, two-stage cohort study to evaluate the utility of a PCU in predicting post-FC UTI. From our real-world experience including over 2000 patients, we observed a low and clinically acceptable risk of UTI—with no incidence of sepsis—when FC was performed in asymptomatic patients, with urinalysis suggesting the presence of “infection”. Before protocol introduction, FC would have been cancelled in all patients with “infection” on a PCU. Overall, 6.8% had UTI (as per our clinical definition) within 2 wk of FC, with a 2.6% rate of culture-proven symptomatic infection, similar to that reported in some literature [3,7,10] and lower than that in others [6,8]. Thus, we suggest that automatic cancellation is not merited and may delay the diagnosis of urological pathology whilst financially burdening health services. Prior to the protocol, many patients with a positive PCU were postponed more than once and significance of the delay would have been dependent on the indication—for BC surveillance or VH, it could be 6 wk, and for all other indications, it would likely be longer.

Our robust follow-up protocol was pragmatic and reflective of real-world practice, with an overestimation of observed “UTI”. More than half of the patients recorded as having developed UTI, by our definition, were treated on clinical suspicion without culture-proven infection, and fewer than half of those who reported “UTI” symptoms on telephone survey actually received antibiotics. This raises the question as to whether a significant proportion of patients routinely prescribed antibiotics for post-FC “UTI” may be suffering self-limiting, instrumentation-related symptoms rather than true symptomatic bacteriuria. Furthermore, our 2-wk follow-up period was relatively long and may have included a cohort that developed sporadic UTI unrelated to their FC, particularly the patients with a history of recurrent infection. Just over 10% of patients were not contactable by telephone—in such patients, we recorded a UTI if there was evidence of post-FC bacteriuria and/or receipt of antibiotics in their electronic prescription. Thus, we may have recorded post-FC UTI in these patients who were not even symptomatic for UTI.

Urinalysis is a simple, noninvasive test used to detect the presence of urinary leucocyte esterase and nitrites as
markers of “UTI”; however, the presence of associated symptoms is considered a superior predictor of infection to urinalysis alone [18]. It has poor predictive values for infection in asymptomatic patients [19] and cannot reliably distinguish between UTI and asymptomatic bacteriuria (ASB), particularly in elderly patients [20]. One meta-analysis concluded that urinalysis has a satisfactory negative predictive value for UTI when both leucocyte esterase and nitrites are absent [21]; however, a negative result does not completely exclude UTI [22] and false positives are common. This supports the premise of our study.

Within our pragmatic study, we did not send negative PCU specimens for C&S and thus we do not have sufficient data to evaluate the true diagnostic accuracy of leucocyte esterase and nitrites for detecting pre-FC bacteriuria. We observed a higher risk of UTI in patients with positive pre-FC C&S compared with those having negative culture; however, the rate remained low with no increased sepsis risk. Whilst our data discourage automatic cancellation on the basis of a PCU, we continue to advocate culturing positive specimens to guide antibiotic therapy.

Our pilot phase aimed to evaluate safety and feasibility of, and compliance with the protocol. Following discussion of the initial results and with departmental consensus, we assigned dedicated personnel to ensure robust prospective follow-up of patients via phone call and electronic clinical records in a cohort study. Our microbiology colleagues advised that single-dose AP could be considered, at the cystoscopist’s discretion in “high-risk” patients with a positive PCU. AP is well established for transurethral procedures [23] and an RCT by Johnson et al [8] demonstrated a reduced risk of post-FC bacteriuria with single-dose AP, supported by a meta-analysis [24]. However, routine treatment of ASB may contribute to antimicrobial resistance and expose patients to adverse events [25] with potential healthcare financial implications. Furthermore, neither the EAU [12] nor the Scottish Intercollegiate Guidelines Network (SIGN) [26] recommend routine treatment of ASB. Herr [27] evaluated the role of AP in bladder tumour patients undergoing FC and observed that 4.5% developed febrile UTI when pre-FC C&S was positive, compared with 11.1% when the culture was negative. We observed an elevated risk of UTI in patients with bladder tumour on FC. Of the 135 patients with a tumour, 21 (15.6%) had a positive PCU and would have been automatically cancelled before the protocol, with potential delay-induced adverse oncological outcomes. AP in all “high-risk” patients may be overtreatment; therefore, we advise that patients considered to be at a “high risk” are counselled appropriately and even supplied with a self-start prescription should they develop UTI symptoms.

4.1 Limitations

The main limitation of our study was absence of a pre-protocol comparison cohort; however, this was not feasible as the standard practice was to automatically cancel FC when a PCU was positive. As the objective of this pragmatic
Table 3 – Association between risk factors, findings on FC, and risk of post-FC UTI (as per our definition) when stratified according to PCU results

| Risk factor (n)                      | Infection on PCU (LE and/or N) | n    | Total Post-FC UTI, n (%) |
|-------------------------------------|---------------------------------|------|-------------------------|
| Recurrent/persistent UTI (256)      | +                               | 57   | 7 (12.3)                |
|                                     | -                               | 199  | 20 (10.1)               |
| Diabetes (281)                      | +                               | 68   | 6 (8.8)                 |
|                                     | -                               | 213  | 12 (5.6)                |
| Previous urothelial cancer (596)    | +                               | 114  | 10 (8.8)                |
|                                     | -                               | 484  | 27 (5.6)                |
| Indwelling ureteric stent (44)      | +                               | 38   | 3 (7.9)                 |
|                                     | -                               | 6    | 0                       |
| Indwelling catheter (70)            | +                               | 46   | 3 (6.5)                 |
|                                     | -                               | 24   | 2 (8.3)                 |
| Immunosuppression (85)              | +                               | 22   | 6 (2.7)                 |
|                                     | -                               | 63   | 3 (4.8)                 |
| FC finding (n)                      |                                 |      |                         |
| Bladder tumour (135)                | +                               | 21   | 4 (19.0)                |
|                                     | -                               | 114  | 12 (10.5)               |
| Bladder stone (19)                  | +                               | 4    | 0                       |
|                                     | -                               | 15   | 1 (6.7)                 |
| Bladder outlet obstruction (363)    | +                               | 50   | 2 (4)                   |
|                                     | -                               | 313  | 23 (7.3)                |
| Urothelial red patch (100)          | +                               | 32   | 1 (3.1)                 |
|                                     | -                               | 68   | 10 (14.7)               |
| Opaque urine/bladder sediment (44)  | +                               | 29   | 2 (6.9)                 |
|                                     | -                               | 15   | 2 (13.3)                |

FC = flexible cystoscopy; C&S = culture and sensitivity; LE = leucocyte esterase; N = nitrites; PCU = pre-cystoscopy urinalysis; UTI = urinary tract infection.

Table 4 – Logistic regression analysis evaluating association between variables and risk of post-FC UTI

| Variable (n)          | Univariate OR | 95% CI     | p value | Multivariate OR | 95% CI     | p value |
|-----------------------|---------------|------------|---------|-----------------|------------|---------|
| Demographics          |               |            |         |                 |            |         |
| Age (1996)            | 1.00          | 0.99–1.02  | 0.53    |                 |            |         |
| Female gender (806)   | 1.47          | 1.04–2.09  | 0.03 *  | 1.31            | 0.91–1.89  | 0.14    |
| Risk factors          |               |            |         |                 |            |         |
| Recurrent/persistent UTI (256) | 1.76  | 1.13–2.75  | 0.01 *  | 1.72            | 1.09–2.73  | 0.02 *  |
| Diabetes (281)        | 0.93          | 0.55–1.55  | 0.77    |                 |            |         |
| Previous urothelial cancer (596) | 0.87  | 0.59–1.29  | 0.48    |                 |            |         |
| Indwelling ureteric stent (44) | 1.00  | 0.31–3.27  | 1.00    |                 |            |         |
| Indwelling catheter (70) | 1.05  | 0.42–2.66  | 0.91    |                 |            |         |
| Immunosuppression (85) | 1.04          | 0.45–2.43  | 0.93    |                 |            |         |
| PCU                   |               |            |         |                 |            |         |
| Any infection (LE and/or N; 372) | 1.70          | 1.14–2.52  | 0.009 * | 1.61            | 1.07–2.40  | 0.02 *  |
| Bladder tumour (135)  | 1.95          | 1.12–3.39  | 0.02 *  | 2.22            | 1.27–3.90  | 0.005 * |
| Bladder stone (19)    | 0.76          | 0.10–5.72  | 0.79    |                 |            |         |
| Bladder outlet obstruction (363) | 1.01  | 0.65–1.59  | 0.95    |                 |            |         |
| Urothelial red patch (100) | 1.75  | 0.91–3.36  | 0.09    |                 |            |         |
| Opaque urine/bladder sediment (44) | 1.38          | 0.49–3.91  | 0.55    |                 |            |         |

CI = confidence interval; FC = flexible cystoscopy; LE = leucocyte esterase; N = nitrites; OR = odds ratio; PCU = pre-cystoscopy urinalysis; UTI = urinary tract infection.

* Statistically significant result.

study was to observe real-world practice, our protocol was developed for guidance and the use of AP in “high-risk” patients was at the discretion of the cystoscopist. Thus, there may have been cases when AP was not given. Existing guidelines published by the Infectious Diseases Society of America [28] and the AUA [13] on “high-risk” patients who may receive pre-FC AP are inconsistent with sparse supporting literature. Thus, our definition of a “high-risk” patient was based on departmental consensus, which may differ from practice elsewhere. For example, we hypothesised that patients with ureteric stents or indwelling catheters—with bacterial colonisation—were at a “high
risk”; however, existing literature appears to contradict this theory, suggesting that upper urinary tract bacteriuria is a more reliable predictor of sepsis than if the specimen was obtained from the bladder [29]. Some of the variables included in our model as risk factors for UTI were based on subjective clinician-reported findings, for example, “BOO”, which was not urodynamically proven, and “opaque urine”, which is not always recorded in cystoscopy reports. Thus, we acknowledge that the subanalysis including these variables is likely underpowered and is merely an observation of a small subset in our study cohort.

5. Conclusions

FC in asymptomatic patients with a PCU suggesting “infection” appears to be safe within the framework of a pragmatic, real-world protocol, with a clinically acceptable low risk of culture-proven UTI and without the risk of sepsis. Avoiding automatic cancellation would enhance service efficiency whilst minimising anxiety and treatment delay in patients with urological pathology, particularly BC. Further consideration should be given to prophylactic or “self-start” antibiotics in specific patient cohorts when appropriate.

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Study concept and design: Mariappan.

Acquisition of data: Trail, Cullen, Fulton, Clayton, McGregor, McWilliam, Dick.

Analysis and interpretation of data: Trail, Mariappan.

Drafting of the manuscript: Trail, Mariappan.

Critical revision of the manuscript for important intellectual content: Mariappan.

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