1   Meatal Swabs Contain Less Cellular Material and are Associated with a Decrease in

2   Gram Stain Smear Quality Compared to Urethral Swabs in Men

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10  **Running Title:** Meatal swabs perform poorly in Gram stain testing

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16  **Abstract:**

17  Urethral swabs are the test of choice for point-of-care Gram stain testing to diagnose

18  *Neisseria gonorrhoeae* (NG) and non-gonococcal urethritis (NGU) in men. As an

19  alternative to urethral swabs, meatal swabs have been recommended for collection of

20  urethral discharge to diagnose NG and *Chlamydia trachomatis* (CT) in certain

21  populations by nucleic acid amplification testing (NAAT), as they are a less invasive

22  collection method. However, as meatal swabs could be sampling a reduced surface

23  area and result in fewer collected epithelial cells when compared to urethral swabs, the

24  adequacy of meatal swab specimens to collect sufficient cellular material for Gram stain

25  testing remains unknown. We enrolled 66 men who received either a urethral swab or a

26  meatal swab and compared the cellular content and Gram stain failure rate. We

27  measured the difference in swab cellular content using the Cepheid Xpert® CT/NG

28  sample adequacy control crossing threshold and determined the failure rate of gram

29  stain smears (GSS) due to insufficient cellular material. Meatal smears were associated

30  with a significant reduction in cellular content ($P$ = 0.0118), which corresponded with a

31  significantly higher GSS failure rate compared to urethral swabs (45% vs. 3%

32  respectively, $P$ <0.0001), in the absence of discharge. When discharge was present,

33  there was no difference between urethral and meatal swabs. Therefore, if GSS testing

34  is being considered for point-of-care diagnosis of NG or NGU in men, meatal swabs

35  should be avoided in the absence of a visible discharge.

36

37  **Introduction**

38  *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections continue to rise

39  with 1.4 million and > 350,000 cases reported, respectively, in the United States in 2015

40  (1); though non-gonococcal urethritis (NGU) remains the most common form of

41  urethritis in men (2). For screening at-risk individuals, the Centers for Disease Control

42  and Prevention (CDC) recommends highly sensitive nucleic acid amplification testing

43  (NAAT) of urine or a urethral swab of urethral secretions (3). Meatal swabs have been

44  suggested as a less invasive alternative to urethral swabs for specimen collection for

45  NAAT testing and are amenable to patient collection by eliciting less discomfort (4).

46  Although not yet FDA-approved or CDC-recommended for NAAT testing in men, meatal

47  swabs are recommended for NAAT testing in prepubertal boys with discharge, given

48  concerns about urethral trauma from urethral swabs (3,7).  In men, self-obtained meatal

49  swabs appear to be equivalent to clinician-collected urethral swabs for diagnosing

50  CT/NG infection by NAAT, although there are mixed reports of the sensitivity of this

51  sample type (5, 6). Currently, no rapid (< 30 minutes) point-of-care NAAT test is

52  available to diagnose NG or NGU; and Gram stain smear (GSS) testing of urethral

53  secretions remains the test of choice in settings where rapid diagnosis is needed and

54  microscopy can be performed. The 2015 Sexually Transmitted Diseases Treatment

55  Guidelines specify that GSS testing of male urethral secretions is appropriate for

56  diagnosing NG or NGU, though no preferred swab type is indicated for specimen

57  collection.  Meatal swabs are recommended as an alternative for collecting urethral

58  secretions in specific populations (7), though they have yet to be approved for NAAT

59  testing in men. In contrast to NAAT, which amplifies nucleic acids from lysed cells, GSS

60  testing requires collection of intact cells. As meatal swabs may sample a smaller

61  surface area than urethral swabs, and also sample a higher proportion of cornified

62  squamous epithelium from the meatus, it is possible that the number of intact cells

63  collected using a meatal swab may be insufficient to reliably diagnose NG or NGU by

64  GSS testing. To address this concern, we enrolled both symptomatic and asymptomatic

65  men and systematically assigned them to receive either a meatal or urethral swab and

66  measured the swab cellular content using the Cepheid Xpert® CT/NG sample

67  adequacy control crossing threshold ($SAC_{CT}$) (8) and also determined the failure rate of

68  GSS testing for each swab type. The $SAC_{CT}$ is an internal control of the Xpert® CT/NG

69  assay and denotes the cycle number at which human hydroxymethylbilane synthase, a

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70  single-copy housekeeping gene, is first detected by real-time PCR amplification.

71  Included in each assay to ensure specimen sample adequacy (9), the $SAC_{CT}$ is

72  inversely proportional to the amount of cellular material present in the specimen. The

73  primary outcome of our study was to determine if meatal swabs were associated with a

74  lower cellular content and a higher GSS failure rate, compared with urethral swabs. A

75  secondary objective was to determine how the meatal swab was influenced by the

76  presence or absence of discharge.

77

78  **Results**

79      66 men were included in this study (Table 1). Participants were 20 to 69 (mean

80  29) years of age, and 56 (89%) were black. 27 men (41%) had visible discharge on

81  genital examination. Swab collection (meatal vs. urethral) was alternated such that 33

82  men provided a urethral swab and 33 men had a meatal swab taken. No difference in

83  age, race, symptoms, prior STI history, or number of sex partners in the last 30 days

84  was identified between the groups. 9 (14%) men had Gram-negative intracellular

85  diplococci (GNID) present on GSS and 20 men (30%) were diagnosed with NGU. The

86  Xpert® CT/NG assay, performed on both swab and voided urine specimens, diagnosed

87  20 men with CT and/or NG: 8 men were positive for CT alone, 4 men for both CT and

88  NG, and 8 men for NG alone.

89      To assess whether meatal swabs were associated with a decrease in cellular

90  content, we compared the $SAC_{CT}$ of meatal swabs to urethral swabs. Meatal swabs

91  were associated with significantly higher $SAC_{CT}$ values, indicating they contained less

92  cellular material, compared to urethral swabs (mean 25.6 vs 23.9, $P = 0.0026$, Table 1).

93    This difference in cellular content did not affect the performance of the NAAT since the

94    swab sample NAAT results were 100% concordant with the urine NAAT results (data

95    not shown).

96        We then assessed the failure rate of GSS prepared using urethral and meatal

97    swabs, with failure defined as an absence of cellular material on microscopy (*i.e.*

98    "quantity of cells not sufficient" [QNS]). The GSS QNS rate of meatal swabs was

99    significantly higher compared with urethral swabs (45% vs. 3%, *P* <0.0001). Despite no

100   difference in the frequency of signs or symptoms of urethritis between the two groups,

101   meatal swabs were associated with significantly lower number of GSS with PMN

102   between 2-5 (3% vs. 33%, *P* = 0.0011, Table 1) than urethral swabs, which is reflected

103   in the high GSS failure rate.

104   To determine if the increased QNS rate in meatal GSS was associated with less cellular

105   content, we stratified the $SAC_{CT}$ results by QNS status. As shown in Figure 1A, Gram

106   stains identified as QNS were associated with a higher meatal swab $SAC_{CT}$ (mean 27.4

107   vs 24.1, *P* = 0.0002), indicating that the meatal swabs used to prepare the GSS

108   contained less cellular material.

109       Given our finding that meatal swabs are associated with significantly less cellular

110   material and a higher GSS failure rate compared with urethral swabs, we were

111   interested in establishing how meatal swabs performed when sampling discharge. As

112   shown in Figure 1B, in the absence of discharge, meatal swabs collected significantly

113   less cellular material than urethral swabs (mean $SAC_{CT}$ 27.0 vs 24.4, *P* = 0.0003). If

114   discharge was present, the meatal swab collected significantly more cellular material

115   than a meatal swab from men without discharge (mean $SAC_{CT}$ 23.7 vs 27.0, *P* =

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116  0.0004). Further, in the setting of visible discharge, no difference in the cellular content

117  collected comparing the meatal or urethral swabs was identified (mean $SAC_{CT}$ 23.7 vs

118  23.3, $P$ = 0.4789). Evaluating the GSS failure rate of swabs in the presence or absence

119  of discharge, the highest QNS rates were seen in meatal swabs from men without

120  discharge compared to meatal swabs from men with discharge (68% vs 15%, $P$ =

121  0.0022, Figure 1C) and compared to urethral swabs in men without discharge (68% vs

122  6%, $P$ <0.0001, Figure 1C). In the presence of discharge, meatal swabs were

123  associated with a slight non-significant increase in the QNS rate compared to urethral

124  swabs (15% vs 0%, $P$ = 0.1373, Figure 1C).

125      We then compared the diagnoses (using both Xpert® and GSS results) of all

126  QNS results to assess the number of NG or NGU diagnoses that could have been

127  missed by GSS failures. Of the 16 QNS GSS results, none were NG diagnoses, but

128  three NGU diagnoses (one CT diagnosed by NAAT and two non-CT NGU [defined by

129  discharge on exam]) were included, which highlights that GSS failures from meatal

130  swabs could delay the time to effective treatment (*i.e.,* missed opportunity to evaluate

131  PMNs in point-of-care testing) in the absence of discharge (data not shown).

132

133  **Discussion**

134      Evaluation by GSS of urethral secretions from a urethral or meatal swab remains

135  the test-of-choice for rapid diagnosis of NG or NGU in men with urethritis symptoms,

136  though no preferred swab type is recommended by the 2015 STD Treatment Guidelines

137  for collecting urethral secretions (7). In this study, we compared meatal and urethral

138  swabs from men and used the Cepheid Xpert® CT/NG $SAC_{CT}$ to measure the

139  difference in the amount of swab cellular material and determine the failure rate of GSS

140  testing for each swab type. Not surprisingly, we found that meatal swabs collected

141  significantly less cellular material, compared with urethral swabs, in the absence of

142  urethral discharge. Moreover, meatal swabs were associated with a high GSS failure

143  rate, eliciting a 12-fold increase in QNS GSS rates, compared with urethral swabs, in

144  men without discharge. In the presence of urethral discharge, there was no difference in

145  the cellular content or GSS failure rate between the swab types, indicating that the

146  collection quality of meatal swabs is highly susceptible to the sampling surface area of

147  the urethral meatus and/or may be collecting increased numbers of non-intact cells;

148  limitations that may be overcome by urethral sampling. Additionally, the limitations of

149  meatal swabs may only significantly affect Gram stain testing, which is dependent on

150  the collection of intact cells to evaluate for the presence of GNID and PMNs, whereas

151  NAAT testing is much more sensitive and less likely to be significantly influenced by

152  changes in the swab cellular content. In fact, NAAT testing comparing urine and either

153  swab type demonstrated a 100% concordance rate for the diagnosis of CT and/or NG in

154  our study, despite the meatal swabs containing less cellular material.

155     Although the NAAT performance of self-collected meatal swabs appears

156  comparable to clinician-collected urethral swabs (5) and superior to urine for diagnosis

157  of CT, NG, and trichomonas (6), no study has compared the performance of meatal

158  swabs to urethral swabs for Gram stain point-of-care testing to evaluate urethritis (7). To

159  our knowledge, our study is the first to demonstrate that in the absence of urethral

160  discharge, meatal swabs are inferior to urethral swabs at collecting cellular material,

161  which increases the failure rate of GSS testing. In addition, although there was no

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162 difference in the signs or symptoms between the swab groups, meatal swabs were

163 associated with significantly fewer numbers of GSS with PMN 2-5 (Table 1), suggesting

164 that under-diagnosis of NGU cases may also result when meatal swabs are used for

165 GSS testing.

166 Our findings have important implications for the use of meatal swabs to collect

167 urethral secretions, a practice that may be increasing given that meatal swabs have

168 several advantages over urethral swabs for NAAT testing. Meatal swabs are likely

169 better tolerated than urethral swabs as demonstrated in a comparison study of men who

170 received both a urethral and meatal swab, which found that 76% of men preferred the

171 meatal swab (4). Another study attempted to quantify the discomfort associated with

172 urethral swab collection using a visual analogue pain scale and found that collection of

173 a urethral swab using standard technique (inserting a swab 2 cm into the distal urethra)

174 elicited a median pain score of 52 mm (on a 100-mm pain scale), which correlated with

175 moderate (>30 mm) to severe (>54 mm) pain (10). Furthermore, multiple studies have

176 identified discomfort from urethral swabbing as a major factor that causes men to delay

177 seeking health care (11-13) and participants in adolescent focus groups expressed

178 strong negative emotions when asked about the urethral swab testing process (12, 13).

179 In addition, the ease of obtaining a meatal swab facilitates self-collection for NAAT

180 testing, allowing patients to self-collect specimens at home or in a clinical setting where

181 regular interval screening of asymptomatic, high-risk men is performed. Given that 77%

182 of men preferred self-collection of a meatal swab to provider-collection (14) and over

183 90% of men report self-collection of a penile-meatal swab as "easy" or "very easy" (5,

184 14), it is likely that NAAT testing of self-collected meatal swabs may play an important

185  future role in screening asymptomatic men in busy, high-flow clinical settings or non-

186  clinical settings.

187      Our study has several limitations. We could not evaluate the performance of

188  meatal swabs versus urethral swabs for the diagnosis of NGU or NG by Gram stain as

189  our study wasn't powered to evaluate that outcome. Also, the majority of men in our

190  study were African American, which is reflective of demographic characteristics of

191  clients attending the STD clinic and our results may not be generalizable to other, non-

192  STD Clinic populations. Additionally, the Gram stains were prepared by multiple

193  clinicians, all highly proficient at preparing and reading Gram stain smears. Although no

194  difference in either swab cellular content or the rate of QNS GSS results was associated

195  with any individual clinician (data not shown), we cannot rule out the possibility that

196  differences in provider collection techniques may have influenced our results.

197      In conclusion, in the absence of visible urethral discharge, the use of meatal

198  swabs for point-of-care diagnosis of NG or NGU by GSS testing was associated with a

199  significant decrease in swab cellular content and an increase in GSS failure rates,

200  compared to urethral swabs. Therefore, in the absence of discharge, meatal swabs

201  should be avoided when considering point-of-care testing for NG or NGU in men.

202

203  **Materials and Methods**

204      We recruited Men ≥ 19 years old from the Jefferson County Department of

205  Health (JCDH) STD clinic in Birmingham, Alabama, excluding only men who had voided

206  within the past 60 minutes and those who had received antibiotics with CT/NG activity

207  within the past 30 days. After informed consent was obtained, a directed physical exam

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208     was performed for the presence or absence of discharge and men were alternately

209     assigned to receive either a urethral or meatal swab for specimen collection using a

210     dacron swab. To collect a urethral swab, highly experienced clinicians inserted the swab

211     2cm into the urethra and rotated during insertion and extraction. For meatal swab

212     specimen collection, the swab was positioned perpendicular to the urethral meatus and

213     rolled back and forth several times across the meatus for 5 seconds. Following

214     specimen collection, swabs were immediately rolled onto the surface of a glass

215     microscope slide in preparation for Gram stain of urethral secretions and then placed in

216     an Xpert® CT/NG (Cepheid, Sunnyvale, CA) specimen transport container and stored

217     at 4°C.  Following meatal or urethral swab collection, an initial void urine specimen was

218     collected for CT and NG testing.

219          Gram stain of the smear was performed using standard laboratory procedure and

220     all smears were read by a highly-experienced clinician (JRS), blinded to the physical

221     exam findings and Xpert® CT/NG assay results. After identifying an area of high

222     cellularity using low magnification, the presence or absence of Gram negative

223     intracellular diplococci (GNID) and average number of leukocytes from five contiguous

224     high power fields were determined and recorded using high magnification with oil

225     immersion (1000x). GSS were labeled "Quantity cells not sufficient" (QNS) if no cells

226     were identified by scanning either low or high power magnification. NGU was diagnosed

227     if no GNID were seen and either (1) a discharge was present on exam or (2) ≥2 PMN's

228     per HPF were seen by GSS testing.

229          Xpert® CT/NG testing was performed on both urethral and meatal swab

230     specimens and post-swab urine specimens within 7 days of collection as described in

231    the package insert. For quantification of specimen cellularity, the Xpert® CT/NG sample

232    adequacy control crossing threshold ($SAC_{CT}$) was used. We also tested the

233    performance of each swab type to prepare a GSS by determining the failure rate of

234    GSS testing, defined as lacking sufficient number of cells to evaluate the specimen.

235    This study was approved by the institutional review board of the University of Alabama

236    at Birmingham and the research review committee at JCDH. Bivariate comparisons

237    were evaluated using an unpaired T-test while Fisher's Exact or Chi-square tests were

238    used to test differences between groups. Significance was reported as $P <0.05$ using

239    Prism software (v7.0b; Graphpad Software, Inc., San Diego, CA).

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260    Figure Legend:

261    **FIGURE 1.** Comparison of cellular content and percent QNS in meatal versus urethral

262    swabs in the presence or absence of urethral discharge. *(A)* Meatal swabs that resulted

263    QNS by GSS are associated with a significantly higher $SAC_{CT}$, compared with

264    satisfactory GSS, indicating they contain less cellular material. *(B)* In the absence of

265    discharge, meatal swabs have a significantly higher $SAC_{CT}$ compared to urethral swabs

266    from men without discharge or meatal swabs from men with discharge. In the presence

267    of discharge, there was no difference in the $SAC_{CT}$ between meatal or urethral swabs.

268    *(C)* In the absence of discharge, meatal swabs were significantly more likely to result

269    QNS by GSS compared to urethral swabs from men without discharge or meatal swabs

270    from men with discharge. In the presence of discharge, there was no difference

271    between the swab types. Horizontal lines and whiskers denote the mean and 95% CI,

272    respectively. $SAC_{CT}$ values were obtained from the Xpert® CT/NG assay.

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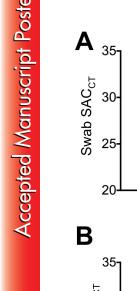| TABLE 1. Characteristics of Study Participants | | | | |
|---|---|---|---|---|
| Characteristic | Total ($n$ =66) | Urethral Swab ($n$ = 33) | Meatal Swab ($n$ = 33) | $P$-value |
| Age, mean (range) | 29 (20 – 69) | 29 (20 – 60) | 29 (20 – 69) | 0.9720 |
| Race, $n$ (%) | | | | 0.2920 |
|   AA | 56 (89%) | 28 (85%) | 28 (93%)[a] | |
|   Caucasian | 7 (11%) | 5 (15%) | 2 (7%)[a] | |
|   Other | 0 | 0 | 0[a] | |
| Prior STI | 43 (65%) | 25 (76%) | 18 (55%) | 0.0724 |
| Partners, $n$ last 30 days Mean (range) | 1.6 (0 – 7) | 1.8 (0 – 7) | 1.5 (0 – 4) | 0.4472 |
| Discharge Present, $n$ (%) | 27 (41%) | 14 (42%) | 13 (39%) | 0.8040 |
| Gram Stain, $n$ (%) | | | | |
|   QNS | 16 (24%) | 1 (3%) | 15 (45%) | **< 0.0001** |
|   GNID positive | 9 (14%) | 3 (9%) | 6 (18%) | 0.2891 |
|   GNID negative | | | | |
|     PMN < 2 | 9 (14%) | 7 (21%) | 2 (6%) | 0.0749 |
|     PMN 2 – 5 | 12 (18%) | 11 (33%) | 1 (3%) | **0.0011** |
|     PMN ≥ 5 | 20 (30%) | 11 (33%) | 9 (27%) | 0.5989 |
| Xpert® Swab Results | | | | |
|   Neg | 46 (70%) | 25 (76%) | 21 (64%) | 0.2912 |
|   CT+ | 8 (12%) | 2 (6%) | 6 (18%) | 0.1556 |
|   CT+NG+ | 4 (6%) | 2 (6%) | 2 (6%) | > 0.999 |
|   NG+ | 8 (12%) | 4 (12%) | 4 (12%) | > 0.999 |
|   $SAC_{CT}$, mean (range) | 24.8 (21 – 33) | 23.9 (21 – 27) | 25.6 (21 – 33) | **0.0026** |
| Urine $SAC_{CT}$, mean (range) | 26.1 (19 – 32) | 26.3 (19 – 32) | 25.9 (19 – 32) | 0.6147 |

Abbreviations: AA, African American; STI, sexually transmitted infection; GNID, Gram-negative intracellular diplococci; PMN, polymorphonuclear neutrophil; QNS, quantity cells not sufficient; CT, chlamydia; NG, gonorrhea

[a]3 missing

Significance evaluated using Fisher's Exact test or T-test, as appropriate.