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Clinical and microbiological investigation into mixed growth urine cultures

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Abstract

Introduction. Urine samples submitted for investigation of urinary tract infection (UTI) may identify more than one bacterial isolate. These samples may be reported as 'mixed growth urine culture' (MGUC). The clinical significance of MGUC remains controversial.

Hypothesis/Gap Statement. The impact of MGUC on patient management is not known and should be assessed.

Aim. To describe MGUC and assess its impact on patient management.

Methodology. Microbiology laboratory reports (Leeds, UK) were retrospectively analysed and urine cultures reported as MGUC from a 1 week period underwent detailed laboratory analysis. Semi-structured interviews of NHS clinicians' response to MGUC reports were explored for emergent themes.

Results. In 2018, 12.4% (14,323/115,664) of urine specimens processed to detect bacterial pathogens were reported as MGUC. Among a total of 200 MGUC samples identified within 1 week in 2019, detailed laboratory analysis identified 459 bacterial isolates. *Enterococcus species* (30.1%) and *Escherichia coli* (27.5%) were the most frequently isolated and the most frequent organism combination (24%). In total, 65.5% cultures contained two organisms and 82.5% of all MGUC contained at least one *Enterobacterales*. Interviews found clinicians believed MGUC reports represented detection of many commensal bacteria. Clinicians indicated they were more likely to diagnose and treat a UTI when provided with urine culture reports derived from detailed microbial analysis of MGUC, including identity and antibiotic sensitivity of organisms.

Conclusions. This study highlights the potential underuse of information derived from microbiological analysis of urine samples. Interpretive commentary on reports together with education for interpretation of enhanced reports should be explored further to improve outcomes in patients with UTI.

INTRODUCTION

Growth of more than one bacteria in urine culture [mixed growth urine culture (MGUC)] is often regarded as contamination of a urine sample [1]. In total, 11–31% of hospitalized patients with symptomatic urinary tract infection (UTI) have MGUC [2, 3]. However, MGUC may represent a combination of a pathogen and contaminating bacterial species [4–6]. Microbiology laboratories may not report specific organisms in MGUC and instead provide interpretive comments, which suggest a sample is contaminated [1]. This study characterizes MGUC in patients investigated for UTI and assesses how reporting of MGUC impacts decisions to treat patients.

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Keywords: urinary tract infection; UTI; mixed growth urine; urine culture reporting; urine culture contamination.

Abbreviations: GP, general practitioner; LIMs, laboratory information management system; MGUC, mixed growth urine culture; UTI, urinary tract infection.

Supplementary material is available with the online version of this article.

METHODS

Study design and setting

This was a three-phase mixed methods study. Phase 1 was a descriptive analysis of retrospective urine laboratory data. Phase 2 was a microbiological analysis of MGUCs. Phase 3 consisted of semi-structured clinician interviews. Phases 1 and 2 were conducted at a microbiology laboratory processing samples for four secondary care sites and 120 primary care sites (Leeds, UK).

Data collection

Retrospective descriptive analysis (phase 1)

Data from urine samples submitted for testing in 2018 were collected from a laboratory information management system (LIMS) and descriptively analysed.

Detailed microbiological analysis (phase 2)

A total of 219 consecutive MGUCs were identified on the LIMS (21 to 27 January 2019). Samples with >1 bacterial isolate with $>10^4$ colony forming units were retrieved from storage [MAST URI chrome 96-well microtitre set (MAST Group)], sub-cultured onto a Cysteine Lactose Electrolyte Deficient agar (E and O) and identified using standard procedures [7] or by MALDI Biotyper system (Bruker) for *Enterobacterales*.

Semi-structured interviews (Phase 3)

Legitimate gatekeepers (primary care site managers, a microbiology consultant and a pathology clinical director) were contacted to identify clinicians managing patients with suspected UTI. Clinician interviews lasted 20 to 60 min. Clinician participants were questioned guided by an interview topic guide (Supplementary Material S1, available in the online version of this article) and presented with hypothetical urine culture reports representing MGUC reports with/without named bacteria and antibiotic sensitivities (Supplementary Material S2 and S3) [8]. Participant's propensity to prescribe antibiotics based on these reports was determined. Interviews were manually transcribed verbatim at a general level of detail then thematically analysed using a framework method [9, 10].

Sample size determination

Phases 1/2 sample sizes were pragmatic based on time available. Phase 3 required representation from community-based clinicians and hospital-based clinicians. Hospital clinicians were represented by microbiology trainees who have dual roles as clinicians.

RESULTS

Phase 1: retrospective descriptive analysis

Overall, MGUC was identified in 14323/115664 (12.4%) urine samples [sample types: 33.6%(423/1258) bag specimen, 25.8% (2223/8600) catheter, 12.1% (3438/28422) clean catch, 10.4% (414/71535) midstream and 14.1% (825/5849) unspecified] with rates highest in patients over 65 years (8061/41760, 19.3%) and under 1 year old (509/2727, 18.7%).

Phase 2: Detailed microbiological analysis

Of 200 urine cultures reported as MGUC and available for analysis 65.5, 29, 1.5 and 0.5% had two, three, four and five isolates, respectively. In total, 4% MGUCs were found to be pure cultures. The most frequent bacterial species were Enterococcus spp. (30.07%) and *Escherichia coli* (27.45%) (Fig. 1). In total 82.5% of MGUC contained at least one Enterobacterales. The most frequent organism combination in MGUC was *E.coli* and Enterococcus spp. (24%) (Table 1).

Phase 3: semi-structured interviews

Participant characteristics

Primary care clinicians (n=5) and duration of experience: general practitioners (GPs): 14, 10 and 2 years, and Advanced Clinical Practitioners: 3 and 4 years. Hospital clinicians with clinical microbiology experience (n=3) with <1, 3 and 6 years' experience.

Findings

Five themes, made up of subthemes, are presented, with representative quotes in Table 2.

Theme 1: Perception of current MGUC reports

Clinicians' dilemma: all primary care clinicians expressed finding reports of MGUC challenging to interpret. Some expressed frustration in not having a clear-cut answer to resist pressure from patients to prescribe unnecessary antibiotics. Clinicians described that MGUC reports without organism species and susceptibility reported were of limited clinical value as they did

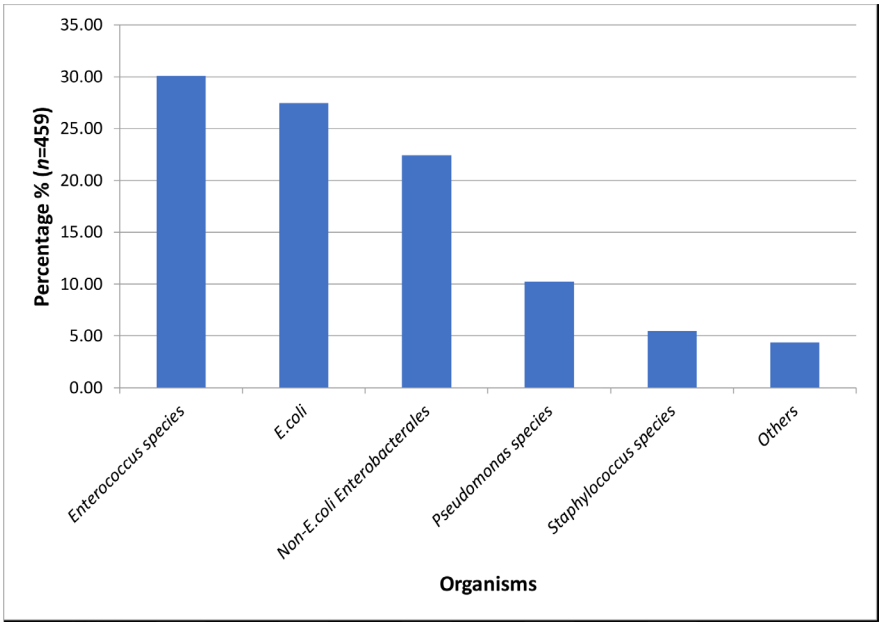

Fig. 1. Organisms identified in 200 mixed growth urine cultures.

not provide additional useful information. Clinicians had concerns for either prescribing unnecessary antibiotics or missing 'significant UTI'. *Repeat sampling difficulties*: some clinicians reported difficulty in obtaining clean repeat urine specimens, and a likelihood mixed growth would result from repeated culture. Participants identified that sometimes requests for repeat urine culture are not completed due to resolution of symptoms or inconvenience to the patient.

Theme 2: approaches to management of patients with MGUC

Interpretation: many regard MGUC of less significance and of no concern for UTI unless there was a 'strong' clinical suspicion. A minority of participants conveyed that patients have a role by re-presenting if they remain symptomatic. *Repeat sampling*: most clinicians would repeat sampling in symptomatic patients and those with indeterminate symptoms. *Empirical antibiotic treatment*: in addition to repeat sampling, clinicians would prescribe an empirical course of antibiotics where a patient is symptomatic or with indeterminate symptoms. One primary care clinician highlighted that when with uncertainty in the clinical evidence and the diagnosis of UTI, antibiotics may be prescribed as part of a diagnostic work up.

Theme 3: clinicians' prescribing propensity

Perception: some clinicians felt alternative reports including organisms identities/sensitivities should not change their prescribing practice but would only help to decide a timely course of antibiotics should they decide to treat. Adding that it would help them to know the trend of organisms in the mixed growth should a patient have persistent MGUC. *Increased tendency to prescribe antibiotics:* when given alternative reports including organism identities/sensitivities compared to a report of MGUC only, primary care clinicians were likely to diagnose and treat a UTI with less concern for contamination, given their awareness of the presence of a pathogenic bacteria (*E. coli*).

Table 1. Bacterial species combinations with rates of ≥3% identified from 200 urine samples with mixed growth

Species combination	no. (%)
E. coli and Enterococcus sp.	48 (24%)
Pseudomonas sp. and Enterococcus sp.	10 (5%)
E. coli and *Klebsiella pneumoniae*	9 (5%)
E.coli, Enterococcus sp. and Pseudomonas sp.	7 (3.5%)
Enterococcus sp. and staphylococcus sp.	6 (3%)
E. coli and *Pseudomonas* sp.	6 (3%)

Table 2. Qualitative results of clinicians review of mixed growth urine reports

Theme 1: summary of the perception of current mixed growth urine culture reports	
Clinicians' dilemma	'… They're a bit confusing really…they're not that helpful really, because they don't really confirm one thing or another' no. 3 primary care clinician
Repeat sampling difficulties	'We would probably hold off and repeat the sample and try and get a cleaner sample but that's not always possible… we might not manage it though we might not get any more' no. 4 primary care clinician
Theme 2: approaches to management of patients with mixed growth	
Interpretation	'…mixed growth is seen as less significant on the ward, we wouldn't necessarily act on it unless there were big clinical suspicions' no. 7 recently qualified trainee doctor
Repeat sampling	'…if they still had symptoms, I think I would repeat the sample and see if we can get something a bit more definite…' no. 3 primary care clinician
Empirical antibiotics treatment	'… if she didn't have every kind of symptoms but she had some symptoms…I might be tempted to try some antibiotics, see if it's UTI…' no. 3 primary care clinician
Theme 3: clinicians' prescribing propensity	
Perception	'…the only reason why this is useful is somebody who is getting these UTIs all the time, you sometimes look at it and you're like oh it's exactly the same organism that they're getting all the time or actually this is changing every time why is it changing…' #2Primary care clinician
Increased tendency to prescribe antibiotics	'…so there are two bugs picked up here the E-coli would worry me and so I would treat that…' #4Primary care clinician
Theme 4: clinicians' expectations for improved MG reports	
Additional information	'So if the person maybe has another line that says 'no treatments required' that more or less reiterate what I was thinking but skin and enteric flora means 'so what?'… You know, what do I do next?…' #1Primary care clinician
	'You could just write positive culture with antibiotics 123… that's all I want to know' #2Primary care clinician
	'…sometimes it would be better if they were picked out (identified)…but I think in reality that's not practicable… it would be a huge amount of work for the lab…' #5Microbiology trainee
Theme 5: misconceptions	
Growth characteristics	'that's (enteric flora report) made me think there was more of a mixture. and when you report this as enterococcus (MGUC report with additional information), are you saying there's only two bugs that you can see there?' #4Primary care clinician
Significance of culture and indication to prescribe antibiotics	'…so when they say likely colonisation and somebody has a raging fever how do you know it's not an infection but it is colonisation but like anything else I respect the judgement of microbiology so when they say likely colonisation even when I think it's an infection sometimes I just tell the patient that we've grown something but the lab says it's not enough concern and then we just see how you go. if things get worse you can then just at that point treat' #1Primary care clinician
Benefits of microbiology rotations	'…I think prior to this job my perception was that if you see a urine available on the system and it's shown E-coli that's growing…usually you would normally have acted, thinking patient has probably got UTI of some sort and I would act on it' #7Recently qualified trainee doctor

Theme 4: clinicians' expectations for improved MGUC reports

Additional information: primary care clinicians felt that their clinical decision making for diagnosis and management of UTI would be improved by the provision of additional information on a MGUC report. This included comments on the significance of culture, suggestion for further action, organisms' identity and sensitivities.

Theme 5: misconceptions

Growth characteristics: primary care clinicians were unsure what exactly MGUC represented possessing the misconception that current MGUC reports represented complex growth of numerous gut flora. Disbelief was expressed when presented with the hypothetical report naming organisms of *E. coli* and *Enterococcus* spp. only. *Significance of culture and indication to prescribe antibiotics*: primary care clinicians incorrectly believed that listed organisms with sensitivities on a report is an indication to prescribe antibiotics. Moreover, when presented with hypothetical reports with organisms listed together with suggested antibiotics, clinicians took this as instruction from the laboratory that antibiotics treatment was required. *Benefits of microbiology rotations:* the two specialist registrars with dual roles as clinicians conveyed an understanding that reports from the laboratory are *'not the be-all and end-all'*. They both expressed suspicions that their non-microbiologist colleagues may be unable to interpret reports of MGUC accurately and/or act appropriately. A recently qualified trainee doctor reported having similar misconceptions prior to his microbiology training post.

DISCUSSION

Clinicians in our study reported relying on urine culture reports to guide clinical decision-making when there is uncertainty in clinical evidence. However, clinicians believed MGUC without species or antibiotic susceptibility reported represents contamination despite evidence that multiple bacterial species can cause symptomatic UTI [4–6]. Previous studies have reported similar rates of MGUC containing only two organisms, (65.5%) as this study [1, 11]. However in this study, clinicians incorrectly believed that MGUC represented complex growth of many bacteria, leading clinicians to assume infection was unlikely and antibiotic therapy unwarranted. This suggests reporting MGUC without species detail may result in failure to diagnose lower UTI, leading to an

increase in upper UTI caused mostly by Enterobacterales [12]. Individual clinician's attitude to antibiotic prescribing determined the likely implication of MGUC on a patient's health outcome. When there is uncertainty in clinical evidence for UTI, some primary care clinicians reported they would repeat sampling in addition to prescribing an empirical course of antibiotics. This group of clinicians were cautious; prescribing antibiotics rather than risking a patient deteriorating. There were also clinicians who would not prescribe antibiotics but would repeat samples until they ascertain the presence of an infection, sometimes even when a patient is symptomatic. These highlight ineffective communication between the microbiology laboratory and clinicians. Consequently, patients with symptomatic UTI may not receive timely antibiotic treatment, leading to infection progressing. An increase in UTI and unnecessary use of antibiotics both have implications for increased antimicrobial resistance [12]. This study suggests that clinicians might alter their decision making, to increase antibiotic prescribing if provided with additional information on MGUC reports. MGUC was found in a significant proportion of urine samples (12.4% of all positive urine cultures), and almost all MGUC (82.5%) contained a recognized uropathogen in the form of an Enterobacterales. Therefore, a significant number of people may have missed UTI diagnosis or unnecessary antibiotics. Further research on the effect of educational training on interpretation of urine culture reports to guide clinical decision making in primary care could provide clinicians with greater confidence in patient management.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The study was designated a service evaluation; therefore, did not require ethical approval from the UK National Health Service (NHS) Health Research Authority. To meet academic requirements ethical approval was obtained from the University of Leeds (Ref: HREC17-013). Permission to interview clinicians in the community was obtained from West Yorkshire R and D (Ref: 001_19_01_18_0000 (service evaluation)) and each clinician's written informed consent was obtained.

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