Case report on a swift shift in uropathogens from *Shigella Flexneri* to *Escherichia Coli*: a thin line between bacterial persistence and reinfection.

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**Case report**

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Abstract

Background: Urinary tract infections (UTI) are mostly caused by bacteria. Urine cultures are usually a definitive measure to select the appropriate antibiotics for the elimination of a uropathogen and subsequent recovery from the infection. However, the preferred antibiotics as determined by urine culture and sensitivity may still not eliminate the infection and would require further examination to ascertain the cause of treatment failure which could be unresolved bacteriuria, bacterial persistence, immediate reinfection with a different uropathogen or misdiagnosis.

Case presentation: A 2-years 7 months-old female was admitted in the Regional hospital of Buea following persistent fever. An auto medication with amoxicillin was reported. Urinalysis was done on the first day and the sediment of the cloudy urine revealed many bacteria and few pus cells. Ceftriaxone was prescribed as empirical treatment and a request for urine and blood culture was made. Three days after admission, the temperature and CRP were 39.0°C and 96 mg/l respectively. The urine culture results (>10^5 CFU/ml of *Shigella flexneri* sensitive to ofloxacin) were presented to the doctor on the 4th day of admission. Patient was put on ofloxacin. Three days after, the temperature (38.5°C) and CRP (24mg/l) were still elevated. The blood culture result came out negative. A second urine culture was requested which came back positive (>10^5 CFU/ml of *Escherichia coli* resistant to ofloxacin and sensitive to meropenem and amikacin). Ofloxacin was discontinued and the patient put on meropenem and amikacin. The third urine culture recorded no significant growth after 48 hours of incubation. The patient was discharged looking healthy once more with a normal body temperature.

Conclusion: Antibiotics tailored towards the elimination of a particular bacterial species may as well provide a favorable environment for other bacterial species that are resistant to it in the course of treating a UTI episode. This apparent treatment failure may first of all require a second urine culture for confirmation rather than considering the possibilities of a misdiagnosis.

Background

Urinary tract infection (UTI) annually affects about 150 million people globally [1]. Although other microorganisms have been reported to cause UTI, it is mostly caused by bacteria and usually treated with antibiotics [2]. Most common uropathogens include *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus Mirabilis*, *Enterococcus sp*, *Staphylococcus saprophyticus*, and *Pseudomonas aeruginosa* [3, 4]. UTI caused by *Shigella sp* have been identified in rare occasions [5–8].

Although contamination is usually considered when more than one bacterial species is isolated from urine, some UTI are actually caused by 2 bacterial species acting simultaneously [9, 10]. However, a rapid and successive shift from one bacterial species to another (following antimicrobial therapy) in the course of a particular UTI episode has not been reported before to the best of our knowledge. An understanding on how to identify and manage such infections is of paramount importance in making clinical decisions for patients with complicated UTI.
Case Presentation

A 2 years 7 months-old female with a body mass of 12.8kg was admitted in the Regional hospital of Buea on the 31st of March 2019 after a 4-day persistent fever, polyarthritis and abdominal pain but no vomiting nor diarrhea. The patient who lives in an urban area with access to drinking water had no history of diarrhea for the past 1 month and neither did the relatives living with her. The parents admitted that for the past 8 months she always talks whenever she feels like urinating or passing out stool. An auto medication with amoxicillin (aminopenicillin) 250mg sirop was reported (5ml twice a day for 3 days).

Upon examination, the patient had moderate jaundice of the sclerae, soft abdomen with no hepatomegaly nor splenomegaly. The temperature upon admission was 38.7°C. The blood test results of the patient are summarized on table 1. Urinalysis was done on the first day and the sediment of the yellow, cloudy urine revealed many bacteria and few pus cells although nitrate reduction and leucocyte esterase were not detected. Ceftriaxone (third generation cephalosporin) was prescribed as empirical treatment and a request for urine and blood culture was made. After being given the relevant instructions, the mother collected mid-stream urine from the child directly into the designated sterile container. Three days after admission, the temperature and CRP were 39.0°C and 96 mg/l respectively. Ceftriaxone was discontinued and a combined therapy of ampicillin (aminopenicillin) and gentamicin (aminoglycoside) was introduced.

Table 1: Summary of blood tests results
| Date               | Tests                                                                 | Results  | Reference interval | Interpretation |
|--------------------|-----------------------------------------------------------------------|----------|--------------------|-----------------|
| 31st March 2019    | Malaria test (microscopy and rapid diagnostic test)                   | Negative | -                  | Negative        |
|                    | C-reactive protein                                                   | 48mg/l   | <6mg/l             | Positive        |
|                    | Hemoglobin                                                           | 8.9      | 10.4-14.0          | Low             |
|                    | WBC ($10^3$ cells/ul)                                                | 28.5     | 4.0-12.0           | High            |
|                    | Neutrophil %                                                         | 45.2     | 40-60              | Normal          |
|                    | Lymphocyte%                                                          | 43.1     | 20-40              | High            |
|                    | Platelet ($10^3$ cells/ul)                                           | 269      | 150-400            | Normal          |
| 2nd April 2019     | Malaria test (microscopy)                                            | Negative | -                  | Negative        |
|                    | C-reactive protein                                                   | 96       | <6mg/l             | Positive        |
|                    | Hemoglobin                                                           | 8.6      | 10.4-14.0          | Low             |
|                    | WBC ($10^3$ cells/ul)                                                | 15.2     | 4.0-12.0           | High            |
|                    | Neutrophil %                                                         | 43.2     | 40-60              | Normal          |
|                    | Lymphocyte%                                                          | 45       | 20-40              | High            |
|                    | Platelet ($10^3$ cells/ul)                                           | 375      | 150-400            | Normal          |
|                    | Urea                                                                 | 18       | 10-50              | Normal          |
|                    | Creatinine                                                           | 0.6      | 0.6-0.9            | Normal          |
|                    | ALT ($U/l$)                                                          | 24       | <37                | Normal          |
|                    | AST ($U/l$)                                                          | 26       | <31                | Normal          |
| 9th April 2019     | C-reactive protein                                                   | 48mg/l   | <6mg/l             | Positive        |
|                    | Hemoglobin                                                           | 9.8      | 10.4-14.0          | Low             |
|                    | WBC ($10^3$ cells/ul)                                                | 18.8     | 4.0-12.0           | High            |
|                    | Neutrophil %                                                         | 59.2     | 40-60              | Normal          |
|                    | Lymphocyte%                                                          | 29.0     | 20-40              | Normal          |
|                    | Platelet ($10^3$ cells/ul)                                           | 371      | 150-400            | Normal          |

Gram staining of the urine sediment revealed gram negative rods which grew on Cystine–Lactose–Electrolyte-Deficient (CLED) agar (figure 1A) and Eosine Methylene Blue (EMB) as small colourless non-mucoid colonies later on identified biochemically using Enterosystem 18R (Liofilchem, Italy) to be *Shigella flexneri* (susceptible to Ofloxacin [second generation fluoroquinolone] and meropenem [carbapenem]). The urine culture results (table2) were presented to the doctor on the 4th day of admission with patient recording a temperature of 40°C and CRP of 24mg/l. Following the antimicrobial sensitivity test, ampicillin and gentamicin were discontinued and patient was put on ofloxacin and paracetamol injection (60mg/kg to bring down the temperature). Three days after, the temperature (38.5°C) and CRP (24mg/l) were still elevated. The blood culture result came out negative. A second urine culture and a urinary tract ultrasound was then requested. The latter did not reveal any abnormality in the urinary tract of the patient. The gram stain of the second urine sample revealed gram negative rods which produced pure yellow colonies on CLED agar (figure 1B) and presented a metallic sheen on EMB agar following subculture. This was later on identified biochemically (Enterosystem 18R [Liofilchem, Italy]) to be *Escherichia coli* (resistant to Ofloxacin and susceptible to Meropenem and
Amikacin [aminoglycoside]. Following this result, Ofloxacin was discontinued and the patient was put on Meropenem and Amikacin IV injections for 7 days. There was a progressive decrease in temperature and CRP over these 7 days with the third day recording a temperature of 37.2°C and CRP of 12mg/l. A third urine culture was requested and no significant growth was observed after 48 hours of incubation. The patient was discharged upon completion of treatment on the 18th of April 2019 looking healthy once more with a normal body temperature.

Table 2: Summary of Urine culture results

| Date            | URINE CULTURE | 1st | 2nd | 3rd |
|-----------------|---------------|-----|-----|-----|
| Collection of sample | 1st April 2019 | 8th April 2019 | 15th April 2019 |
| Release of results | 4th April 2019 | 11th April 2019 | 17th April 2019 |

| Date            | URINE CULTURE | 1st | 2nd | 3rd |
|-----------------|---------------|-----|-----|-----|
| Collection of sample | 1st April 2019 | 8th April 2019 | 15th April 2019 |
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Discussion And Conclusion

Some cases of UTI caused by bacteria happen to be bacteria coming from the gastrointestinal tract and entering the urinary tract via faeces. As a matter of fact, *E. coli* which is known to be the most common uropathogen usually enters the urinary tract as a faecal contaminant especially in women (short distance between the anus and urethral meatus)[11]. The *Shigella* and of course the *E. coli* we have in this case report most likely entered the urinary tract as faecal contaminants. Unfortunately, stool culture was not done to confirm this. However, the question here is: Did the “faecal contaminant” succeed in establishing itself as a uropathogen in the urinary tract? Not every bacterial growth from urine culture is considered as a UTI or as a uropathogen. Other parameters need to be taken into consideration in order to distinguish between contamination and infection. These include direct WBC count, nitrate reduction, proteinuria (evidence of inflammation from the urinary tract) leucocyte esterase, colony count of bacterial growth etc [12–14]. We considered all of this (as seen in table 2) before arriving at the fact that *Shigella* was a causative agent of the UTI episode.

*Shigella* and *Escherichia* are closely related phenotypically [15] and their genetic makeup is about 80-90% similar [16]. These similarities may also be reflected in their virulence factors as some studies have shown that *Shigella flexneri* also possesses the *sat* gene [17–20] found in uropathogenic *Escherichia coli* (UPEC) and known to code for a secreted autotransporter toxin that elicits cytopathic effect on bladder and kidney cells in the course of a urinary tract infection [21]. This may explain why a UTI initially caused by *Shigella flexneri* could easily undergo a swift and unnoticeable change in uropathogen to *Escherichia coli* as both bacteria probably affect the urinary tract in a similar way due to some similarities in their pathogenicity and virulence. If both bacterial isolates do not share the same antimicrobial sensitivity profile, treatment with an antibiotic that can eliminate the initial causative agent but not the “successor” would most probably give rise to a recurrent infection.

A recurrent infection is usually associated with unresolved bacteriuria, bacterial persistence or reinfection [22]. The clinical findings and laboratory diagnosis of this patient presents a rare case of reinfection which apparently looks like bacterial persistence. The fact that the patient’s condition presented an unexpected prognosis with a complete and abrupt change in uropathogen species during the same UTI episode made it quite difficult to distinguish bacterial persistence from reinfection. Although the initial treatment with ofloxacin following the first urine culture was effective (it eliminated the *Shigella flexneri*), it also gave room for ofloxacin resistant *Escherichia coli* to swiftly proliferate and colonize the urinary tract. As such, the overall outcome revealed an apparent treatment failure and it boils down to this question: What are the steps to consider when a treatment failure is recorded even after administering the appropriate antibiotics as determined by urine culture and sensitivity?

Treatment failure after urine culture and sensitivity is often linked to obstructive pyelonephritis (requiring a renal ultrasound) or misdiagnosis [23, 24]. As such, some common ways of addressing this in clinical practice is usually to also consider different conditions that mimic the signs and symptoms of UTI. Some
of these conditions may include kidney stone [25], painful bladder syndrome (interstitial cystitis)[26], possible renal tract malignancy, renal tuberculosis, urethritis and some sexually transmitted infections [27]. Since most of these conditions are seldom found in children [28–31], we still required more evidence to exclude a UTI for this patient, thus the need for a second urine culture. The second urine culture was quite necessary in this context as it helped to eliminate the possibilities of misdiagnosis and presented an unusual, rapid reinfection of the urinary tract by a completely different bacteria species. Although a second urine culture is recommended for treatment failure [27], urinalysis is what is commonly done to exclude or include a possible on-going UTI episode despite treatment [32] especially in resource limited settings like ours. In addition to the fact that it is less specific and does not directly guide the choice of antibiotics as compared to urine culture, urinalysis on its own cannot identify a short-term reinfection (especially in the case of our patient) nor detect a polymicrobial UTI episode.

Polymicrobial infections often lead to dramatic and unexpected outcomes in the aptitude of antibiotics to eliminate bacteria [33]. Based on the fact that we isolated pure colonies from the first two meticulously done urine cultures, this case report apparently looks like a non-polymicrobial UTI episode which lead to a dramatic and unexpected outcome following therapy. However, this may have been a polymicrobial infection which initially had a *Shigella* dominance.

In conclusion, antibiotics tailored towards the elimination of a particular bacterial species may as well provide a favourable environment for other bacterial species that are resistant to it in the course of treating a UTI episode. This can indicate an overall treatment failure and may first of all require a second urine culture for confirmation rather than considering the possibilities of a misdiagnosis.

**List Of Abbreviations**

UTI: Urinary tract infection

CFU-colony forming unit

WBC: White blood cells

RBC: Red blood cells

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

CLED: Cystine Lactose Electrolyte Deficient

EMB: Eosin Methylene Blue

CRP: C-reactive protein
Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
A signed consent for publication was obtained from the father of the child in this report

Availability of data and materials
All data generated or analysed during this study are included in this published article

Competing interests
The authors declare that they have no competing interests

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Authors' contributions
KAT did laboratory analyses and wrote the manuscript
FDP clinically followed up the patient and reviewed the manuscript
YSK did laboratory analyses
HDM reviewed the manuscript

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**Figures**

A) 1st Urine culture: Profuse growth (>10⁵CFU/ml) of *Shigella flexneri*

B) 2nd Urine culture: Profuse growth (>10⁵CFU/ml) of *Escherichia coli*

**Figure 1**

Bacterial growth on CLED agar after 24 hours of incubation of patient urine sample