Urology Case Reports 46 (2023) 102312

Contents lists available at ScienceDirect

Urology Case Reports

journal homepage: www.elsevier.com/locate/eucr

Treatment of chronic relapsing urinary tract infection with antibiotics selected by AtbFinder

George V. Tetz [a,*], Kristina M. Kardava [a], Maria F. Vecherkovskaya [a], Michael D. Tsifansky [b,c], Victor V. Tetz [a]

[a] Human Microbiology Institute, New York, NY, USA
[b] Department of Pediatrics, George Washington University (GWU), Washington, DC, USA
[c] Divisions of Cardiac Critical Care Medicine and Pulmonary, Children's National Hospital, Washington, DC, USA

ARTICLE INFO

Keywords:
Antibiotics
AtbFinder
Drug resistant
Susceptibility testing
Urinary tract infection

ABSTRACT

We report the case of a 46-year-old patient who, after renal cancer surgery, developed a recurrent urinary tract infection that lasted for more than 2 years. Despite repeated antibiotic courses, including broad-spectrum drugs chosen using conventional antibiotic susceptibility testing, multiple reinfections followed. The patient was successfully treated once antibiotics were selected with AtbFinder. Unlike routine antimicrobial susceptibility methods, which select antibiotics effective only against a "lead bacterial pathogen," AtbFinder identifies antibiotics that target the mixture of bacteria at the infection site. This case demonstrates the ability of AtbFinder to successfully select antibiotics for the treatment of relapsing urinary tract infections.

1. Introduction

Conventional phenotypic or genotypic antimicrobial susceptibility testing (AST) frequently fails to identify optimal and effective antibiotics.[1,2] In patients with recurrent urinary tract infections (UTIs), antibiotics selected with these tests frequently fail to eradicate infections resulting in relapses. In the present report, we describe a clinical case, whereby a novel diagnostic test AtbFinder was used successfully to select antibiotics for a patient with recurrent UTI.

2. Case presentation

A 46-year-old man underwent resection of the right kidney in February 2020 due to a cystic variant of renal cell carcinoma complicated with a urinary fistula. Three weeks post-surgery, the patient developed a UTI. A standard microbiological laboratory test identified *Enterococcus faecalis* and *Pseudomonas* spp. In urine and, based on disk-diffusion AST, meropenem and clindamycin were prescribed. The response was insufficient and the bacteria persisted for the next two weeks, which prompted treatment with meropenem and levofloxacin (Fig. 1).

Nevertheless, the patient was still infected with *E. faecalis* and reinfected with *Achromobacter xylosoxidans*. In June 2020, *E. faecalis* and reinfection with *Pseudomonas aeruginosa* were confirmed, but due to the absence of clinical symptoms the patient was left untreated. Within a month, clinical symptoms of UTI appeared and *P. aeruginosa* was detected in urine; hence, the patient was administered fosfomycin, as suggested by conventional AST. However, the infection recurred and in August 2020 the patient was administered another course of fosfomycin due to persistence of *P. aeruginosa* along with reinfection with *Escherichia coli*. In February 2021, *P. aeruginosa* and reinfection with *Klebsiella pneumoniae* were identified, prompting treatment with a course of cefepime according to AST data. By April 2021, recurrence of *P. aeruginosa* and *E. faecalis* was noted and the patient was treated with ceftriaxone. During the next months, *P. aeruginosa* was detected in urine and, based on AST results, levofloxacin and cefepime were administered, but the infection recurred every time. Finally, in March 2022, the treating doctor prescribed a therapy based on antibiotic identification with AtbFinder.

Whereas routine AST identified only *P. aeruginosa*, AtbFinder detected *P. aeruginosa*, *Staphylococcus aureus*, *A. xylosoxidans*, and *K. pneumoniae* in the same urine sample. Accordingly, cefepime, moxifloxacin, cefepime + amikacin, meropenem + amikacin, and piperacillin/tazobactam + tobramycin were identified as effective by microbroth dilution, but ineffective by AtbFinder (Table 1). Instead, the latter identified ceftriaxone + amikacin, levofloxacin + azithromycin, and piperacillin/tazobactam + levofloxacin as effective (Fig. 2).

* Corresponding author. 101 Avenue of the Americas, New York, NY, 10013, USA.
E-mail address: g.tetz@hmi-us.com (G.V. Tetz).

https://doi.org/10.1016/j.eucr.2022.102312
Received 12 December 2022; Accepted 28 December 2022
Available online 28 December 2022
2214-4420/© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

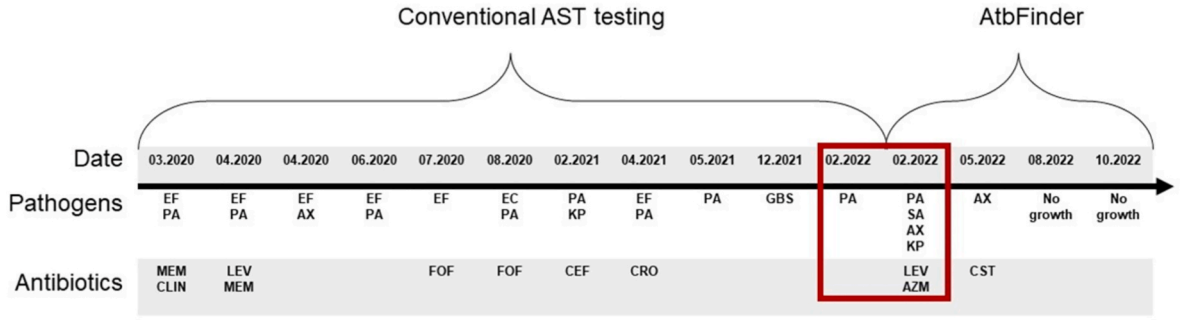

Fig. 1. Timeline of recurrent UTIs.
Timeline of the disease. The column for each timepoint describes the pathogen identified with conventional microlab or AtbFinder methods, such as *E. faecalis* (EF), *P. aeruginosa* (PA), *A. xylosoxidans* (AX), and *K. pneumoniae* (KP), as well as the antibiotics used for the corresponding treatment, including levofloxacin (LEV), meropenem (MEM), fosfomycin (FOF), cefepime (CEF), ceftriaxone (CRO), azithromycin (AZT), and colistin (CST). The red square identifies the initiation point of AtbFinder-based therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Comparison of antibiotic efficacy between conventional AST and AtbFinder.

Well number	Antibiotic	Antibiotic efficacy	
		Conventional AST	AtbFinder
		PA	PA; SA; AX; KP
A1	Azithromycin	–	–
A2	Amikacin	–	–
A3	Amoxiclav	–	–
A4	Cefalexin	–	–
A5	Cefepime	+	–
A6	Cefotaxime	–	–
A7	Ciprofloxacin	–	–
A8	Clindamycin	–	–
B1	Colistin	–	–
B2	Co-trimoxazole	–	–
B3	Fosfomycin	–	–
B4	Furagin	–	–
B5	Furazidine	–	–
B6	Levofloxacin	–	–
B7	Meropenem	–	–
B8	Moxifloxacin	+	–
C1	Nitrofurantoin	–	–
C2	Piperacillin/tazobactam	–	–
C3	Teicoplanin	–	–
C4	Tigecycline	–	–
C5	Tobramycin	–	–
C6	Cefepime + amikacin	+	–
C7	Cefepime + ciprofloxacin	–	–
C8	Cefepime + meropenem	–	–
D1	Cefepime + piperacillin/tazobactam	–	–
D2	Cefepime + tobramycin	–	–
D3	Cefepime + levofloxacin	–	–
D4	Ceftriaxone + piperacillin/tazobactam	–	–
D5	Ceftriaxone + amikacin	–	+
D6	Ceftriaxone + levofloxacin	–	–
D7	Ceftriaxone + Meropenem	–	–
D8	Ceftriaxone + tobramycin	–	–
E1	Levofloxacin + amikacin	–	–
E2	Levofloxacin + azithromycin	–	+
E3	Levofloxacin + tobramycin	–	–
E4	Meropenem + amikacin	+	–
E5	Meropenem + azithromycin	–	–
E6	Meropenem + ciprofloxacin	–	–
E7	Meropenem + levofloxacin	–	–
E8	Meropenem + tobramycin	–	–
F1	Piperacillin/tazobactam + amikacin	–	–
F2	Piperacillin/tazobactam + azithromycin	–	–
F3	Piperacillin/tazobactam + ciprofloxacin	–	–
F4	Piperacillin/tazobactam + levofloxacin	–	+
F5	Piperacillin/tazobactam + meropenem	–	–
F6	Piperacillin/tazobactam + tobramicin	+	–
F7	Piperacillin/tazobactam + Fosfomycin	–	–
F8	Control	**N/A**	–

"+" antibiotic is effective (absence of bacterial growth).
"-" antibiotic is ineffective (presence of bacterial growth).

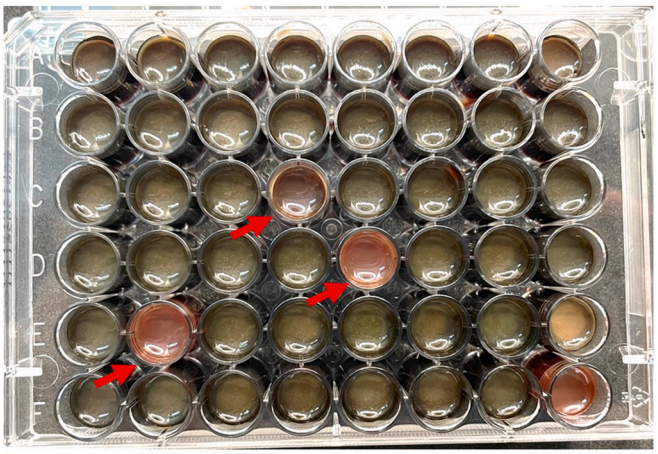

Fig. 2. Image of a 48-well AtbFinder plate, showing bacterial growth after 12 h of cultivation at 37 °C.
The agar in each well is supplemented with one or several antibiotics at concentrations deemed effective in urine. Well F8 represents an antibiotic-free control. No bacterial growth is displayed by wells C4 (ceftriaxone + amikacin), D5 (levofloxacin + azithromycin), and E2 (piperacillin/tazobactam + levofloxacin), highlighted with red arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The patient was eventually treated with a combination of levofloxacin and azithromycin, which resulted in the rapid disappearance of clinical symptoms. At the check-up visit in May 2022, *A. xylosoxidans* was detected; however, no clinical data supported ongoing UTI. AtbFinder identified colistin, cefepime + levofloxacin, and tigecycline as effective, and the patient was treated with colistin for 5 days. At the next follow-up visits in August and October 2022, no bacterial growth in urine was detected using either conventional AST or AtbFinder.

3. Discussion

One of the reasons for the failure of conventional AST to select effective antibiotics effective against recurrent UTI is the reliance on the antibiotic response of the lead UTI pathogen within a pure bacterial culture. However, conventional AST neglects the occurrence of multispecies biofilms during UTI, where bacteria are up to 1000 times more tolerant to antimicrobials than corresponding planktonic cells.[3] Moreover, the lead pathogen in multispecies biofilms could be additionally protected by collective antibiotic resistance, when an antibiotic resistance factor released by even non-virulent bacteria, which are often fewer in number, may protect an entire community.[4] Finally, standard AST is unable to detect persisters or account for inter-microbial communication via quorum sensing, Teazeled (TezR) receptors, and the TR-receptor system that upregulate resistance genes.

The recently developed AtbFinder, used in this study overcomes the above limitations.[5] By recapturing polymicrobial biofilms from the biosamples it can identify effective and ineffective antibiotics by employing a "whole community response" to antibiotics instead of filtering a single lead bacterium. AtbFinder takes into consideration critical "real-life" factors required for the effective selection of antibiotics, such as biofilm growth, the presence of persisters, modulation of antibiotic resistance by quorum sensing and TezRs, and collective antibiotics resistance, not taken into consideration by routine AST.

AtbFinder is a 48-well plate filled with proprietary developed TGV agar that supports growth of a diverse bacterial population, including bacteria that are frequently missed by culture with a standard nutrient medium due to low viable counts in a biological sample and inocula. In each well, the agar is supplemented with one or several antibiotics at a concentration that reflects their penetration into different tissues.

In this study, a variant of AtbFinder designed for the selection of antibiotics in patients with UTIs, was supplemented with antibiotics taken at concentrations achievable in urine. Urine was plated directly on the agar without isolation of a pure culture. Following incubation at 37 °C for 4 h, bacterial growth on the agar surface determined the effectiveness of antibiotic treatment. Antibiotics selected by AtbFinder terminated recurrent UTIs that had been unsuccessfully treated with multiple courses of antibiotics indicated as effective by routine AST. That happened because besides *P. aeruginosa*, which was identified in urine by a conventional microlab assay, AtbFinder identified also *S. aureus*, *A. xylosoxidans*, and *K. pneumoniae*, so antibiotics were evaluated based on their efficacy against mixed biofilms cultured from the biological sample. The presented case report highlights the advantage of the "whole microbial community response" to antibiotics utilized by AtbFinder for patients with UTIs.

4. Conclusion

Data from the current case support the hypothesis that the antibiotics selected based on a novel principle of a "whole microbial community response" are clinically more effective than conventional routine AST methods. AtbFinder is fundamentally different from AST, offering a combination of phenotypic testing and a high speed of antibiotic selection. With as little as 4h turnaround time compared with 48–96h required by standard culture-based AST, AtbFinder may become a valuable tool for selecting more effective antibiotics replacing empirical therapy.

Consent

This study was approved by the Institutional Board Review (PA-3340/22, 2022) and followed the principles outlined in the Declaration of Helsinki. The patient provided written informed consent. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of interest

Nothing to declare.

Author contributions

KK, VT, GT conceived and supervised the research. VM, KK, GT, VT and MT analyzed the data, and wrote the manuscript. KK and GT edited and helped to draft the final manuscript. All authors contributed to the article and approved the submitted version.

Funding

Nothing to declare.

Acknowledgements

Nothing to declare.

References

1. Ersoy SC, Heithoff DM, Barnes L, et al. Correcting a fundamental flaw in the paradigm for antimicrobial susceptibility testing. *EBioMedicine*. 2017;20:173–181.
2. Tetz G, Tetz V. Overcoming antibiotic resistance with novel paradigms of antibiotic selection. *Microorganisms*. 2022;10:2383.
3. Josephs-Spaulding J, Krogh TJ, Rettig HC, et al. Recurrent urinary tract infections: unraveling the complicated environment of uncomplicated rUTIs. *Front Cell Infect Microbiol*. 2021;11.
4. Vega NM, Gore J. Collective antibiotic resistance: mechanisms and implications. *Curr Opin Microbiol*. 2014;21:28–34.
5. Tetz G, Tetz V. Evaluation of a new culture-based AtbFinder test-system employing a novel nutrient medium for the selection of optimal antibiotics for critically ill patients with polymicrobial infections within 4 h. *Microorganisms*. 2021;9:990.