Treatment of recurrent urinary tract infections in a 60-year-old kidney transplant recipient – last-chance antibiotics and phage therapy

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Case report

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Abstract

Background: The article underlines the problem of antimicrobial resistance in transplant departments where wide-spectrum antibiotics must often be used as first line treatment for immunocompromised patients. This applies especially to kidney transplant recipients who suffer from urinary tract infections. Additional means to control infections and support treatment methods are much needed in departments treating transplant patients.

Case presentation: This article presents a case of a 60-year-old patient after kidney transplantation repeatedly admitted to the hospital due to recurrent urinary tract infections, including an episode of urosepsis, caused by *Klebsiella pneumoniae* producing extended-spectrum beta-lactamases (ESBL). Kidney transplantation was performed due to renal insufficiency caused by polycystic kidney disease, without removing of the patient's own kidneys. As a consequence of numerous episodes of urinary tract infections (12 episodes within 15 months since transplantation), the patient developed chronic infection caused by ESBL-producing *K. pneumoniae* which showed variable susceptibility to carbapenems and full susceptibility to colistin only. In the meantime, the patient developed accompanying urinary tract infection caused by a vancomycin-resistant *Enterococcus faecium* and subsequent colonisation of the gastro-intestinal tract by this strain. In an attempt to curb the *K. pneumoniae* infection, bacteriophage therapy was applied on the experimental basis, coordinated by the Phage Therapy Unit of the Hirsfeld Institute in Wrocław, Poland. Probiotics were also used in an attempt to modify the bacterial gut colonisation. Eventually, the patient fully recovered following nephrectomy of his own left kidney in which cysts were suspected to be the reservoir of bacteria causing recurring infections. In this article we discuss some treatment methods complementary to classic antibiotic therapy, in times when antimicrobial resistance is on the rapid rise.

Conclusions: It is necessary to further research methods of decreasing our reliance on antibiotics in view of falling susceptibility to those medicines. Phage therapy or altering patient's microbiome can give us an edge in tackling infections which today are treated solely with antimicrobials. This would be of great significance to transplant departments.

Background

Infections in patients after solid organ transplantation are more common when compared to the rest of the population. This is due to a number of factors, i.e. administered immunosuppression, exposure to healthcare-associated pathogens as well as altered anatomy of the operated site [1, 2]. Additionally, many patients suffer from comorbidities such as hypertension or diabetes (pre-existing or post-transplant) which further strain the immune system [3, 4]. Most common infections during the first months following organ transplantation have bacterial origin and are usually treated with antibiotics [1, 5].

Urinary tract infections in kidney transplant recipients

Kidney is the most frequently transplanted solid organ, represented by 927 kidney transplantation procedures (KTX) out of 1390 total solid organ transplantations performed in Poland in 2018 [6]. This makes urinary tract infections (UTIs) an every-day challenge for hospital departments and ambulatory care centres which provide treatment for kidney transplant recipients [7]. The most common single pathogen among transplant patients causing UTI is *Escherichia coli*. According to various studies, its presence varies from 29% [8] to 61.3% [9] in urine cultures sampled from kidney transplant recipients. In comparison, in the non-transplant population, *E. coli* is responsible for UTIs in over 80% of cases [10]. Other bacteria responsible for UTIs in the immunocompromised patients include *Proteus* spp., *Staphylococcus* spp., *Enterococci* spp., *Pseudomonas* spp., and *Klebsiella* spp. (the latter in approx. 10% of patients) [11]. Non-bacterial pathogens such as *Candida* spp. or viruses (cytomegalovirus, BK virus) should also be considered when diagnosing UTI in patients with immunodeficiency [7]. Watchfulness is needed as UTIs may contribute to acute injury of the allogenic kidney [12, 13].

Antimicrobial resistance in transplantation

In the light of antibiotic resistance (AMR) emerging worldwide, treatment of infections is becoming an alarming problem faced by many healthcare institutions [14]. Identification of colonisation with multidrug-resistant bacteria may be useful for the future prophylaxis or empirical treatment choices [15]. When infection is suspected, wide-spectrum antibiotics administered intravenously are often the first choice in solid-organ transplant recipients, as for example meropenem for treatment of Gram-negative bacterial diseases. Targeted de-escalation should be done, if possible, as soon as antibiograms are obtained [16]. In all cases, exposure to antibiotics can lead to the development of resistant strains of bacteria or to gastro-intestinal infections caused by *Clostridium difficile* [17, 18]. The latter demand the use of additional antibiotics which catalyse the infection-antibiotic-resistance cycle. There are potential ways to alleviate the burden of repeated treatment with antibiotics, some of which will be raised in the Case Presentation and summarised in the Discussion section.

Polycystic kidney disease

Among underlying reasons for renal insufficiency leading to kidney transplantation is polycystic kidney disease (PKD) – a genetic disorder causing kidneys to appear enlarged and remodelled by numerous cysts present in their structure. It can be of a recessive (ARPKD) or dominant (ADPKD) type. PKD may lead to end-stage kidney disease (ESKD) leaving a patient in need for renal replacement therapy [19]. Around 10% of all patients in Europe with ESKD suffer from ADPKD [20]. Cysts in patient's own kidneys not removed during or after transplantation may become a source of recurrent infections promoted by the administration of immunosuppression.

Case Presentation

A 60-year old male patient after allogenic KTX performed 6 months earlier due to kidney failure caused by PKD was admitted to the Department of Transplantation Medicine in Warsaw with fever of over 38.5 °C, accompanied by chills and dysuric symptoms. Two months earlier, he was subjected to a transurethral

resection of the prostate due to diagnosis of prostate adenocarcinoma (Gleason Score: 4 + 3) without perineural or vascular invasion. Within half a year from the KTX to the reported admission, the patient had already been hospitalised 3 times due to UTIs, including an episode of urosepsis, all caused by *Klebsiella pneumoniae* producing extended-spectrum beta-lactamases (ESBL) susceptible to carbapenems. Prior to KTX there was no medical record of UTIs in this patient. The patient's daily immunosuppression scheme was 5 mg prednisone and 3 mg tacrolimus at that time (TAC_0 in serum 4.6–7.6 ng/ml). Mycophenolate was withdrawn due to previous infections. Upon reported admission, the laboratory results showed an increase of C-reactive protein (CRP) level up to 52 mg/L (normal range: 0.0–9.0 mg/L), elevated serum creatinine of 1.8 mg/dL (normal range: 0.6–1.3 mg/dL with patient's stable creatinine at 1.4–1.6 mg/dL), leukocyte count of 11 G/L and leukocyturia. After securing blood and urine samples for microbiological cultures, meropenem was administered in slow (3-hour) intravenous infusions in a dose adjusted to the eGFR. It was later confirmed that the infection was caused by ESBL-producing *K. pneumoniae*. However, this time the strain had intermediate susceptibility to all carbapenems and full susceptibility to colistin only which was immediately administered in addition to meropenem.

In the course of antibiotic therapy, the patient improved both clinically and on the laboratory findings, lowering serum creatinine from 1.8 to 1.4 mg/dL. However, on the 12. day of treatment with both meropenem and colistin, colistin was discontinued due to suspected nephrotoxicity which manifested in the increase of creatinine from 1.4 to 1.7 mg/dL again while the initial infection seemed to have been treated. However, according to the control urine culture taken at that point, ESBL-producing *K. pneumoniae* was eliminated from urine yet vancomycin-resistant *Enterococcus faecium* (VRE) was identified in the urinary tract. Antibiotic therapy was then modified to meropenem with linezolid. Both antibiotics were administered for the following 14 days. At the same time, a rectal swab confirmed colonisation of the patient with VRE and an 8-strain probiotic (Vivomixx®) was introduced to modify the patient's intestinal microbiota. After over a month of treatment with wide spectrum antibiotics, the patient was discharged from the hospital with remission of clinical symptoms of UTI, CRP level of 0.6 mg/L, without leukocyturia but with occasional erythrocyturia and elevated serum creatinine of 1.70 mg/dL. Other laboratory findings obtained by the end of that hospitalisation showed elevation in the serum levels of aminotransferases (increase of aspartate transaminase from 13 to 51 U/L and alanine transaminase from 19 to 140 U/L) most likely due to intensive and lengthy antimicrobial therapy. Blood cultures were negative throughout the whole course of infection. Future urine cultures and control rectal swab done after over one month from discharge confirmed successful eradication of VRE from the GI tract.

In the following seven months, the patient was hospitalized another four times due to the recurrent UTIs caused by ESBL-producing *K. pneumoniae* of variable sensitivity to carbapenems and full susceptibility to colistin. During each hospitalisation he was treated with meropenem alone or meropenem with colistin lasting 12 to 14-days that resulted in temporary resolution of UTI symptoms. Serum creatinine levels in that period varied from 1.5 mg/dL to 2.0 mg/dL. An ultrasound examination performed during one of the hospitalisations revealed dynamic increase in the width of the pelvis of the transplanted kidney up to

21 mm in the anterior-posterior plane and its wall thickness of 2 mm, with dilation of the ureter up to 4 mm in the upper part that could correspond with the ongoing infections. For this reason, a double JJ stent was placed into the widened ureter for 10 weeks. However, this procedure did not prevent the relapse of UTIs of the usual aetiology.

At this point, the patient was referred to the Phage Therapy Unit (PTU) at the Hirszfeld Institute of Immunology and Experimental Therapy PAS in Wrocław, Poland, which conducts experimental phage therapy (PT) of infections caused by bacteria resistant to antibiotic treatment [21]. After giving his informed consent, the patient started intrarectal application of the specific phage preparation against the ESBL-producing *K. pneumoniae* strain at a dose of 10 ml twice daily. Specificity of the PT against current ESBL-producing *K. pneumoniae* strain isolated from the patient's urine was confirmed in the phage typing procedure.

On the fifth day of PT, the patient's body temperature increased to 37.2 °C, dysuric symptoms occurred with pain in the right lumbar area where one of his own polycystic kidneys was located. He was admitted to the Department of Transplantation Medicine in Warsaw once more where laboratory results showed massive leukocyturia with erythrocyturia, elevated CRP of 14.9 mg/dL and serum creatinine level of 2.37 mg/L. On the ultrasound examination of the patient's own kidneys (Fig. 1) they were described as containing numerous cysts. Some of the cysts were separated, filled with dense content and had calcified walls. Treatment with meropenem was initiated based on the urine culture presented by the patient upon admission showing the usual aetiology of ESBL-producing *K. pneumoniae*. The identified strain was fully susceptible to carbapenems. The application of the phage preparation was continued throughout the whole hospitalisation alongside meropenem. After 18 days of combined treatment, gradual remission of clinical symptoms was observed. CRP and serum creatinine level decreased to 0.82 mg/L and 1.61 mg/dL, respectively, with no leukocyturia. However, an attempt to suspend meropenem administration resulted in reoccurrence of leukocyturia and elevation of CRP. Therefore phage and antibiotic treatment was continued.

Due to recurrent episodes of UTI (12 episodes within 15 months from KTX, all resulting in hospitalisations, including urosepsis), both own kidneys presenting with cysts showing content suspected of infectious character, and ineffective earlier treatment interventions, the patient was eventually qualified for a planned resection of the own right polycystic kidney. The choice of the kidney was based on ultrasound imaging exams, a CT scan (Fig. 2) performed 7 months after KTX and patient reporting pain in the right lumbar area. The above-mentioned CT was the only one performed after KTX due to chronic graft insufficiency. The decision about the side of nephrectomy was agreed upon a day before the intervention at a meeting of radiologists who defined the right kidney as the suspected source of recurring infections. Nonetheless, the final choice was made by surgeons who decided to remove the opposite – left – kidney due to its intraoperative presentation. This procedure resulted in complete remission of the UTIs and erythrocyturia in this patient. Meropenem was administered throughout the period of the surgery whereas PT was stopped a day before (it lasted for 29 days in total).

At present, almost 3 years after removal of the left kidney and over 4 years after KTX, the patient presents neither laboratory nor clinical signs of UTIs. He has not been hospitalised ever since the left-sided nephrectomy. He undergoes regular ambulatory monitoring by a transplant specialist. Laboratory control performed around the time of writing this article showed no clinical signs of infection, no leukocyturia, no erythrocyturia, CRP within normal range and stable serum creatinine level of 1.58 mg/dL.

Discussion

In the case described above, cysts in the patient's own right kidney proved to be the main source of recurrent infections with ESBL-producing *K. pneumoniae* and of erythrocyturia. Scheduled removal of the infected organ proved to be the most successful intervention. Nonetheless, since *K. pneumoniae* strains pose serious threat due to their increasing resistance, the administration of 'last-chance' antibiotics, phage therapy as well as probiotics would be discussed here as novel or additional approaches to managing bacterial infections.

Colistin

Colistin which was administered at different points during treatment is considered a last-chance antibiotic from a group of polymyxins. It is used against infections caused by multi-drug-resistant bacteria, not-susceptible to any other antimicrobials available. Despite its wide spectrum of action, the decision to use colistin is problematic due to its neurotoxicity and nephrotoxicity [22]. The *mcr-1* gene located in a plasmid making bacteria resistant to colistin was already discovered in isolates collected from animals in 2011 (China) and first described in 2015 by Liu and colleagues [23]. Resistance to colistin, although not present in the described case, has already been reported in various bacterial cultures collected from humans [24–26]. This poses a global threat in the era of widespread national and international travels [27].

Therapy with bacteriophages (phage therapy)

Following the CT scan of the patient's urinary tract, it was suggested to perform resection of at least one of the polycystic kidneys (nephrectomy). However, the patient did not agree due to risks involved, i.e. extensive range of surgery, potential rupture of kidney cysts with hemorrhage and immunosuppression impeding recovery after such a vast procedure. Experimental therapy with bacteriophages was chosen instead. After over a year from KTX, the reported patient initiated supportive experimental treatment with phages at the Phage Therapy Unit at the Hirsfeld Institute in Wrocław, Poland. This method uses viruses to attack and destroy bacteria responsible for infection. A hundred years after the first clinical phage application by Felix d'Herelle [28] and its abandonment with the introduction of antibiotics which seemed easier to produce, stock and administer, phage therapy experiences a renaissance. Nowadays, with better understanding of its mechanism of action, immunology and procurement methods, phage therapy gets a second look [29]. In view of accelerating bacterial resistance to once effective medicines, increasing number of new studies herald phage therapies as one potential getaway from the post-antibiotic era.

The mechanism of action of phages resembles classic virus-host interaction. Phages target a concrete type of bacterium based on their surface receptors, inject their genetic material into the cell and cause destruction of the prokaryote host by massive internal reproduction [30]. They do not target eukaryotic cells [31]. While safety profiles of antibiotics have been well documented, implications of introducing phages into human body are still being examined. GI administration is a common route, although controversies exist about the transition of phages through the gut wall into the bloodstream [32, 33]. Some researchers describe beneficial impact on the human immune system thanks to phages interaction with human microbiota and gut epithelium [34]. Humoral response to phages should also be considered when planning PT, although production of anti-phage antibodies must not always correlate with good response to PT [35]. Other questions arise in the case of immunocompromised patients, although in a 2008 literature review by Borysowski J. and Górski A. [36], phage therapy was concluded safe and advisable also to patients whose own immune response is weakened. Moreover, 'transplantation' of selected phages in allotransplantation to treat acute graft-versus-host disease has been recently speculated based on the anti-infection, anti-inflammatory and immunomodulatory phage properties [36].

Currently, there are no therapies with phages officially recommended in the European Union or the United States yet the research is ongoing [38]. PTU at the Hirszfeld Institute is the first PT dedicated centre in the EU [21]. It conducts PT in outpatients based on the rules of a 'therapeutic experiment' (compassionate use) according to the relevant Polish law regulations, the Declaration of Helsinki and a PT protocol approved by the bioethics committee. Reported patient initiated his phage treatment in-between episodes of UTIs which were treated with antibiotics. It was discontinued shortly after removal of the polycystic kidney. Due to the concomitant use of meropenem, it is difficult to assess the efficacy of PT in this case. Nonetheless, it cannot be excluded that it could have helped to control the infection in the transplanted kidney as well as in the not-resected patient's own kidney. It is possible that shortly after its beginning, PT could have resulted in selection of phage resistant *K. pneumoniae* strain that required additional antibiotic application. Interestingly, a synergistic effect between meropenem and anti-*Acinetobacter baumannii* phage was recently reported [39].

It is most likely that kidney cysts were the source of infections non-penetrable to an optimal degree by either antibiotics or phages. Removing such a reservoir of infection proved to be the most effective intervention. However, subsequent and current results confirm that 29 days of phage lysate application was safe. Those results support our previous observations confirming general safety of PT, echoing results presented recently by Kuipers et al. who described a case of a renal transplant recipient successfully treated with meropenem and bacteriophages for ESBL-positive *K. pneumoniae* UTI [21; 40].

Probiotics

Probiotics and prebiotics are used to restore healthy gut microbiota in patients undergoing treatment with antibiotics. Destabilisation of the host's intestinal microbiological balance may contribute to a wide variety of disorders – from diarrhoeal infections with *C. difficile* to autoimmune diseases or neurological and psychological disorders [41]. Extensive research is ongoing to understand better the complex interlinks between general health and bacteria, fungi or viruses which naturally populate our GI

tract [42, 43]. At the same time, patients may suffer from GI dysbiosis and microbiological imbalances months or even years after a course of antimicrobials [44, 45].

The reported patient was given an 8-strain probiotic during the first described hospitalisation with two goals in mind. Firstly, in order to maintain microbiological balance in his microbiota when undergoing intensive treatment with broad-spectrum antibiotics (meropenem, colistin, linezolid). Secondly, such step was undertaken in order to help replace colonisation with VRE with beneficial microorganisms. The GI colonisation was considered eradicated upon later control. However, according to a 2018 research paper published by Zmora et al. [46], probiotics given empirically may not always bring the benefits expected. Some hosts resist the supplemented bacteria and simply eliminate them from the system. Another study published by the same team showed that optimal results were achieved with autologous fecal microbiome transplants (aFMT) where patients' microbiotas were sampled, preserved and reintroduced after antibiotic therapy was over. The gut populations returned to their pre-disruptive state within days following an aFMT intervention. In the latter study, probiotics were even hindering the process of repopulation of the GI tract with desirable microorganisms [47]. This can give a twist in how we look at one-size-fits-all commercial probiotics.

Conclusion

Kidney transplant recipients who represent a group of immunocompromised patients suffer from urinary tract infections more often than the general population. In some cases, changed anatomical site or presence of cysts may create infection reservoir and impede successful treatment interventions. This results in higher exposure to antibiotics of such patients which further promotes the emergence of drug-resistant organisms such as e.g. carbapenem-resistant Enterobacteriaceae and vancomycin-resistant Enterococci. Colistin is a last-resort antibiotic for an increasing number of patients but pathogens resistant to polymyxins have already been described. Infection as well as colonisation with multidrug-resistant organisms pose threats to all patients, especially transplant patients, therefore alternatives to complement or reduce the use of antibiotics are being explored. Administration of bacteria-specific bacteriophages, although still not confirmed in standard clinical trials, is a method which has the potential to become therapeutic choice in fight against certain types of infections. Probiotics used alongside antibiotics may help maintain microbiological balance in the patient's GI tract during and after treatment with antimicrobials. However, their efficacy varies widely. It is necessary to further research methods of decreasing our current reliance on antibiotics in view of ever evolving AMR.

Declarations

Author contributions

OR - writing the article, case analysis

RM - case analysis

DMS – collection and/or assembly of data

AG – critical revision of the article

MD – final approval of the article

All authors reviewed and accepted the manuscript.

Competing interest

AG and RM have filed patent applications for anti-bacterial use of bacteriophages. OR, DMS, MD declare no potential conflict of interest.

Data availability

No datasets were generated or analysed during the current study.

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Abbreviations

ADPKD – Autosomal Dominant Polycystic Kidney Disease

aFMT – autologous fecal microbiome transplants

AMR – antibiotic resistance

ARPKD – Autosomal Recessive Polycystic Kidney Disease

CRE – carbapenem-resistant Enterobacteriaceae

CRP – C-reactive protein

eGFR – estimated glomerular filtration rate

ESBL – extended-spectrum beta-lactamases

ESKD – end stage kidney disease

GI tract – gastrointestinal tract

KTX – kidney transplantation, kidney transplant

PKD – Polycystic Kidney Disease

PT – phage therapy

UTI(s) – urinary tract infection(s)

VRE – vancomycin-resistant Enterococci

References

1. Gospodinova, M., Todorov, I., Bakardzhiev, I. Infections in transplanted patients. *Clin Res Dermatol Open Access* 2018; 5(1): 1-5.
2. Patel, R., Paya, C.V.: Infections in solid-organ transplant recipients. *Clinical Microbiology Reviews* 1997; 10(1), 86-124.
3. Yoo, H.Y., Thuluvath, P.J. The effect of insulin-dependent diabetes mellitus on outcome of liver transplantation. *Transplantation* 2002; 74(7): 1007-1012.
4. Tovikkai, C., Charman, S., Praseedom, R., Gimson, A., van der Meulen, J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open*. 2015; 5(5): e006971-e006971.
5. Kritikos, A., Manuel, O. Bloodstream infections after solid-organ transplantation. *Virulence* 2016; 7(3): 329–340.
6. Information Bulletin 2019. [Accessed: December 2 , 2019].
http://www.poltransplant.pl/Download/Biuletyn_2_28_2019.pdf
7. Giessing, M. Urinary tract infection in renal transplantation. *Arab Journal of Urology* 2012; 10: 162–168.
8. Chuang, P., Parikh, C., Langone, A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. *Clin Transplant*. 2005; 19(2): 230-235.
9. Grekas, D., Thanos, V., Dioudis, C., Alivanis, P., Tourkantonis, A. Treatment of urinary tract infections with ciprofloxacin after renal transplantation. *Int J Clin Pharmacol Ther Toxicol*. 1993; 31(6): 309–311
10. Kahlmeter, G.: The ECO.SENS project: a prospective, multinational, multicentre epidemiological survey of the prevalence and antimicrobial susceptibility of urinary tract pathogens—interim report. *Antimicrob. Chemother*. 2000; 46(Suppl. 1):15–22.

11. Säemann, M., Hörl, W. Urinary tract infection in renal transplant recipients. *Eur J Clin Invest.* 2008;38:58-65.
12. Rice, J.C., et al. Renal allograft injury is associated with urinary tract infection caused by *Escherichia coli* bearing adherence factors. *Am J Transplant.* 2006; 6(10): 2375–83.
13. Bien, J., Sokolova, O., Bozko, P. Role of Uropathogenic *Escherichia coli* Virulence Factors in Development of Urinary Tract Infection and Kidney Damage. *Int J Nephrol.* 2012; 2012: 1-15.
14. Cervera, C., et al.: Multidrug-resistant bacteria in solid organ transplant recipients. *Clin Microbiol Infect.* 2014; 20 (Suppl 7): 49–73.
15. Len, O., Garzoni, C., Lumberras, C., Molina, I., Meije, Y. et al. Recommendations for screening of donor and recipient prior to solid organ transplantation and to minimize transmission of donor–derived infections. *Clinical Microbiology and Infection.* 2014; 20: 10-18.
16. Hand, J., Patel, G. Antimicrobial stewardship in transplant patients. *Curr Opin Organ Transplant.* 2019; 24(4): 497-503.
17. Chalmers, J.D., Akram, A.R., Singanayagam, A., Wilcox, M.H., Hill, A.T. Risk factors for *Clostridium difficile* infection in hospitalized patients with community-acquired pneumonia. *Journal of Infection.* 2016; 73(1): 45–53.
18. Vardakas, K.Z., Konstantelias, A.A., Loizidis, G., Rafailidis, P.I., Falagas, M.E. Risk factors for development of *Clostridium difficile* infection due to BI/NAP1/027 strain: a meta-analysis. *International Journal of Infectious Diseases.* 2012; 16: e768–e773.
19. Spithoven, E.M., Kramer, A., Meijer, E., Orskov, B., Wanner, C. et al: Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. *Kidney Int.* 2014; 86(6): 1244-1252.
20. Bisceglia, M., Galliani, C., Senger, C., Stallone, C., Sessa, A. Renal Cystic Diseases. *Adv Anat Pathol.* 2006; 13(1): 26-56.
21. Międzybrodzki, R., et al.: Clinical aspects of phage therapy. *Adv Virus Res.* 2012; 83: 73-121.
22. Falagas, M., Grammatikos, A., Michalopoulos, A. Potential of old-generation antibiotics to address current need for new antibiotics. *Expert Rev Anti Infect Ther.* 2008; 6(5): 593-600.
23. Liu, Y., et al.: Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases.* 2016; 16(2): 161-168.
24. McGann, P., et al: *Escherichia coli* Harboring mcr-1 and blaCTX-Mon a Novel IncF Plasmid: First Report of mcr-1 in the United States. *Antimicrob Agents Chemother.* 2016; 60(7): 4420-4421.
25. Berrazeg, M., Hadjadj, L., Ayad, A., Drissi, M., Rolain, J. First Detected Human Case in Algeria of mcr-1 Plasmid-Mediated Colistin Resistance in a 2011 *Escherichia coli* Isolate. *Antimicrob Agents Chemother.* 2016; 60(11): 6996-6997

26. Rossi, F., et al. Emergence of colistin resistance in the largest university hospital complex of São Paulo, Brazil, over five years. *The Brazilian Journal of Infectious Diseases*. 2017; 21(1): 98-101.
27. Blyth, D., Mende, K., Maranich, A., Beckius, M.L., Harnisch, K.A. et al. Antimicrobial resistance acquisition after international travel in U.S. travelers. *Trop Dis Travel Med Vaccines*. 2016; 2(1).
28. Sulakvelidze, A., Alavidze, Z., Morris, J.G. Jr Bacteriophage therapy. *Antimicrob Agents Chemother*. 2001; 45, 649-659.
29. Górski, A., et al: Phage therapy: What have we learned? 2018; 10(6). pii: E288.
30. Delbruck, M.: The growth of bacteriophage and lysis of the host. *J Gen Physiol*. 1940; 23(5): 643-660.
31. Lehti, T., Pajunen, M., Skog, M., Finne, J. Internalization of a polysialic acid-binding Escherichia coli bacteriophage into eukaryotic neuroblastoma cells. *Nat Commun*. 2017; 8(1).
32. McCallin, S., et al. Safety analysis of a Russian phage cocktail: from metagenomic analysis to oral application in healthy human subjects. 2013; 443: 187–196.
33. Międzybrodzki, R., et al. Means to facilitate the overcoming of gastric juice barrier by a therapeutic staphylococcal bacteriophage A5/80. *Microbiol*. 2017; 8: 467.
34. Górski, A., et al. Bacteriophage translocation. *FEMS Immunology & Medical Microbiology*. 2006; 46(3): 313-319.
35. Łusiak-Szelachowska, M., et al. Antiphage activity of sera during phage therapy in relation to its outcome. *Future Microbiol*. 2017; 12: 109-117.
36. Górski, A., Jończyk-Matysiak, E., Międzybrodzki, R., Weber-Dąbrowska, B., Borysowski, J. "Phage transplantation in allotransplantation": Possible treatment in graft-versus-host disease? *Front Immunol*. 2018; 9: 941.
37. Borysowski, J., Górski, A. Is phage therapy acceptable in the immunocompromised host? *International Journal of Infectious Diseases*. 2008; 12(5): 466-471.
38. Nilsson AS: Pharmacological limitations of phage therapy. *Ups J Med Sci*. 2019: 1-10. doi: 10.1080/03009734.2019.1688433.
39. Schooley, R.T., Biswas, B., Gill, J.J., Hernandez-Morales, A., Lancaster, J., et al. Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. *Antimicrob Agents Chemother*. 2017; 61(10). pii: e00954-17.
40. Kuipers, S., Ruth, M.M., Mientjes, M., de Sévaux, R.G.L., van Ingen, J. Successful treatment of chronic relapsing urinary tract infection with bacteriophages in a renal transplant recipient - a Dutch case report. *Antimicrob Agents Chemother*. 2019; pii: AAC.01281-19.
41. Hemarajata, P., Versalovic, J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol*. 2012; 6(1): 39-51.
42. Cani, P.D. Human gut microbiome: hopes, threats and promises. 2018; 67(9): 1716-1725.
43. Ding, R.X., et al. Revisit gut microbiota and its impact on human health and disease. *J Food Drug Anal*. 2019; 27(3): 623-631.

44. Jernberg, C., Löfmark, S., Edlund, C., Jansson, J. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME J.* 2007; 1(1): 56-66.
45. Dethlefsen, L., Relman, D. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences.* 2010; 108(Supplement_1): 4554-4561.
46. Zmora, N., et al. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell.* 2018; 174(6): 1388-1405.e21.
47. Suez, J., et al. Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT. *Cell.* 2018; 174(6): 1406-1423.e16.

Figures

Figure 1

Ultrasound performed 3 weeks before the planned nephrectomy. The patient's own kidneys contain numerous cysts (in the picture – right kidney). Some cysts are separated, filled with dense content and have calcified walls.

Figure 2

CT performed 8 months before the performed nephrectomy. Both left and right kidneys are shown as enlarged and remodelled by the cysts. The left kidney appears larger.