A patient presenting with cholangitis due to *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* successfully treated with intrabiliary colistine

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Abstract

Anatomical barriers for antibiotic penetration can pose a particular challenge in the clinical setting. *Stenotrophomonas maltophilia* (SM) and *Pseudomonas aeruginosa* (PA) are two pathogens capable of developing multiple drug-resistance (MDR) mechanisms. We report the case of a 56-year-old female patient with a permanent percutaneous transhepatic biliary drainage (PTBD), who was admitted to our hospital with a cholangitis due to a MDR *Escherichia coli* strain. Upon admission, culture-guided antimicrobial therapy was conducted and the biliary catheter was replaced, with poor clinical response. Subsequently, SM and PA were detected. Treatment with fosfomycin and colistine was initiated, again without adequate response. Systemic colistine and tigecycline along with an intrabiliary infusion of colistine for 5 days was then used, followed by parenteral fosfomycin and tigecycline for 7 days. The patient was then successfully discharged. This is the first case report we are aware of on the use of intrabiliary colistine. It describes a new approach to treating cholangitis by MDR bacteria in patients with a PTBD.

Introduction

The emergence of multi-drug resistant (MDR) bacteria is of growing concern worldwide. This was highlighted in particular by Rice (2008) with his well-known article describing the ESKAPE group of pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia* along with other MDR bacteria from the *Enterobacteriaciae sp* family, *Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter sp*.), which includes the most common bacteria that cause hospital-acquired infections world-wide.[1] We are particularly interested in one microorganism belonging to this group, *Pseudomonas aeruginosa*, and in another from a different genus which is not part of this group, *Stenotrophomonas maltophilia*.

P. aeruginosa is a gram-negative non-fermenting bacillus, known to degrade a wide range of organic molecules for its own nutritional processes. It is mainly an opportunistic pathogen. Its outer membrane OprF porin has an exclusion limit of 500 KDa, which confers on this bacteria its natural immunity to many antibiotics and helps promote punctual mutations of its chromosome. Other mechanisms of antibacterial resistance are the co-expression of OprD porin, which further diminishes its permeability (especially to carbapenems), and the MexEF-OprN efflux pump as well as the mutations of DNA-girase/tropoisomerase IV.[2]

S. maltophilia has recently emerged as an important global opportunistic pathogen, which, according to previous papers, represents the most worrisome threat among the unusual non-fermenting gram-negative bacilli to hospitalized patients.[3,4] It can be mainly in nutrient-poor water sources, and is frequently co-isolated with *P. aeruginosa* in cystic-fibrosis patients.[3] It is naturally resistant to many classes of antibiotics due to its low permeability, efflux pumps, antibiotic-modifying enzymes and biochemical feeding processes.[3] It is also capable of acquiring resistance via plasmids, transposons, integrons, and biofilm formation.[3] The reported mortality rate in patients who develop a clinically overt infection due to *S. maltophilia* vary from 14% to 69%.[3,4]

In three studies, the incidence of patients presenting with cholangitis caused by MDR bacteria was reported to be between 14.8% and 42% of all cases, without sub-group differentiations.[5-7] In a retrospective analysis, the MDR-related cholangitis risk factors identified were: nosocomial infection, longer hospital stay before bacteremia, previous hospitalization within 90 days, antibiotic use in the previous 90 days, prior biliary intervention, and presence of an indwelling biliary catheter.[6] In these retrospective studies *P. aeruginosa* accounted for 3% to 16% of isolates and no cases of *S. maltophilia* were reported.[5-7]

Reports on the treatment of biliary tract infections (BTI) caused by MDR bacteria are largely outdated and heterogeneous. Furthermore, identifiable mortality risk factors at 30 days in patients with bacteremic cholangitis include, among others, the use of inappropriate definitive antibiotic regimens, but not the use of an inappropriate initial antibiotic regimen, thus highlighting the importance of culture-guided therapy in these patients.[6,7] This approach was also described in patients with a percutaneous transhepatic biliary drainage (PTBD), being a very important measure, alongside mechanical source control, namely prophylactic replacement of the PTBD, in patients with long-term drainage and in patients with overt cholangitis and/or sepsis.[8]

In a recent article on two case reports of patients with cholangitis caused by *P. aeruginosa*, the serum concentrations of colistimethate and the creatinine levels were obtained sequentially. These patients received prolonged cycles of multiple antibiotics to eradicate the infection, with documented subtheurapeutic levels of colistimethate, despite well-standardized intravenous regimens. They both developed adverse effects caused by the

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use of this drug or other antibiotics.[9]

Health-care related cholangitis has been associated with a risk of ceftazidime-resistant *P. aeruginosa*, extended-spectrum β-lactamase (ESBL) producing gram-negative bacteria, third-generation cephalosporine-resistant strains, ampicillin-resistant *Enterococcus sp.*, and methicillin-resistant gram-positive cocci.[7] The authors of this report concluded that in their population, patients with a nosocomial BTI could be adequately treated with an empirical cycle of a carbapenem, piperacillin-tazobactam or an aminoglycoside, while waiting from the culture results. Furthermore, in case of a community-acquired BTI, the use of a third-generation cephalosporin and metronidazole should be considered as initial empirical antimicrobial therapy.[7]

There is only one reported case of biliary sepsis caused by *S. maltophilia.* The patient was successfully treated with intravenous tigecycline.[3] According to a worldwide collection of strains of this bacterium, susceptibility reports indicate the use of tigecycline, levofloxacin, and TMP-SMX, as potential options.[10]

Case Report

This case report refers to a 56-year-old Mexican woman, whose past medical history includes the placement of a permanent external biliary catheter following a complete stricture of a biliodigestive anastomosis (choledochojejunostomy) secondary to a biliary duct injury during a laparoscopic cholecystectomy in 2009. In the following two years, she had recurrent episodes of cholangitis by ESBL producing *Escherichia coli*, which were treated with broad spectrum antibiotic regimens in an outpatient setting. Despite this comprehensive treatment, biliary cirrhosis developed.

Symptoms began 21 days prior to her admission with general malaise, fever up to 101.8°F (38.8°C), jaundice, diminished drainage through the biliary catheter and a mild, dull pain in the right upper quadrant of her abdomen. After 5 days with no improvement, the patient saw her physician. Blood and bile were cultured and she was empirically treated with cephalexin in an outpatient setting.

Three days later, bile culture results reported ESBL producing *E. coli.* She was switched to imipenem-cilastatin for 10 days. The abdominal pain completely disappeared, but she kept having intermittent low-grade fever, nausea, poor oral tolerability, jaundice and low drainage through the biliary catheter. After the imipenem-cilastatin cycle, a new bile culture was taken and showed persistence of ESBL producing *E. coli*.

The patient was then admitted to our hospital's internal medicine ward with low-grade fever of 100.4°F (38.0°C), general malaise and exacerbated generalized jaundice. The complete blood count (CBC) showed a hemoglobin level of 11.7 g/dL, with preserved corpuscular volume and mean concentration of corpuscular hemoglobin, 137-thousand platelets per cubic millimeter, and 3.7-thousand total leucocytes per cubic millimeter, but with 54% neutrophils and 36% total lymphocytes. Total bilirubin was 124.1 mcmol/L (7.26 mg/dL), at the expense of direct bilirubin, along with significant increases in alkaline-phosphatase and liver enzymes. Creatinine was 55.7 mcmol/L (0.63 mg/dL). Ultrasound in the upper-abdominal region showed only dilation of the intrahepatic biliary tree and chronic inflammatory changes of the liver. No evidence of biliary or splenic abscess was detected.

Upon admission, the biliary catheter was replaced and the tip of the catheter and the bile were cultured again. The gram-stain showed only gram-negative bacilli. The patient was administered empirically an intravenous regimen of meropenem (1 g every 8 hours) and colistine (loading dose 370 mg, followed 12 hours later by 150 mg every 8 hours), while waiting for the culture results.

Stenotrophomonas maltophilia and *Pseudomonas aeruginosa* were isolated. *Stenotrophomonas maltophilia* proved to be resistant to TMP-SMX, and sensitive to tigecycline with a growth ratio of inhibition (GRI) of 22 mm. The *Pseudomonas aeruginosa* isolate was sensitive to carbapenems, fosfomycin (GRI 26 mm) and colistimethate (GRI 16 mm). After 5 days of treatment with meropenem and colisitine, and based on the isolate sensitivity reports, antimicrobial therapy was switched to intravenous fosfomycin (6 g every 6 hours) and ticegycline (50 mg every 12 hours) with an initial good response. However, after 72 hours, the patient had a new episode of fever and chills. New blood and biliary cultures were taken. Other sources of infection were investigated, but none was found. The bile gram-staining showed again gram-negative bacilli, and the culture report showed the same two bacteria with no changes in terms of sensitivity in the antimicrobials report.

A second PTBD replacement was performed and tigecycline plus colistine (same doses as before) were administered intravenously. Given the known poor biliary tissue penetration of the latter and the lack of clinical improvement with previous antibiotic schemes, a topic preparation was formulated with 30 mg of colistine in 2 cc of normal sterile saline 0.9%, based on a review of the literature about its intrathecal and intraventricular use, and on the authors' own experience on the use of topic colistine in treating patients with meningitis caused by MDR gram-negative rods (namely *Acinetobacter baumanii*).[11,12] Written informed consent and authorization was obtained from the patient and the preparation was administered through the biliary drainage system, closing it afterwards for 3 hours, every 24 hours.

After 5 days of this antimicrobial regimen, colistine, both systemic and topic, had to be discontinued due to a country-wide lack of supply of the antibiotic. The biliary catheter was changed once more and a 7-day cycle of fosfomycin and tigecicline was administered, after which the patient was discharged with negative bile cultures, normal white-blood cells on the CBC and complete remission of symptoms.

A total of 13 days of outpatient and 21 days of inpatient antimicrobial treatment were completed; all blood cultures were negative, and no alterations in creatinine, urine output or neurological status were presented during treatment.

After discharge, the patient was followed up every two months in an outpatient setting. No new episodes of cholangitis occurred, despite bacterobilia was documented continuously (with frequent isolations of ESBL producing *E. coli* and *Pseudomonas aeruginosa*). Her PTBD was changed prophylactically every 6 months to prevent cholangitis, without any further complications.

The bacterial detection and sensitivity reports were generated using the automated microbroth dilution system called MicroScan autoSCAN4 (Siemens Healthcare Diagnostics Inc., Erlangen, Germany), except for the sensitivity analysis for colistimethate, fosfomycin and tigecycline, which were performed with Bio-Rad antibiotic disks (Bio-Rad Clinical Diagnostics, Hercules, CA, USA).

Discussion and Conclusions

This is the first case report we are aware of on the use of intrabiliary colistine. Community -acquired cholangitis is a difficult infection to treat on its own. The reports on therapeutic options in case of multi-drug resistant bacteria in this particular anatomical site are few and heterogeneous.[6,7] The assessment of risk factors (biliary manipulation and previous infections) and pharmacokinetic considerations played a key role in the decision to use a topical treatment in this patient, since systemic colistimethate has no biliary excretion. Our case illustrates a new approach to treat cholangitis caused by MDR bacteria in patients with PTBD. Further knowledge is now being gained on the topical use of this agent in other clinical pictures, like the intra-vesical irrigation in patients with persistent urinary tract infections caused by MDR pathogens, or intrathecal and intraventricular administration in patients with *Acinetobacter baumanii* meningitis.[11-14]

However, there is no standardized consensus on how to prepare topical dilutions of colistine for irrigation. Based on the evidence presented in this case report, our approach proved an effective and safe clinical solution for our patient and could be considered in other patients with the same clinical picture.

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