CASE REPORT

Pulmonary exacerbation due to colistin-resistant *Stenotrophomonas maltophilia* in a Bulgarian cystic fibrosis patient

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In patients with cystic fibrosis (CF) lung damage secondary to chronic infection is the main cause of death. Treatment of lung disease to reduce the impact of infection, inflammation and subsequent lung injury is therefore of major importance. As *Pseudomonas aeruginosa* is the dominant pathogen in CF patients it has been the major target of all treatment strategies, possible antibiotic regimens and recommendations for years. More sophisticated antibiotic therapies introduced over the last decades have helped to improve the prognosis in cystic fibrosis, but then new multidrug-resistant pathogens emerged.

We present a case of cystic fibrosis in a 16-year-old boy with pulmonary exacerbation due to colistin-resistant *Stenotrophomonas maltophilia*. This case raises some interesting questions regarding the antibiotic policy and treatment options in our country for patients with CF and multidrug-resistant strains. Colistin is used at present in Bulgaria as a strategic last option for the CF patients but with the advent of new more drug-resistant strains therapeutic approach should change - for instance, there should be restrictions imposed on the use of levofloxacin and trimethoprim/sulfamethoxazole which are regarded as "cheap and not so potent" antibiotics suitable for any infection and use them only in strict dependence on the respective culture results.

INTRODUCTION

Cystic fibrosis is the most common lethal autosomal recessive hereditary disorder in Caucasians.¹ The prognosis of the disease is substantially dependent on the chronic respiratory infection and inflammation, a hallmark of CF.² Antibiotic therapy aims at eradicating *Pseudomonas aeruginosa*, the major bacterial pathogen in CF, after early lung infection, and improved regimens to treat chronic *P. aeruginosa* infection have played a major role in increasing median survival of CF patients to 40 years during the last decades.³ However, during the last 5 years, reported survival rates appear to have reached a plateau⁴ and one of the reasons could be the emergence of new highly-resistant non-pseudomonas strains characteristic for CF such as *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia* species⁵. In a

recently published study for respiratory bacteriology in CF patients authors found that the average annual percent change in overall prevalence and incidence significantly decreased for *P. aeruginosa* and *B. cepacia* complex; almost did not changed for *A. xylosoxidans* while in contrast significantly increased for *S. maltophilia*.⁶

CASE REPORT

We present a case of cystic fibrosis in a 16-year-old boy treated in the clinic in March 2015 for pulmonary exacerbation – fever up to 38°C, calf pain, increased cough with greenish expectoration, weight loss and fatigue. The boy was well known in the clinic, diagnosed with CF since infancy, with homozygous $\Delta F508$ mutation and a chronic *Pseudomonas aeruginosa* infection according to the Leeds definition⁷, requiring 4 to 5 intravenous

antibiotic courses per year and regular inhalation therapy with TOBI® until July 2014, when colistin® was introduced in his treatment plan, alternating with TOBI®. After hospitalization in July 2014 the patient needed oral antibiotic courses (trimethoprim/sulfamethoxazole and ciprofloxacin) in addition to the inhalation scheme and azithromycin 3 times weekly for 3 months. In March 2015 his lung function deteriorated with a forced expiratory volume in 1 s (FEV₁) of 22.4% from predicted. Blood results including urea, glucose and electrolytes and liver biochemistry were unremarkable. Erythrocyte sedimentation rate was elevated and full blood count showed signs of infection. A chest radiograph showed emphysema, bronchiectasis and new inflammation changes consistent with his known cystic fibrosis and new exacerbation. The sputum culture grew *Stenotrophomonas maltophilia* (first time for this patient). Bacterial identification was done by the BBL Enteric/Nonfermenter ID System (Becton

Dickinson). Antimicrobial susceptibility testing was performed by the E-test (LIOFILCHEM) according to the Clinical and Laboratory Standards Institute (CLSI) 2014 recommendations.⁸ For *S. maltophilia* the MIC interpretative breakpoints are available only for ticarcillin-clavulanic acid, ceftazidime, minocycline, levofloxacin, trimethoprim/sulfamethoxazole, and chloramphenicol. Other agents may be approved for therapy, but according to the CLSI, their performance has not been sufficiently studied to establish disk diffusion breakpoints.⁸ Antibigrams in a study of *S. maltophilia* (isolated from snakes) demonstrated that the most effective antibiotics against these isolates were TMP-SMX, levofloxacin, ofloxacin, colistin, and gentamicin.⁹ A combination of doxycycline and aerosolized colistin was successfully used to treat persistent *S. maltophilia* ventilator-associated pneumonia when high-dose TMP-SMX therapy was ineffective.¹⁰ Regarding colistin, the breakpoints established

Table 1. Antimicrobial results of our patient and the percentage of resistant strains towards each antimicrobial in 4 different studies. (Ref. 16, 21, 22, 29)

Antimicrobial	% Resistant strains					MIC ₅₀ (mg/liter)	MIC ₉₀ (mg/liter)	Range (mg/liter)	
	Our patient	P. Goncalves-Vidigal (2011)	P.S Gabriel (2004)	H Nazik (2007)	K. E. N. Milne (2012)			Low	High
MIN	R	NA	NA	NA	3.8	2	4	0.25	16
SXT	R	0	84	0	12.7	0.5	> 32	0.012	> 32
DOX*	R	NA	11	NA	13.7	4	16	0.5	16
CHL	R	NA	NA	NA	24.4	16	64	2	> 256
LVX	S	7.7	NA	NA	37.5	4	> 32	0.25	> 32
COL*	R	30.8	19	NA	55	8	> 256	0.125	> 256
GEN*	R	NA	65	64	84	> 256	> 256	1	> 256
TIM	R	19.5	50	NA	64.1	256	> 256	1	> 256
AMK	R	NA	NA	55	86.5	> 256	> 256	8	> 256
CIP*	R	3	85	17	73.7	16	> 32	0.5	> 32
CAZ	R	29.4	NA	45	89.6	> 256	> 256	2	> 256
TOB	R	NA	74	73	91.2	256	> 256	2	> 1024
TZP	R	NA	92	45	91.2	> 256	> 256	16	> 256
PIP	R	NA	NA	NA	100	> 256	> 256	256	> 256
IPM	R	NA	97	100	100	> 32	> 32	> 32	> 32
MEM	R	NA	92	100	100	> 32	> 32	32	> 32

NA- no data in the article

MIN, minocycline; SXT, co-trimoxazole; DOX, doxycycline; CHL, chloramphenicol; LVX, levofloxacin; COL, colistin; GEN, gentamicin; TIM, ticarcillin/clavulanate; AMK, amikacin; CIP, ciprofloxacin; CAZ, ceftazidime; TOB, tobramycin; TZP, piperacillin-tazobactam; PIP, piperacillin; IPM, imipenem; MEM, meropenem.

CLSI-approved interpretive standards for *S. maltophilia*.

* CLSI-approved interpretive standards for *P. aeruginosa*

for *P. aeruginosa* were applied.⁸ The strain was resistant to ceftazidime, ticarcillin/clavulanic acid, minocycline, trimethoprim/sulfamethoxazole and colistin, and susceptible only to levofloxacin. In **Table 1** we compare the data for our patient with the resistance level of other studies. We adjusted the therapy with levofloxacin, discontinued colistin and left only TOBI® (due to history for chronic *P. aeruginosa* infection) for inhalation.

DISCUSSION

Chronic infection is the main determinant of morbidity and mortality in individuals with cystic fibrosis (CF).⁴ The bacteria most commonly believed to be pathogenic in CF include *P. aeruginosa*, *S. aureus*, *H. influenzae*, *S. maltophilia*, *A. xylosoxidans*, and *B. cepacia* complex. It is suggested that *S. maltophilia* is a low pathogenic species as it has limited growth in sputum from chronically infected CF patients¹¹ which may be due to low O₂ availability in the endobronchial mucus in CF patients¹² caused by the intense O₂ consumption by activated PMNs¹³.

In the 1960s and 1970s, *P. aeruginosa* was initially not realized as a pathogen for CF patients and there were still reports until 1990 questioning its significance, while nowadays a huge part of the therapy in CF is targeted in eradicating and preventing this bacterium. The similarities in biofilm formation of *S. maltophilia* poses same concerns for its significance in CF.⁵ Since 2010 its presence has been also part of the monitored variables in CF patients for the registry. Data from several CF centres worldwide indicate that the prevalence of *S. maltophilia* has increased in recent years.¹⁴ Many retrospective studies show conflicting data about whether *S. maltophilia* is associated with lung function decline, but in one of the recent papers by Pompillo, its role in lung pathology is discussed.¹⁵ Chronic *S. maltophilia* infection is an independent risk factor for pulmonary exacerbation.^{16,17}

S. maltophilia exhibits intrinsic resistance to broad-spectrum antibiotics, including beta-lactams and aminoglycosides; and thus the treatment options are limited.^{18,19} Recommended antibiotics for therapy against *S. maltophilia* infections in patients with CF are minocycline, doxycycline, trimethoprim/sulfamethoxazole, colistin, and ticarcillin/clavulanic acid.¹⁶ Regarding antimicrobial susceptibility, only a few studies have performed susceptibility testing for *S. maltophilia* on samples from CF patients.²⁰ Goncalves-Vidigal *et al.* in a recent study demon-

strated that tigecycline (not available in Bulgaria) and trimethoprim/sulfamethoxazole exhibit 100% activity against *S. maltophilia*, while colistin, ceftazidime, and ticarcillin/clavulanic acid exhibited low activity against this pathogen.¹⁶ Their results are not consistent with the higher resistance rates for trimethoprim/sulfamethoxazole in USA CF patients²¹ but are in concordance with a Turkish study from 2007 confirming trimethoprim/sulfamethoxazole as the most active antibiotic (all isolates were susceptible) and levofloxacin getting the second place with susceptible 82% of isolates²².

These studies claim that colistin demonstrates limited activity against *S. maltophilia* isolates from CF patients. However, CLSI guidelines have not yet established specific breakpoints as interpretive criteria for colistin (administered through inhalation and not parenterally) against *S. maltophilia*.⁸

The case is interesting for us due to microorganism susceptibility only to levofloxacin, an antibiotic used very often even for minor infections, and resistant to all other available antibiotics on the market (including trimethoprim/sulfamethoxazole and colistin). In Bulgaria, to the best of our knowledge so far, all tested *S. maltophilia* strains were 100% susceptible to colistin [unpublished data]. This fact could be due to the very high cost of the antibiotic that should be paid by the National Health Insurance fund since April 2016²³, and up until now the patients have had to pay for it themselves, and not all of them could afford it. Also, colistin was re-introduced to our market just last year and we are using it as antibiotic of last resort in all multidrug-resistant gram-negative infections in CF patients.²⁴

Another point of concern for our patient is also the high prevalence of self-treatment with antibiotics in Bulgaria, found as acceptable from 73% of the studied representative part of Bulgarian population.²⁵ Research conducted in southern Europe indicate that between 75% and 94% of the total use of antibiotics occurs in outpatient care.²⁶ At present in Bulgaria antibiotics such as levofloxacin (our only option for the patient) and trimethoprim/sulfamethoxazole counted as “cheap and not so potent” antibiotics are widely accepted and prescribed even when not needed.²⁷ Additionally, although in 2009 in Bulgaria a strict antibiotic policy was introduced for obligatory prescription for antibiotics, recent journalistic investigation showed that buying antibiotics without prescription

in pharmacies is still easily done.²⁸

To the best of our knowledge, this is the first CF patient with isolated *S. maltophilia* resistant to colistin in Bulgaria. We will continue to monitor the patient closely in future to re-evaluate the therapy according the isolated microorganism susceptibility.

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Обострение заболевания легких в результате резистентной к колистину *Стенотрофомонас мальтофилии* (*Stenotrophomonas maltophilia*) у пациента из Болгарии с кистозным фиброзом

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Обострение заболевания легких
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колистину *Стенотрофомонас*
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monas maltophilia) у пациента
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У пациентов с кистозным фиброзом (CF), с повреждением легких, которое является вторичным по отношению к главной инфекции, это является основной причиной смертных случаев. Ввиду этого, лечение заболевания легких, направленное на сокращение воздействия инфекции, воспаления и последующего повреждения легких, имеет основное значение. Поскольку бактерия *Псевдомонас аэругиноза* (*Pseudomonas aeruginosa*) является основным патогеном у пациентов с CF, она и есть главная цель всех терапевтических стратегий, возможных режимов с приемом антибиотиков и многолетних рекомендаций. Более современные терапии с приемом антибиотиков, внедренные в течение последних десятилетий, способствуют улучшению прогноза при наличии кистозного фиброза, но наряду с этим появляются и новые патогены с множественной лекарственной устойчивостью.

Представляем случай кистозного фиброза у 16-летнего мальчика с обострением заболевания легких в результате резистентной к колистину бактерии *Стенотрофомонас мальтофилии*. Из данного случая проистекает ряд интересных вопросов относительно антибиотической политики и возможностей лечения в нашей стране пациентов с CF штаммами с множественной лекарственной устойчивостью. На данный момент лекарство "Колистин" используется в Болгарии как стратегическая последняя возможность для пациентов с CF, но имея ввиду появление новых, еще более устойчивых к лекарствам штаммов, терапевтический подход должен измениться: необходимо введение ограничений – к примеру на употребление Левофлоксацина, Триметоприма и Сульфаметоксазола, которые считаются "дешевыми и не настолько мощными" антибиотиками, подходящими для любой инфекции, с их применением в строгой зависимости от соответствующих результатов исследований посева.