Antimicrobial resistance: concerns of healthcare providers and people with CF

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Word count: 3099 words (abstract 173 words)

Key words: cystic fibrosis, antimicrobial resistance, survey

Abstract

Background: Chronic lung infections and their treatment pose risks for the development of antimicrobial resistance (AMR) in people with cystic fibrosis (PWCF). In this study, we evaluated the attitudes of healthcare providers' (HCP) and PWCF or their parents' toward AMR within the international CF community.

Methods: HCP and PWCF identified through listservs and CF-related organizations were asked to complete an AMR centered survey, with additional questions on antimicrobial stewardship (AMS) for HCP. Descriptive analyses are reported.

Results: The responding 443 HCP and 464 PWCF/Parents were from 30 and 25 countries, respectively. Sixty-two percent of HCP and 56% of PWCF stated they were "very concerned" about AMR, with *Pseudomonas spp.* and *Burkholderia spp.* considered the most concerning organisms for both HCP and PWCF/Parents. Non-tuberculous mycobacteria were of greater concern to HCP compared to PWCF/Parents. There was a discrepancy regarding AMR education to PWCF, with 80% of HCP stating having discussed this with PWCF/Parents, but only 50% of PWCF recalling such discussions.

Conclusion: These results highlight that AMR is relevant to CF HCP and PWCF internationally, indicating that educational tools and research are warranted.

INTRODUCTION

Antimicrobial resistance (AMR) broadly defined, refers to the inability of antimicrobials to effectively inhibit the growth of or kill a given microorganism.[1] AMR is increasing among microbial opportunists, which is a major concern for healthcare providers (HCP), patients, and the general public. In CF, the emergence of AMR is multi-factorial due to chronic lung infections with bacterial adaptation and to the use of chronic suppressive antibiotic therapy with additional antibiotics for exacerbations.[2,3,4,5] In CF care centers in the USA, proportions of people with CF (PWCF) with multi-drug resistant (MDR) *Pseudomonas aeruginosa* isolated from respiratory cultures has increased over time and is now 25-30%.[5] Yet, greater use of antibiotics has been historically associated with better patient outcomes in CF, making the concept of using less antibiotics to decrease AMR challenging and situation dependent.[6,7,8]

The increasing prevalence of AMR may require re-addressing antibiotic use more carefully in CF.[9] Measures to address AMR have led to the development of hospital and community antimicrobial stewardship programs (AMS) around the world.[10,11] The goals of AMS programs are to improve the treatment of infections by assisting in selection of antimicrobials, prescribing proper doses and durations, and monitoring for toxicity and other adverse effects.[12]

The AMR in CF International Working Group (funded by European CF Society, U.S. CF Foundation, CF Trust, CF Australia, and CF Canada) was created to inform the CF community on important issues related to AMR.[2,13] In order to design educational and/or treatment related interventions, it is important to understand current knowledge and attitudes of the stakeholders regarding AMR. The aim of this study was to assess the current knowledge, concerns, and educational needs of the CF community (i.e. PWCF or their parents, termed here PWCF/Parents) and HCP with regards to AMR. Further, we surveyed HCP about AMS resources in their practice environment and attitudes towards AMS.

METHODS

A subgroup of the International Working Group developed a survey to explore five topics: 1) knowledge of AMR; 2) level of concern and perceived risks; 3) perceived consequences of AMR; 4) desired information; 5) preferred information sources. HCP were asked an additional six questions related to AMS. The initial survey was pilot tested by ten internationally recruited HCP and eight PWCF from three CF centers. After modifications based on feed-back from pilot testers, the surveys (Survey Monkey) were distributed internationally to HCP and PWCF/Parents in July 2018 through the Cystic Fibrosis Foundation, the European Cystic Fibrosis Society, CF Canada, and CF Australia and were open for one month. Details of distribution and the complete survey are available in an online Supplement. Percentages were calculated as proportion of valid answers to each question. Data for sub-groups of PWCF/Parents are shown when relevant differences were noted. Descriptive statistics were performed using MS Excel and JMP®Pro 12.0.1 (SAS Institute).

RESULTS

We received responses from HCP (n=443) with various clinical roles from 30 countries, including 78% where English was the respondent's first language (**Figure 1A).** Providers were involved in pediatric care (44%), adult care (33%), or both age groups (23%). Among physicians, the majority (71%) were respirologists/pulmonologists, 5% were in infectious disease/infection control-epidemiology, and 17% were classified as "other," which included 11 general practitioners. Time engaged in the care of PWCF ranged from < 1 year to > 20 years (most common, 1-5 years (28%)) with an even distribution across the continuum. CF center sizes were evenly distributed in size, with numbers of PWCF ranging in four categories from <50 to >200; the majority reported being in centers with a size of 101-200 PWCF. Among the PWCF/Parents (n=464) who responded, 25 countries were represented and 56% lived in an English-speaking country. The majority were parents of children with CF (**Figure 1B**). Response rates for survey completion was significantly higher for HCP than PWCF/Parents (mean ± SEM. 89.8 ± 0.02% vs. 73.4 ± 0.02%,

p<0.001). Response rates did not differ across topics in either group of respondents.

Knowledge of AMR

The term antibiotic and/or antimicrobial resistance was known to all but one social worker in the HCP group (~100%) and to 96% of PWCF/Parents. Using four vignettes and allowing more than one response, 88% of HCP and 66% of PWCF/Parents selected microbiology-laboratory based definitions of AMR and 61% of HCP and 81% of PWCF/Parents chose vignettes that indicated patient response to therapy as a clinical definition. Respondents were also asked for short descriptors of the term “antimicrobial resistance”. Descriptor responses (more than one answer allowed) were categorized into the following areas: 1) bacterial mechanisms, chosen by 66% HCP and 57% PWCF/Families, with an additional 15% of HCP adding specific microbiology laboratory definitions 2) antibiotic/clinical outcomes-related definitions provided by 4% and 14% of HCP and PWCF/Parents, respectively, and 3) definitions that implicated AMR as a host-related event were given by 1% of HCP and 9% of PWCF/Parents. Nine percent of HCP and 5% of PWCF/Parents provided incomplete responses. Further, 7% of PWCF/Parents were unable to provide their own definition; these rates did not differ by primary language.

Level of concern and perceived risks

A majority of HCP (62%) and PWCF/Parents (56%) rated their concern about AMR as “very concerned”. In contrast, a single HCP and 1% of PWCF/Parents stated not being concerned about AMR. The estimated frequency of AMR in PWCF ranged from “some of the time” (48% HCW and 53% PWCF/Parents) to “most of the time” (42% HCW and 38% PWCF/Parents) to “all of the time” (9% in each group).

A majority of respondents in each group perceived AMR risk to be different in some individuals with CF compared to others. **Table 1** summarizes which situations (more than one answer allowed) or locations (single, ranked answers) were perceived as relevant. When ranking risk factors, a majority of HCP (73%) chose frequent intravenous or oral antibiotics (i.e., frequency <

every 2 months) over prolonged oral antibiotics (15%), >2 inpatient admissions per year (6%), and older age (6%). Among PWCF/Parents the majority (57%) chose frequent antibiotics over prolonged oral antibiotics (21%), >2 inpatient admissions per year (12%), and older age (10%).

Pseudomonas spp. (69%, 69%) and *Burkholderia spp.* (55%, 43%) were most concerning to HCP and PWCF/Parents, followed in frequency (52%) by non-tuberculosis mycobacteria (NTM) among HCP. Interestingly, HCP were less concerned than PWCF/Parents about *Staphylococcus aureus* in general (12% vs. 28%), but concerns for methicillin-resistant *Staphylococcus aureus* (MRSA) doubled in both groups (25% vs. 47%); MRSA infection is often highlighted in lay media and may lead to worse outcomes in PWCF.[14,15] Other organisms and distributions by country/continent are shown in **Table 2**.

Consequences of AMR

Congruence was high between HCP and PWCF/Parents for perceived consequences of AMR, including the influence of AMR on the choice of antibiotics (89% of HCP and 81% of PWCF/ Parents agree) and AMR adversely affecting life expectancy (88% of HCP and 92% of PWCF agree). There was less congruence for "AMR affects response to antibiotics" (94% of HCP and 78% of PWCF/Parents). We also asked whether "PWCF/Parents did not complete their antibiotic course as prescribed because of concerns of AMR". Among HCP, 86% did not think this occurred, compared to 77% of PWCF/Parents who stated never having not completed therapy. Parents answered "never" in 83% of cases compared to 75% of adults vs. 57% of adolescents with CF. Additionally, 16% of PWCF/Parents stated they rarely had not completed therapy, 2% stated not completing therapy often, and 1% (n=3) responded "always".

Frequency and type of AMR education

Results regarding the estimated frequency of information provided to PWCF/Parents showed a discrepancy between groups in response rate (HCP 89% vs. PWCF/F 73%, $p<0.001$), with equal distribution of missing answers within the sub-groups of PWCF/Parents. The HCP

estimated providing AMR education to PWCF/Parents at a frequency of 38%, 45%, and 17% once a year, every other visit, or every visit, respectively. Among responding PWCF/Parents, only 50% stated that they were given information about AMR, yet this differed by subgroups with 64% of adults and 63% of adolescents with CF compared to 39% of parents remembering this. Only 35% of PWCF/Parents provided an estimated frequency of AMR discussions, with once a year (61%), every other visit (32%) and at every clinic visit (7%) and those estimates were similar across PWCF/Parents subgroups.

Fifty percent of HCP provided free text answers discussing the context in which they provided AMR education. The most common situations were related to antibiotic treatment or to hospital admissions (jointly 66%), 17% discussed AMR when new or newly resistant bacteria were isolated, 9% discussed AMR as part of routine education or when prompted by PWCF/Parents, and 8% had various/other responses. PWCF/Parents stated that the following information was included (>1 option): definition of AMR (61%), infection control measures (61%), and antibiotic overuse (38%).

Responses about current resources PWCF/Parents utilized to obtain information on AMR were similar between the groups and showed that the preferred source of information was communication from their CF team (**Figure 2**). Open comments further suggested that flyers and handouts would be desired followed by national or international CF specific websites.

Expectations and attitudes towards Antimicrobial Stewardship among HCP

Response rate for the AMS questions was 86%. Available resources reported by respondents were pharmacists (69%), infectious disease consultation (65%), and local written exacerbation guidelines (55%). Fewer had a formal AMS program (39%), pre-approval process for restricted antibiotics (41%), and post-prescription feedback and audit (8%) in their institution. Most respondents perceived that choosing and dosing antibiotics appropriately and reducing AMR were the main goals of AMS (**Figure 3**). When asked whether they believed that AMS

programs preserved the activity of antibiotics, a higher proportion thought this to be true in people without CF (71%) vs. people with CF (55%). About a third stated that they didn't know whether AMS was helpful in those without CF (26%) or those with CF (34%). The effect of AMS in managing CF exacerbations was considered to be "a large impact" by 32% of HCP and "to have some impact" by 58%.Ten percent thought AMS would have "minimal to no impact". Stewardship activities considered useful during CF exacerbations included: choice of antibiotics (83%), duration of antibiotics (78%), dose of antibiotics (68%), therapeutic drug monitoring (63%), minimizing drug interactions (53%), and avoiding toxicity (50%). Nine percent of respondents stated that they did not know the benefit of AMS during exacerbations.

DISCUSSION

A survey of over 900 HCP and PCWF/Parents from over 30 countries illustrated that AMR was thought to be important to care and that responses between HCP and PWCF/Parents were largely congruent. A majority of HCPs and PWCF/Parents were "very concerned" about AMR and listed frequent use of antibiotics as the most important risk factor. A high proportion of HCP and PWCF/Parents felt that AMR affected life expectancy. Concerns about person-to-person transmission of infection as a source for AMR was listed by over 50% of respondents (PWCF/Parents > HCP) (**Table 1**). This is an important finding as such concerns may affect the likelihood of PWCF attending appointments, which was mentioned in open text by some PWCF/Parents. This also stresses the need for ongoing focus on infection prevention, education, and control measures. Interestingly, most HCPs believed they discussed AMR with PWCF/Parents; however, fewer PWCF/Parents remembered receiving this information, especially parents. This highlights the need for HCP to provide better means of education, e.g. written handouts.

A recent priority-setting exercise, involving both the lay and clinical CF communities, identified the negative effects of antibiotics (including development of antimicrobial resistance) as one of

the top research priorities.[16,17] This is consistent with answers given by PWCF in surveys conducted through the U.S. CF Foundation, where PWCF listed respiratory microorganism detection and treatment as the top research priority.[18,19] However, a central paradox of CF care is that, whilst antibiotic resistance is prevalent, there appears to be little relationship between the results of antibiotic susceptibility testing and clinical response to antibiotic treatment.[2,20,21]

Such a paradox may be compounded by historical data from U.S. CF centers showing better pulmonary outcomes with higher intravenous antibiotic use;[7,8,22] this was not seen in a more recent study using the UK CF Patient Registry.[23]

This study has limitations. Given the self-selection of respondents, they may be more aware of AMR and AMS compared to other people in professional and lay communities. The English language survey may have limited response rate among non-native English speakers in Europe; however, this did not seem to affect results by those who took the survey. Additionally, surveys were subject to recall bias and responses were restricted to the questions asked on the survey. Although the survey included 27 and 23 questions for HCP and PWCF/Parents, respectively, the response rate did not decrease towards the later questions.

Our findings imply that “road testing” of specific approaches to patient education about AMR (such as infographics and podcasts) and looking at the effectiveness of different media (social media vs. written material from the CF center) would be of particular interest. Both HCPs and PWCF/Parents would like to see research that evaluates antibiotic therapy to maximize effectiveness and avoid the emergence of resistance.[16,18,24] This may include measures to reduce the need for antibiotics, such as eradication strategies[25,26] to prevent development of persistent infection, systematically evaluating the duration of antibiotics for exacerbations (STOP2 and Ped. STOP trial)[27,28] and measures of infection prevention and control.[29] There is a need to understand how microbiologic lab testing can best inform treatment decisions as current microbiology susceptibility methods of testing may not mimic CF airways growth conditions.[30,31]

Other suggestions for AMS have recently been proposed, such as strengthening relationships between CF clinical and AMS teams, in order to consider implementing stewardship strategies.[9] The disconnect between antibiotic strategies and clinical outcomes suggest that both basic science and translational approaches are needed. As an immediate direction, HCP should enhance their discussions about AMR during CF clinic visits to educate a broader audience given that PWCF/Parents want to learn about AMR from their providers.

Acknowledgements:

The authors would like to thank the Cystic Fibrosis Foundation for facilitating research through Community Voice, the European Cystic Fibrosis Foundation, CF Canada, and CF Australia for facilitating research through their patient communities to support this work. Additionally, we would like to thank all the adults with cystic fibrosis and family members across North America, Europe, and Australasia, who participated for sharing their insights.

The authors wish to acknowledge the work of the other members of the Antimicrobial Resistance in Cystic Fibrosis International Working Group: Shawn Aaron (Ottawa General Hospital, Ottawa, Canada), Pierre-Regis Burgel (Paris Descartes University, Paris, France), Catherine Byrnes (Auckland Hospital, Auckland, New Zealand), Rafael Canton (Hospital Universitario Ramón y Cajal, Madrid, Spain), Miquel Ekkelenkamp (University Medical Center Utrecht, Utrecht, Netherlands), Peter Gilligan (UNC Healthcare, Chapel Hill, NC, USA), Alison Holmes (Imperial College London, London, United Kingdom), Helle Krogh Johansen (University of Copenhagen, Copenhagen, Denmark), Barbara Kahl (University Hospital Münster, Münster, Germany), Timothy Kidd (The University of Queensland, Brisbane, Australia), John LiPuma (University of Michigan, Ann Arbor, MI, USA), Holly Maples (University of Arkansas for Medical Sciences, Little Rock, USA), Stacey Martiniano (Children's Hospital Colorado, Aurora, USA), Susanna McColley (Children's Hospital of Chicago, Chicago, USA), Andrew Morris (University Health Netwok, Sinai Health System, Toronto, Canada), Michael Parkins (University of Calgary, Calgary, Canada), Felix Ratjen (Hospital for Sick Children, Toronto, Canada), Jason Roberts (Royal Brisbane and Women's Hospital, Brisbane, Australia), Anand Shah (Royal Brompton Hospital, London, UnitedKingdom), Pradeep Singh (University of Washington, Seattle, USA), Ranjani Somayaji (University of Calgary, Calgary, Canada), Giovanni Taccetti (Anna Meyer Children's University Hospital, Florence, Italy), Michael Tunney (Queen's University Belfast, Belfast, United Kingdom), Francoise Van Bambeke (Université catholique deLouvain, Brussels, Belgium), Kevin Winthrop (Oregon Health and Science University, Portland, USA), Edith Zemanick(Children's Hospital Colorado, Aurora, USA).

Drs. Elborn and Muhlebach and Ms. Hempstead have nothing to disclose.

Dr. Bullington reports a grant outside this work from the Cystic Fibrosis Foundation.

Dr. Smyth reports a grant and personal fees from Vertex, speaker honorariums and expenses from Teva and Novartis, and a patent on alkyl quinolones as biomarkers of pseudomonas aeruginosa infection outside of this work.

Dr. Drevinek reports personal fees from Vertex, Proteostasis, and Corbus Pharmaceuticals outside of this work.

Dr. Walters reports grants from Gilead and an Astrazeneca consultancy outside of this work.

Dr. VanDevanter reports personal fees from AbbVie, Albumedix, AN2, Aradign, Armata, Arrevus, Calithera, Chiesi USA, Cipla, Cystic Fibrosis Foundation, Corbus, Eloxx, Enbiotix, Eveo, Galephar, Horizon, IBF, ICON Clinical Sciences, Ionis, Kala, Merck, Microbion, NDA, Protalix, PTC, Pulmocide, Recida, Savara, Vast, and Vertex outside of this work.

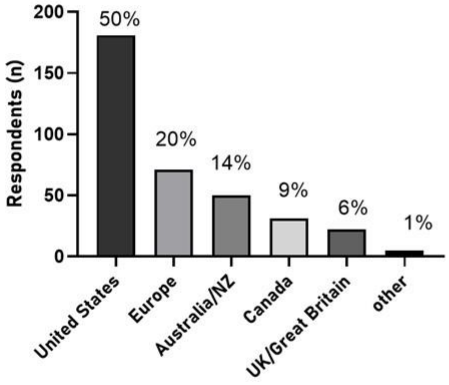
Dr. Flume reports grants outside of this submitted work from the European Cystic Fibrosis Society, the Cystic Fibrosis Foundation, Cystic Fibrosis Trust, Cystic Fibrosis Canada, Cystic Fibrosis Australia, Novartis, and Novoteris. Dr. Flume also receives personal fees from Insmed outside of this submitted work.

Dr. Bell reports grants and other support from Vertex, Galapagos, and AbbVie outside of this work.

Figure Legends

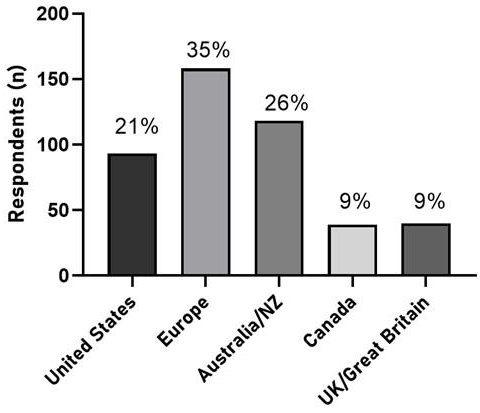
Figure 1: Characteristics of Respondents for **A)** Health care providers (HCP) showing country of current work and their role in CF care; **B**) People with CF (PWCF) with country. Fourteen did not provide a response regarding their role/connection to CF. Abbreviations: Inf Ctr = Infection control/Hospital epidemiology. Inpt = inpatient; SW= Social worker

1



Role in CF care	% of respondents
Physician	48
CF nurse specialist	16
CF pharmacist	10
Physical- Resp. therapist	9
Other (self defined)	7
Other groups (Inf. Ctrl; inpt nurse; dietician, SW, Advanced care practioner)	10

2



PWCF sub-group	% Respondents
Parent of CF child	57% of all respondents
Child is 0 - 3 years	21% of parents
Child is 4 - 6 years	17%
Child is 7 - 13 years	33%
Child is 14<18 years	28%
Adolescent (14 -18 yrs) w CF	2% of all respondents
Adult with CF	41% of all respondents
Adult 18 - 25 years	17%
Adult 26 - 35 years	41%
Adult > 35 years	82%

Figure 2: Sources where HCP perceive PWCF get information about antimicrobial resistance; and where PWCF state they get their information about AMR. Respondents checked all that applied.

Figure 3: Healthcare provider responses to questions on the goals of antimicrobial stewardship in CF. Respondents were allowed to check more than one answer.

Tables

Table 1: Perceived situational and location-specific risk factors by HCP and PWCF

Situational risk	% of respondents		Location-specific risk	% of respondents	
	HCP	**PWCF**		**HCP**	**PWCF**
Cycled inhaled antibiotics	31.5	29.3	Home	3.0	1.7
Country of residence	28.5	21.4	School or work	1.8	6.4
Frequent inpatient antibiotics	81.1	63.1	CF outpatient clinic appointment	28.2	22.0
Any hospitalization	31.9	40.5	Inpatient admissions	53.1	47.0
Frequent outpatient antibiotics	78.8	66.3	Non-CF medical appointment	7.2	9.0
Same antibiotics within 3 months	54.9	48.4	Non-healthcare crowded areas	6.7	13.9
Transmission among PWCF	51.4	56.6	Other / no response	<1	<1
CFTR mutation	16.9	17.9			
Other	5.8	5.6			

Table 1: 397 healthcare providers (HCP) and 341 people with CF (PWCF) responded to the situational risk questions. Respondents were able to choose more than one answer for situational risks. Responses to the location-specific risk questions came from 401 HCP and 345 PWCF. Only one choice was allowed for this question.

Table 2

HCP and PWCF concern by organism for AMR

Organism	Australia/New Zealand n=58		Europe n=122		USA/Canada n=239	
	% of respondents		% of respondents		% of respondents	
	HCP	**PWCF**	**HCP**	**PWCF**	**HCP**	**PWCF**
Pseudomonas	38 (66)	77 (65)	65 (53)	94 (48)	163 (68)	72 (55)
Burkholderia	28 (48)	41 (35)	63 (52)	55 (28)	115 (48)	56 (42)
Staphylococcus	5 (9)	30 (25)	11 (9)	38 (19)	32 (13)	30 (23)
NTM	32 (55)	25 (21)	55 (45)	41 (2)	114 (48)	31 (23)
MRSA	9 (16)	49 (42)	22 (18)	60 (31)	66 (28)	55 (42)
Streptococcus	0	13 (11)	1 (1)	18 (9)	5 (2)	19 (14)
Stenotrophomonas	3 (5)	8 (7)	12 (10)	10 (5)	31 (13)	7 (5)
Aspergillus	1 (2)	23 (19)	6 (5)	23 (12)	18 (8)	24 (18)
Influenza virus	0	12 (10)	1 (1)	5 (3)	3 (1)	12 (9)

Table 2: Healthcare providers' (HCP) and people with cystic fibrosis (PWCF) level of concern by organism for antimicrobial resistance (AMR) shown by continent. Percentage of respondents (%) by continent exceeds 100 as participants could choose up to two organisms. NTM – non-tuberculous mycobacteria. MRSA – methicillin resistant *Staphylococcus aureus*.

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