ANTIMICROBIAL RESISTANCE IN CYSTIC FIBROSIS

Final Report for the international Working Group/Task force

June 6, 2020

Background:

The prevalence of antimicrobial resistance (AMR) among microbial pathogens is increasing and is a high priority worldwide for interventions from antibiotic stewardship to new antibiotic development (http://www.who.int/antimicrobial-resistance/en/). Increasing AMR prevalence is driven by the widespread use of antibiotics. It is also of concern that the current antibiotic drug development pipeline has few new products and in the past 25 years there have been no new classes of antibiotics.[1] This is particularly true for antibiotics targeting Gram-negative bacteria and specific initiatives have been commenced in Europe and the USA to accelerate drug development in this area.[1]

AMR is commonly encountered in bacteria isolated from the airways of people with cystic fibrosis (CF). This is an expected finding given the high use of antibiotics in CF patients. Chronic inhaled antibiotics are standard of care in patients with chronic airway infection due to *P. aeruginosa* and are frequently used for other non-fermenting Gram-negative (NFGN) bacteria.[2,3] Long term oral and inhaled antibiotics are used to treat non-tuberculous mycobacteria (NTM) infection as well. Antibiotics are also used intermittently to treat exacerbations of lung infection and early infection with *Pseudomonas* for eradication[2,3].

However, in people with CF who have chronic airways infection, the interpretation of the significance of AMR is challenging. Traditional microbiologic teaching is that when antibiotics are used to treat a pathogen to which it is resistant based on *in vitro* susceptibility testing, there will be poor clinical outcomes.[4,5] This experience regarding AMR is derived from the treatment of acute infections, but the biology of a chronic infection is significantly different; there is frequently a discordance between *in vitro* test results and clinical outcomes. More specifically, treatment with an antibiotic to which a cultured pathogen is resistant *in vitro* does not necessarily correlate with a poor clinical outcome in patients with CF.[5] This is a particular problem in people with chronic *P. aeruginosa* and other NFGN infections.[6] There are a number of factors which may explain this discordance. AMR defined by achievable systemic drug concentrations may not be applicable to bacteria residing in sputum where significantly higher concentrations of antibiotic may be achieved by topical (inhaled) delivery.[7] Technical issues including limited sampling of bacterial colonies, significant phenotypic and variability within clonal populations, and variations in antimicrobial testing, among others, make interpretation of AMR difficult.[8,9]

These issues lead to a lack of clarity for stakeholders including people with CF, clinicians, the pharmaceutical industry, and regulatory bodies, as to the relevance of AMR and how this should influence antimicrobial drug development and usage in the treatment of CF lung disease. It is also possible that these issues are relevant to other types of chronic lung infection in other airways diseases such as chronic obstructive pulmonary disease (COPD) and bronchiectasis.

The increasing survival of people with CF will result in greater lifetime exposure to antibiotics.[10] Some bacteria are intrinsically resistant while others have acquired resistance following antibiotic

exposure.[11] Antibiotics remain a key therapeutic in CF and have likely contributed to the survival gains in the past 4 decades. Minimizing the induction of AMR by the careful use of antibiotics is important to maintain the value of current drugs and protect the value of future compounds while not compromising patient care.[12] Antimicrobial stewardship (AMS) will therefore not follow conventional practice and needs to be specifically contextualised for people with CF.

We proposed a working group to develop guidelines on the interpretation of AMR for clinical care in CF and to consider the implications of AMR on antimicrobial stewardship. This project was funded jointly by the Cystic Fibrosis Foundation, the European Cystic Fibrosis Society, CF Canada, CF NZ/Aus, and the UK Trust. This progress report is submitted to provide an update on the activities thus far.

Original Objectives

- Describe current and developing definitions and methodologies for determining antimicrobial resistance
- Understand how chronic infections differ from acute infections with respect to the microbiological assumptions regarding AMR
- Assess the value of current susceptibility testing including the frequency and timing of testing
- Offer guidance for the use of antimicrobial resistance testing in the conduct of clinical trials by the pharmaceutical industry and regulatory agencies.
- Explore how antimicrobial stewardship plays a role with respect to AMR in people with CF.
- Set key research priorities for the development of appropriate future application of AMR diagnostics to improve patient outcomes

Original Key deliverables

1. Manuscripts describing the work and consensus statements
    a. Definitions and methodologies, including role of future methods, key questions
    b. Results of systematic reviews and Delphi consensus
2. Symposium for presentation to the CF community
3. White paper with recommendations for industry and regulatory agencies

Work Accomplished:

1. We established a committee of content experts (participants listed in Appendix 1) using the following criteria:
    a. Representation of all stakeholders
    b. Respected content experts in the CF community
        i. Microbiology
        ii. Pharmacy
        iii. Clinicians (pulmonary and infectious diseases, pediatric and adult)
    c. Engagement of junior scholars.
    d. Engagement of regulatory agencies
    e. Input from patients and families
2. Conducted two face-to-face meetings.

    a. NACFC (November 2017) to establish workplan and initiate individual working groups.
    b. Artimino (September 2018) to review work completed to that point and prepare for presentation at NACFC 2018.
3. The Working Group was divided into Teams that had ongoing phone meetings on an ongoing schedule.
    a. Team 1: Established definitions used by all working groups and in all publications. This group completed the original goal and published two reviews on AMR to broaden reach to both CF and infectious disease audiences (see Appendix 2: publications, Kidd et al, Waters et al). An update was presented in a symposium at NACFC 2018, a symposium at ECFC 2019, and the American Society of Microbiology conference in 2019 (see Appendix 3: presentations).
    b. Team 2: This group completed a systematic review of the literature resulting in a published manuscript (see Appendix 2: publications, Somayaji, et al). An update was presented in a symposium at NACFC 2018 and a symposium at EFCF 2019 (see Appendix 3: presentations).
    c. Team 3: This group conducted a Delphi iterative survey of the committee to develop consensus on final recommendations, which was published in Journal of Cystic Fibrosis (see Appendix 2: publications, Zemanick, et al). An update was presented in a symposium at NACFC 2018 and a symposium at EFCF 2019 (see Appendix 3: presentations).
    d. Team 4: This was an objective added following our initial face-to-face meeting when it became apparent that we should be engaging with the antimicrobial stewardship community. This group published a manuscript in the Journal of Cystic Fibrosis (see Appendix 2: publications, Cogen, et al). An update was also presented in a symposium at NACFC 2018 and a symposium at EFCF 2019 (see Appendix 3: presentations). An invited review is currently being drafted for publication in *Infection Control and Hospital Epidemiology.*
    e. Team 5: This group was charged with engagement of patients and families. An internationally distributed survey of patients, families and healthcare providers was completed to identify key aspects that must be addressed in providing education. This group published a manuscript in the Journal of Cystic Fibrosis (see Appendix 2: publications, Bullington, et al).

<u>Future plans</u>

This Working Group has fulfilled the majority of the goals set at the beginning. More manuscripts have been published than were initially envisaged and a strategic engagement with external stakeholders, particularly in the infectious diseases disciplines, have been established. The Working Group would be interested in further discussions with the sponsors to determine if an extension of the Working Group would be considered to undertake the following tasks:

1. To engage with the pharmaceutical industry, including small and medium-sized entities (SME), and governmental stakeholders such as the regulatory bodies (FDA and EMA), BARDA, New Medicines and antimicrobial catapults and similar organisations internationally. The aim of this would be to develop a white paper charting out the context challenges and

roadmap for development of effective antimicrobial therapy in the era of highly effective modulator therapy. This would focus on the development of effective antimicrobial treatments, including formulation and delivery, minimising any effects on the development of clinically relevant AMR.

2. To develop an educational toolkit for people with CF and healthcare professionals involved in CF care and management. This would provide material for stakeholders in infectious diseases and hospital administration to provide clear rationale for the use of antibiotics, particularly long-term inhaled antibiotics.

References

1. Kostyanev T, Bonten MJ, O'Brien S, Steel H, Ross S, François B, Tacconelli E, Winterhalter M, Stavenger RA, Karlén A, Harbarth S, Hackett J, Jafri HS, Vuong C, MacGowan A, Witschi A, Angyalosi G, Elborn JS, deWinter R, Goossens H. The Innovative Medicines Initiative's New Drugs for Bad Bugs programme: European public-private partnerships for the development of new strategies to tackle antibiotic resistance. J Antimicrob Chemother. 2016 Feb;71(2):290-5.
2. Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC; Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic Fibrosis Pulmonary Guidelines: Treatment of Pulmonary Exacerbations. Am. J. Respir. Crit. Care Med. 2009 Nov;180(9):802-8.4978611.
3. Döring G, Flume P, Heijerman H, Elborn JS; Consensus Study Group. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. J Cyst Fibr. 2012 Dec;11(6):461-79.
4. Gilligan PH. Infections in patients with cystic fibrosis: diagnostic microbiology update. Clin Lab Med. 2014 Jun;34(2):197-217. doi:10.1016/j.cll.2014.02.001. Review. PubMed PMID: 24856524.
5. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, Ranganathan SC, Waters VJ, Ratjen FA. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant Staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc. 2014 Sep;11(7):1120-9.
6. Hurley MN, Ariff AH, Bertenshaw C, Bhatt J, Smyth AR. Results of antibiotic susceptibility testing do not influence clinical outcome in children with cystic fibrosis. J Cyst Fibr 2012 Jul;11(4):288-92.
7. Wenzler E, Fraidenburg DR, Scardina T, Danziger LH. Inhaled Antibiotics for Gram-Negative Respiratory Infections. Clin Microbiol Rev. 2016 Jul;29(3):581-632.
8. Waters V, Smyth A. Cystic fibrosis microbiology: Advances in antimicrobial therapy. J Cyst Fibros. 2015 Sep;14(5):551-60.
9. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, Ranganathan SC, Waters VJ, Ratjen FA. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant Staphylococcus aureus, Gram-negative bacteria, and multiple infections. Ann Am Thorac Soc. 2014 Sep;11(7):1120-9.
10. Burgel PR, Bellis G, Olesen HV, Viviani L, Zolin A, Blasi F, Elborn JS; ERS/ECFS Task Force on Provision of Care for Adults with Cystic Fibrosis in Europe.. Future trends in cystic fibrosis demography in 34 European countries. Eur Respir J. 2015 Jul;46(1):133-41
11. Sherrard LJ, Tunney MM, Elborn JS. Antimicrobial resistance in the respiratory microbiota of people with cystic fibrosis. Lancet. 2014 Aug 23;384(9944):703-13.
12. McCaughey G, Gilpin D, Elborn JS, Tunney MM. The future of antimicrobial therapy in the era of antibiotic resistance in cystic fibrosis pulmonary infection. Expert Rev Respir Med. 2013 Aug;7(4):385-96

Appendix 1: Participants

Chairs		
J. Stuart Elborn	UK	Adult clinician
Patrick A. Flume	USA	Adult clinician
Valerie Waters	Canada	Infectious diseases
Scott C. Bell	Australia	ECFS, Adult clinician
Dutch VanDevanter	USA	Facilitator
Europe		
Michael Tunney	UK	Pharmacist, microbiologist
Rafael Canton	Spain	Microbiologist
Miguel Ekkelenkamp	Netherlands	Microbiologist
Françoise Van Bambeke	Belgium	Microbiologist
Anand Shah	UK	Adult clinician/early career clinician
Pierre –Regis Burgel	France	Adult clinician
Barbara Kahl	Germany	Microbiologist
Pavel Drevinek	Czech Republic	Microbiologist
Giovanni Taccetti	Italy	Pediatric clinician
Helle Krogh-Johanssen	Denmark	Microbiologist
Alison Holmes	UK	Antimicrobial stewardship (ID)
USA		
Pradeep Singh	USA	Microbiologist
Kevin Winthrop	USA	Infectious diseases
Marianne Muhlebach	USA	Pediatric clinician
Peter Gilligan	USA	Microbiologist
John Lipuma	USA	Infectious diseases
Suzanna McColley	USA	Pediatric clinician
Wendy Bullington	USA	Pharmacist
Lisa Saiman	USA	Infectious diseases
Edith Zemanick	USA	Pediatric clinician
Stacey Martiniano	USA	Early career clinician
Holly Maples	USA	Antimicrobial stewardship (Pharm)
Canada		
Michael Parkins	Canada	Infectious diseases
Felix Ratjen	Canada	Pediatric clinician
Shawn Aaron	Canada	Adult clinician
Ranjani Somayji	Canada	Early career clinician
Andrew Morris	Canada	Antimicrobial stewardship (ID)
Australia/NZ		
Jason Roberts		Pharmacist
Tim Kidd		Microbiologist
Cass Byrnes		Pediatric clinician
Others		
Drucy Borowitz	USA	CFF, Patient/family representative
Alan Smyth	UK	Patient/family representative
Mair Powell	Europe	EMA representative
John Alexander	USA	FDA representative

Appendix 2: Publications

Flume PA, Waters VJ, Bell SC, VanDevanter DR, Elborn JS. Antimicrobial resistance in cystic fibrosis: does it matter? J Cyst Fibros 2018; 17: 687-689.

Kidd TJ, Canton R, Ekkelenkamp M, Krogh Johansen H, Gilligan P, LiPuma JJ,. Bell SC, Elborn JS, Flume PA, VanDevanter DR, Waters VJ. Defining antimicrobial resistance in cystic fibrosis. J Cyst Fibros 2018; 17: 696-704.

Somayaji R, Parkins MD, Shah A, Martiniano SL, Tunney MM, Kahle JS, Waters VJ, Elborn JS, Bell SC, Flume PA, VanDevanter DR. Antimicrobial susceptibility testing (AST) and associated clinical outcomes in individuals with cystic fibrosis: a systematic review. J Cyst Fibros 2019; 18: 233-240.

Waters VJ, Kidd TJ, Canton R, Ekkelenkamp MB, Johansen HK, LiPuma JJ, Bell SC, Elborn JS, Flume PA, VanDevanter DR, Gilligan P, on behalf of the Antimicrobial Resistance International Working Group in Cystic Fibrosis. Reconciling Antimicrobial Susceptibility Testing and Clinical Response in Antimicrobial Treatment of Chronic Cystic Fibrosis Lung Infections. Clin Infect Dis 2019; 69: 1812-1816.

Zemanick E, Burgel PR, Taccetti G, Holmes A, Ratjen F, Byrnes CA, Waters VJ, Bell SC, VanDevanter DR, Elborn JS, Flume PA. Antimicrobial susceptibility testing in cystic fibrosis: A Delphi approach to defining best practices. J Cyst Fibros. 2019 Oct 31:S1569-1993(19)30919-1. doi: 10.1016/j.jcf.2019.10.006. Online ahead of print).

Cogen JD, Kahl BC, Maples H, McColley SA, Roberts JA, Winthrop KL, Morris AM, Holmes A, Flume PA, VanDevanter DR, Waters V, Muhlebach MS, Elborn JS, Saiman L, Bell SC. Finding the relevance of antimicrobial stewardship for cystic fibrosis. J Cyst Fibros 2020; https://doi.orgf/10.1016/j.jcf.2020.02.012.

Bullington W, Hempstead S, Smyth A, Drevinek P, Saiman L, Waters VJ, Bell SC, VanDevanter DR, Flume PA, Elborn S, Muhlebach M. Antimicrobial resistance: concerns ofin healthcare providers and people with CF. J Cyst Fibros (in press).

Appendix 3: Presentations

A. NACFC November 2018: Antimicrobial Resistance in Cystic Fibrosis
    a. What do we mean by antimicrobial resistance? (Timothy Kidd)
    b. What is the clinical relevance of antimicrobial resistance? (Ranjani Somayaji)
    c. Recommendations for use of antimicrobial resistance testing in clinical practice (Edith Zemanick)
    d. What is the role for antimicrobial stewardship in CF? (Lisa Saiman)
B. ECFC June 2019: Antimicrobial Resistance in CF – are we overusing antibiotics?
    a. Introduction: defining resistance (Stuart Elborn)
    b. Managing AMR in clinical practice – consensus from clinician (Anand Shah)
    c. Resistance testing in selection of therapeutic antibiotics (Helle Krogh Johansen)
    d. Antibiotic stewardship – is it possible I NCF? (Scott Bell)
    e. AMR: what do our teams and patients know? (Marianne Muhlebach)
C. American Society of Microbiology Microbe Conference June 2019 (San Francisco, CA)
    a. Antimicrobial resistance in CF lung Pathogens: The interface of clinicians, microbiologists, pharmacists and infection preventionists (Meet the expert symposium with Valerie Waters and Peter Gilligan)