

## ANTIMICROBIAL RESISTANCE IN CYSTIC FIBROSIS

*Progress Report for the international Working Group/Task force*

March 14, 2019

### 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.<sup>1</sup> 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.<sup>1</sup>

AMR is commonly encountered in bacteria and fungi 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 other non-fermenting Gram-negative (NFGN) bacteria.<sup>2,3</sup> Long term oral and inhaled antibiotics are used to treat non-tuberculous mycobacteria (NTM) infection. Antibiotics are also used intermittently to treat exacerbations of lung infection and early infection with *Pseudomonas* for eradication<sup>2,3</sup>.

However, in people with CF who have chronic airways infection, the interpretation of AMR is challenging. Traditional microbiologic teaching is that when antibiotics are used to which the pathogen is resistant based on *in vitro* susceptibility testing, there will be poor clinical outcomes.<sup>4,5</sup> This experience regarding AMR is derived from 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.<sup>5</sup> This is a particular problem in people with chronic *P. aeruginosa* and other NFGN infections.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8,9</sup>

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.<sup>10</sup> Some bacteria are intrinsically resistant while others have acquired resistance following antibiotic

exposure.<sup>11</sup> 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.<sup>12</sup> 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 thus far:

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. Each working Group has had ongoing phone meetings on an ongoing schedule.
4. Working Group 1: Establish definitions that will be used by all working groups and in all publications. This group has completed the original goal and published a review on AMR and submitted another review (see Appendix 2: publications). An update was also presented in a symposium at NACFC 2018 and will be part of a symposium at EFCF 2019 (see Appendix 3: presentations).
5. Working Group 2: This group completed a systematic review of the literature resulting in a published manuscript (see Appendix 2: publications). An update was also presented in a symposium at NACFC 2018 and will be part of a symposium at EFCF 2019 (see Appendix 3: presentations).
6. Working Group 3: This group conduct a Delphi iterative survey of the committee to develop consensus on final recommendations. A manuscript is near completion and will be submitted to the Journal of Cystic Fibrosis. An update was also presented in a symposium at NACFC 2018 and will be part of a symposium at EFCF 2019 (see Appendix 3: presentations).
7. Working Group 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 is working on a manuscript (State of the Art review) intended to be submitted to Infection Control & Hospital Epidemiology (ICHE) as well as a planned submission to the Journal of Cystic Fibrosis. These will be intended to inform the two readerships about the special challenges of CF that are relevant to a stewardship program. An update was also presented in a symposium at NACFC 2018 and will be part of a symposium at EFCF 2019 (see Appendix 3: presentations).
8. Working Group 5: This group is charged with engagement of patients and families. An internationally distributed survey of patients, families and healthcare providers has been completed to identify key aspects that must be addressed in providing education. Two manuscripts are in preparation to present these results. Abstracts will also be submitted to ID-week and NACF 2020.

#### Next steps:

- Prepare for symposium to be presented at ECFC 2019 (see Appendix 3: presentations)
- Submit manuscripts as noted above
- Research priorities will be in Delphi manuscript
- Connect with federal medical agencies (completed work has already been sent to FDA)

#### References

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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.
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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

<b>Chairs</b>		
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
<b>Europe</b>		
Michael Tunney	UK	Pharmacist, microbiologist
Rafael Canton	Spain	Microbiologist
Miguel Ekkelenkamp	Netherlands	Microbiologist
Françoise Van Bambeke	Belgium	Microbiologist
Anand Shah	ECR	Adult 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)
<b>USA</b>		
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)
<b>Canada</b>		
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)
<b>Australia/NZ</b>		
Jason Roberts		Pharmacist
Tim Kidd		Microbiologist
Cass Byrnes		Pediatric clinician
<b>Others</b>		
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**

### *In press:*

Flume PA, Waters VJ, Bell SC, VanDevanter DR, Elborn JS. Antimicrobial resistance in cystic fibrosis: does it matter? *J Cyst Fibr* 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 Fibr* 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 Fibr* (in press).

### *Submitted:*

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. Submitted to *Clin Infect Dis*

### **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)