Effect of anti-*staphylococcal* antibiotic prophylaxis upon isolation and colonisation with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and their resistant variants in cystic fibrosis

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Short title: Antistaphylococcal prophylaxis effects in CF

Acronym: APEC

Duration of study: June 2012 – September 2012

Trial Sponsor: University of Nottingham

Funding Source: No funding sought

STUDY PERSONNEL AND CONTACT DETAILS

Sponsor: Contact name	University of Nottingham Mr Paul Cartledge Head of Research Grants and Contracts Research Innovation Services King's Meadow Campus Lenton Lane Nottingham NG7 2NR
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Study Coordinating Centre:	Child Health School of Clinical Sciences University of Nottingham

SYNOPSIS

Title	Effect of anti-*staphylococcal* antibiotic prophylaxis upon isolation and colonisation with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and their resistant variants in cystic fibrosis
Acronym	APEC
Short title	Anti-*staphylococcal* prophylaxis effects in CF
Chief Investigator	Prof Alan Smyth
Objectives	To determine the effects of anti-*staphylococcal* antibiotic prophylaxis upon patients with CF in terms of clinical and microbiological outcomes
Study Configuration	Observational cohort longitudinal study
Setting	Cystic Fibrosis Foundation Registry, UK Cystic Fibrosis Trust Registry 2002-2010
Sample size estimate	Assuming the infection prevalence of the UK is 7% and the US prevalence is 10% at age 4 years the number needed in each cohort would be US (n= 3813) and UK (n= 1271), we have over 90% power to detect a significant difference ($p<0.05$) in *S. aureus* infection between the two countries. therefore the sample size should be large enough even to detect a small difference in bacterial infection
Number of participants	For the 8 year period 2002-2010 we estimate the number of newborns diagnosed with CF and included in the registries to be – Approximately 1880 individuals for the UK CF register Approximately 7680 individuals for the US CF register
Eligibility criteria	All patients diagnosed with CF at birth and details registered on each of the registries.
Description of interventions	A comparison in the acquisition of bacteria in those in the UK who receive anti-staphylococcal antibiotics and those who do not. Parallel descriptive study of the experience of acquisition of these bacteria in the USA.
Duration of study	8-year observation period.
Outcome measures	Primary outcomes Time to first isolation of *S. aureus*, *P. aeruginosa*, MRSA and MDR-PA

	Secondary outcomes 1. Prevalence of *S. aureus*, *P. aeruginosa*, MRSA and MDR-PA in each cohort 2. Incidence of first isolation MRSA and MDR-PA 3. Number of isolates of *S. aureus* and *P. aeruginosa* in first 3 years of life. 4. To investigate the effect of bacterial colonisation on lung function, FEV_1 % predicted, BMI/Weight/Height, O_2 requirement, Hospitalisations, Death
Statistical methods	Multivariate Cox regression for primary analyses

ABBREVIATIONS

CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFT	UK Cystic Fibrosis Trust
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
IRB	Institution Review Board
MDR-PA	Multiply drug-resistant *Pseudomonas aeruginosa*
NHS	National Health Service
REC	Research Ethics Committee
R&D	Research and Development department
MRSA	Methicillin Resistant *Staphylococcus aureus*

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STUDY BACKGROUND INFORMATION AND RATIONALE

Internationally there is a considerable degree of consensus regarding the standards of care patients with cystic fibrosis (CF) should receive[1-5]. The prompt and aggressive management of infection is central to the strategy of deferring and preventing chronic lung infection[2]. Once chronic infection is established, eradication is usually not possible and there is a strong association between lung infection, morbidity, quality of life and survival[6].

The issue of antibiotic prophylaxis for *S. aureus* remains contentious. A recent Cochrane review[7] and the UK CF Trust working group recommends the use of *S. aureus* prophylaxis. However, the concern regarding the possibility of selection of resistant strains of *P. aeruginosa* prompts the Cystic Fibrosis Foundation to recommend refraining from its use.

Recently the US have experienced a rapid increase in the incidence of MRSA in the general population, with most of these infections originating in the community. Infection in patients with CF has risen correspondingly.

STUDY OBJECTIVES AND PURPOSE

We wish to determine, whether antibiotic prophylaxis for *S. aureus* confers a positive or negative outcome for patients with CF, in terms of microbiological efficacy (*S. aureus* isolation), complications (*P. aeruginosa*, MRSA and MDR-PA isolation) and clinical outcomes.

PURPOSE

PRIMARY OBJECTIVES

(1) Time to first isolation *S. aureus*,
(2) Time to first isolation *P. aeruginosa*

SECONDARY OBJECTIVES

5. Prevalence of *S. aureus*, *P. aeruginosa*, MRSA and MDR-PA in each cohort
6. Time to first isolation MRSA and MDR-PA
7. Number of isolates of *S. aureus* and *P. aeruginosa* in first 3 years of life.
8. Clinical Outcomes- Lung function, FEV_1 % predicted, BMI/Weight/Height, O_2 requirement, Hospitalisations
9. Death

STUDY DESIGN

Epidemiological observational cohort registry study

STUDY CONFIGURATION

The primary analysis will utilise the UK CF Trust Registry to compare the time to first infection, incidence and prevalence of *S. aureus* and *P. aeruginosa*. The US CFF Registry will be used to describe the incidence and time to first infection of *S. aureus* and *P. aeruginosa* in the United States.

STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

The study uses data from the two ongoing cohort registries of patients with cystic fibrosis from the United Kingdom and the United States. The analyses will commence when the data has been obtained. Both registries have been designed to track the health of people with cystic fibrosis in order to provide health care professionals and researchers information about how treatments effect people with CF and to help in the development of guidelines for treatment in order to improve health care for these patients. Patients regularly contribute data yearly and during clinical encounters.

The data capture of oral antibiotics was not recorded until 2002 in the CFF trust registry and therefore the start date of the study will be in 2002. Therefore there will be just less than 10 years of follow-up data in each of the cohorts.

Inclusion criteria

All new patients joining the registry from 2002 at birth (generally registered within 5 months of birth).

Exclusion criteria

Informed consent

Patients provide informed consent to the each of the registries prior to their inclusion in the database.

STATISTICS

Methods

The initial analysis will involve the UK CF Trust Registry to determine the time to first infection, prevalence and incidence of *S. aureus*, *P. aeruginosa,* MRSA and MDR-PA in those that do, and do not receive anti-staphylococcal antibiotic prophylaxis. The secondary analysis will involve a parallel analysis of the US CFF Registry to describe the age at first isolation, prevalence and incidence of the organisms of interest. Direct comparisons between the two populations are difficult and so the US analysis will act as a description of the experience of these infections in another setting.

For the main analyses, we will use birthdate as the start time and the follow-up time will be determined by the time to first acquisition of *S. aureus* and also time to first acquisition of *P. aeruginosa.* We will examine the data to determine if the use of antibiotic treatment changes the time to acquisition using Cox Proportional Hazard regression model. The US CFF Patient Registry does not capture anti-*Staphylococcal* prophylaxis specifically but will capture treatment of pulmonary exacerbation which, in the setting of *Staphylococcus aureus* infection, will include anti-staph treatment. In the UK sample, we will evaluate the time to acquisition in a similar model but with the additional covariate of use of anti-*Staphylococcal* prophylaxis. The proportional hazards assumption will be assessed in both models with graphic inspection and assessment of Schoenfeld residuals. Secondary analyses will examine time to acquisition of MRSA and MDR-PA; we will compare the median time to

acquisition with 95% CI's between the US and the UK. A sensitivity analyses will be conducted in those who attain a minimum of 4 cultures a year to determine if the effects are the same in this population.

The data will then be examined again using logistic, linear or Cox regression as determined by the type of outcome variable to determine how colonisation with *S. aureus* bacterial infection effect clinical outcomes (longitudinal change in weight percentile, height percentile and BMI percentile, lung function, and pulmonary exacerbation) and death. To assess the impact of colonisation on longitudinal measures of growth, nutrition and lung function, mixed effects linear regression will be employed. To assess the impact of *S. aureus* bacterial infection on exacerbation rate, a Poisson regression model will be employed. This model will be examined for over dispersion and if there is evidence of this then we will use a negative binomial response All measure of effects will be investigated for potential confounding factors. All data will be analyzed in Stata or SPSS.

Sample size and justification

In 2008 in the UK there were 235 newly diagnosed patients added to the registry[8]. Assuming a relatively stable accrual, the study population in the UK will be approximately 1880 individuals. In the US there were 960 newly diagnosed patients in 2008[9] resulting in a study population of over 7680 individuals. We will not be undertaking a direct statistical comparison between the two Registries and will use all data available.

Limitations
The background prevalence of MRSA in the USA and the UK differs, illustrated by a 6.3 fold excess community acquired MRSA bloodstream rate in the USA[10]. As a result, conclusions based on the differences between rates of isolation of MRSA in the cohorts will require consideration of these background differences. In addition, consideration must be given to other confounders including differences in environment (and the background incidence of MRSA/MDR-PA), healthcare systems and characteristics of patients in both countries.

Time to first isolation of the bacteria of interest depends upon respiratory sampling at intervals. Differences between the cohorts in frequency of respiratory sampling could influence the time at which a respiratory isolate is identified.

ETHICAL AND REGULATORY ASPECTS

The study will not commence until the Patient Registry Committee of the CFF Registry, and the University of Nottingham Medical School Ethics Committee (IRB) have approved the study protocol.

RECORDS

No patient identifiable information will be requested from the CFF Registry. Patient data is automatically given a unique identifier (CFF Patient number) at source at the Registry. Date of birth, or age at clinical encounter data will be requested so that age of acquisition of our outcomes may be calculated.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and any relevant regulatory authorities (see

above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

STUDY CONDUCT

Study conduct will be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

Study data and evidence of monitoring and systems audits will be made available for inspection as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

It is the policy of the CFF to protect patient information from unauthorized access or use at all times and to assure that this information will only be utilized, transferred, and/or stored in sanctioned and approved ways to provide the strictest confidentiality of the patients listed in the national Patient Registry database. No personal identifiable information will be used in this study.

PUBLICATION AND DISSEMINATION POLICY

Results of this study will be disseminated by way of presentation at national and international conferences and submission for publication in peer reviewed journals.

The Registry Committee may be consulted on any publications resulting from use of the requested data. This will help assure that the interpretations and conclusions of the authors are accurate and consistent with the scientific objectives initially stated in the proposal. It is helpful to the Registry Committee for you to specify all proposed collaborators/co-authors at the time of your data request.

When abstracts, exhibits, invited papers or manuscripts are prepared using the CF Patient Registry data, the work must carry a credit line to the Cystic Fibrosis Foundation. The CF Foundation requires that no individually identifiable information from the CF Patient Registry shall be included in publications, and other written products based on the data request.

When abstracts, poster presentations, or manuscripts are accepted by a scientific organization, one copy of said paper, or a suitable description of the exhibit, shall be forwarded to the CF Foundation on notice of such acceptance, together with the name of the publication or the organization accepting it, and the time and place of the scientific meeting.

At the time manuscripts are submitted for publication, the CF Foundation requires simultaneous submission of said manuscripts to the CF Foundation to provide the opportunity to review the manuscript, track use of Registry data and to verify the credit line for the CF Patient Registry.

STUDY FINANCES

Funding source

MH is funded by the Wellcome Trust by a Clinical Research Training Fellowship.

REFERENCES

1. CF Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK: Cystic Fibrosis Trust; 2001.
2. Cystic Fibrosis Trust. Antibiotic treatment for cystic fibrosis - Report of the UK Cystic Fibrosis Trust Antibiotic Working Group; 2009.
3. Flume PA, Mogayzel PJ, Jr., Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al. Cystic Fibrosis Pulmonary Guidelines: Treatment of Pulmonary Exacerbations. Am J Respir Crit Care Med. 2009 November 1, 2009;180(9):802-8.
4. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ, Jr., Willey-Courand DB, et al. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. Am J Respir Crit Care Med. 2007 November 15, 2007;176(10):957-69.
5. Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. J Cyst Fibros. 2005 Mar;4(1):7-26.
6. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol. 2002 Aug;34(2):91-100.
7. Smyth A, Walters S. Prophylactic antibiotics for cystic fibrosis. Cochrane Database Syst Rev. 2003(3):CD001912.
8. UK Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2008 Annual Report: UK Cystic Fibrosis Trust; 2009.
9. Cystic Fibrosis Foundation Patient Registry. 2008 Annual Data Report: Cystic Fibrosis Foundation; 2008.
10. Lessa FernandaÂ C, Mu Y, Davies J, Murray M, Lillie M, Pearson A, et al. Comparison of Incidence of Bloodstream Infection with Methicillin• Resistant Staphylococcus aureus between England and United States, 2006-2007. Clinical Infectious Diseases. 2010;51(8):925-8.