Early Respiratory Bacterial Detection and Antistaphylococcal Antibiotic Prophylaxis in Young Children with Cystic Fibrosis

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Abstract

Rationale: Consensus is lacking regarding antistaphylococcal antibiotic prophylaxis use for young children with cystic fibrosis. Prophylaxis is recommended in the United Kingdom, but it is recommended against in the United States.

Objectives: To test the hypothesis that antistaphylococcal antibiotic prophylaxis is associated with a decreased risk of *Staphylococcus aureus* acquisition but no increased risk of *Pseudomonas aeruginosa* acquisition.

Methods: We undertook a longitudinal observational study of children with cystic fibrosis who were recruited from birth (or from their first registry entry in the period) and followed until the age of 4 years (1,500 d) using 2000–2009 data from the UK Cystic Fibrosis Trust and Cystic Fibrosis Foundation registries. Children were excluded if they had a positive culture result for *S. aureus* or *P. aeruginosa*, or if they were receiving inhaled antibiotics, at the first encounter. Time to first *S. aureus* and *P. aeruginosa* detection in the UK/U.S. cohorts was compared using a Cox proportional hazards model. A UK-based analysis compared the same for those receiving flucloxacillin with those who received no prophylaxis. We included

the following covariates: sex, age at registry entry, dornase alfa use, genotype, and center size.

Results: The primary analysis comprised 1,074 UK and 3,677 U.S. children. The risk of first detection was greater in U.S. children than in UK children for *S. aureus* (hazard ratio [HR], 5.79; 95% confidence interval [CI], 4.85, 6.90; $P < 0.001$) and *P. aeruginosa* (HR, 1.92; 95% CI, 1.65, 2.24; $P < 0.001$). In the UK analysis, we compared 278 children receiving flucloxacillin and 306 receiving no prophylaxis. Flucloxacillin was not associated with a reduced risk of *S. aureus* detection (HR, 1.22; 95% CI, 0.74, 2.0; $P = 0.43$), but it was associated with an increased risk of *P. aeruginosa* detection (HR, 2.53; 95% CI, 1.71, 3.74; $P < 0.001$). None of the covariates significantly affected the risk estimate in either analysis.

Conclusions: The risk of first detection of *S. aureus* and *P. aeruginosa* was greater in the United States than in the United Kingdom. In the United Kingdom, the risk of first *P. aeruginosa* detection was increased among those receiving flucloxacillin compared with those who received no prophylaxis. These observational findings should be examined in randomized controlled trials.

Keywords: cystic fibrosis; children; antibiotics; prophylaxis; infection

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The hallmark of cystic fibrosis (CF) lung disease is increased susceptibility to chronic endobronchial infection (1). *Staphylococcus aureus* is the most common respiratory pathogen in infants and young children with CF (2), the detection of which is independently associated with lower respiratory tract inflammation (3). In the United Kingdom, prophylactic antibiotics are administered with the aim of preventing infection with *S. aureus* (4). U.S. registry data for young children with CF show a prevalence of 60 to 70% for *S. aureus* and a prevalence of around 20% for *Pseudomonas aeruginosa* (5). In the United Kingdom, comparable registry figures are 14% for *S. aureus* and 21% for *P. aeruginosa* (6).

Internationally, the issue of antibiotic prophylaxis for *S. aureus* is controversial (7–9). The evidence supporting the use of antistaphylococcal therapy is summarized in a Cochrane review whose authors concluded that although prophylaxis appeared to reduce the detection of *S. aureus*, no effect on clinical status was observed, and the significance of the increased rate of *P. aeruginosa* detection seen in one trial was uncertain (10). Nevertheless, the Cochrane review (10) and the UK Cystic Fibrosis Trust working group (4) recommend the use of *S. aureus* prophylaxis until 3 years of age. In contrast, concerns regarding the possibility of the emergence of *P. aeruginosa* and uncertainty regarding clinical benefit prompted the Cystic Fibrosis Foundation in the United States to recommend against prophylaxis (9). As a result, *S. aureus* prophylaxis is in general not practiced in the United States.

Our objective in the present study was to test the hypothesis that antistaphylococcal antibiotic prophylaxis confers a positive microbiologic outcome for children with CF (prolongation of the time to first *S. aureus* detection), without an increase in microbiologic complications (reduced time to first detection of *P. aeruginosa*).

Methods

We aimed to identify the first occasion when *S. aureus*, *P. aeruginosa*, and methicillin-resistant *S. aureus* (MRSA) was detected for each child and to describe the time to first infection for each cohort. The registry committees of the UK Cystic Fibrosis Trust Registry and the Cystic Fibrosis Foundation

in the United States approved the requests for data. The institutional review board at the University of Nottingham Medical School approved the protocol.

The Registries

We retrieved data for 2000–2009 inclusive from the UK Cystic Fibrosis Trust Registry and the Cystic Fibrosis Foundation National Patient Registry. In the U.S. registry, data from each clinical encounter are entered into the registry (see Figure E1 in the online supplement). The UK registry, however, documents annual data. As a result, clinical encounters of the year are reviewed and summarized at the annual review, traditionally in the child's birth month. It is the date of the annual review and the detail of the annual summary that are recorded in the registry.

To make the U.S. registry data as equivalent as possible to the United Kingdom's for the primary (United Kingdom vs. United States) analysis, we annualized the U.S. data by condensing the encounter-level data into a single record per calendar year. This was achieved by identifying the encounter nearest to the child's birthday. For the variables of interest, this entry summarized the activity in the previous year. This is described in more detail in the online supplement.

Study Population

Our cohorts comprised children with a diagnosis of CF enrolled in the registries before the age of 1,500 days (approximately 4 yr). We chose the age of 4 years to maximize the time for children to have a bacterium isolated from their respiratory samples, 1 year beyond the time period that UK guidelines recommend antistaphylococcal antibiotic prophylaxis be used. Routine practice in the United Kingdom is for children to have a respiratory sample taken at each clinical encounter (four to six times per year), and in the United States, samples are taken quarterly. We excluded children with *S. aureus* (methicillin susceptible or resistant) or *P. aeruginosa* isolates at their first registry encounter. We excluded those receiving inhaled tobramycin or colistin at their first registry encounter, because these children were likely to have already acquired *P. aeruginosa*. We also excluded those children with only one registry entry.

We unexpectedly identified a cohort of children in the United Kingdom who were

documented as not receiving antibiotic prophylaxis. As a result, we were able to undertake two analyses.

Analyses

In the primary analysis, we evaluated the time to first detection of infection in children with CF in the United Kingdom (where *S. aureus* prophylaxis is recommended until 3 years of age) and the United States (where *S. aureus* prophylaxis is not practiced in the first 3 yr of life). We were also able to undertake a secondary analysis evaluating time to first infection with *S. aureus* and *P. aeruginosa* among children in the United Kingdom recorded as receiving flucloxacillin prophylaxis versus no prophylaxis. There were a number of children in the UK registry recorded as receiving a number of different oral antibiotics given over a prolonged time, making it unclear whether these were prophylactic antibiotics. We therefore limited the analysis of prophylactic antibiotics in the United Kingdom to children in whom the same chronic antibiotic—or no antibiotic—was recorded over 2 successive years. Owing to the small number of children who consistently received an antibiotic other than flucloxacillin, these children were also excluded. Thus, the final comparison was between those who received flucloxacillin and those who received no prophylaxis.

Analytic Methods

For the survival analyses, failure time was defined as the time to first detection of *P. aeruginosa* or *S. aureus*, respectively. Children not acquiring these organisms during follow-up were censored either at the last data entry before the age of 1,500 days or at the end of the study (December 31, 2009) for those not reaching the age of 1,500 days. We determined whether country (United States/United Kingdom) or the use of antibiotic prophylaxis (for the UK-based analysis) was associated with the time to first detection using a Cox proportional hazards regression model after confirming that the proportional hazards assumptions were not violated on the basis of Schoenfeld residuals. Potential confounding factors (sex, age at registry entry, dornase alfa use, genotype [homozygous Phe508del, other] and center size) were included if they individually resulted in a 10% or greater change in the estimate (11). Kaplan–Meier plots were

constructed to illustrate the survival analysis.

We undertook several sensitivity analyses to detect any effects of decisions made in the protocol on the final results. These are described in the online supplement. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used for reporting (12). All data were analyzed with Stata/SE version 12 software. The protocol is available in detail in the online supplement.

Results

Primary Analysis Cohort Derivation and Characteristics

For the years 2000–2009, there were 2,325 individuals in the UK registry and 11,002 individuals in the U.S. registry younger than 1,500 days old at registry entry. After excluding children who were receiving inhaled tobramycin or colistin at the first annualized registry entry ($n = 474$ in the United Kingdom; $n = 1,589$ in the United States), those in whom *S. aureus* or *P. aeruginosa* was detected at their first entry ($n = 272$ in the United Kingdom; $n = 5,104$ in the United States), and those with only one registry entry ($n = 505$ in the United Kingdom; $n = 745$ in the United States), the final study cohort consisted of 1,074 UK children and 3,564 U.S. children (Figure 1). As shown in Table 1, the characteristics of children included in and excluded from the final cohorts, as well as those of the UK and U.S. cohorts, were similar with the exception of a much higher prevalence of dornase alfa use in the United States.

Primary Analysis: Comparison of Detection of Bacteria between United Kingdom and United States

The risk of first detection of *S. aureus* (methicillin-sensitive *S. aureus*) was significantly greater in the U.S. cohort than in the UK cohort (hazard ratio [HR], 5.79; 95% confidence interval [CI], 4.86, 6.90; $P < 0.001$) (Figure 2). Similarly, the risks of first detection of *P. aeruginosa* (HR, 1.92; 95% CI, 1.65, 2.23; $P < 0.001$) and MRSA (HR, 5.66; 95% CI, 3.35, 9.57; $P < 0.001$) (Figure 2) were significantly greater in the United States than in the United Kingdom. None of the model estimates were changed by 10% or more following inclusion of sex,

CF genotype, dornase alfa, or age at registry entry as covariates.

To determine if the method of cohort selection exerted a significant effect on the results, a sensitivity analysis was conducted that included all children younger than 1,500 days old. Another sensitivity analysis was performed to determine if the direction of effect changed over the time period of the study by comparing the periods 2000–2004 and 2005–2009. For both sensitivity analyses, the estimates of the HRs were similar to the original analyses (see online supplement).

Secondary Analysis: UK-based Comparison of Flucloxacillin versus No Prophylaxis

Of all the 2,325 children in the UK registry, 1,696 children were documented to have received a consistent regimen (either a consistent antibiotic class or no chronic antibiotics). Of the 1,074 children included in the UK cohort of the UK/U.S. analysis, 470 were excluded from this secondary analysis owing to inconsistent antibiotic prophylaxis ($n = 442$) or consistent use of prophylaxis with an antibiotic other than flucloxacillin ($n = 28$). We included 604 children with 2 or more years of data in the analysis, of whom 326 received flucloxacillin and 278 received no prophylaxis (Figure 1).

Distribution of prophylactic antibiotic use by center was examined (Figure E2) and demonstrated a spectrum of use across centers. The characteristics of the UK cohort, comparing those included with those excluded from analysis, are shown in Table 2.

Time to First Detection of *S. aureus* and *P. aeruginosa*

Sixty-four children experienced their first *S. aureus* culture detection during 1,023.9 person-years at risk. Flucloxacillin use was not associated with risk of first detection of *S. aureus* (HR, 1.22; 95% CI, 0.74, 2.0; $P = 0.43$). One hundred thirteen children had their first *P. aeruginosa* detection during 970.7 person-years at risk, with those receiving flucloxacillin having a significantly increased hazard (HR, 2.53; 95% CI, 1.71, 3.74; $P < 0.001$) compared with those receiving no prophylaxis. There was no association detected between prophylaxis use and detection of MRSA (HR, 1.57; 95% CI, 0.1, 25.2; $P = 0.75$). Inclusion of sex, age at entry to the registry,

dornase alfa use, genotype, and center size as covariates did not significantly affect the risk estimates for any of the models.

Sensitivity Analysis

To determine if the results of the UK-based analysis were similar to those with the most complete data of those children up until the age of 3 years (as per UK guidance regarding duration of prophylaxis) and to consider if time trends exerted an effect over the duration of the study, further sensitivity analyses were conducted, the results of which were not significantly different from the original results (presented in the online supplement).

Discussion

To our knowledge, this study is the first observational study to examine the effect of *S. aureus* antibiotic prophylaxis in infants with CF on microbiologic outcomes using “real-world” data, and it furthers the debate regarding risks and benefits. In this retrospective study describing the first detection of *S. aureus* and *P. aeruginosa* in the United Kingdom and the United States, we found that the risk of first detection of both organisms is significantly increased in the United States compared with the United Kingdom. Unexpectedly, we discovered a cohort of children in the United Kingdom who were not documented to be receiving antistaphylococcal antibiotic prophylaxis. We therefore undertook an analysis of a cohort of children in the United Kingdom who either consistently received flucloxacillin or received no prophylaxis. We found that flucloxacillin use does not appear to be associated with a reduced risk of first detection of *S. aureus*. However, flucloxacillin use does appear to be associated with an increased risk of first detection of *P. aeruginosa*.

Our findings differ from the conclusions of authors of a Cochrane review who found that antistaphylococcal prophylaxis resulted in a reduction in the proportion of children isolating *S. aureus* (10). The Cochrane review considers only randomized controlled trials, which may in part explain this difference. Furthermore, only two of the included studies involved flucloxacillin, and both of these were open-label studies comparing continuous flucloxacillin

Figure 1. Illustration of derivation of cohorts for comparisons of 1) United Kingdom versus United States and 2) UK flucloxacillin versus no prophylaxis. MRSA = methicillin-resistant *Staphylococcus aureus*.

prophylaxis with “as-required” arms instead of placebo. Researchers in the only double-blind randomized trial of antibiotic prophylaxis used cephalexin and saw a delay in detection of *S. aureus* but an increase in detection of *P. aeruginosa* (13), an observation that is consistent with our data. An Australian observational study using bronchoalveolar lavage–based microbiological sampling found that co-amoxiclav (amoxicillin-clavulanate) antibiotic prophylaxis use was not

associated with detection of either *P. aeruginosa* or *S. aureus* (14), though there was a nonsignificant excess of *P. aeruginosa* isolates in the prophylaxis group. It is possible that the Australian study did not have sufficient power to detect a significant difference.

There is a contradiction that lies within these data: In the United States (where antibiotic prophylaxis is not administered), the risk of first detection of *P. aeruginosa* is greater than in the United Kingdom. Yet,

when examining the UK data, we observed that those administered prophylaxis have a reduced time to first *P. aeruginosa* infection compared with those not given prophylaxis. It is likely that the observed differences in risk of detection of *P. aeruginosa*, *S. aureus*, and MRSA between the United States and United Kingdom are due to differences in ecological conditions in the two countries (e.g., very different rates of microbial colonization in the general and CF populations and major differences in the

Table 1. Baseline characteristics of UK and U.S. registries before and after cohort selection

	All Children Aged <1,500 d at Registry Entry (n [%] or Median [IQR])		Included in Final Cohort (n [%] or Median [IQR])	
	United Kingdom	United States	United Kingdom	United States
No. of subjects	2,325	11,002	1,074	3,564
Male	1,169 (50.3%)	5,512 (50.1)	562 (52.3%)	1,806 (49.3%)
Female	1,156 (49.7%)	5,490 (49.9)	512 (47.7%)	1,758 (50.7%)
Age at entry, d	475 (351, 975)	352 (319, 717)	381 (225, 691)	354 (322, 718)
Diagnosed by screening/PNS	815 (35.1%)	3,550 (32.3%)	417 (38.8%)	955 (26.8%)
BMI z-score	0.4 (−0.3, 1.1)	0.3 (−0.5, 0.9)	0.36 (−0.5, 1.1)	0.26 (−0.5, 1.0)
Dornase alfa (ever in first 1,500 d)	158 (6.8%)	4,157 (37.8%)	71 (6.6%)	1,171 (32.9%)
Homozygous Phe508del*	1,271 (54.7%)	5,094 (46.3%)	588 (54.8%)	1,665 (46.7%)

Definition of abbreviations: BMI = body mass index; IQR = interquartile range; PNS = prenatal screening.

Cohorts comprise those included in UK/U.S. analysis as percentage (IQR) for children up to just over 4 years of age (1,500 d).

*Percentage of total, including those with missing or unknown genotype data after annualization of U.S. data.

healthcare systems) rather than to any association with staphylococcal prophylaxis. In fact, the finding of a significantly earlier age of first detection of *S. aureus* in the United States than in the United Kingdom is not surprising, given the previously identified threefold greater annual prevalence of methicillin-sensitive *S. aureus* and an eightfold greater annual prevalence of MRSA in U.S. CF centers than in the United Kingdom (15). The

nasopharyngeal carriage of *S. aureus* among healthy children in the United Kingdom is unknown, whereas such carriage has been reported to be as high as 48% in the United States (16) and 36% in the Netherlands (17).

It is known that more sampling opportunities provide a greater chance of isolating an organism should it be present. The European Cystic Fibrosis Society and UK Cystic Fibrosis Trust standards of

care suggest that patients should be seen every 1–3 months (7, 8); however, although this may be commonplace for young children, anecdotally the true frequency of visits is likely to lie at the upper end of the range. In the U.S. dataset, where data from every clinic visit are documented, the median gap between visits for children under 4 years (1,500 d) old was 53 days (interquartile range, 28–89 d). The more frequent sampling in the United

Figure 2. Kaplan-Meier plot of time to first acquisition of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA) in the United Kingdom and the United States, truncated at 3 years. CI = confidence interval.

Figure 3. Kaplan-Meier plot of time to first acquisition of *Staphylococcus aureus* and *Pseudomonas aeruginosa* by prophylaxis use in the United Kingdom, truncated at 3 years. CI = confidence interval.

States could have contributed to the observed higher detection rates, but again they are unlikely to explain the entire effect.

Owing to the differences in the way data are recorded in the two registries, namely that the U.S. data consist of encounter-based data, whereas the UK data consist of an annual summary of the previous year, an immortal time bias (a period of time where it is not possible to detect a bacterial isolate) could exist. We annualized the U.S. data to minimize this

source of bias. The size of the observed effect, in combination with the significant differences between prevalence of infection in the two countries, suggests that immortal time bias is unlikely to account for all the observed differences.

One potential explanation for the increased risk of *P. aeruginosa* infection among those receiving flucloxacillin in the UK analysis is reverse causation—that patients were actually receiving *treatment* of persistent symptoms rather than prophylaxis. If that were the case, these

individuals would have been sicker, with more structural lung disease, and consequently at increased risk of *P. aeruginosa* infection. The fact that *S. aureus* detection rates were similar between these two groups argues against reverse causation to some degree.

In the earlier years of the UK registry, a substantial proportion of individuals had incomplete data (29% in 2001). However, the proportion with incomplete data has steadily decreased over time (11% incomplete in 2014). Our sensitivity analyses suggest that changes in the completeness of data did not have a significant effect on our findings. The time period of this study (2000–2009) includes a period when newborn screening was not widely implemented in either the United Kingdom or the United States. Furthermore, microbiological laboratory techniques may have changed. These factors may limit the generalizability of our findings.

The polymicrobial nature of CF lung infection is increasingly appreciated (18). Those with good lung function host greater lung microbial diversity than their counterparts with poorer lung function or who experience frequent exacerbations (19, 20). The effect of prophylactic antibiotics on this complex ecosystem is unknown. This question is particularly significant, given that the effect of intravenous antibiotics on the microbiome appears to be limited in terms of quantitative microbiology but significant in terms of bacterial diversity (20, 21). It may be that chronic exposure to prophylactic antibiotics disrupts the fecal and/or respiratory microbiome, providing a favorable ecosystem for opportunistic bacteria such as *P. aeruginosa*.

Table 2. Baseline characteristics of children included in and excluded from UK comparison

	No Prophylaxis	Flucloxacillin Prophylaxis	P Values between Included Groups	Excluded	P Values for Included vs. Excluded Groups
No. of subjects	278	326	—	1,721	—
Male	159 (57.0)	167 (50.9)	0.16	843 (49.0)	0.04
Age at entry, d	410 (277, 773)	383.5 (270, 699)	0.06	547 (359, 1,085)	<0.001
BMI z-score	0.46 (−0.47, 1.20)	0.37 (−0.46, 1.08)	0.47	0.44 (−0.29, 1.15)	0.52
Dornase alfa (ever in first 1,500 d)	18 (6.5%)	21 (6.4%)	1.0	119 (6.9%)	0.78
dF508/dF508*	151 (54.3%)	179 (54.9%)	0.94	941 (54.7%)	1.0

Definition of abbreviation: BMI = body mass index.

Data are presented as count (percent) or median (interquartile range).

*Percentage of total including those with missing or unknown genotype data.

The large numbers of children from the two countries providing data to the registries is a significant strength. One important limitation of our study is that it relies on oropharyngeal and cough swabs, which are known to have relatively low sensitivity and specificity for lower airway infection (22, 23), particularly because *S. aureus* colonization of the upper airways of healthy children is common (16). Thus, our results describing upper airway cultures may not be generalizable to lower airway infection. We also do not have adherence data in either registry.

Given these limitations, these data should be interpreted with caution. Nevertheless, these results will be concerning to those who endeavor to postpone the age at which infection with either *S. aureus* or *P. aeruginosa* is first

acquired. Infection with *S. aureus* in the 1960s and 1970s had a devastating effect in young children. However, the improved management, standards of living, nutrition, and subsequent survival of children with CF is such that the spectrum of disease seen in this earlier era does not reflect the current situation (24). This might mean that the balance of risks and benefits of staphylococcal prophylaxis has changed: The tenet of “first do no harm” appears to be apt.

A randomized controlled trial of antistaphylococcal prophylaxis in the United Kingdom has commenced (<http://www.nets.nihr.ac.uk/projects/hta/142223>). The trial will address the biases of the previous studies. It will also be important in the future to determine the effect of such antibiotic administration on the flora of the

lungs of young children with CF to explain the findings of the randomized controlled trial in microbiological terms. ■

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