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Staphylococcus aureus in cystic fibrosis: problem bug or an innocent bystander?

A common organism

Staphylococcus aureus is a commonly encountered organism in day-to-day living. However, the epidemiology is complicated by three different patterns of carriage. Up to 60% of the population hosts the organism at any one time and, while ~20% are considered "persistent carriers" due to their status of being continuous hosts of the same strain, a further 20% never host *S. aureus* and so are considered non-carriers [1]. *S. aureus* is commonly encountered in childhood with nasopharyngeal carriage among healthy children as high as 48% in the USA [2] and 36% in the Netherlands [3]. *S. aureus* carriage varies markedly by occupation, as do the proportions of those who carry antibiotic resistant strains (methicillin-resistant *S. aureus* (MRSA)) [1].

Epidemiology

In children with cystic fibrosis (CF) infection rates appear to vary considerably over time. The direction of this change appears to be locality specific: *S. aureus* infections have risen dramatically in the USA over time from 30% in 1990 to 60% in 2016 [4]. This is supported by a randomised trial in the USA from 1987 to 1989, reporting 30.4% of infants in the placebo group had *S. aureus* isolated from the respiratory tract [5]. Data for the UK over the same time period is less easily obtained, but appears to show the opposite trend. In 1994 Weaver *et al*. [6] reported a randomised trial of anti-staphylococcal antibiotic prophylaxis in 38 babies where 60% of babies in the non-prophylaxis group had *S. aureus* cultured from their respiratory tract. The Cochrane review [7] reports data from the Chatfield study (1991) in which 37% of children in the placebo group cultured *S. aureus*. Current data from the UK CF Registry suggest that the proportions of children in whom *S. aureus* is detected is reducing, with 16% of 0–3 year-olds and 23.7 of 4–7 year-olds documented as having intermittent *S. aureus* infection in the UK [8].

Infection rates also vary considerably by country. While comparisons of infection rates between countries is wrought with methodological difficulties, significant differences between the UK and USA have been reported in terms of age at first infection [9], and a three-fold greater annual prevalence of methicillin-sensitive *S. aureus* and an eight-fold greater annual prevalence of MRSA in US CF centres compared to those in the UK [10].

Rates throughout Europe appear equally varied; however, direct comparisons are complicated by the markedly different population size of patients and registry coverage rates of patients in each country. The European Cystic Fibrosis Society Patient Registry

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(2015) reports the proportion of children with chronic *S. aureus* infection by country. This varies from as low as 8% in the UK to 68% in Latvia [11]. In adults with CF, *S. aureus* infection rates appear to reduce with increasing age through adulthood [4, 8].

Infection or respiratory commensal?

While it is established that *S. aureus* is a relatively common organism isolated from patients with CF, the role that *S. aureus* plays in influencing respiratory health is less clear. The main challenge in this regard is determining true infection from colonisation. As implied by the high carriage rates in the healthy population, not all isolation from the upper respiratory tract represents lower respiratory tract infection. The paucity of evidence supporting any particular approach for managing *S. aureus* infection in young children is acknowledged [12].

Microbiology

In vitro and animal model studies suggest that those with CF exhibit dysregulated inflammatory responses to *S. aureus* [13] and the organism may even survive within macrophages [14]. *S. aureus* is equally implicated in early lung damage in such studies [15] and detection is independently associated with lower respiratory tract inflammation [16].

Just as *Pseudomonas aeruginosa* may select a mode of growth to promote chronic infection, so may *S. aureus* by selecting for small colony variants (SCVs). SCVs are part of the regular growth cycle, but, under particular conditions, this phenotype may predominate and form a persistent, intracellular, infection in the host through intrinsic antibiotic resistance without evoking the host immune response [17].

There is also an increasing body of literature that describes the complexities of co-infection with *S. aureus* and *P. aeruginosa*. Unfortunately, much of this is contradictory. There is evidence to suggest that, within the competitive niche of the CF lung, *P. aeruginosa* may force *S. aureus* to use a suboptimal metabolism strategy that eventually renders *S. aureus* unviable [18]. However, others have shown similar competitive strategies exhibited by *P. aeruginosa* may actually confer a survival benefit to *S. aureus*, protecting it from the effects of commonly used aminoglycoside antibiotics [19].

Clinical effects of infection

Chronic infection with *S. aureus* is similarly difficult to understand. High bacterial density, frequent exacerbations, evidence of inflammation (elevated interleukin-6 levels), presence of *S. aureus* SCVs and co-infection with *Stenotrophomonas maltophilia* appear to be particular risk markers for more severe lung disease [20]. SCVs appear to be a particular risk for worse lung function in the paediatric age group [21]. Illustrating the complexity, however, in another series *S. aureus* infection in the absence of other infections appeared to be a marker for more mild disease [22].

Can we prevent infection, and is there a cost?

In terms of management, the first consideration is whether prevention of infection in young children is both possible and confers benefit. The Cochrane review, which considered four trials of which one was a double-blind randomised controlled trial, concluded that fewer children receiving prophylaxis had a positive isolate of *S. aureus* [7]. The clinical consequences of this remain unclear. The only double-blind randomised trial of antibiotic prophylaxis used cephalexin and observed a delay in detection of *S. aureus*, but an increase in detection of *P. aeruginosa* [5]. This competing tension has led to differing approaches internationally [23–25]. In the UK, anti-staphylococcal antibiotic prophylaxis in the form of flucloxacillin, is recommended for the first 3 years. In the USA, prophylaxis is recommended against.

An Australian observational study using bronchoalveolar lavage-based microbiological sampling found that co-amoxiclav (amoxillin–clavulanate) antibiotic prophylaxis use was not associated with either detection of *P. aeruginosa* or *S. aureus* [26], although an excess of *P. aeruginosa* isolates was noted in the prophylaxis group. Continuous anti-staphylococcal prophylaxis was associated with increased isolation of *P. aeruginosa* in an analysis of German CF Registry data [27] and more recently flucloxacillin was associated with an increased risk of earlier age of first *P. aeruginosa* detection [9].

Calls for an adequately powered randomised controlled trial of anti-staphylococcal antibiotic prophylaxis have been made for at least 20 years [28]. Fortunately, the CF-START trial (www.nets.nihr.ac.uk/projects/hta/142223; https://doi.org/10.1186/ISRCTN18130649) is now underway and so an answer to this critical question should be available to inform practice in the future.

MRSA

MRSA may be of particular concern as this has been associated with an increased rate of decline in lung function (as measured by forced expiratory volume in 1 s) [29] and an increased risk of death [30]. The potential for eradication of newly acquired MRSA infection has recently been demonstrated [31, 32], although the clinical sequelae of this has yet to be

demonstrated. Unfortunately evidence to support eradication of chronic MRSA infection is currently lacking [33].

A pragmatic approach, but more evidence is needed

When confronted with a positive *S. aureus* isolate in a patient with CF, management decisions are difficult and so largely dependent on the individual circumstances and clinical condition. The pragmatic approach to early infection in young children is to treat positive cultures as they present; acknowledging that in upper airway cultures the potential for treating an upper airway commensal is high. Equally, the approach to managing the first MRSA isolate should be to attempt eradication with an approach that appears to be effective [32].

The questions of what are the optimal approaches for prevention of early infection and how best to manage patients with chronic infection remain accompanied by considerable uncertainty. One comfort is that we should have the answer to at least one of these questions in the near future.

Conflict of interest

None declared.

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