Sugar sweet and deadly?

The recent report by Bartholdson *et al.* (2008) demonstrating production of large amounts of exopolysaccharide (EPS) by organisms of the *Burkholderia cepacia* complex (Bcc), which changed the phenotype from non-mucoid to mucoid when the bacteria were exposed *in vitro* to a variety of sugar alcohols including mannitol, fructose and sucrose, raises a worrying scenario. Mannitol as an inhaled therapy appears to increase the hydration of airway secretions and thus promote airway clearance, with demonstrated improvements in lung function (Jaques *et al.*, 2008; Minasian *et al.*, 2007). As Bartholdson and colleagues highlight, cystic fibrosis (CF) patients infected with Bcc have been excluded from the clinical trials of mannitol in order not to confound results, given the potential adverse impact of some of these strains on lung function decline. In Australia, 4.1 % of all CF individuals are infected with Bcc, but the prevalence rises with increasing age (Australian CF Data Registry Report 2005). Similar or higher prevalence of Bcc infection has been reported from Europe, the USA and Canada (Lambiase *et al.*, 2006). The obvious concern is that despite the findings of Bartholdson and colleagues, mannitol will be prescribed in Bcc-infected patients. The large multi-centre studies of hypertonic saline (Elkins *et al.*, 2006) and azithromycin (Saiman *et al.*, 2003) have also excluded patients with Bcc infection; however, these treatments are now frequently prescribed in this patient population (unpublished observations). Interestingly, strains of the more virulent ET12 strain of *Burkholderia cenocepacia* did not produce EPS following growth on mannitol, and the critical determinant here appears to be the *bce* gene cluster, with ET12 strains possessing an 11 bp deletion that prevented *bce* upregulation by mannitol and thus EPS production. Paradoxically therefore, mannitol may not be of great concern when administered to patients infected with the ET12 strain, but

may have adverse consequences when used in the setting of what are generally considered less virulent strains.

The other consideration from a microbiological perspective prompted by the study of Bartholdson and colleagues is the impact of increased sugar moiety availability to Bcc in the setting of CF-related diabetes (CFRD). To our knowledge, no comprehensive longitudinal study has been undertaken of the impact of CFRD on Bcc infection. Insulin therapy for CFRD has been shown to improve lung function and nutritional indices as well as reduce the prevalence of positive sputum cultures for *Streptococcus pneumoniae* and *Haemophilus influenzae*, suggesting that abnormal glucose homeostasis may promote infection in CF (Lanng *et al.*, 1994). Assessment of sugar moieties has not been undertaken in CF sputum, but levels of fructose and other sugar alcohols are elevated in the serum of patients with diabetes and are likely to be similarly increased in airway secretions in patients with CFRD, providing a favourable substrate for bacterial growth (Kawasaki *et al.*, 2002). The findings of Bartholdson and colleagues would also suggest that the lungs of patients with CFRD may promote bacterial virulence, i.e. EPS production by Bcc. Careful analysis of the impact of CFRD on CF patients with Bcc infection is required but will need international collaboration to ensure sufficient patient numbers to provide statistical power. New therapies such as mannitol will require close scrutiny in patients with Bcc infection, although the evidence indicates that this therapy will be of benefit in those infected with *P. aeruginosa*, who

constitute the vast majority of the CF population.

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Charles J. Dorman, Editor-in-Chief

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Sugar sweet and deadly: author's response

Drs Reid and Bell provide thoughtful and informative comments on our recent report (Bartholdson *et al.*, 2008), which describes the production of exopolysaccharide (EPS) in the presence of mannitol, and other sugar alcohols, by the *Burkholderia cepacia* complex (Bcc). My co-authors and I are grateful for these insights. We would also point out that the

role of EPS in the pathogenesis of Bcc may demonstrate additional idiosyncrasy and subtlety in these organisms relating to a suggested similarity between the Bcc and the characteristic conversion to a mucoid, alginate-producing phenotype observed in *Pseudomonas aeruginosa* during the chronic stages of infection in individuals with cystic fibrosis (CF). In our study, we were initially surprised to observe a lack of EPS biosynthesis in the highly virulent *Burkholderia cenocepacia* ET12 lineage. However, as we suggested, loss of mucoidy in *B. cenocepacia* isolates could provide a striking contrast with the pathogenesis of *P. aeruginosa*. Zlosnik *et al.* (2008) recently observed that isolates of *B. cenocepacia* are frequently non-mucoid, and also a surprising mucoid to non-mucoid conversion in sequential isolates from chronically infected patients. As they suggest, Bcc EPS could be responsible for the persistence of Bcc in CF airways, whilst loss of EPS could lead to enhanced

virulence. The influence of this change in EPS phenotype on mannitol therapy in individuals with CF, including CF-related diabetes, is unclear.

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