

## Antimicrobial susceptibility testing of *Burkholderia cepacia* complex (BCC)

### The organism

The *B. cepacia* complex (BCC) is a group of closely-related species that are ubiquitous in nature and found particularly in soil and water.<sup>1-4</sup> Clinically they are predominantly associated with chronic pulmonary infection in patients with cystic fibrosis, but may also cause infections in immunocompromised patients, including those with Chronic Granulomatous Disease.

### Antimicrobial resistance

BCC are resistant to many antimicrobial agents. A lack of binding sites on the lipopolysaccharide of BCC leads to intrinsic resistance to the cationic antimicrobials, polymyxins and aminoglycosides.<sup>5</sup> BCC can also be resistant to many or all available  $\beta$ -lactams due to a combination of impermeability and inducible chromosomal  $\beta$ -lactamases.<sup>6,7</sup> Apart from intrinsic low outer membrane permeability,<sup>8</sup> at least one efflux pump system has been described that confers intrinsic resistance to tetracycline, chloramphenicol and ciprofloxacin.<sup>9</sup> The potential presence of these resistance mechanisms means that multiple drug resistance is common. In one study, 50% of isolates were resistant *in vitro* to all 10 commonly used agents tested.<sup>10</sup>

### Treatment

A recent Cochrane Systematic Review concluded "There is a lack of trial evidence to guide decision making and no conclusions can be drawn from this review about the optimal antibiotic regimens for cystic fibrosis patients with chronic *Burkholderia cepacia* complex infections. Clinicians must continue to assess each patient individually, taking into account *in vitro* antibiotic susceptibility data, previous clinical responses and their own experience."<sup>11</sup> Unfortunately, evidence to describe a relationship between the *in vitro* susceptibility to any specific antimicrobial agent and clinical outcome is lacking. This is due to a potential mismatch between the *in vivo* and *in vitro* expression of resistance as BCC are known to exist in biofilms *in vivo*, and may also invade and survive inside airway epithelial cells and macrophages.<sup>12</sup> Also BCC is frequently treated as a mixed infection, with combinations of antimicrobials, so that it can be impossible to correlate the outcome with specific activity of a particular antimicrobial agent against BCC.

### Antimicrobial susceptibility testing

It is not currently possible to establish MIC breakpoints for BCC organisms as:

- There is no evidence to describe a relationship between MIC and outcome.
- BCC is frequently part of a mixed infection
- The MIC distribution of BCC for relevant antimicrobials is wide and encompasses the non-species related pharmacodynamic breakpoint. Therefore the epidemiological cut-off value cannot be used to define the wild-type population as either susceptible or resistant.

Susceptibility testing methodology is problematic:

- MIC determination by the ISO broth microdilution (BMD) method with Mueller-Hinton broth yields reproducible results.
- MIC determination by the gradient strip method is less reproducible than BMD.

- The correlation between the MIC by the ISO BMD method and disk diffusion zone diameters is poor when tested by EUCAST (on MH agar) or BSAC (on Isosensitest agar) methods.

### Recommendations

While the ISO BMD method may give reproducible MIC results (gradient MIC and disk diffusion methods are not reproducible), it is currently not possible to recommend susceptibility testing of BCC organisms to guide patient therapy.

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