



Antimicrobial Susceptibility Testing of *Burkholderia cepacia* complex

The organism

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

Antimicrobial resistance

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

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.”¹¹ Unfortunately evidence to describe a relationship between the *in vitro* susceptibility of any specific antimicrobial 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.¹² 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 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 cannot be used to define the wild-type population as susceptible or resistant.

Methodologically, susceptibility testing is problematic:

- MIC testing by the ISO Broth Microdilution (BMD) method using Mueller-Hinton broth yields reproducible results.
- The results from Gradient strip testing are less reproducible.
- The correlation between ISO BMD MIC and disc zone diameters is poor when testing by EUCAST (MH agar) or BSAC (Isosensitest agar) methods.



Recommendations

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

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