Candida and antibiotic-associated diarrhoea

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ABSTRACT

The role of Candida in antibiotic-associated diarrhoea (AAD) has been controversial for many years. Since Candida exists physiologically in the gastrointestinal tract, the presence of small numbers of Candida organisms in stool has therefore been considered normal, and thus non-pathogenic. Increased Candida counts have been linked to the development of diarrhoea in antibiotic-treated patients. However, recent findings have not confirmed this. To date, there is no convincing evidence that Candida may cause AAD in adults.

Keywords Antibiotic-associated diarrhoea, Candida, diarrhoea, therapy

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The role of Candida spp. in antibiotic-associated diarrhoea (AAD) has been controversial for many years. Reported cases of AAD associated with Candida that responded to antifungal treatment, and the presence of high faecal counts of Candida (≥10⁵ CFU/mL stool) in patients with AAD, supported this association. However, the publication of a few anecdotal case reports of suspected Candida-associated AAD failed to establish convincingly that Candida may be a causative agent of AAD [1–4], and several recent studies have attempted to elucidate the relationship between Candida spp. and AAD in more detail.

A study involving 395 patients, with or without diarrhoea, and independent of antibiotic treatment, investigated the presence and numbers of Candida spp. in stool. It was shown that the rates of isolation of Candida from faeces and Candida overgrowth in AAD patients did not differ from those of patients without diarrhoea who were also taking antibiotics. Candida overgrowth among patients with diarrhoea who were not taking antibiotics was less frequent than among AAD patients, but the frequency of Candida isolation was the same. In control subjects without diarrhoea who were not taking antibiotics, the frequencies of Candida isolation and overgrowth were less common than in all the other groups. Exploratory analysis using different cut-off values for the definition of Candida overgrowth (10³, 10⁴, 10⁵, 10⁶ or 10⁷ CFU/mL stool) yielded qualitatively similar results: in all calculations, Candida overgrowth was significantly less common in the control group than in all the other groups [5]. It was suggested that the decrease of bacteria in the stool, caused by either antibiotic therapy or dilution in watery stools, resulted in increased counts of Candida [5].

It has also been hypothesised that a fungal toxin or toxin-like substances may cause AAD [1,3,6]. Candida produces two main virulence factors, namely secreted aspartyl proteinases (Saps) and phospholipases, and both virulence factors have been investigated recently to determine their possible role in AAD. All strains of Candida albicans obtained from AAD patients and controls produced Saps, with no significant difference in the amount produced between the two groups [5]. In addition, the production of phospholipase by faecal Candida isolates from patients with AAD did not differ from that of controls [7]. It can be concluded from these studies that the major fungal virulence factors, Saps and phospholipase, are not responsible for AAD in adults.

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Another study, prompted by the presence of elevated *Candida* counts in AAD patients, investigated the faecal environment and its influence on the growth of *Candida* spp. Physiologically, the indigenous microflora forms a dense layer of mucus that competes successfully with yeasts for adhesion sites, and produces inhibitor substances such as short-chain fatty acids and secondary bile acids. *C. albicans* adhesion is reduced and the growth of *Candida* is suppressed further by the competition for growth-limiting nutrients [8–10]. It was shown [11] that the superior growth of *Candida* in stool fluid from AAD patients, compared to that from healthy subjects, was caused by a reduction in soluble growth-inhibiting factors (e.g., short-chain fatty acids and secondary bile acids) for *Candida*, and increased availability of growth and nutrient factors for the indigenous microflora. The study demonstrated that a normal intestinal bacterial microflora is important in maintaining a balanced intestinal micro-ecology with low counts of *Candida*. It has also been shown that a reduction, by itself, in the population of certain anaerobic bacteria, plus the subsequent reduction in the metabolism of undigested fibre and starch to short-chain fatty acids (in particular, butyrate), causes AAD [12].

The theory that *Candida* may cause AAD was also based on studies concerning antifungal treatment and anecdotal case reports of rapid abatement of gastrointestinal symptoms following antifungal therapy. However, the design of most of these studies did not include controls, and the reports are based on small numbers of investigated patients. In one study, five of seven patients with *Candida* overgrowth and AAD were treated successfully with nystatin [1]. In another study, two of nine patients with AAD and *Candida* overgrowth received nystatin, and their stools solidified within 6 days [4]. Among a further ten patients with diarrhoea and *Candida* in their stools, all responded to nystatin treatment [3]. However, two of these ten patients did not have AAD, and four patients had received antibiotic treatment with clindamycin, which is known to cause soft stools and diarrhoea in up to 25% of cases [13]. In the remaining patients, other causes of diarrhoea (e.g., post-radiation colitis, toxic or pharmacological effects of antibiotics) were not excluded.

Large trials comparing rates of *Candida* isolation among antibiotic-treated patients, with and without diarrhoea, have been undertaken to clarify the role of *Candida* in AAD. The resulting data show that both antibiotic therapy and diarrhoea itself are responsible for increased faecal counts of *Candida* [5,11], which leads to the conclusion that the increase is a result of antibiotic treatment or diarrhoea (leading to disturbance of the indigenous intestinal microflora and short-chain fatty acids) rather than a cause of AAD. The fact that the fungal toxins Saps and phospholipase are not responsible for AAD in adults has been established [5,7], and there is no convincing evidence to date that *Candida* overgrowth can cause AAD in adults.

REFERENCES