Trends in Microbiology

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Review

Involvement of Bacteria Other Than *Clostridium difficile* in Antibiotic-Associated Diarrhoea

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Antibiotic-associated diarrhoea (AAD) is a common and unintended consequence of antibiotic use. *Clostridium difficile* is the most common infectious aetiology of AAD; however, only approximately 25% of all AAD cases are associated with *C. difficile* infection, with the aetiology in the majority of cases remaining undetermined. Numerous other bacterial infectious agents have been implicated in AAD, including *Clostridium perfringens*, *Staphylococcus aureus*, and *Klebsiella oxytoca*. AAD is a complex disease that is influenced by the host, the infectious agent involved, and numerous clinical factors, including antibiotic treatment regimes. This review re-examines AAD and presents current perspectives on this disease, with a particular focus on the current understanding of bacterial causes other than *C. difficile* and the virulence factors involved in pathogenesis.

Antibiotic-Associated Diarrhoea: A Current Perspective

For almost a century, the treatment of bacterial infections has largely relied on antibiotics. Consequently, antibiotic resistance has emerged as one of the most serious health threats worldwide. In the USA, over 2 million people annually acquire serious infections with bacteria that are resistant to at least one of the antibiotics used to treat them, with at least 23 000 deaths resulting from these infections (http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf). Many more of these people die from other conditions that are complications of an antibiotic-resistant infection (http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf). One such complication is AAD, which often results from the unintended disruption of the protective gut microbiota, leading to opportunistic infection and diarrhoeal disease. Although this review focuses on infectious AAD, there are also several noninfectious mechanisms of AAD pathogenesis, including the direct toxicity of antibiotics, and metabolic alterations related to dysbiosis caused by antibiotic treatment [1].

C. difficile is the most common known AAD cause, accounting for most fatal cases [2]. However, only approximately 25% of cases can be attributed to this bacterium [3]. Several other infectious aetiologies have been identified, including *C. perfringens*, *S. aureus*, and *K. oxytoca* (Table 1, Key Table) [4–21], although often an infectious aetiology cannot be identified.

The focus of research on AAD has thus far been on *C. difficile*. However, the surprisingly low recovery rate of *C. difficile* as the AAD causative agent, coupled with the present worldwide interest in antibiotic resistance, gut health, microbiota and dysbiosis, has broadened the context and perspectives on AAD research. With this increasing global interest in AAD, more clinical evidence is becoming available to support a role for other bacterial pathogens in disease.

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C. difficile is the main infectious cause of AAD but only causes up to 25% of all cases. In the majority of AAD cases, no infectious aetiology can be determined, suggesting unknown infectious or non-infectious causes.

C. perfringens, *S. aureus*, and *K. oxytoca* have been identified as other infectious causes of AAD. However, due to inadequate screening and epidemiological analysis, data supporting the prevalence of non-*C. difficile* bacterial pathogens in AAD is lacking.

Clinical and research efforts have begun to examine non-*C. difficile* AAD pathogens. This has included specific mechanisms relating to gut dysbiosis, bacterial pathogenesis, and the host response in AAD. This increased understanding of AAD will undoubtedly lead to better clinical outcomes.

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Key Table

Table 1. A Comparative Analysis of Antibiotic-Associated Diarrhoea (AAD) by Known Associated Bacterial Pathogens

	Clostridium difficile	*Clostridium perfringens*	*Staphylococcus aureus*	*Klebsiella oxytoca*
AAD Isolate Features				
Associated Strain Characteristics and Toxins	Toxins: toxin A (TcdA), toxin B (TcdB)	Type A strains; Toxin: CPE (plasmid-encoded)	MRSA strains; Toxins: SEs, LukED leucotoxin	Toxin: Tilivalline
Toxin Mechanisms	Glycosylation of small Rho GTPases	Pore-formation, disruption of tight junction proteins	SEs: superantigenic, nonspecific T cell activation; LukED: pore-formation, immune cell death	Unknown
Clinical Features				
Diarrhoea	Mild to severe diarrhoea	Loose watery stool, possibly containing blood and mucus	Large volume diarrhoea, greenish in colour	Bloody diarrhoea
Endoscopy	Colitis with pseudo-membranes	Not known	Enterocolitis with dilation & fluid accumulation. Small intestine: pseudo-membranes; Colon: wall thickening, diffuse mucosal hyperaemia	Right-sided haemorrhagic colitis with hyperaemia
Primary Implicated Antibiotics	Clindamycin; cephalosporins; fluoroquinolones; broad-spectrum penicillins	Broad-spectrum penicillins; cephalosporins; co-trimoxazole; trimethoprim	Fluoroquinolones; cephalosporins	β-lactams; fluoroquinolones
Other Implicated Drugs	PPI	PPI	Not known	Not known
Risk of Relapse?	Yes	Yes	Not known	Not known
Animal Infection Model	Yes	No	No	Yes
Laboratory Diagnosis	Detection of toxin production, genes, and cytotoxicity (primarily of TcdB)	Detection of CPE production and *cpe* gene	Culture, detection of SE production (commercial methods not available for all SEs)	Culture, commercial biochemical tests, detection of cytotoxicity
Treatment	Discontinuation of inciting antibiotics and supportive care			
	Metronidazole; vancomycin; faecal microbiota transplantion	Metronidazole	Vancomycin; faecal microbiota transplantion	No other treatment generally necessary

Risk Factors for AAD

Antibiotic treatment is important for the development of AAD, and is integral to its diagnosis. However, there are several other factors that have also been associated with an increased risk of AAD. The role of antibiotics and other risk factors are discussed below.