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IN THIS ISSUE

Burkholderia cepacia: a Complex Problem for More than Cystic Fibrosis Patients

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Abstract

It is always surprising to find that an organism we know only from the clinical laboratory is a "player" in other venues. Therefore, it was with some fascination that we learned that *Burkholderia cepacia*, long known as a pathogen in cystic fibrosis patients, is also the number one organism isolated from product recalls. We recount the story of this amazing organism, which has a place in the clinical, agricultural, and pharmaceutical sectors.

Burkholderia cepacia, formerly *Pseudomonas cepacia*, has long been linked to causing infections in cystic fibrosis (CF) patients [1]. It is surprising to find, therefore, that *B. cepacia* is the number one microorganism involved in product recalls. It is particularly a problem for non-sterile products. Here, we examine the diversity and versatility of *B. cepacia* and the breadth of problems it can cause [2].

B. cepacia has a multi-faceted story as a human pathogen; it is also an environmental contaminant, particularly of non-sterile pharmaceutical products [3] and a biocide used in the agricultural industry for bioremediation [4]. It is so adaptable to low-nutrient environmental conditions that it can consume practically any carbon source in its environment. Thus, *B. cepacia* can support itself under conditions that would kill almost any other organism.

In 1992, the organism, formerly known as *Pseudomonas cepacia*, was renamed *Burkholderia*. The name was given in honor of Walter H. Burkholder, who first identified the microorganism as the cause of rot of onionskin (*cepacia* is Latin for "like onion") [5].

B. cepacia Complex in Human Infection

There are actually 18 genomovars in the *B. cepacia* complex [6]. They have been uncovered since the advent of phenotypic and newer molecular methods used to place organisms in their proper taxonomic categories. *B. cepacia*, *Burkholderia multivorans*, and *Burkholderia cenocepacia* are the most important species involved in human infection. Although most human infections from *B. cepacia* are connected to CF, *B. cepacia* also causes endocarditis, catheter-associated urinary tract infections, septic arthritis, peritonitis, wound infections, and intravenous-catheter-associated bacteremias. Most infections occur in persons with underlying health issues [4]. It has also been reported as the causative agent of "foot rot" in U.S. troops training in swampy areas of northern Florida or at war in the Mekong Delta in Vietnam. In its most severe presentation, about one-third to one-half of CF patients die of "*cepacia* syndrome," a rapidly fatal necrotizing pneumonia [5].

The organism is difficult to eradicate because of its resistance to multiple antibiotics [6]. Similarly, *B. cepacia* is intrinsically resistant to a wide range of disinfectants, including chlorhexidine gluconate, benzalkonium chloride, cetylpyridinium chloride, citric acid, diazolidinyl urea, hydrogen peroxide, lactic acid, methylparaben, potassium sorbate, prophyparaben, sodium citrate, and sodium hypochlorite [5,7,8].

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Identification of *B. cepacia*

B. cepacia organisms are free-living, non-fermenting Gram-negative rods typically found in soil and water. They have a characteristic dirt-like odor. Their laboratory identification is complicated by the fact that most commercial systems fail to identify *B. cepacia* [9]. Isolates are commonly misidentified as *Burkholderia gladioli*, *Stenotrophomonas maltophilia*, or *Ralstonia* spp. [5]. There are several important biochemicals to identify *B. cepacia* [6]. Key biochemical methods include the oxidase test (positive), as well as utilization of lysine decarboxylase and ONPG (*ortho*-nitrophenyl-β-galactoside). MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight mass spectrometry) has also been used successfully for the identification of *Burkholderia* spp. [6].

Oversight of Pharmaceutical Products

All products are supposed to be manufactured under "good manufacturing practices" whether sterile or non-sterile [5]. The FDA requires manufacturers to define each product's necessary quality criteria. This is part of the FDA's quality initiative and is called Quality by Design. Product recalls are handled by the FDA's Division of Manufacturing and Product Quality, which is part of the Center for Drug Evaluation and Research (CDER). Within CDER, the Division of Manufacturing and Product Quality monitors manufacturer quality. *B. cepacia* is the most frequently isolated bacterial contaminant in pharmaceuticals (Table 1) [3]. In general, microbial contamination includes Gram-negative rods, Gram-positive cocci, yeasts, and molds. However, among all these organisms, *B. cepacia* is the number one species isolated. Between 2004 and 2011, 37/77 (47%) Gram-negative-rod contaminants were *B. cepacia*; among all organisms, 36/103 (34%) were *B. cepacia* [7]. This finding is undoubtedly because *B. cepacia* is found in water and many manufacturers do not consider the water source as a potential reservoir. That and other reasons for contamination of pharmaceutical products are shown in Table 2. In the case of *B. cepacia*, with its propensity to form biofilms and ability to survive in the presence of preservatives, any break in technique can result in its contaminating any pharmaceutical. What should the manufacturer consider when deciding how to manufacture a product? The most important points are shown in Table 3.

Table 1. Cases of *B. cepacia* contamination involved in FDA recalls[a]

Baby and adult wipes
Nasal spray
Anticavity rinse
Skin cream
Cosmetics
Soaps
Eyewash
Alcohol-free mouthwash
Surgical prep cloths
Electrolyte solution
Radiopaque preparations
Hair dyes
Albuterol nebulizers
Children's liquid Tylenol
Povidone-iodine

[a] Adapted from references 14 to 23.

Recent Cases

The CDC recently reported a multistate outbreak of *B. cepacia* infections occurring in primary ventilated patients in hospital intensive care units; the patients did not have CF, which makes the *B. cepacia* infections that much more unusual [10]. The CDC subsequently reported that *B. cepacia*-contaminated docusate may have been the vehicle in at least one state. Docusate is a stool softener commonly aerosolized in intubated patients. At the same time of the multistate outbreak in the United States, an outbreak of *B. cepacia* in Adelaide, Australia, at South Australia's Royal Adelaide Hospital was linked to a tainted mouthwash, Chlorofluor Gel

Table 2. Reasons for contamination of pharmaceutical products[a]

Inadequate cleaning procedures
Use of an unsuitable type of water to clean equipment, e.g., use of potable water for cleaning, which can have as much as 1,000 CFU of bacteria/ml
Poor maintenance of water systems
Lack of scheduled maintenance
Lack of proper sanitization
Failure to perform quality control on water system at recommended intervals
Poor water system design, e.g., stagnant water in dead leg, which allows biofilm development
Inadequate testing of raw materials, e.g., inadequate microbiological analysis; contaminated raw materials
Inadequate procedures, e.g., improper storage of raw materials; inadequate sterilization of final product
Inadequate validation of environmental monitoring of critical product surfaces and equipment

[a] Adapted from reference 5.

Table 3. Criteria to be evaluated prior to deciding how to manufacture any product[a]

How the product will be used, e.g., topical application, injection, intravenous infusion
Nature of product, i.e., whether it has preservatives, should be sterile, or is nonsterile
Who is the intended recipient, i.e., neonates, infants, elderly, immunocompromised
Effect if the patient has a particular disease, infection, or accompanying organ damage
Effect of accompanying immunosuppressive agent

[a] Adapted from reference 5.