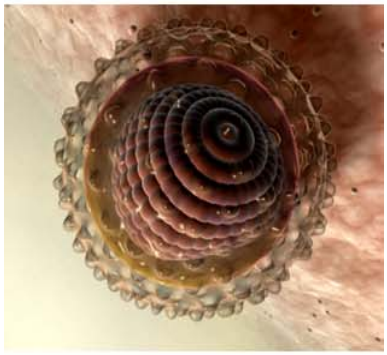
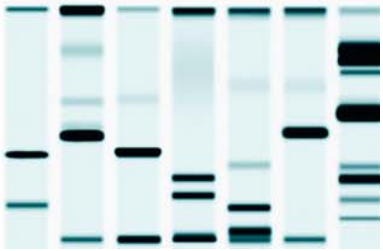
Clostridium difficile – the bad news and possibly good news





LONDON, UK----18 November 2008----ExpertREACT. Recently two distinct pieces of news contributed to the momentum of global interest regarding the hospital "superbug" *Clostridium difficile* **(C.diff).** Firstly, in the US, a new APIC survey suggested colonization and incidence of CDI was higher than previously thought. Secondly, Optimer Pharmaceuticals published results from one Phase III study for OPT-80 suggesting the rate of disease recurrence after treatment was lower than the gold-standard oral vancomycin.

Clostridium difficile (C.diff) is a Gram-positive bacterium, which can harmlessly colonize the gut of humans. Colonization with C.diff does not always cause disease except in people that are mainly older than 65 years and have undergone intensive antibiotic therapy. In these population(s), which reside mainly in the hospital and long-term care facilities, rates reach 30-40% because the normal flora of the gut is diminished. In vulnerable patients the bacterium causes disease (CDI) by producing toxins that cause inflammation and colitis. Outcomes range from mild diarrhea to severe-complicated disease where patients experience fever, tachycardia and psuedomembranous colitis. Mortality rates can reach 6-30% but in some patients with toxic megacolon who require surgical intervention or colectomy, mortality can reach 35-50%.

Across the globe the measurement of "true" CDI incidence has in recent years become increasingly important. It is imperative that national healthcare policy makers understand accurately the burden of disease so that measures, both near and long-term, can be put in place to combat a growing problem that some observers mention is worse than MRSA. When asked, most experts perceive that in their hospitals/units the incidence of CDI is growing and in some countries, the disease is becoming associated with increased severity, mainly due to certain strains e.g. ribotype 027/NAP1. However, in many countries, mandatory reporting of all CDI cases is still not required so it is easy to speculate on historical and future trends based on local viewpoints. In the EU only the UK, Belgium and Ireland have mandatory surveillance whereas for example, in Spain and Italy, CDI is not a notifiable disease and no active surveillance is performed (1). In 2009, a pan-European surveillance study will be released allowing better comparison better EU countries (1).

In the US, cases of CDI are also not nationally reportable although other surveillance techniques have been used to estimate disease burden. These include the national inpatient sample administered by the Agency for Healthcare Research and Quality (AHRQ) which measures primary and secondary discharge diagnoses from a sample of hospitals in 28 states. Another system known as the CDC's Biosense system covers a large number of US hospitals, measuring CDI but is only at the prototype stage. Despite this lack of a robust active national reporting system, generally CDI incidence in the US is reported to be increasing with an approximately doubling over the past 3-5 years. The National Hospital Discharge Survey (NHDS) data suggests that around 290,000 people were discharged with a CDI diagnosis in 2005 (2). Moreover, CDI is believed to have contributed to the death of ~20,000 people between1999-2005 (3).

The new APIC (Association for Professionals in Infection Control) survey (results released November 11, 2008) is reportedly the largest and most comprehensive study of its kind where ~12,000 members were asked to collect data regarding their patients and C.diff status (colonization status and infection) on one day during May-August 2008 (4). The survey covered around 47 states and 12.5% of acute care hospitals. Bearing in mind the weakness of reporting systems currently in place, the results from the study are striking and add to the urgency of stepping up preventative action. The APIC survey data showed that 13 out of every 1000 inpatients in the survey were "either infected or colonized" with C.diff a rate presumed to be 6.5-20 times higher than previous incidence estimates. Again the majority of disease was in the >60 yrs group with comorbidities and represented an initial episode. APIC say that each day 300 Americans could be killed by CDI.

Another important observation from the APIC data, and particularly relevant to search for new prevention and treatment strategies was the fact that ~40% of the C.diff cases were likely to be recurring or relapsing disease. It is well documented that a patient experiencing an initial episode of CDI, that is then treated with vancomycin (oral) or metronidazole, in around 20-30% of case fails therapy and suffers disease recurrence or relapse, often due to a new strain of C.diff (~50% of cases). In these cases the immunological status of patients is believed to be strongly linked to clinical outcome associated with CDI.

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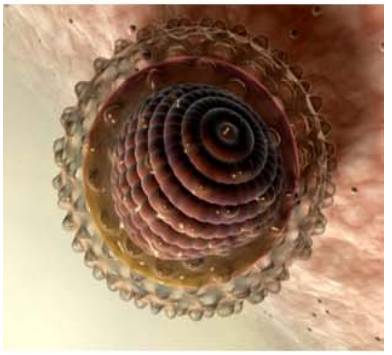

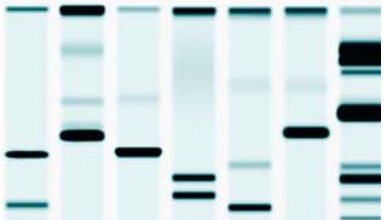

Currently, there are no tried and tested treatments for patients that suffer from multiple recurring/relapsing CDI with many physicians being unsure of next steps or resorting to techniques with little evidence of their effectiveness. In order to combat this issue e a number of approaches are being explored in the current R&D pipeline. Sanofi Pasteur, with its acquisition of Acambis has the only active C.diff vaccine in clinical development soon to be recruiting for a Phase II (POC) study in patients experiencing a first-event of CDI (Clinical trial identifier: NCT00772343). The vaccine will be used in combination with antibiotics to observe any possible reduction in the disease recurrence rate. If successful, the vaccine could later be investigated for prophylatic vaccination of >65yrs individuals in the community, a public health strategy long advocated by this research consultancy. Other notable biological approaches being pursued include monoclonal antibodies against C.diff toxins (Medarex).

US-based Optimer Pharmaceuticals have been pursuing a more traditional approach with the development of the novel macrocyclic antibiotic, OPT-80. The concept here is that the use of a narrow spectrum agent may selectively target pathogenic C.diff and preserve the integrity of the normal gut flora essential to continued bowel health. OPT-80 is being studied in two large Phase III studies one of which is completed and reported top-line results recently (5). The Optimer data indicates that in comparison to the gold-standard vancomycin, OPT-80 (200mg/bid) exhibited roughly half the rate of disease recurrence (13-15%) versus Vancocin (125mg) (24-25%) meeting the trial non-inferiority endpoint. In both the Per protocol (microbiologically evaluable) and modified to Intent-to-Treat data sets (mITT), OPT-80 also had ~10% higher global cure rates defined as an exploratory endpoint in patients that did not suffer a recurrence.

The OPT-80 is encouraging news and likely to provide an additional option for physicians treating first-line CDI. The results of the additional Phase III study will be critical as it is well known that large variability rates between CDI trials have occurred in terms of measuring disease recurrence. In addition, it will be of interesting to observe the performance of OPT-80 versus vancomycin specifically in severe CDI disease. For Optimer getting OPT-80 licensed and marketed will bring commercial rewards probably best maximized with a marketing partner. It will be resource intensive justifying a higher branded price of OPT-80 versus Vancomycin which is soon to lose exclusivity.

References:

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4) The Association for Professionals in Infection Control and Epidemiology. Inc. (APIC). National Prevalence Study of Clostridium difficile in U.S Healthcare Facilities. Press Release, November 2008. Available at: http://www.apic.org/AM/Template.cfm?Section=National_C_Diff_Prevalance_Study&Template=/CM/HTMLDisplay.cfm&ContentID=12183. Accessed November 2008.

5) Optimer Pharmaceuticals News Release, November 10, 2008. Available at: http://www.optimerpharma.com/news.asp?news_story=69&page_num. Accessed November 2008.

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