The spread of hypervirulent *Clostridium difficile* PCR Ribotype 027 in Europe

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Background: Since 2002, increasing rates of *Clostridium difficile*-associated infections (CDI) with a more severe course, higher mortality and more complications have been reported in Canada, USA and Europe. This increased virulence is assumed to be associated with higher amounts of toxin production by a strain belonging to PCR ribotype 027, toxinotype III (Type 027).

Methods: Following the first cases of *C. difficile* Type 027 in Europe, a network of microbiologists and epidemiologists from national reference centers was established. *Clostridium difficile* strains were sent to National Reference laboratories for further investigations. The Reference laboratory in Leiden confirmed most of the first isolated Type 027 isolates in each country.

Results: As of April 2008, *C. difficile* Type 027 was found in 16 European member states and in Switzerland. Seven countries only reported sporadic cases of Type 027. Of these 7 countries, 2 countries reported on patients with infections acquired abroad in countries known to be affected by Type 027. One country reported an outbreak with the index patient having acquired PCR ribotype 027 during stay in a foreign hospital. England and Wales, Belgium, France, Luxembourg, Finland and The Netherlands reported a high number of hospitals affected by Type 027. Application of a recently developed Multi-Locus Variable Number of Tandem Repeat Analysis (MLVA) for *C. difficile* on isolates from individual countries revealed specific subtypes in some countries. Type 027 isolates were generally susceptible to clindamycin and resistant to erythromycin, however clindamycin-resistant, erythromycin-resistant, *ErmB* positive Type 027 strains have been found in Switzerland, France and Ireland. In contrast, erythromycin-susceptible, clindamycin-susceptible strains were found in Denmark and Germany. Information on the attributable mortality was available from France (4%) and The Netherlands (4.1%). Systematic surveillance studies have been developed in all countries affected by Type 027, but they differ considerably in design.

Conclusions: *C. difficile* PCR ribotype 027, toxinotype III has been found in more than 250 hospitals in 17 countries and is rapidly spreading in Europe.

doi:10.1016/j.ijid.2008.05.098
Infection control: 1) Single room or cohort, 2) barrier precautions, 3) avoid rectal thermometers, 4) chlorhexidine 1000 ppm room cleaning, 5) early detection, 6) BioQuell - experimental and 7) outbreak - control antibiotics and soap for hand hygiene.

Prevention of relapses: Avoid "bad" Abx and antiperistaltics; role of probiotics and gastric pH control - unknown.

doi:10.1016/j.ijid.2008.05.100

34.004

Managing CDAD: Current and Upcoming Approaches

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The epidemiology, clinical severity and case-fatality ratio of Clostridium difficile infection (CDI) changed dramatically with the emergence of a toxin hyperproducing strain (BI/NAP1/027) in North America and Europe since 2000. These changes have stimulated the quest for novel therapeutic approaches, and a re-examination of the comparative efficacy of metronidazole versus oral vancomycin. Unfortunately, tolevamer, the only novel treatment evaluated so far in phase 3 trials, has proven inferior to comparators, and metronidazole and vancomycin remain the two most commonly used drugs. The major advantage of metronidazole is its low price. The major advantage of orally administered vancomycin lies in its more favorable pharmacokinetics. Facilitating vancomycin-resistant enterococci colonization/infection is a potential drawback of both drugs.

With the development of a prospectively validated scoring system, the IDSA/SHEA expert committee will define severe CDI as any patient with a leukocytosis $\geq 15000/mm^3$ or a creatinine increased by $\geq 50\%$ from baseline. For patients with mild-to moderate CDI (leukocytosis $<15000/mm^3$ and creatinine $<1.5 \times$ baseline), there is no evidence that vancomycin is superior to metronidazole (even for intermediate outcomes), and metronidazole and vancomycin remain the two most commonly used drugs. The major advantage of metronidazole is its low price. The major advantage of orally administered vancomycin lies in its more favorable pharmacokinetics. Facilitating vancomycin-resistant enterococci colonization/infection is a potential drawback of both drugs.

The randomized controlled trials published so far used intermediate outcomes rather than outcomes that now preoccupy clinicians: the frequency of complications or recurrences. Pending the development of a prospectively validated scoring system, the IDSA/SHEA expert committee will define severe CDI as any patient with a leukocytosis $\geq 15000/mm^3$ or a creatinine increased by $\geq 50\%$ from baseline. For patients with mild-to moderate CDI (leukocytosis $<15000/mm^3$ and creatinine $<1.5 \times$ baseline), there is no evidence that vancomycin is superior to metronidazole (even for intermediate outcomes), and metronidazole and vancomycin should be preferred. For patients with severe CDI not infected with BI/NAP1/027, there is reasonable evidence that the better pharmacokinetics of vancomycin translate into a lower probability of complications. For those infected with BI/NAP1/027, the superiority of vancomycin remains to be proven. About one fourth of patients treated with either metronidazole or vancomycin will experience at least one recurrence. There is now some evidence that the more common post-metronidazole recurrences will experience at least one recurrence. There is now some evidence that the more common post-metronidazole recurrences documented recently in some centers may have corresponded to re-infections among patients who remained exposed in the hospital environment.

doi:10.1016/j.ijid.2008.05.101