

Key research issues in *Clostridium difficile*

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Clostridium difficile is an emerging pathogen that causes *C difficile*-associated diarrhea, an important nosocomial infection. Control of this infection remains a challenge, and much needs to be determined about the antimicrobial resistance of the organism, antibiotic stewardship, contamination of the patient environment, and various host factors that determine susceptibility or resistance to infection. A national symposium focusing on *C difficile* infections, the *Clostridium difficile* Symposium on Emerging Issues and Research, was hosted on November 23, 2004, by the Department of Medical Microbiology and Infectious Diseases at the University of Manitoba, Winnipeg, Manitoba, in partnership with the Canadian Institutes of Health Research. This symposium, which aimed to summarize key research issues regarding *C difficile* infections in Canada, had the following objectives: to provide a forum for learning and discussion about *C difficile* and its impact on the health of Canadians; to identify the key research issues that should be addressed; and to explore potential research funding opportunities and collaboration. The present report summarizes key research issues identified for *C difficile* infections in Canada by addressing four major themes: diagnosis and surveillance, infection prevention and control, antibiotic stewardship, and clinical management.

Key Words: *Clostridium difficile*; Diarrhea; Research issues

Clostridium difficile is an emerging pathogen that causes *C difficile*-associated diarrhea (CDAD), an important nosocomial infection (1-5). Control of this disease remains a challenge, and much remains to be determined about the antimicrobial resistance of the organism, antibiotic stewardship, contamination of the patient environment and various host factors that determine susceptibility or resistance to infection. On November 23, 2004, the Department of Medical Microbiology and Infectious Diseases (University of Manitoba, Winnipeg, Manitoba), in partnership with the Canadian Institutes of Health Research, hosted a national symposium focusing on *C difficile* infections – the *Clostridium difficile* Symposium on Emerging Issues and Research. This national symposium, sponsored by the Institute for Infection and Immunity (Canadian Institutes of Health Research), had the following objectives: to provide a forum for learning and discussion about *C difficile* and its impact on the health of

Enjeux clés de la recherche sur *Clostridium difficile*

Clostridium difficile est l'agent pathogène émergent qui est à l'origine de la diarrhée à *C difficile*, une importante infection nosocomiale. Le contrôle de cette infection reste difficile et beaucoup de questions sont encore en suspens notamment au sujet de la résistance de cet agent pathogène aux antibiotiques, du choix de l'antibiothérapie la plus appropriée, de la contamination de l'environnement du patient et de divers facteurs liés à l'hôte et déterminant sa sensibilité ou sa résistance à l'infection. Un symposium national sur les infections à *C difficile* (Symposium sur les nouveaux enjeux et la recherche sur *C difficile*) a été organisé le 23 novembre 2004 par le département de microbiologie médicale et d'infectiologie de l'Université du Manitoba à Winnipeg, au Manitoba, en partenariat avec les Instituts de recherche en santé du Canada. Ce symposium, qui visait à résumer les principales problématiques liées à l'infection à *C difficile* au Canada, s'était donné pour objectifs de fournir une tribune aux praticiens afin qu'ils échangent, débattent et se renseignent au sujet de *C difficile* et de son impact sur la santé des Canadiens; d'identifier les principaux thèmes de recherche à explorer et d'étudier les possibilités de financement et de collaboration pour la recherche sur cet agent pathogène. Le présent rapport résume les grandes questions qu'il reste encore à résoudre au sujet de *C difficile* au Canada et propose trois thèmes principaux : le diagnostic et la surveillance, la prévention et le contrôle de l'infection, le choix de l'antibiothérapie et la prise en charge clinique.

Canadians; to identify the key research issues that should be addressed; and to explore potential research funding opportunities and collaboration. Presentations are available on the University of Manitoba Web site (6).

The present report summarizes key research issues identified for *C difficile* infections in Canada by addressing four major themes: diagnosis and surveillance, infection prevention and control, antibiotic stewardship, and clinical management.

DIAGNOSIS AND SURVEILLANCE

- Canada-wide surveillance of CDAD in hospitals, long-term care facilities and the community is required.
- Surveillance database development considerations:
 - Establishment of standard definitions and forms;
 - Importance of surveillance for research, and the interrelationship between the two;

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- Surveillance to be developed to impact future directions of research; and
- Information systems support to decrease burden on human resources for diagnosis and surveillance.
- Reasons for an increased risk of transmission should be identified using modelling of potential factors (eg, shared bathrooms).
- Identification of strain characteristics; establishment of *C difficile* strain collection systems, including historical, current and future strains; the development of molecular typing systems; genome sequencing of selected strains; virulence gene analysis; and antimicrobial susceptibility testing of *C difficile*.
- Diagnostic issues, including diagnostic testing algorithms, diagnostic turnaround time benchmarks and their impact on patient outcomes, global cost and environmental transmission; enhanced diagnostics directly from stool specimens (to bypass the need for detecting and growing strains); sample collection guidelines; and the development of standardized guidelines that include the laboratory in the definitions of disease.
- Evaluation of animal and human CDAD linkages.
- The environment as a spore reservoir, specifically, issues related to environmental hygiene practices and the evaluation of optimal interventions.

INFECTION PREVENTION AND CONTROL

Symposium participants discussed and prioritized the following issues: environmental decontamination; infection control surveillance, infection control interventions, institution and community issues, and identification of at-risk individuals.

Environmental decontamination

- Develop an environmental infection control group with the following elements:
 - A country-wide, national approach;
 - The conduct of well-controlled, randomized trials;
 - The conduct of scientific research and analysis using available and future data; and
 - The formation of a National Centre for Environmental Infection Control.
- Establish the importance of carriage of *C difficile* and/or environmental acquisition in relation to the development of disease.
- Determine the role of screening for carriage as a means of stratifying risk.
- Determine the importance of *C difficile* carriage in patients or health care workers, or health care environment colonization, in risk of transmission and subsequent development of disease.
- Environmental cleaning:
 - Cleaning agents/sporicides;
 - ◆ Establish the efficacy of products, such as hydrogen peroxide, bleach, alcohol, alcohol gels, glutaraldehyde; determine product efficacy

in different situations (eg, outbreak versus nonoutbreak settings); standardize protocols for evaluating product efficacy and the concentration of agents; and

- ◆ Determine the impact of cleaning products on the physiology of *C difficile*, specifically as they pertain to the induction of sporulation.
- Establish the type and frequency of cleaning, particularly during outbreaks, in comparison with nonoutbreak settings, particularly:
 - Protocols for cleaning, both during outbreak and nonoutbreak settings;
 - Define 'adequate cleaning';
 - Relative importance of the cleaning agent and physical removal;
 - The role of cleaning, disinfection and sterilization; and
 - Importance of contact time for the cleanser and the type of cleanser.
- Establish standards for acute care and long-term care settings for cleansers and cleaning.
- Determine the need for reusable clean, sterile or disposable patient care equipment (eg, bedpans).
- Establish standards for the frequency of cleaning and type of cleanser for commodes, bathrooms and other shared equipment, such as chairs, beds, telephones and other equipment in patient rooms.
- Equipment issues:
 - Determine standards for multiple-use devices for patients with *C difficile*, specifically as they pertain to cleaning, storing and reuse;
 - Establish the utility of dedicated equipment, including a cost-benefit analysis;
 - Determine the relative cost effectiveness of increasing human resources versus dedicated equipment; and
 - Determine the costs of effective strategies for environmental decontamination.

Infection control surveillance

- Establish a standardized definition for CDADs.
- Data collection forms:
 - For national, regional and/or facility-specific surveillance, standardize data collection forms to collect the following information: risk factors; diagnosis; antibiotics; and laboratory and clinical information to incorporate into existing national systems for data collection.

Infection control interventions

- Handwashing:
 - Randomized trials for efficacy of gels, soaps, etc; and
 - Consider effectiveness of agents against micro-organisms other than *C difficile*.

- Isolation and cohorting:
 - Level of contact precautions needed
 - ◆ Impact of universal gloving and gowning; and
 - ◆ Importance of the physical plant: sinks; room layout; number of single rooms; single versus shared bathrooms; a trial to determine if isolation works; single versus multibed rooms; when to discontinue isolation; screening and what to do with positive results; acute care versus rehabilitation, chronic care and long-term care.
- Education:
 - The impact of teaching hospital staff about cleaning;
 - Credentialing staff based on their knowledge of infection prevention; and
 - Knowledge of risk factors and prescribing practices.
- Staffing:
 - Impact of *C difficile* on staffing levels, incidence and transmission, including nursing, nursing assistants, orderlies, housekeeping staff and medical staff.
- Equipment cleaning:
 - Difference made by surface material;
 - Sterilization versus cleaning of devices and cleaning frequency; and
 - Impact on housekeeping, staff, patients and environment
 - ◆ Toxicity;
 - ◆ Environmental impact.

Institution and community

- Patient transfers:
 - Interfacility
 - ◆ Frequency of transfer and impact on transmission;
 - ◆ Use of modelling to determine the impact of these transfers.
 - Intrafacility
 - ◆ Authorization to transfer based on symptoms and risk factors;
 - ◆ Cost-effectiveness of screening and preemptive isolation; and
 - ◆ Use of modelling to determine the impact of transfers on *C difficile* transmission.
- Outpatient CDAD:
 - Define an outpatient case and determine bacteria rates;
 - Risks of transmission in the community and in acute care;
 - Risk to health care workers of acquiring CDAD; and
 - Epidemiology of community CDAD.
- Identification of at-risk individuals.

- Screening:
 - Cost-benefit analysis;
 - Relationship to disease (sensitivity and specificity).

ANTIBIOTIC STEWARDSHIP ISSUES

Antibiotic stewardship issues included clinical as well as basic science issues:

Hospital formulary considerations

- Whether antibiotics should be further restricted in hospitals, including the use of clindamycin, second- and third-generation cephalosporins, amoxicillin, ampicillin, amoxicillin/clavulanate and fluoroquinolones such as ciprofloxacin, gatifloxacin, levofloxacin and moxifloxacin.
- Whether antibiotics should be rotated or cycled to minimize CDAD.
- Randomized comparative studies on antimicrobial restriction versus no restrictions, considering the individual patient level and institutional level.

Treatment considerations

1. Performing routine or annual susceptibility testing to assess the prevalence and incidence of antibiotic resistance with *C difficile*.
2. Understand the fundamental immunobiology in *C difficile*-associated diarrhea.
3. Understand the role that antibiotics play on the colonic flora to allow *C difficile* to overgrow and express toxins, using in vitro and animal models:
 - How normal human flora protects from CDAD and the importance of not disturbing the normal flora of *Bacteroides fragilis* to minimize overgrowth with *C difficile*.
 - The effects that antibiotics have on *C difficile*, specifically with regard to strain selection, toxin A and B expression, effects on bacterial adherence and invasion, and the effect on spore burden and excretion.
 - The roles that vancomycin, metronidazole, fusidic acid, bacitracin, probiotics, resins and intravenous immunoglobulin have on strain selection, toxin A and B expression, bacterial adherence and invasion, and spore burden and excretion.
 - The roles that each of the above have in the treatment of CDAD, as well as the appropriate duration of treatment for primary infection of CDAD and relapses.
 - The role of antibiotic resistance in the treatment of CDAD with metronidazole and vancomycin.
 - The frequency of susceptibility testing with *C difficile*.
 - The role of antitoxin treatment.
 - The role of a CDAD vaccine.
 - The effects that antibiotics have on the colonic flora, using animal models.

- The basic immunobiology of patients with CDAD.
 - Randomized comparative trials of IVIG.
 - Randomized comparative trials of bio-restoration, including rectal enemas, or long-term oral therapy.
4. The role of proton pump inhibitors (PPIs) in CDAD, specifically:
- The effect of PPIs on strain selection.
 - The effect on toxin A and B expression.
 - The effects on bacterial adherence and invasion.
 - The effects on spore burden/excretion.
 - Whether we should restrict PPIs in hospitals and the community, and whether we should monitor all patients on PPIs in the hospital.

CLINICAL MANAGEMENT ISSUES, AND PHARMACOLOGICAL AND VACCINE PREVENTION

- The determination of risk factors that will predict a severe or fulminant course versus disease resolution once a patient develops CDAD.
- A national consensus regarding definitions of mild, moderate and severe CDAD; these definitions can be applied to studies, and could be based on various clinical laboratory parameters (could be similar to the Apache 3 score for sepsis, the Anthonisen criteria for chronic obstructive pulmonary disease exacerbation, and the Child-Pugh-Turcotte score for liver disease). Studies could then focus on clinical efficacy of adjunctive treatment with subgroup analysis.
- The pathogenesis of CDAD:
 - New antimicrobials to be developed for the treatment of CDAD; and
 - The role of adjunctive therapy, including IVIG, toxin binders, sporicidal agents, agents to induce sporulation (spores are pathogenically inert), bacteriophages, spores/phages, stool enemas and probiotics.
- Use of probiotics at the time of antibiotic administration.
- The role of monoclonal antibodies to prevent adhesion of *C difficile*.
- The role of immunity in disease manifestation (eg, the presence or absence of disease and severity).
- Whether the humoral versus cellular immunity or both are important to minimize or prevent CDAD disease.
- The role of passive immunization with IVIG:
 - How to test whether IVIG preparations have antitoxin antibodies;
 - The correlation with antitoxin titres in clinical outcome;
 - The standardization of IVIG preparations; and
 - The optimal dosing and timing of IVIG and whether colostrum could also be used.
- The need and role for a vaccine to provide active immunization.
- Type of vaccine required, whether it be a toxoid (successful in piglet), a live attenuated vaccine, a whole-cell inactivated vaccine or a killed vaccine.
- Who to vaccinate and when to vaccinate.

SUMMARY

The control of CDAD remains a challenge; much needs to be determined about antimicrobial resistance of the organism, antibiotic stewardship, contamination of the patient environment and the various host factors that determine susceptibility or resistance to infection. The present report summarizes the important research issues identified by a national symposium and provides the foundation on which to develop a research agenda for this important Canadian problem.

SPEAKERS AND FACILITATORS: The symposium, chaired by Dr Greg Hammond (Winnipeg), consisted of presentations on various aspects of *C difficile* infections, including the spectrum of clinical illness, diagnosis and surveillance of *C difficile* infections, pathogenesis, molecular typing and epidemiology, infection control and treatment. Speakers included Dr Mark Miller (Montreal), Dr Michelle Alfa (Winnipeg), Dr Tom Louie (Calgary), Dr Allison McGeer (Toronto), Dr Vivian Loo (Montreal), Dr Mike Mulvey (Winnipeg), Dr Louis Valiquette (Sherbrooke) and Dr Judy Bray (Canadian Institute for Health Research, Ottawa). Presentations were followed by breakout sessions on the following themes: Diagnosis and Surveillance Issues (Dr Michelle Alfa – facilitator; Dr Samira Mubareka – recorder); Infection Control Issues (Dr John Embil – facilitator; Dr Phil Lagace-Wiens – recorder); Antibiotic Stewardship Issues (Dr George Zhanel – facilitator; Dr Alfred Gin – recorder); and Clinical Issues (Dr Joanne Embree – facilitator; Dr Don Vinh – recorder).

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