TITLE: Bleach versus Accelerated Hydrogen Peroxide for *Clostridium difficile* and Norovirus Disinfection: A Review of the Clinical Effectiveness and Safety

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CONTEXT AND POLICY ISSUES:

Nosocomial infections are a major cause of patient morbidity and mortality, and result in significant costs to the healthcare system.[1-3] *Clostridium difficile* and noroviruses are commonly occurring pathogens in healthcare facilities, and infection control programs are often put in place to limit the spread of these and other infections.[4] An estimated 20% to 40% of nosocomial infections are attributed to cross-infection by way of the hands of health care personnel, and contamination of the hands can occur by either touching patients or contaminated environmental surfaces.[1] As such, environmental cleaning is one of the interventions used to control the spread of infectious organisms in healthcare facilities. A Canadian study found that the products used in cleaning and disinfection of *C. difficile* in acute care hospitals varies considerably across the country, and that two products that are often used for disinfection in these facilities are bleach (sodium hypochlorite) and accelerated hydrogen peroxide.[5] The relative effectiveness of these disinfectants in controlling pathogens should be considered in developing policy for environmental cleaning. Given that these disinfectants must be used by hospital workers who are subjected to frequent exposure, as well as near patients whose health is already compromised, relative safety must also be a consideration.

The aim this review is to assess the evidence for the relative effectiveness and safety of bleach and accelerated hydrogen peroxide for *C. difficile* and norovirus disinfection in healthcare facilities. A review of published evidence-based guidelines will be conducted to summarize disinfection practices in other jurisdictions.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness and safety of bleach versus accelerated hydrogen peroxide for *Clostridium difficile* or norovirus disinfection?

2. What are the guidelines for use of bleach or accelerated hydrogen peroxide for *Clostridium difficile* or norovirus disinfection?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, EBSCOhost CINAHL, The Cochrane Library (Issue 8, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2000 and August 13, 2010. No filters were applied were applied to limit the retrieval by study type.

SUMMARY OF FINDINGS:

The literature review yielded 79 citations, and 31 reports were selected and retrieved for further screening. Screening resulted in the exclusion of 18 reports. Reasons for exclusion were: not a comparative study (n=9), wrong comparator(s) (n=4), hydrogen peroxide was vapor or dry mist formulation (n=3), not the interventions of interest (n=1), and duplicate study (n=1). The 13 remaining relevant reports included two systematic reviews,[6,7] two non-randomized comparative studies,[8,9] and nine guidelines.[10-18] Both the non-randomized studies related to *C. difficile*.[8,9] All of the non-comparative studies assessed the effectiveness of environmental cleaning with bleach only (five in *C. difficile*, and four in norovirus). None of the selected studies were assessments of the relative safety of bleach and accelerated hydrogen peroxide.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, the systematic reviews are presented first, followed by the non-randomized studies and the evidence-based guidelines.

Systematic reviews

Hsu et al.[6] published a systematic review in 2010 of prevention practices in endemic healthcare-associated *C. difficile* infection. The authors included studies that assessed the effectiveness of a strategy for the prevention of *C. difficile* infection in a hospital setting, either provided a risk or rate ratio or provided data to calculate these measures, and used clinically important outcomes. Studies published from 1966 to 2009 were considered. Four studies assessing environmental decontamination were identified; three of which used hypochlorite solution (bleach), and one of which used a hydrogen peroxide vapor. A summary of the three studies on hypochlorite solution are provided in Table 1.

Table 1: Studies of environmental decontamination with hypochlorite solution reviewed by Hsu et al.[6]

Author	Design	Pre and post intervention infection rates	Comments
Mayfield et al. (2000)	Before-after intervention study	Bone marrow transplant unit: 8.6 cases/1000 patient days vs. 3.3 cases/1000 patient days, (hazard ratio=0.37, 95%CI: 0.19-0.74) General medicine: 3.0 cases/1000	Noted study limitations include lack of complete data on antineoplastic and antimicrobial doses and duration, lack of evidence of

Table 1: Studies of environmental decontamination with hypochlorite solution reviewed by Hsu et al.[6]

Author	Design	Pre and post intervention infection rates	Comments
		patient days, no significant change after intervention Neurosurgical ICU: 1.3 cases/1000 patient days, no significant change after intervention	environmental contamination, and lack of direct observation of housekeeping technique and compliance
Wilcox et al. (2003)	Non-randomized cross-over control study	First ward: 8.9 cases/100 admissions vs. 5.3 cases/100 admissions ($p<0.05$) Second ward: 3.5 cases/100 admissions vs. 4.7 cases/100 admissions ($p<0.05$)	No limitations or conclusions were reported
McMullen et al. (2006)	Randomized control trial of education versus education + bleach	Education + bleach: 3.1 cases/1000 patient days vs. 2.7 cases/1000 patient days ($p=0.42$). Change in education alone group not stated.	Concluded that bleach might not impact endemic C. difficile infection rates

The authors also noted a fourth study, also by McMullen et al.(2007), that was not formally included in the review because it was done in the setting of an outbreak. This was a before-and-after intervention study that looked the use of hypochlorite solution in medical and surgical intensive care units. The pre- and post infection rates in the medical intensive care unit were 16.6 cases/1000 patient days and 3.7 cases/1000 patient days, respectively (relative risk <0.22, 95% CI: 0.09-0.56). Rates in the surgical intensive care unit were 10.4 cases/1000 patient days and 3.9 cases/1000 patient days, respectively (significance not reported). The studies by Mayfield et al, Wilcox et al, and McMullen et al. (2007) used 1:10 household bleach, and the bleach concentration used by McMullen et al. (2006) was not stated. While the results of this review were inconclusive, the authors noted that the Centers for Disease Control currently recommend chlorine-containing solutions for environmental disinfection in areas of ongoing *C. difficile* transmission.

Harris et al.[7] published a systematic review and meta-analysis of infection control measures for norovirus in semi-enclosed settings in 2010. Eligible studies included reports of outbreaks of norovirus infection in enclosed or semi-enclosed settings (ie. hospitals, nursing homes, cruise ships), and reports that included attack rates or enough information to allow calculation of attack rates. Studies published up to July 2008 were considered. Twenty-nine papers describing studies in which infection control measures were applied were identified. Infection control measures included hand washing, environmental cleaning, and restrictions for infected staff. Environmental cleaning was identified as an important control measure in 16 of the 29 papers, and 14 of these studies occurred in healthcare settings. All 16 papers mentioned the use of bleach solution. The authors reported that shortened outbreaks were claimed in 10 of the published papers, however the authors' analyses found no evidence for shorter duration of outbreaks or lower attack rates where control measures were used. It should be noted that

these results were in regard to control measures in general, and specific data on the use of hypochlorite solution were not presented.

Non-randomized studies

In a controlled laboratory experiment, Fawley et al.[8] (2007) compared the efficacy of hospital cleaning agents and germicides against six different strains of vegetative and spore forms of epidemic and nonepidemic *C. difficile*. The authors considered five different cleaners, among which included an accelerated hydrogen peroxide solution (G-Force; JohnsonDiversey) and three chlorine-containing solutions, one of which was a detergent with hypochlorite solution (Dispatch; Caltech Industries). The authors conducted three series of experiments. First, they determined the minimum inhibitory concentrations (MICs) of germicides that prevent visible bacterial growth, and tested agents at a range of dilutions of 1/1.024 to 1/4 of the manufacturer's recommended working strength. Second, they assessed spore viability at 0, 10, 20, and 30 minutes of exposure to the germicides.. Finally, the impact of subinhibitory concentrations of germicides on sporulation rates was assessed. With regard to results on MICs, the suggested manufacturer's working concentration for the hypochlorite solution was 5,500 parts per million (ppm) hypochlorite, and the MIC as a proportion of the working concentration was 1/64. For the accelerated hydrogen peroxide solution, the suggested working concentration was 1:64 dilution and the MIC as a proportion of the working concentration was 1/128. The authors noted that the manufacturers of the accelerated hydrogen peroxide solution did not state the concentration of hydrogen peroxide used. The results on efficacy of solutions against spore germination showed immediate and complete prevention with the three chorine-containing products, while exposure to the hydrogen peroxide product after 30 minutes did not result in a significant reduction compared with controls. With the experiments on the effect of subinhibitory concentrations of cleaning agents/germicides on sporulation rates, the authors noted that in general, sporulation rates for each epidemic *C. difficile* strain were significantly greater than other strains tested, particularly PCR ribotype 001. Mean sporulation capacity (proportion of a cell population that is in spore form) was 13% for all strains not exposed to a cleaning agent or germicide, but was significantly increased by exposure to the hypochlorite solution (24%) and the hydrogen peroxide solution (33%). By contrast, exposure to the two other chlorine-containing agents (dichloroisocyanurates) did not affect sporulation rates. The authors stated that the poor efficacy of the hydrogen peroxide solution was unexpected, but that the concentration of active hydrogen peroxide in the working solution was unknown and may have been insufficient to kill spores. While the hypochlorite solution was effective against spore germination, it had high sporulation rates, and the authors stated that their results supported the use of dichloroisocyanurate-containing germicides. In a letter to the editor regarding this study,[19] it was argued that the results on higher mean sporulation rates in the hypochlorite solution were not as relevant as the other study findings, as testing was conducted with MICs which should not be extrapolated to environmental surface disinfection on the macroscopic level.[19]

Perez et al.[9] (2005) also conducted a controlled laboratory experiment on the activity of selected microbiocides against the spores of *C. difficile*. The strain of *C. difficile* tested was a local clinical isolate obtained from a child in the Ottawa area and was designated as CHEO. The four disinfectants tested are shown in Table 2.

Table 2: Disinfectants tested in Perez et al.[9]	
Disinfectant	**Composition**
Chlorine dioxide (ClO_2)	124.59 ml distilled water 0.263 ml domestic bleach (5.25% sodium hypochlorite) 0.35 ml concentrated hydrochloric acid 0.112 ml 24.67% sodium chlorite
Acidified bleach	One part domestic bleach Two plus six parts hard water One part commercial white vinegar (5%)
Domestic Bleach	0.54 ml domestic bleach (5.25%) with 5 ml hard water for 5000 mg/L dilution. Dilutions of 3000 mg/L and 1000 mg/L were also tested.
Virox STF (Virox Technology, Oakville ON)	Disinfectant based on accelerated hydrogen peroxide, containing 7% (70,000 mg/L) hydrogen peroxide, tested undiluted.

The second tier of a quantitative carrier test was used to assess the sporicidal activity of the disinfectants. Stainless steel disks acted as hard environmental surfaces, with each one being contaminated with 10µL test spore suspension. After incubation, the action of the disinfectants was stopped with a neutralizer and the contents of the vials were filtered. Filters were then placed on agar recovery mediums (plates) and incubated at 36° Celcius ± 1°. Colony-forming units (CFU) were counted at day 2 and day 5, and $\log_{10}$ reductions in spore titers were calculated. Times required for microbiocides to inactivate *C. difficile* spores were tested and estimated. Acidified bleach, regular bleach at 5000 mg/L dilution, and the Virox solution all inactivated *C. difficile* spores within 10 minutes. The 3000 mg/L dilution of bleach required 15 minutes to inactivate *C. difficile* spores, and the 1000 mg/L dilution required 15 to 25 minutes. The authors noted that stainless steel does not represent all the hospital surfaces that may place different demands on disinfectants. They also noted that the numbers of spores in their study may have been higher than what might be found on environmental surfaces, however, so were the volumes of disinfectants used in the tests. The authors suggested that the sporicidal products tested in their experiment may be more appropriate for eliminating severe or long-standing *C. difficile* contamination, and not be used routinely because of potential hazards to personnel and patients.

Guidelines and recommendations

Of the nine guidelines that were retrieved, five[10-14] related to *Clostridium difficile* infection, one[15] related to noroviruses, and three[16-18] applied to both.

Clostridium difficile

The Health Protection Network of Scotland published guidance in 2009 on the prevention and control of *C. difficile* infection in healthcare settings.[10] The levels of evidence for recommendations made in this guidance were graded using the systematic literature review by Vonberg et al.[11] The guidance for environmental cleaning was that after cleaning with warm water and detergent, hard surfaces in residents' rooms and toilets that tolerate bleach should be wiped with a bleach (hypochlorite) based disinfectant that is diluted to 1,000 ppm. This recommendation was assigned a Hospital Infection Control Practices Advisory Committee (HICPAC) category of implementation in clinical practice of IB, meaning that it was strongly recommended for implementation and strongly supported by some experimental, clinical, or epidemiological studies and a strong theoretical rationale. The authors of this guideline did not

recommend the use of hypochlorite solutions above 1,000 ppm because of possible corrosion of metal surfaces and potential respiratory problems due to vapors, and suggested that a risk assessment of the use of bleach should take into consideration the general health and risk factors of residents and patients as well as the health and safety of staff in the facility.

In 2008, Vonberg et al.[11] published an evidence-based guideline to be used in the review or production of local protocols for the control of nosocomial *C. difficile* infection in Europe. The guidelines were created based on a systematic review of the literature, and recommendations were assigned HICPAC categories for implementation in clinical practice. The authors guidance was that regular environmental disinfection of rooms of *C. difficile* patients should be done using sporocidal agents, ideally chlorine-containing agents of at least 1,000 ppm available chlorine, with the choice of cleaning regimen being dependent on local policy. This recommendation was based on level 2b evidence (individual cohort studies, including low-quality randomized controlled trials), and was assigned a HICPAC category of implementation of IB.

Dubberke et al.[12] (2008) authored the Society for Healthcare Epidemiology of America / Infectious Diseases Society of America recommendations for the prevention of *C. difficile* in acute care hospitals. The method used to review and summarize the evidence for these guidelines was not described, however quality of evidence was graded and strength of recommendations was made using a scale adapted from the Canadian Task Force on the Periodic Health Examination. It was recommended that facilities consider using a 1:10 dilution of sodium hypochlorite for environmental disinfection in outbreak settings and settings of hyperendemnicity in conjunction with other infection prevention and control measures, and that the bleach solution should have a contact time of at least 10 minutes. The strength of this recommendation was assigned a B category (moderate evidence to support a recommendation for use) and a grade II for the quality of evidence on which this recommendation was based (evidence from at least one well designed clinical trial, without randomization; from cohort or case-control analytic studies; from multiple time series; or from dramatic results from uncontrolled experiments). The authors also recommended that toxicity to patients and staff and damage to equipment and the environment from diluted sodium hypochlorite use be avoided, but did not outline specific measures.

The Department of Health in London (U.K.) published guidance on dealing with *C. difficile* infection in hospitals in 2008.[13] This guidance updated and replaced earlier guidance published by the Department of Health. It aligned its recommendations with the 2006 Health Act, and drew on several other advisory and guidance documents for *C. difficile* infection. The recommendations called for at least daily cleaning of rooms and bed spaces of *C. difficile* patients using chlorine-containing cleaning agents (at least 1,000 ppm). All bathroom facilities used by these patients should be cleaned after each use with a chlorine cleaning agent (at least 1,000 ppm). In addition, terminal cleaning of a mattress, bed space, bay, or ward should be thorough and be cleaned with a chlorine solution (at least 1,000 ppm). It was also recommended that chlorine-containing cleaning agents be made up to correct concentrations and stored in accordance with manufacturers' instructions, with particular attention to compliance with health and safety regulations. All recommendations were based on B graded strength of evidence (strongly recommended and supported by non-RCT studies and/or by clinical governance reports and/or the 2006 Health Act).

The Ontario Ministry of Long-Term Care published an update of best practices for the management of *C. difficile* in all health care settings in 2007.[14] The document was developed by the Provincial Diseases Advisory Committee (PIDAC) using an evidence-based and consensus approach. Guidance for environmental cleaning suggested that the use of hypochlorite solution-based products for disinfection may be considered in patient-care areas where there are multiple cases or ongoing transmission of *C. difficile* (in consultation with Infection Prevention and Control and Occupational Health and Safety, Centres for Disease Control 2004). However, organizations may alternatively consider the use of new disinfectant products with in vitro evidence of sporicidal activity. Guidance also stated that compatibility of products and occupational exposures must be considered. These guidelines were further updated in 2009,[18] and stated that both sodium hypochlorite (1000 ppm) and accelerated hydrogen peroxide (4.5%) had shown activity against *C. difficile* spores. It was also noted in these guidelines that the use of a sporicidal agent should be considered in consultation with Infection Prevention and Control and Occupational Health and Safety.

Norovirus

The Ontario Ministry of Long-Term Care 2009 *Best Practices for Environmental Cleaning for Infection Prevention and Control in All Health Care Settings* [18] addressed contact precautions for norovirus. The authors stated that products used for disinfection of norovirus must have an appropriate virucidal claim. There were no recommendations made for specific disinfectants, however the authors noted that some jurisdictions (US, UK) recommend bleach at 1000 ppm concentration.

Chadwick et al.[15] (2000) co-authored a report of the Public Health Laboratory Service Viral Gastro-enteritis Working Group in the U.K. which made recommendations for the management of hospital outbreaks of gastro-enteritis due to small round structured viruses (SRSVs), including Norwalk-like viruses. Details on the review of the evidence were not given. Categories of recommendation were based on the categories used by the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. The authors recommended that 1,000 ppm hypochlorite be used to disinfect hard surfaces after cleaning. The level of this recommendation was Category II: strongly recommended and viewed as effective by experts in the field and by the working group, based on strong rationale and suggestive evidence, even though definitive studies may not have been done.

General hospital infection

Pratt et al.[16] published national evidence-based guidelines for preventing healthcare-associated infections in National Health Service hospitals in England in 2007. The guidelines were developed based on a systematic review and quality assessment of the literature. Evidence classification and guidance recommendation levels used were those employed by the National Institutes for Clinical Excellence (NICE).The guidelines identified four distinct interventions, one of which was hospital environmental hygiene. Studies relating to *C. difficile* and norovirus, among other hospital infections, were mentioned in the literature review. The authors recommended that the use of hypochlorite and detergent should be considered in outbreaks of infection where the pathogen concerned survives in the environment and environmental contamination may be contributing to spread. This recommendation was classified as a level D, which meant that is was based on level 3 evidence (non-analytic studies), level 4 evidence

(expert opinion, formal consensus), or extrapolated from well-conducted case-control or cohort studies with low risk of bias and a moderate probability of a casual relationship.

Siegal et al.[17] and the Healthcare Infection Practices Advisory Committee co-authored guidelines for isolation precautions with the aim of preventing transmission of infectious agents in healthcare settings. These guidelines were published through the Centers for Disease Control (CDC) in the US in 2007. Guidelines were based on a review of the literature, and guidance was assigned HICPAC categories for implementation in clinical practice. *C. difficile* and norovirus were among the hospital infections addressed in the literature review. Guidance recommended the use of Environmental Protection Agency (EPA)-registered disinfectants that have microbiocidal activity against the pathogens most likely to contaminate the patient-care environment, and to use these disinfectants in accordance with manufacturers' instructions. This guidance was assigned HICPAC categories IB and IC (category IB has been previously described, and category IC means that it is required for implementation, as mandated by federal and/or state regulation or standard). In an accompanying appendix which outlined precautions for different types of infection, the authors suggested that hypochlorite solutions may be required for cleaning where there is continued transmission for both *C. difficile* and for noroviruses.

Limitations

The literature search did not yield any randomized studies of sodium hydrochlorite versus accelerated hydrogen peroxide in either *C. difficile* or norovirus infection. Given the practical difficulties in carrying out such a study, it may be unlikely that one will be done.

The two comparative studies in *C. difficile*[8,9] were both laboratory studies, and did not take place in real world settings, where multiple factors may influence outcomes.

Comparative studies of the two disinfectants in norovirus were not identified, and there was no evidence for accelerated hydrogen peroxide alone in norovirus. Although several authors and guidelines noted potential toxicity of the disinfectants,[9,10,12-14] no safety studies were identified.

Only two of the nine guideline documents retrieved were from a Canadian jurisdiction. The other guidelines were from the UK, Europe, and the US and may not be generalizable to the Canadian setting.

In general, guideline recommendations for the use of bleach were not based on higher-level evidence.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

With regard to the evidence in *C. difficile*, the systematic review conducted by Hsu et al.[6] considered only studies of bleach and findings were inconclusive. The laboratory study by Fawley et al.[9] suggested that high concentrations of bleach (5000 mg/L) are superior to accelerated hydrogen peroxide in preventing spore germination, however the concentration of hydrogen peroxide in this study was unknown. The laboratory study by Perez et al.[8] suggested that high concentrations of bleach (5000 mg/L) were comparable to an accelerated hydrogen peroxide (7%) solution in inactivating *C. difficile* spores, while lower concentrations of bleach

required longer contact times than both these comparators to attain the same efficacy. The reviewed guidelines all recommend the use of bleach in environmental cleaning, although some suggest lower concentrations than that found to be most effective by Perez et al. The results from Perez et al.[8] suggested that longer contact times would be required in environmental cleaning with the concentrations suggested in some of the reviewed guidelines. Recent Ontario guidelines[18] recommended use of sporicidal agents that have demonstrated activity against *C. difficile* spores, and noted that both bleach and accelerated hydrogen peroxide had shown this activity.

For the evidence in norovirus, the systematic review by Harris et al.[7] was limited in its presentation of results on environmental cleaning, only bleach was considered as a disinfectant among the studies reviewed, and no conclusions could be drawn from this report. No other relevant studies in norovirus were found. Three guidelines[15-17] recommended the use of bleach for environmental cleaning for the control of norovirus infection in healthcare settings, and Ontario guidelines[18] did not specify antibacterial agents in their recommendations.

While it is possible that an accelerated hydrogen peroxide solution may be as effective as bleach in preventing the spread of *C. difficile* and norovirus in healthcare settings, very little evidence was found examining the effectiveness of accelerated hydrogen peroxide. All the reviewed guidelines recommended hypochlorite solution for environmental cleaning, and Ontario guidelines also mention accelerated hydrogen peroxide (4.5%) as being effective in *C.difficile*. No safety studies were found to permit comparison of possible relative toxicity; however several authors addressed this concern, with some suggesting that products should be used according to manufacturers' recommendations, while taking the general health and risk factors of patients and staff into consideration.

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