Published in final edited form as:

Crit Care Med. 2010 August ; 38(8 0): S324–S334. doi:10.1097/CCM.0b013e3181e69f05.

Recognition and Prevention of Hospital-Associated Enteric Infections in the Intensive Care Unit

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Abstract

Objectives—To review the causes and extent of hospital-associated infectious diarrhea and associated risks in the general hospital ward and ICU, to compare microorganisms with similar symptoms in order to aid in recognition that will lead to timely and appropriate treatment and control measures, and to propose infection prevention protocols that could decrease human process errors in the ICU.

Design—Literature review describing epidemiology, comparison of microbial characteristics for potential hospital-associated enteric pathogens, diagnosis, and prevention, especially if important in the ICU, and particularly in regard to *Clostridium difficile*.

Results—Enteric organisms that most commonly cause hospital-associated infectious diarrhea in acute care settings and the ICU are *C. difficile*, rotavirus, and norovirus, although others may also be important, particularly in developing countries.

Conclusions—In order to successfully recognize and control infectious diarrhea in the ICU, intensivists should be aware that epidemiology, risks and prevention measures may differ between these microorganisms. In addition, intensivists should be ready to implement systems changes related to notification, isolation precautions and prevention and environmental cleaning in the ICU.

Keywords

Hospital-associated diarrhea; ICU; *Clostridium difficile*; fulminant colitis; rotavirus; norovirus; pseudo-outbreak; prevention; control

Introduction

Patients are at increased risk for developing diarrhea in the hospital, with as many as 40% to 90% of some ICU patient populations affected (1, 2). Diarrhea adversely impacts critically ill patients by contributing to dehydration, electrolyte imbalances, hemodynamic instability, malnutrition, and skin breakdown. The etiologies of most cases of diarrhea are non-infectious, and include enteral feeding, fecal impaction, bacterial overgrowth, medications, psychological stress, diagnostic test reagents, certain tumors, endocrine disorders, malabsorption, hypoalbuminemia, intestinal ischemia, or exacerbations of inflammatory

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LDB has no financial disclosures.

ERD – research: Viropharma; consultant: Steris, Becton-Dickinson, Meridian, Merck

bowel disease (3). Infectious causes of diarrhea in the ICU are less common than non-infectious causes, but are a major concern. Infectious diarrhea is typically more severe than non-infectious diarrhea, increasing the likelihood of developing complications such as arrhythmias due to electrolyte abnormalities, cardiopulmonary instability requiring vasopressors and mechanical ventilation, or intra-abdominal catastrophes. Infectious diarrhea in the healthcare setting can also be more problematic than non-infectious causes because the causative agent often can be transmitted from patient to patient, from patient to healthcare worker or vice versa. Hospital-associated infectious diarrhea accounted for 21% of all 223 healthcare-related outbreaks reported to the Centers for Disease Control and Prevention from 1956 to 1979 (4). The most common cause of infectious diarrhea in the ICU is *Clostridium difficile*, a pathogen associated with increasing incidence and severity of infection. *Salmonella*, rotavirus, and norovirus have also been associated with outbreaks in healthcare facilities including the ICU (Table 1).

Recognition and diagnosis of infectious diarrhea in the ICU

It is essential to consider an infectious etiology in an ICU patient with diarrhea, especially if the patient has > 3 bowel movements per day, blood or mucus in the stool, vomiting, severe abdominal pain, and/or fever (Table 2). Establishing the diagnosis is important not only to initiate specific treatment for the patient with diarrhea, but also so measures to prevent the spread of the causative organism to other patients and staff in the ICU can be implemented. Person-to-person spread is the most common form of transmission, and *C. difficile* is the most common causative pathogen of healthcare-associated enteric infection outbreaks. However, it is also important to also keep in mind that intestinal pathogens of interest in the United States are still present in the food supply and contaminated food has been implicated as a vehicle in some hospital-associated enteric infection outbreaks. The United States preliminary surveillance FoodNet data from the Communicable Disease Center indicates that none of the *Healthy People 2010* targets for reduction of foodborne pathogens has been met as of 2008 (14). Enteric pathogens in this report included *Campylobacter*, *Listeria*, *Salmonella*, *Shigella*, Shiga toxin-producing *Escherichia coli* 0157, *Yersinia* and *Cryptosporidium*. In addition, rotavirus and norovirus, typically considered causes of gastroenteritis in the community, are the most common etiologies of hospital-associated diarrhea in children (15–18). Hospital-associated outbreaks due to these pathogens also have occurred in adults (15–18). Persons aged 50 years, the very young, and immunocompromised patients who develop diarrhea with these pathogens are at greatest risk for hospitalization, infection and ultimately death. Several of these organisms can be shed post-infection, have a carrier state, or have cysts that are resistant to most disinfectants. Hospital outbreaks through patient-to-patient or health care worker-to-patient transmission and contamination of food in the hospital have occurred.

If the index of suspicion is high enough to warrant testing for an intestinal pathogen, there are a wide number of potential causative pathogens and no single test is able to detect all of them. Table 2 contains enteric bacteria, viruses and parasites that have been or could potentially be involved in hospital-associated diarrhea, in developed and developing countries. Although these organisms share diarrhea as a common element, they may differ markedly in mode of transmission, incubation period, and duration of illness. In addition, seasonal outbreaks are part of the infection cycle in some, and attention to temporality can aid in preliminary identification of the pathogen.

Reliable and accurate laboratory diagnostic tests are critical for identification that cannot be made by the clinical presentation of the diarrheal illness alone. In some cases insensitive or nonspecific characteristics of the test assay have delayed correct treatment and resulted in incorrect control measures and economic loss (19–22). In addition, spatial characterization

of an outbreak can be examined using strain typing, and this can be important to determine whether strains are endemic or epidemic for control measures. However, typing is not readily available in most clinical laboratories in developed countries and in resource poor areas. There is usually a delay in generating this information for infection control in developed regions due to need for reference laboratories with highly trained personnel to perform specialized techniques.

In terms of when to culture stool for enteropathogenic bacteria other than *C. difficile*, it has been shown that a modified “3-day rule” is a safe and cost-effective cut-off for rejecting stool samples of adult in-patients due to low yield of enteric pathogenic bacteria detected in patients hospitalized for at least three days (<1%), as compared to the yield if the specimen was collected within three days (2.6%–6.4%) (23, 24). The same conclusion was obtained when children were included in a similarly designed study (25). This rule allows the laboratory to discard the stool sample if the patient has been in the hospital >3days, unless there are exceptions. Proposed exceptions to the “3-day rule” rule were neutropenia (<0.5 × 10⁶ cells/ml), Human Immunodeficiency Virus (HIV) infection, suspected non-diarrheal manifestation of enteric infection (erythema nodosum, mesenteric lymphadenitis, polyarthritis, fever of unknown origin), patient >65 years with co-morbidities causing end-organ damage, or a suspected hospital-acquired outbreak (26). Good communication between the ICU and the laboratory should be maintained, since some of these organisms may have a latency period and others a prolonged incubation time. There have been no formal studies on ICU patients in regard to a “3-day rule”.

Epidemiologic and Microbial Characteristics that are Important for Prevention and Control

Bacteria

Clostridium difficile—*Clostridium difficile* is an anaerobic, spore-forming bacillus that produces two exotoxins, toxin A and toxin B. These toxins cause intestinal pathology by disruption of the actin cytoskeleton and induction of neutrophil migration and mucosal inflammatory cascades (27–29). This organism was first reported in the stools of healthy infants in 1935 (30). *C. difficile* was relatively unnoticed for the next four decades, until Tedesco recognized the association of clindamycin with colitis in 1974 (31). Shortly thereafter, Bartlett and colleagues identified *C. difficile* as the major cause of antibiotic-associated colitis and the primary causative agent of pseudomembranous colitis (32).

Epidemiolog: In adults, *Clostridium difficile* is now the leading cause of infectious hospital-associated diarrhea in the United States, Canada, and Europe, and is being recognized increasingly in other parts of the world (33–34). Since *C. difficile* infection (CDI) is not yet a reportable disease in the United States as in the United Kingdom and some European countries, the true burden on health and health care spending, including the intensive care unit, is not really known (35).

National estimates indicate that the incidence of CDI increased from 5.5 cases per 10,000 population in adults (>17 years old) discharged from hospitals in the year 2000 to 11.2 cases per 10,000 in the year 2005 (36, 37). This represents a 23% average crude increase annually from 2000–2005, which contributed to 1.3% increase in overall hospitalizations (36). Data from acute care, ICU, cancer, cardiac, children’s, long-term and rehabilitation hospitals were collected on one day between May and August 2008, for 1,443 patients with CDI from 648 hospitals (12.5% of all medical facilities) (38). The point prevalence of *C. difficile* infection (CDI) was 13/1000 patients either infected or colonized. This was extrapolated to 7,178 affected inpatients on any given day. Overall 30-day mortality in patients with CDI in the

ICU was almost 40% during 2004–2005, and 6% mortality was directly attributable to CDI in the ICU (39, 40)

There are a constellation of interacting variables that might explain the increased incidence and severity of CDI. These include clonal expansion of the hypervirulent BI/NAP1/027 epidemic strain of *C. difficile*, lack of timely recognition of severe CDI, changes in medication prescribing practices, and increased and more complex patient co-morbidities in an increasingly aging or immunocompromised population (41–46). The BI/NAP1/027 clone has recently been implicated in several large outbreaks, with an associated increase in CDI severity (44, 45, 47, 48). Increased virulence of BI/NAP1/027 is thought to be due to its ability to produce 16–23 times more toxin A and toxin B, respectively. This strain also produces “binary toxin”, and this may also contribute to increased CDI severity (44, 49, 50).

Clinical presentation: *C. difficile* can cause a range of syndromes from asymptomatic colonization, to a mild self-limited diarrhea, to a life threatening colitis. Fatal ileitis in the absence of colonic involvement with *C. difficile* has also been recently described (51). Common symptoms of CDI include a watery, foul-smelling diarrhea, nausea, mild abdominal pain or cramping, and fever. CDI can rapidly progress to fulminant colitis with systemic inflammatory response syndrome and shock, resulting in death within hours or weeks. Although diarrhea is considered the hallmark for symptomatic CDI, abdominal pain and lack of diarrhea could indicate ileus with toxic megacolon. It is important to recognize many patients in the ICU have risk factors associated with severe CDI, such as advanced age, immunosuppression, and hypoalbuminemia, because recent data indicate oral vancomycin is superior to metronidazole for treating severe CDI (42, 52, 53). To date there is not a validated set of markers, either clinical or biologic, that can be used to predict morbidity and mortality.

Risk Factors: Independent risk factors for CDI include exposure to antimicrobials, age >60 years, exposure to other patients with CDI, residence in a chronic care facility, gastric acid suppression, and severe underlying disease (54–56). Others important risk factors for CDI seen in the ICU include recent surgery, immunosuppression, and a newly recognized risk, pregnancy (57, 58). It can be difficult to identify patients at risk for CDI in the ICU because many patients in the ICU have the risk factors listed above.

Antimicrobial exposures are the most common, and potentially modifiable risk factor for CDI in the ICU setting. Antimicrobials increase the risk for CDI by altering protective gut flora. Historically, clindamycin, ampicillin, and cephalosporins were the antimicrobials associated with the greatest risk for CDI (59). More recently, fluoroquinolones have emerged as another antimicrobial strongly associated with CDI (60). Prolonged courses of antibiotics and the exposure to multiple antibiotics also are associated with CDI (60).

CDI has also been associated with gastric acid suppressive agents, such as H₂-receptor antagonists and proton pump inhibitors (PPIs) (55, 56). These medications are almost universally used in the ICU to help reduce the risk of stress-associated mucosal damage (61). Clostridial spores survive at gastric pH 1, but gastric acid may inhibit the germination of spores into vegetative, toxin producing, cells. This may explain the increased risk of CDI associated with gastric acid suppression (62). In addition, CDI is associated with tube feeds, and in particular post-pyloric tube feeds (63–66). This provides additional evidence that gastric acid, despite not killing *C. difficile* spores, may be important in the prevention of CDI.

Laboratory studies: *C. difficile* testing is recommended for adults and children 1 years old with unexplained diarrhea associated with antibiotic use. There are several laboratory-

based methods to diagnose CDI, and they all have advantages and disadvantages. Most commonly employed are tests to detect toxin A and/or B from the stool of a patient with diarrhea. The cell culture cytotoxicity assay is the most sensitive method to detect toxin from stool. However it takes 24 to 72 hours for results, it requires the ability to maintain cell cultures, and it is relatively expensive. The most common method to diagnose CDI in the United States is with enzyme immunoassays (EIA) to detect both toxins. These tests are rapid with same day results and are inexpensive. The disadvantage of these assays is they are less sensitive than most other laboratory-based assays to diagnose CDI.

Other tests that detect *C. difficile* in the stool include stool culture for *C. difficile*, EIAs that detect glutamate dehydrogenase (GDH), and polymerase chain reaction (PCR)-based tests. Stool culture for *C. difficile* is the most sensitive method for detecting *C. difficile* in the stool, but it is expensive, labor intensive, and takes 48 to 96 hours for results. EIAs that detect GDH are highly sensitive, but they are not specific. Some facilities use a GDH EIA as a screen, and confirm positives with a cell culture cytotoxicity assay (67). PCR-based assays appear highly sensitive and specific, but they are expensive and require specialized equipment (68).

Prevention: There are two primary approaches for preventing CDI: preventing transmission and exposure to *C. difficile*, and decreasing risk of infection if exposure to *C. difficile* occurs. Recommendations for preventing CDI in acute care facilities have been published recently (69). Included in the published recommendations are methods to facilitate diagnosis and implementation of prevention measures. These will be covered in the “Prevention and Control Measures” section, as they are pertinent for all infectious, transmissible causes of diarrhea in the healthcare setting.

The main mechanism of *C. difficile* spread is via fecal-oral transmission of the spores from person to person. The infectious dose₅₀ (ID₅₀) is not known in humans, but humans with CDI are reported to excrete 10⁷–10⁹ spores/gram of feces, and fewer than 10 spores are able to cause disease in hamsters (70, 71). Health care workers, including physicians, spread the spores on their hands or on medical equipment, and spores can be isolated from the environment weeks or months after discharge of an infected person (72, 73). Basic measures to prevent transmission of CDI in the healthcare setting include conducting CDI surveillance, placing patients with CDI in contact precautions, and monitoring of hand hygiene, contact precaution, and environmental cleaning practices compliance.

Although *C. difficile* spores are resistant to alcohol and standard hospital disinfectants used to clean patient rooms, it is not recommended to routinely avoid alcohol-based hand hygiene products after caring for a patient with CDI or to routinely use diluted bleach or other agents with activity against spores for environmental cleaning. Several studies have failed to demonstrate an increase in CDI with the use of alcohol-based hand hygiene products, and sporicidal environmental disinfectants can be difficult to use and have not been consistently associated with a reduction in CDI (74–81). However, it is recommended to consider preferentially washing hands with soap and water rather than using alcohol-based hand hygiene products and to use bleach for environmental cleaning in outbreak settings if compliance with hand hygiene, contact precautions, and environmental disinfection are otherwise considered adequate.

Decreasing the risk of CDI if *C. difficile* transmission occurs, involves antimicrobial stewardship. The first line of defense against developing CDI after *C. difficile* exposure is healthy gut flora. Antimicrobial stewardship, by decreasing the number of patient on antimicrobials and/or decreasing high risk antimicrobial exposures, decreases the number of patients at risk for CDI if *C. difficile* exposure occurs. This in turn will also decrease *C.*

difficile transmission by decreasing the number of patients with CDI contributing to the spread of *C. difficile*. Antimicrobial stewardship programs focused on restriction of a single antimicrobial and programs focused on improving antimicrobial prescribing practices have led to reductions in CDI, including an outbreak due to the NAP1 strain (82–84).

Salmonella enterica—*Salmonella enterica* is a facultative, intracellular Gram negative enteric bacillus, whose species contains >2500 serotypes. Most human infections worldwide are caused by *S. enterica* subsp. *enterica* serotypes *typhi*, *typhimurium*, and *cholerasuis*, and *enteritidis* causes most of the food-borne illness in the United States (85, 86). The infectious dose where 50% are infected (ID₅₀) for nontyphoidal disease varies from 200-1 million bacilli (87). *S. typhi* is more apt than nontyphoidal *Salmonella* in causing bacteremia and invasive disease.

Epidemiology: Worldwide estimates of nontyphoidal *Salmonella* infection are from 200 million to 1.3 billion, with 3 million deaths annually (88). An estimated 1.4 million people in the United States are infected with nontyphoidal *Salmonella* annually (14). The reported 2007 incidence was 14.9 cases per 100,000, and this has been stable since 2004. Reservoirs for *Salmonella* include humans, poultry, swine, reptiles, dogs and cats. Fecal-oral transmission occurs by way of water, eggs, dairy, and other products, with recently recognized unpasteurized orange juice as a vehicle (86, 89). Typically thought of as a community pathogen, *Salmonella* frequently causes disease in the healthcare setting. Although *Salmonella* is typically associated with contaminated food, secondary transmission can occur in the healthcare setting by direct person to person spread or indirectly from contaminated fomites (such as endoscopes). Up to 35% of cases of *Salmonella* in the US are healthcare-associated, *Salmonella* caused >50% of outbreaks in nursing homes between 1975 and 1987, and 81% of nursing home deaths from foodborne illness (case fatality rate of 3.8%) (90).

Risk factors: Age <20 years or >70 years are associated with an increased risk of infection due to *Salmonella*. Neonates are at the greatest risk for infection after exposure due to relatively decreased stomach acid, and the elderly due to co-morbidities. In addition, immunocompromised states due to HIV, chemotherapy or aplastic anemia also are recognized as increasing risk of Salmonellosis (85, 91, 92).

Clinical presentation: Salmonellosis can present with acute gastroenteritis, enteric fever, bacteremia, extraintestinal infection, or as an asymptomatic, chronic carrier state. There can be fairly significant abdominal pain that is similar to that of inflammatory bowel disease or pseudoappendicitis (87). Gastroenteritis is highest during May through October in temperate climates. Antibiotics are usually not indicated since gastroenteritis is self-limited in otherwise healthy people. The exceptions are moderate or severe disease, the presence of bacteremia, sickle cell disease or prosthetic grafts, and extraintestinal disease, or disease in immunocompromised hosts (85, 87, 93).

Laboratory Studies: Stool culture is the main stay of diagnosis, but sensitivity decreases after the first week of illness or with antibiotic therapy. Blood cultures are indicated with persistent fever or signs of sepsis. *Salmonella* is a reportable disease, and local reporting requirements should be followed. In order to characterize an outbreak, highly discriminative nucleic acid typing methods of the serovar can be done (94).

Prevention: A single case of *Salmonella* infection should prompt an investigation as to whether the infection is healthcare-associated. Many healthcare-associated outbreaks of *Salmonella* start with contaminated food. Outbreak investigations should evaluate food

handling practices as well as potential patient-to-patient and healthcare worker-to-patient transmission. Since the hospital case/outbreak could be part of a larger epidemic, it is important that the ICU works closely with infectious diseases specialists, infection prevention and control personnel, and public health officials. Standard hospital disinfectants and alcohol-based hand hygiene products are effective against *Salmonella* species. Contact precautions are reserved for incontinent or diapered patients to control institutional outbreaks.

Viruses

Rotavirus—*Rotavirus* is non-enveloped virus with a double-stranded, segmented RNA genome. Rotavirus is found worldwide and infects almost all children by 2–3 years of age (95). The incidence of gastroenteritis due to rotavirus is the same in developed and developing countries, but mortality is higher in impoverished regions with malnutrition and poor access to medical care (96).

Epidemiology: Transmission is primarily by the fecal-oral route, and dry conditions in the winter may help facilitate spread (97, 98). Ninety-one to 94% of hospital-acquired infectious diarrhea cases in children are due to viruses, including the ICU, and rotavirus causes 31–87% of these cases (16, 99–101). Rotavirus is excreted from affected infants at 10^8 – 10^{11} virions/gm feces, and can occur prior to symptoms, with prolonged shedding during convalescence. Spread of rotavirus among NICU infants from the hands of health care workers and visitors, with subsequent transmission to the regular ward has occurred (101). In the United States, rotavirus hospital-acquired diarrhea alone increased hospitalization cost from \$500–\$2500 per case, but the total economic burden is not yet known (102).

Clinical presentation: The primary risk factor for rotavirus is exposure of a non-immune person to a person with symptomatic infection. Immunity after an initial episode is incomplete, but subsequent episodes of illness are less severe. The incubation period for rotavirus is typically around two days and symptoms can last three to eight days. Profuse watery diarrhea with dehydration and electrolyte abnormalities are generally more severe in infants and children with rotavirus infection than with diarrhea caused by other common enteric pathogens (103–105). Vomiting is more common and prolonged with rotavirus compared to other pathogens as well. In immunocompromised children, rotavirus can be associated with chronic diarrhea, prolonged shedding and extraintestinal infection (106). Rotavirus has caused severe infections in adults, including some deaths (18).

Laboratory Studies: Since it is difficult to distinguish gastroenteritis due to rotavirus from other causes of gastroenteritis on clinical grounds alone, confirmation of the diagnosis is important for complicated cases, in immunocompromised patients, and for epidemiologic infection control purposes. Rotavirus detection is possible by many assays, but enzyme-linked immunoassay for VP2 and 6 are widely used (107). Reverse-transcriptase PCR (RT-PCR) on stool samples is more sensitive than enzyme-linked immunoassays for rotavirus and is now the major diagnostic test. Some of these tests have the ability for fine type discrimination of P and G types for epidemiologic studies (108, 109).

Prevention: All patients with rotavirus infection should be placed in contact precautions for the duration of their illness. Rotavirus is very hardy and resists inactivation by chlorination found in sewage effluents and drinking water (98, 110). However, it is inactivated by antiseptics with >40% alcohols, free chlorine >20,000 ppm, >10,000 ppm iodine, phenol-based compounds, and calcium chelators (111). A commercial disinfectant spray with 79% ethanol and 0.1% *o*-phenylphenol (Lysol) prevented transmission from fomites to human

volunteers, and quaternary ammonium products were found to be no more effective than tap water (112). Rotavirus survival decreases markedly with high humidity.

Norovirus: *Norovirus* is a single-stranded positive-sense RNA virus that is a member of the Calicivirus group. It is found worldwide, and causes an estimated 23 million cases in the United States annually (113, 114). Norovirus gastroenteritis comprises 17–46% of viral, hospital-associated gastroenteritis in children (115–117). Seroprevalence studies indicate norovirus exposure occurs in early childhood, and 90% of older children and adults have been exposed (118).

Epidemiology: Norovirus hospital-associated outbreaks have occurred both in pediatric and adult patients on the general wards and in the intensive care unit (Table 1). The major mode of transmission is person-to-person by fecal or vomitus-oral route (115, 116). Rapid secondary spread from patients to health care workers, low infectious dose, very short incubation time, and survival in feces and vomitus, necessitate rapid recognition of norovirus for implementation of control measures and to prevent patient morbidity and economic loss (117). In one large outbreak involving a coronary care unit and psychiatry wards, the high attack rate for patients and health care workers resulted in unit closures, extensive disinfection, furloughing or cohorting staff, and cost an estimated \$658,000 (19).

There are also cases of norovirus pseudo-outbreaks and norovirus outbreaks being mistakenly attributed to other pathogens. In several NICU outbreaks in Europe, false positive results from different manufacturers of norovirus antigen enzyme immunoassays resulted in implementation of prevention measures that were costly and unnecessary. A rapidly disseminating outbreak that was originally attributed to *C. difficile* but was really due to norovirus occurred in a hospital where *C. difficile* was endemic (119). Conversely, efforts to abort a norovirus outbreak resulted in a reduction in CDI (120–123).

Clinical presentation: The primary risk factor for norovirus is exposure of a non-immune patient to a patient shedding norovirus. Immunity to norovirus appears to be strain specific, and wanes after several months. The incubation period is 24 to 48 hours, but can be as short as 12. In general, abdominal cramping and/or nausea can occur gradually or abruptly, followed by vomiting and/or diarrhea. Fever up to 101°–102° can occur, and diarrhea, although it can be profuse, typically lasts only 24 to 60 hours (Table 2).

Laboratory studies: Specific diagnosis requires laboratory confirmation because the signs and symptoms of norovirus gastroenteritis are not characteristic. Unfortunately testing for norovirus is not routinely performed in clinical laboratories in the United States. Sensitive and specific antigen enzyme immunoassays on stool are valid for detection as long as the monoclonal antibody panel can detect antigenic variants of the capsid protein (124, 125). Highly sensitive RT-PCR is also useful for detecting and genotyping norovirus in stool, food and environmental samples (126). Immunoassays have been used for diagnosis of antibody to the virus, with titer rise within 10–14 days of onset (127, 128). Serology can be useful, because diarrhea is generally short-lived and limits the time available to collect samples for characterizing outbreaks.

Prevention: It is extremely important that intensivists recognize norovirus gastroenteritis early, due to the debilitating nature of the disease, the explosiveness of outbreaks, the high infectivity and stability of the virus (19). Patients who are incontinent or diapered should remain in contact precautions for the duration of their illness. Special attention needs to be paid to environmental cleaning, even if surfaces do not appear to be soiled. It may be necessary to clean the environment with bleach (500 ppm available chlorine) during outbreaks. Although norovirus is relatively resistant to alcohol, there is no evidence that

alcohol-based hand hygiene products are not effective for hand decontamination. Aerosolization as a mode of infection may occur, and those who are engaged in cleaning heavily infected areas of vomitus and feces may benefit by wearing masks (12, 129).

Parasites

Much of the developing world has a relatively high endemic burden of parasitic and bacterial enteric pathogens, unlike developed countries. It is possible that parasites, such as *Giardia lamblia* and *Cryptosporidium* may be underestimated causes of hospital-associated infection in developing countries due to their low infectious doses, but the incidence of these diseases are unclear. Hospital-associated parasitic gastrointestinal infections in the United States are extremely rare. However, one must still maintain vigilance in the hospital for spatially related cases, during large community outbreaks of water-borne *Cryptosporidium*, or temporal increase in *Cyclospora* cases in association with contaminated water or food.

Cryptosporidium—*Cryptosporidium* species are protozoan parasites with a world-wide distribution, and infection occurs after ingestion of the oocyst. Increase in cases typically occurs in warm, moist months with peaks from July through September in temperate zone countries (130). It is transmitted by fecal-oral route, and large outbreaks have occurred due to surface water contamination in the United States (131). It is estimated that 300,000 people are affected each year in the United States in the absence of an outbreak (113). Cryptosporidiosis is particularly problematic in HIV-AIDS, in immunosuppressed transplant patients, and children with primary immunodeficiencies (132–134). Hospital-associated infection has been reported in health care workers spatially related to patients (135, 136). However, there appears to be low transmission risk, even between those with HIV-AIDS, with standard precautions of gloving and hand washing (136).

Clinical presentation: The development of symptoms is variable and seems to be strain-dependent, ranging from mild and self-limited to more severe (137). In immunocompetent persons, cryptosporidiosis is less likely to cause vomiting than other causes of gastroenteritis, and relapses may follow a diarrhea-free period of days to weeks (138). Cryptosporidiosis in HIV has decreased in incidence due to improved highly active retroviral therapy (139). However, chronic diarrhea is characterized by frequent, foul-smelling bulky stools with development of malabsorption and malnutrition, or less frequently, voluminous watery diarrhea.

Laboratory studies: The sensitivity and specificity for acid-fast staining of the oocyst in stool is poor, requiring >500,000 oocysts/ml, and it can be confused with *Isospora* and *Cyclospora* (140, 141). Although antigen-detection immunoassays have specificity and sensitivities from 66%–100%, there have been pseudo-outbreaks due to false positive results (142, 143). Nested PCR has been described for detection of *Cryptosporidium* in stool (144).

Prevention: Patients incontinent of stools or diapered should be placed in contact precautions for the duration of their illness. *Cryptosporidium* is difficult to eradicate from hard surfaces. Oocysts can remain infectious for six months if kept moist, and are extremely resistant to chlorination (two hour exposure to 5% bleach), especially in the presence of fecal material (145, 146). In addition, oocysts are also resistant to various concentrations of alcohols, phenol, iodophors and quaternary ammonium compounds, but a 1000-fold decrease in infectivity occurs with a four minute exposure to 6–7% hydrogen peroxide (147). Despite the resistance of *Cryptosporidium* oocysts to multiple agents, standard hospital disinfectants can be use in the absence of an institutional outbreak.

Prevention and Control Measures—The National Academy of Engineering and the Institute of Medicine recently recommended using systems engineering approaches for improving the health care delivery system (148, 149). This recommendation was based on observations that the current care delivery system isn't designed to support care of complex patients, requiring multiple providers and services (150). The rapid increase in *C. difficile* hospital-associated infection and disease severity are examples of this. Systems engineering encompasses coordination, synchronization and integration of complex systems of personnel, information, and financial resources.

In the ICU, specific systems should be in place to decrease the occurrence of human error in recognizing, treating and controlling hospital-associated intestinal infections. Once diarrhea has been recognized, clearly delineated protocols that pertain to identifying the cause and reducing the risk of transmission of infectious agents to others should be implemented. These protocols involve the infection prevention and control department, nurses, physicians, support staff, visitors, and housekeeping staff. For *C. difficile*, pharmacy should be included as well in the development of treatment and prevention protocols. Protocols must be formatted so they are easily accessible to clinical staff caring for patients and it is easy to clearly identify the policies for specific syndromes and/or pathogens.

Recognition that patient has diarrhea or ileus: The first step to preventing the spread of an infectious cause of gastroenteritis is recognizing which patients have compatible clinical syndromes, and prompt initiation of diagnostic, treatment, and prevention protocols. Usually, the nursing staff in the ICU is the first to become aware that the patient's stooling pattern has deviated from normal. All patients with diarrhea that might be due to a transmissible agent should immediately be placed in contact precautions if they are incontinent of stool or diapered. Since *C. difficile* is the overwhelmingly most common cause of infectious diarrhea in adult hospitalized patients, many healthcare facilities allow nurses to send stool for *C. difficile* testing by means of a standing order or a telephone order if there is concern for CDI. These order sets can be altered as needed for ongoing outbreaks due to other pathogens or other patient populations (i.e. pediatric). Results of diagnostic testing can then be used to guide additional prevention efforts and treatment.

Verbal and electronic communication that a pathogen has been found: Appropriate clinical personnel must be alerted immediately when an epidemiologically important enteric pathogen is identified. At a minimum, ICU staff caring for the patient, the treating intensivist, and the infection prevention and control department should be notified. These steps allow treatment to be adjusted if needed, initiation of appropriate prevention measures (if not already done), and surveillance initiation by infection prevention and control personnel. The method by which these personnel are notified will depend on where the test is performed and existing infrastructure. Methods in which the alert may not be noted immediately (e.g., FAX) should not be the sole method for reporting the alert.

Isolation precautions and hand hygiene: Methods facilitating adherence to proper infection control procedures and policies must be in place. If any measures beyond standard/universal precautions are necessary, place clearly visible signs to indicate what precautions are necessary outside of the patient's room. For contact precautions, dedicated patient care equipment is placed in the room and gowns and gloves are made readily available to all people before entering the room. Assign responsibility for monitoring the availability and restocking of supplies to specific healthcare personnel. Alcohol-based hand hygiene products should be easily accessible.

Environmental cleaning: Cleaning responsibilities and protocols are to be clearly defined for the particular pathogen. For example it is uncommon for housekeepers to be responsible

for cleaning medical equipment in patient rooms, such as ventilators. Specific ICU staff must be assigned to clean the ventilators and any other equipment for which housekeeping staff are not responsible. Environmental disinfectants are often purchased in concentrated form and diluted prior to use. Systems need to be in place to ensure cleaning agents that are not typically used for daily cleaning are mixed in the proper proportions and applied as directed if they are needed for specific pathogens.

Conclusion—The three most common hospital-associated enteric pathogens in the United States, *C. difficile*, norovirus, and rotavirus, cause significant morbidity, and economic losses due to unit closures and furloughing of staff. Lag in diagnosis and treatment can be devastating to the already fragile ICU patient. When considering a causative pathogen, it is important to consider not only symptomatology, but also patient risk factors, spatial/temporality of cases in the rest of the hospital, and current outbreaks in the community.

Hand-in hand with correct recognition of etiology is prompt implementation of preventive measures. This can be encouraged by designing systems that facilitate indicated isolation precautions, healthcare worker compliance with the precautions, and environmental decontamination.

Acknowledgments

Financial Support: National Institutes of Health Grant 1K23AI065806-01A2 (ERD)

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Table 1
Selected Intensive Care Unit Hospital-Associated Intestinal Infection Studies

Reference	Study Purpose	Location	Type	Outcome	Pathogen
Walters (1982) (5)	Identify cause of PMC ¹ , CDI ² increase, transmission in ICU	Large tertiary care hospital in Australia	Observational; outbreak of CDI	<i>C. difficile</i> spores in environment for weeks; isolated PMC patients to control outbreak	<i>C. difficile</i> ; cytotoxin by tissue culture (CT-TC) ³ bacterial culture
Foulke (1989) (6)	CDI Management and prevention in ICU	Large academic tertiary care hospital in US ⁴ (California)	Observational; outbreak over 2-week period	Contaminated enemas, NG ⁵ tubes, bed sheets/pans; patients put on enteric precautions; cleaning; teaching	<i>C. difficile</i> ; CT-TC
Singh-Naz (1996) (7)	Hospital-acquired diarrhea (HAD) and Rotavirus (RV)-Risk factors in PICU (pediatric)	Large academic tertiary care hospital in US (Washington DC)	Prospective cohort 1992-93	Increase with PRISM ⁶ score, surgery, stay, antibiotic therapy >10 days, parenteral nutrition, device utilization; RV 9%	Rotavirus; diagnostic not specified
Archibald (2004) (8)	CDI ICU surveillance for HAD	US hospitals and ICUs	Review by CDC NNIS ⁷ in US 1987-2001	Increased in >500-bed hospitals, stay, device use; CDI highest in winter	<i>C. difficile</i> ; diagnostic not specified
Guallar (2004) (9)	Salmonella outbreak in ward from ICU	Large tertiary care hospital in Spain 1998	Observational; outbreak source, control, prevention	AR ⁸ 0,138 per 1000 patient days; immunosuppressed 41% mortality; kitchen source	Salmonella: bacterial culture and typing
Ang (2008) (10)	CDI acquisition rate and outcome in ICU	Large tertiary care hospital in England	Retrospective- all ICU admit from 2004-07 with CDI	mean CDI acquisition in 7 days; overall CDI AM ⁹ 33.9%; older	<i>C. difficile</i> ; toxin A-B EIA ¹⁰
Sommer, 2009 (11)	Norovirus presentation and diagnostics in NICU	Large tertiary care hospital in Austria	Two separate outbreak descriptions in 2007, 2008	Prolonged shedding, outbreak hard to contain	Norovirus; EIA or RT-PCR ¹¹ adenovirus, rotavirus, stool cultures, parasitology

¹ PMC-pseudomembranous colitis

² CDI-*C. difficile* infection

³ CT-TC-*C. difficile* cytotoxin B tissue culture assay

⁴ US-United States

⁵ NG-nasogastric

⁶ PRISM-Pediatric Risk of Mortality

⁷ CDC NNIS-Communicable Disease Center National Nosocomial Infection Surveillance

⁸ AR-attack rate

⁹ AM-attributable mortality

ELA-enzyme immunoassay
// RT-PCR-reverse transcriptase polymerase chain reaction

Table 2

Intestinal Pathogens That May Be Encountered in Health-Care Settings

Organism	Transmission	Syndrome ¹	Incubation Period	Duration	Laboratory Diagnosis	Institutional Control (12)
<i>Staphylococcus aureus</i>	Food (food poisoning); contact (infectious enterocolitis)	V ² , d ³ , a ⁴	2–6 hours	6–12 hours	Culture food, vomitus.	Food poisoning: review food handling; not transmissible from person-to-person. Infectious enterocolitis: contact precautions
<i>Bacillus sp usually cereus</i>	Food	V, D	Emetic toxin-1–5 hours; diarrhea toxin-8–16 hours	24 hours	Culture of food, stool; EMT-PCR ⁵ , DHLT ⁶ serology	Review food handling; not transmissible from person-to-person
<i>Clostridium perfringens</i> type A	Food	D, A, v, f ⁷	7–15 hours	24 hours	culture	Review food handling; not transmissible from person-to-person
<i>Clostridium difficile</i>	Fecal contact; ? food and animals	D, A, F, s ⁸	unknown	variable	EIA ⁹ TC ¹⁰ , culture, PCR	Contact precautions //, soap and water for hand washing; hypochlorite for cleaning if transmissions continues
<i>Clostridium botulinum</i>	Food, soil	d (adults), C ¹² (infant), p ¹³	12–36 hours	variable	Culture stool, food; serology	Review food handling; not transmissible from person-to-person
<i>Salmonella spp</i>	Food, water, fecal contact	d, v, a, F, s	6–48 hours	3–7 days	culture	Review food handling; contact precautions
<i>Shigella spp</i>	Food, water, fecal contact	D, V, A, F	1–3 days	1 day-1 month	culture	Contact precautions
<i>Campylobacter jejuni</i>	Food, fecal contact	D, A, F	12–24 hours	1 week or longer	culture	Contact precautions
<i>Yersinia enterocolitica</i>	Food, fecal contact	D, F, A, v	4–7 days	1–3 weeks	culture	Contact precautions
<i>Escherichia coli (EC)</i> ETEC-enterotoxigenic	Food, water	D, F, A	hours-2 days	5 days or less	PCR for enterotoxin Gene	Contact precautions
EC-EPEC-enteropathogenic	Fecal contact, food, water	D, V, F	16–48 hours	5–10 days	TC, PCR	Contact precautions
EC EIEC-enteroinvasive	Food?	D, f, a	16–48 hours	2–7 days	Culture, PCR	Contact precautions
EC EHEC-enterohemorrhagic	Fecal contact, food, water	D, A, HUS ¹⁴	17–120 hours	2–12 days	Culture, PCR	Contact precautions
<i>Aeromonas spp.</i>	Food	D, F	Unknown	1–7 days	Culture, PCR	Contact precautions
<i>Rotavirus</i>	Fecal contact	D, F, V	24–72 hours	1–4 days	RT-PCR ¹⁵ , EIA, EM ¹⁶	Contact precautions; consistent environmental cleaning, disinfection, frequent diapering
<i>Norovirus.</i>	Fecal, vomitus contact, ? aerosol	D, F, V, h	24 hours	2–3 days	If needed EIA, RT-PCR	Contact precautions; consistent environmental cleaning, disinfection;

Organism	Transmission	Syndrome ¹	Incubation Period	Duration	Laboratory Diagnosis	Institutional Control (12)
<i>Adenovirus</i> subgroups B, F	Fecal contact	F, v, d	Unknown	1–2 weeks		hypochlorite if continued transmission; consider cohorting affected patients to separate airspaces, toilet facilities to interrupt transmission
<i>Cryptosporidium</i>	Fecal contact, food, water	D, F, v, a	1–30 days	5–10 days or chronic	EIA, serology, PCR	Contact precautions; immunocompromised can have prolonged shedding
<i>Cyclospora cayentanensis</i>	Water, food	D, A, f, w ¹⁷ , ei ¹⁸	1–11 days	2–7 weeks or longer	Smear, EIA, PCR	Contact precautions
<i>Entamoeba histolytica</i>	Fecal contact, food, water	D, F, A, ei	Unknown	Variable	Smear, serology, EIA, PCR	Contact precautions
<i>Giardia lamblia</i>	Fecal contact, food, water	D, A, m ¹⁹	1–2 weeks	1–several weeks or longer	Smear, EIA, PCR	Contact precautions

¹ Syndrome-uppercase indicates usual, lowercase indicates occasional

² V-vomiting

³ D-diarrhea

⁴ A-abdominal pain

⁵ EMT-PCR-emetic toxin polymerase chain reaction

⁶ DHLT-diarrhea heat labile toxin

⁷ F-fever

⁸ S-sepsis

⁹ EIA-enzyme-linked immunoassay

¹⁰ TC-tissue culture

¹¹ Contact precautions-use contact precautions for diapered or incontinent patients for duration of illness or to control institutional outbreak and modifications to this (12)

¹² C-constipation

¹³ P-paralysis

¹⁴ HUS-hemolytic uremic syndrome

- ¹⁵ RT-PCR-reverse transcriptase PCR
- ¹⁶ EM-electron microscopy
- ¹⁷ WL-weight loss
- ¹⁸ EI-extraintestinal
- ¹⁹ M-malabsorption. "Table adapted with permission from C. Glen Mayhall (2004)." (13).