Clostridium difficile Infection in Older Adults: Systematic Review of Efforts to Reduce Occurrence and Improve Outcomes

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OBJECTIVE: Provide a systematic review of the primary literature on efforts to reduce *Clostridium difficile* infection (CDI) occurrence and improve outcomes in older adults.

DATA SOURCES, STUDY SELECTION, DATA EXTRACTION: PubMed and CINAHL databases were searched for research studies using search terms CDI, CDI prevention, reduction, control, management, geriatric, elderly, adults 65 years of age and older. The MeSH categories Aged and Aged, 80 and older, were used. A second search of PubMed, CINAHL, National Guideline Clearinghouse, and TRIP databases was conducted for primary, secondary, and tertiary literature for CDI epidemiology, burden, and management in adults of all ages, and prevention and management guidelines. Of the 2,263 articles located, 105 were selected for full review: 55 primary and 50 secondary, tertiary. Primary literature selected for full review included studies of interventions to prevent, reduce occurrence, control, manage, or improve outcomes in adults 65 years of age and older. Patient settings included the community, assisted living, nursing facility, subacute care, or hospital.

DATA SYNTHESIS: The main outcome measures for research studies were whether the studied intervention prevented, reduced occurrence, controlled, managed, or improved outcomes. Studies were conducted in acute or long-term hospitals, with a few in nursing facilities. Interventions that prevented or reduced CDI included antibiotic policy changes, education, procedure changes, infection control, and multi-intervention approaches. There were few management studies for adults 65 years of age and older or for all adults with results stratified by age. Treatments studied included efficacy of fidaxomicin, metronidazole, vancomycin, and fecal microbiota transplant. Though clinical outcomes were slightly less robust in those 65 years of age and older, age was not an independent predictor of success or failure. The current prevention and management guidelines for adults of all ages, as well as special considerations in skilled nursing facilities, extracted from the secondary/tertiary literature selected, are summarized.

CONCLUSION: There are a limited number of studies designed for older adults. Our findings suggest that guideline recommendations for adults are adequate and appropriate for older adults. Exposure to antibiotics and *Clostridium difficile* remain the two major risk factors for CDI, reinforcing the importance of antibiotic stewardship and infection control.

KEY WORDS: Antibiotic stewardship, *Clostridium difficile* infection, Contact precautions, Fecal microbiota transplant, Fidaxomicin, Gastrointestinal, Infection control, Metronidazole, Older adults, Probiotics, Vancomycin.

ABBREVIATIONS: AE = Adverse event, APIC = Association for Professionals in Infection Control and Epidemiology, CDAD = CDI-associated diarrhea, CDI = *Clostridium difficile* Infection, CCDI = Complicated CDI, FMT = Fecal microbiota transplant, IC = Infection control, ID = Infectious disease, mITT = Modified intent-to-treat, PPI = Proton-pump inhibitor, PX-UV = Pulsed-xenon ultraviolet, RCDI = Recurrent CDI, RCT = Randomized controlled trial, SCDI = Severe CDI, SHEA = Society for Healthcare Epidemiology of America, SNF – Skilled nursing facility, WBCs = White blood cells.

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Introduction

Clostridium difficile (CD), an anaerobic, spore-forming, toxin-producing, gram-positive bacterium, is currently the most common nosocomial pathogen in the United States, causing symptomatic *Clostridium difficile* infection (CDI) in some individuals.[1,2] Many people are asymptomatic carriers of CD and should not be treated, but others develop symptomatic infection necessitating prompt appropriate management.[3,4] The CD toxin causes the pathogenesis in the gastrointestinal tract, resulting in patient symptoms of abdominal cramping and diarrhea with three or more watery or loose stools in 24 hours. CDI is defined by acute onset of typical symptoms, including diarrhea, with documented CD or toxin A and B via stool sample, or confirmed pseudomembranous colitis, with no other cause for the diarrhea.[5] Patients may have increased white blood cells (WBCs) and fever, although the increase in WBCs and temperature may not occur as rapidly or to the same degree in older adults as in younger patients.[6,7] Some patients may develop ileus, toxic megacolon,

pseudomembranous colitis, other complications, or even death.[6,8,9] CDI is currently the leading cause of gastroenteritis-associated death in the United States.[8] Although many cases of CDI are acquired in the hospital, CDI in nursing facility residents and in individuals in the community has increased over the past two decades.[1,8,10,11] The majority of community-dwelling individuals who develop CDI visited an outpatient health care setting in the 12 weeks prior to CDI diagnosis.[8,12] The movement of individuals from the hospital to subacute care, nursing facilities, or even assisted living facilities, after a hospital stay, makes it difficult to determine if the nosocomial CDI was from the hospital stay or present health care setting.[5]

Exposure to systemic antimicrobial therapy for other infections and exposure to the CD organism, via the CD spores, are the two major CDI risk factors for all individuals.[1,3] Antibiotics change gastrointestinal microbiota, increasing susceptibility to CD colonization and infection.[9] The spores produced by CD have been found in patient rooms and on the skin one to four weeks after anti-CDI antibiotic therapy.[9] The most common areas for active spores in symptomatic individual's rooms were bedrails, bedside tables, and floor areas by toilets.[9,11] Older adults are at increased risk for developing CDI and have a higher CDI incidence than younger adults because of their increased exposure to antibiotics, increased exposure to health care settings, altered intestinal microbiota, multiple comorbid conditions, decline in renal function, and decline in immune function.[1,6-9] Decreased gastric acidity from age or use of medications that decrease gastric acidity, especially proton-pump inhibitors (PPIs), has also been considered to be a possible risk factor for CDI, as has fecal incontinence.[4,13] Older adults have an increased incidence of severe CDI (SCDI) compared with younger adults.[6] Older adults are also at increased risk for recurrent CDI (RCDI) because of the same risk factors as the initial infection, but also because of increased re-exposure to CD or CD spores remaining in the colon despite therapy.[6] Older adults who develop CDI while in any type of long-term care facility, e.g., long-term acute care hospital, subacute care facility, or nursing facility, after a hospital stay or not, have substantial morbidity and even mortality resulting from multiple factors including their frailty, comorbid conditions, severity of infection, and less robust response to initial antibiotic therapy.[9,10,13]

Prevention guidelines for CDI are written for adults of all ages and primarily focus on prevention measures in the hospital setting.[3,5,11,14] Management guidelines are also written for adults of all ages and base management recommendations on CDI severity, rather than age.[3,5,15] A Society for Healthcare Epidemiology of America (SHEA) position paper on CDI in long-term care facilities, published in 2002, based prevention recommendations on the current hospital-based guidelines at the time.[16]

With the increasing rates of initial CDI, RCDI, and SCDI in older adults, whether in the hospital, nursing facility, assisted living, or community setting, there is a need for an increased understanding of effective CDI prevention and management strategies for older adults to reduce occurrence and improve outcomes. Effective prevention and management is important not only in hospitals, but also in nursing or assisted living facilities, to reduce CD organism transmission and infection. As exposure to antibiotics is one of the two major risk factors for CDI, effective antibiotic stewardship in long-term care could reduce CDI occurrence.[14,16,17] If a nursing facility resident develops CDI, effective CDI infection control (IC) policies could prevent spread of CDI.[14] One national survey and two local surveys of nursing facilities found that nursing facilities usually follow voluntary IC guidelines, but some had no policies and procedures specific to CDI.[18-20] Our objective is to provide a systematic review of the primary literature for senior care pharmacists and other health care professionals working with older adults on published strategies to prevent, reduce occurrence, control, manage, and improve outcomes of CDI in adults 65 years of age and older. To augment the limited published CDI management studies designed specifically for adults 65 years of age and older, we also provide a report and analysis of management studies, published from 2011 onward, inclusive of all adults, that included a number of participants 65 years of age and older where the study outcomes were reported by participant age. In addition to critical analysis of the literature on CDI, we provide a summary of the current

CDI prevention and management guidelines for all adults in the Discussion section.[3,5,11,14,15]

Methods

The PubMed and CINAHL databases were searched for primary literature using key words and MeSH terms relevant to the prevention, occurrence reduction, control, treatment, or management of CDI in older adults. For this review, the definition of older adult was 65 years of age or older, which is reflected in the MeSH categories Aged (65-79) and Aged, 80 and older. The population settings included community, assisted living, nursing facility (or home), subacute care, long-term care, acute care or long-term care hospital, primarily in the United States. Many studies that were indexed for the terms "aged" and "aged, 80 and over," also included younger patients. Within the primary literature search of PubMed and CINAHL databases, the authors excluded primary literature studies not conducted in human patients, studies in languages other than English, case studies, meta-analysis, and review articles. A second search of PubMed, CINAHL, National Guideline Clearinghouse, and TRIP databases was conducted for primary, secondary, and tertiary literature for CDI epidemiology, burden, and management in adults of all ages, both research studies and reviews, and for prevention and management guidelines. This search included meta-analysis, review articles, and case studies, but excluded articles other than English. The search for studies in the primary literature that investigated management strategies for CDI in all adults was conducted to augment the limited published management studies found that were designed to only include participants 65 years of age and older and also to augment the management literature cited in the published guidelines.

Of the 2,263 articles initially located in the literature searches, the three authors selected 105 for full review. Of these, 55 were primary literature articles. Of the 55, 15 were research studies that investigated CDI prevention, reduction, control, treatment, or management exclusive to adults 65 years of age and older and were included in this systematic review and analysis. An additional eight research studies included in this systematic review and analysis investigated management strategies in all adults, included a significant number of adults 65 years of age and older, and reported study results by age. These additional eight research studies were published 2011 to date. Secondary and tertiary literature articles, as well as epidemiologic studies and research studies conducted in all adults, were used for additional information for the manuscript. The results of this systematic review and analysis were summarized based on the type of the intervention used to prevent or manage CDI, type of study conducted (randomized controlled trials [RCT] or observational), setting of the study, country of the study, and effectiveness of the intervention. Additionally, this review was evaluated vis-à-vis the current guidelines for all adults older than 18 years of age and also includes an update on vaccine development to prevent CDI.

Results

Research studies designed to investigate and document the outcomes of interventions for preventing, reducing occurrence, controlling, or managing CDI in adults 65 years of age and older were primarily set in either the acute or long-term hospital setting. Research designs included randomized controlled trials (RCTs) and before and after intervention studies as retrospective reviews. There were very few published studies set in the nursing facility (long-term care facility) and none in the assisted living or community setting with inclusion criteria limiting participants to those 65 years of age and older. Results of the published studies on interventions to prevent, reduce occurrence, or control CDI in adults 65 years of age and older are included in Table 1 and reported in detail below.[21-33] Database searches yielded few published studies designed specifically for adults 65 years of age and older comparing patient outcomes with different management strategies for existing initial or RCDI.[34,35] Database searches for management studies published 2011 onward in all adults to augment these limited findings and provide updated data yielded a few studies that included a number of older adults where participant outcomes were reported by age in the study results.[36-43] The outcomes of CDI management studies published 2011 or later, where study outcomes were

Table 1. Interventions to Prevent, Reduce Occurrence, or Control *Clostridium difficile* Infection[a]

Type of Intervention	Description of Study	Setting of Study	Type of Study	Outcomes of Study	Study Citation
Antibiotic policy changes	Piperacillin-tazobactam added to formulary to use in place of cefotaxime and then cefotaxime use was restricted	Elderly Medicine Unit (5 wards) at the General Infirmaries, a University teaching hospital, UK	Before and after study: retrospective review comparing CDI diarrhea rates pre- vs. postintervention	Reduction in CDI diarrhea rates by 52% ($P = 0.008$)	Wilcox MH, Freeman J, Fawley W et al. (2004)[21]
	Reinforced narrow-spectrum antibiotic policy with a feedback and audit program for prescribers	Three acute care medical wards for geriatric patients in a teaching hospital; participants aged 80 or older, UK	Before and after study: prospective controlled interrupted time series comparison pre- vs. postintervention	Reduction in CDI incidence rate ratios by 0.35 (95% CI 0.17-0.73; $P = 0.009$)	Fowler S, Webber A, Cooper BS et al. (2007)[22]
	Changed antibiotic policy including restricting the use of injectable cephalosporins	Acute care and rehabilitation wards of the Elderly Care Unit for patients 65 years and older of Cork Hospital, Ireland	Before and after study: retrospective analysis comparing CDI diarrhea rates pre- vs. postintervention	Reduction in CDI diarrhea rates (RR = 3.24, 95% CI 1.07-9.84; $P = 0.03$)	O'Connor KA, Kingston M, O'Donovan M et al. (2004)[23]
	Changed the antibiotic policy from an open to a restrictive policy	Elderly Care Unit of four wards for patients 75 years and older of Royal Hospital, UK	Before and after study: retrospective review comparing CDI diarrhea, mortality, & length of hospital stay pre- vs. postintervention	Reduction in CDI diarrhea from 37 to 16 cases ($P = 0.002$); no changes in mortality & length of stay for all patients admitted with infection	McNulty C, Logan M, Donald IP et al. (1997)[24]
Educational approach	Onsite infectious disease consultation service to medical residents instituted	Veterans Administration long-term care facility, 160 beds, US	Before and after study: retrospective review comparing antibiotic use and positive CDI tests pre- vs. postintervention	Antibiotic use decreased by 30% ($P < 0.001$) and rates of change for CDI positive tests declined in the post- vs. preintervention ($P = 0.04$)	Jump RL, Olds DM, Seife N et al. (2012)[25]
Procedure changes	Replacement of electronic thermometers with the single-use disposals	343-bed acute hospital and a 538-bed SNF, US	Before and after study: retrospective review comparing CDI diarrhea rates by patient days pre- vs. postintervention	Reduction in CDI diarrhea from 2.71 to 1.76/1,000 patient days in acute hospital and 0.41 to 0.11/1,000 in SNF	Brooks SE, Veal RO, Kramer M et al. (1992)[26]
	Increased environmental sanitation and use of tympanic thermometers throughout hospital	A 343-bed acute care hospital with predominantly elderly population referred from nursing facilities, US	Before and after study: retrospective review using Poisson regression model to compare relative incidence over time	A risk reduction of 60% for VRE and 40% for CDI (RR = 0.59, 95% CI 0.47-0.67)	Brooks S, Khan A, Stoica D et al. (1998)[27]
	Began use of launderable mattress and bed deck (metal surface below mattress) cover on beds	2 long-term acute care hospitals, A & B, 104 beds total; mean patient age pre & post, 66 +/– 1 and 65 +/– 2 years, respectively, US	Before and after study: retrospective review using Poisson regression model to compare relative incidence	Reduction in the rate of CDI by 47.8% (95% CI 47.1-48.6) in A and 50% (95% CI 47.5-52.7) in B	Hooker EA, Bochan M, Reiff TT et al. (2015)[28]

[a] In long-term facilities or hospitals with geriatric ward(s) where the study participants were adults 65 years of age and older.

Abbreviations: AAD = Antibiotic-associated diarrhea, CDI = *Clostridium difficile* infection, IC = Infection control, IDSA = Infectious Diseases Society of America, MRSA = Methicillin-resistant *Staphylococcus aureus*, SHEA = Society for Healthcare Epidemiology of America, SNF = Skilled nursing facility, VRE = Vancomycin-resistant enterococcus.

Source: References 21-33.

Table 1. Interventions to Prevent, Reduce Occurrence, or Control *Clostridium difficile* Infection[a] (continued)

Type of Intervention	Description of Study	Setting of Study	Type of Study	Outcomes of Study	Study Citation
Combined use of IC practices developed by a multi-disciplinary team and implementation of routine use of a nontouch pulsed-xenon UV disinfection device	After a 1-year baseline preintervention period, IC practices were implemented for a year and then the pulsed-xenon disinfection was added to IC and followed for 15 months	Long-term acute- care hospital, US	Before and after study: retrospective analysis of health care associated CDI pre- vs. postinterventions	CDI rates dropped 56.9% over the 15-month postintervention period of IC + pulsed-xenon disinfection compared with the preintervention baseline period	Miller R, Simmons S, Dale C et al. (2015)[29]
Multi-intervention approach	IC, active surveillance and diagnosis, environmental cleaning and disinfection based on SHEA and IDSA guidelines	Long-term acute-care hospital for the elderly, primarily ventilator-dependent, 50 beds, US	Before and after study: retrospective review using Poisson rate test to compare CDI rates pre- vs. postintervention	Reduction of CDI by 27.6% the first 12 months postintervention and 23% the second 12 months postintervention	Brakovich B, Bonham E, VanBrackle L. (2012)[30]
Multi-intervention approach following bed closures because of CDI and MRSA	Multi-infection control policy of cephalosporin restriction, 7-day time limit on antibiotics, feedback & teaching on infection rates, & emphasis on handwashing	Three acute medical wards for adults > 75 in an acute care hospital, UK	Before and after study: retrospective review comparing CDI and MRSA rates pre- vs. postintervention	Reduction in CDI rates from 3.35% of admissions (36/1,075) to 1.94% of admissions (27/1,392); $P < 0.05$; MRSA from 3.95% to 1.94%; $P < 0.01$	Stone SP, Beric V, Quick A et al. (1998)[31]
Lactobacilli and Bifidobacteria for patients beginning or on 1 or more antibiotics in the preceding 7 days	Treatment group given L & B once daily for 21 days and the control group placebo; participants followed for 12 weeks	Inpatients age 65 years and older, 3 acute care hospitals, UK	Multi-center randomized, double-blind placebo-controlled trial	CDI diarrhea rates of 1.2% (17/1,471) in placebo vs. 0.8% (12/1,470) in treatment group; RR = 0.71 (95% CI 0.34-1.47; $P = 0.35$)	Allen SJ, Wareham K, Wang D et al. (2013)[32]
Recombinant Lactoferrin (an antimicrobial protein found in human breastmilk) grown in rice for patients beginning a new antibiotic course	Treatment group received lactoferrin 5 mg/mL once daily by gastrostomy tube and the control placebo by gastrostomy tube for 56 days	Geriatric Center ventilator rehabilitation unit, US	Randomized controlled trial; n for analyses = 13 placebo, 9 treatment	Reduction in AAD, RR = 0.07, (95% CI 0.001-0.97; $P = 0.023$), but not CDI diarrhea	Laffan AM, McKenzie R, Forti J et al. (2011)[33]

[a] In long-term facilities or hospitals with geriatric ward(s) where the study participants were adults 65 years of age and older.

Abbreviations: AAD = Antibiotic-associated diarrhea, CDI = *Clostridium difficile* infection, IC = Infection control, IDSA = Infectious Diseases Society of America, MRSA = Methicillin-resistant *Staphylococcus aureus*, SHEA = Society for Healthcare Epidemiology of America, SNF = Skilled nursing facility , VRE = Vancomycin-resistant enterococcus.
Source: References 21-33.

clearly reported by age in the results and a significant number of study participants were 65 years of age or older, are included in Table 2.[34-43] The majority of research studies on CDI treatment, published 2011 or later, had inclusion criteria for participants 18 years of age and older, and the study outcomes were not reported by participant age.[44-57] The current guidelines for the management of CDI in adults are written for all adults, regardless of age. Management recommendations are based on disease severity, initial versus RCDI, and prior response to treatment rather than age.[3,5,15] The current guidelines for the prevention, reduction, and control of CDI in all adults are summarized in Table 3, Discussion section, and special considerations for nursing facilities per the Association for Professionals in Infection Control and Epidemiology (APIC) are summarized in Table 4, Discussion section. Because of the limited number of published management studies in older adults and management, per guidelines, decided by disease severity, rather than age, the current guidelines

Table 2. Management Studies of CDI in Adults Where Participants Were 65 Years of Age or Older[a]

Type of CDI Management	Description of Study	Setting of Study	Type of Study	Outcomes of Study	Study Citation
Metronidazole, oral, 500 mg 3 times a day	Multicenter cohort outcomes study of age-stratified patient response rates to inpatient treatment for CDI[b]	Three tertiary academic hospitals, US	Retrospective analysis (univariate and multivariate regression) of age-stratified treatment response; age > 70 (n = 73), age 50-70 (n = 97), age < 50 (n = 72)	Refractory CDI rates after treatment were 37%, 28%, and 22%, respectively, for age > 70, 50-70, & < 50 (P = 0.05), but age was not identified as an independent risk factor of refractory CDI; severity of CDI, severity of underlying illness & increased concomitant antibiotic use likely increased refractory CDI rates for > 70	Pham VP, Luce AM, Ruppelt SC et al. (2015)[36]
Fidaxomicin, oral, 200 mg 2 times a day versus vancomycin, oral, 125 mg 4 times a day, both for 10 days for 1st RCDI	Two multicenter RCTs, n = 1,164, of fidaxomicin vs. vancomycin for CDI; analysis of subpopulation of those enrolled for treatment of 1st RCDI, n = 178, for cure rates and time to 2nd RCDI; time to 2nd recurrence reported by age	Study sites in US, Canada, and Europe	Subgroup analysis of cure of 1st RCDI with fidaxomicin vs. vancomycin (1º end point); subgroup analysis of 2nd RCDI rates within 28 days of cure, results reported by age	Clinical cure of 1st RCDI was 74/79 (93.7%) & 76/83 (91.6%), respectively, for fidaxomicin and vancomycin; 2nd RCDI within 28 days of cure was > 2x for those ≥ 65 than those < 65 (HR = 2.57, 95% CI, 1.26-5.25; P = 0.01)	Cornely OA, Miller MA, Louie TJ et al. (2012)[37]
Fidaxomicin, oral, 200 mg every 12 hours versus vancomycin, oral, 125 mg every 6 hours for 10 days	Multi-center prospective noninferiority RCT; results reported by age (≥ 65 or < 65 years) in subgroup analysis[b]	52 study sites, US & 15 sites, Canada; participants treated inpatient and outpatient	Prospective, multi-center, double-blind, randomized, parallel-group trial to determine and compare CDI clinical cure rates and recurrence rates for fidaxomicin versus vancomycin	Per protocol population, subgroup age ≥ 65: clinical cure rates were 87.6% (99/113) & 88.4% (122/138) for fidaxomicin and vancomycin, respectively; CDI recurrence rates were 18.8% (16/85) & 30.1% (31/103) for fidaxomicin and vancomycin, respectively; P = 0.08	Louie TJ, Miller MA, Mullane KM et al. (2011)[38]
Fidaxomicin, oral, 200 mg every 12 hours, vs. vancomycin, oral, 125 mg every 6 hours each for 10 days	Multi-center, double-blind, randomized, noninferiority trial for acute CDI; modified intention-to-treat (mITT) results reported by age ≥ 65 (n = 273) & < 65 (n = 236)[b]	41 study sites in US and Canada, 45 sites in Europe	Prospective randomized trial; efficacy endpoints of clinical cure, recurrence rates, & sustained response rates in per protocol and mITT populations	Age ≥ 65 results, n = 273, mITT: clinical cure rates of 82.4%, vancomycin, vs. 85.2%, fidaxomicin (P = 0.534); recurrence rates of 27.8%, vancomycin vs. 13.2%, fidaxomicin; sustained response rates of 59.5%, vancomycin, vs. 73.9%, fidaxomicin	Cornely OA, Crook DW, Esposito R et al. (2012)[39]
Metronidazole, oral, 500 mg 3 to 4 times a day versus vancomycin oral (dose not provided), versus no antibiotic	Single-center outcomes study of all patients aged 80 and older with positive CDI assays and CDI clinical course during 1 year (n = 70)[a]	Tertiary care hospital, 850 beds, US	Retrospective review of clinical outcomes of patients aged ≥ 80 who received metronidazole (n = 65), vancomycin (n = 2), or no antibiotic (n = 3) as initial therapy for CDI	18/65 (27.7%) metronidazole-treated patients required change to vancomycin for initial cure; 12/70 (17.1%) patients required treatment for relapse within 90 days; high-peak WBC was independently associated with initial treatment failures (P < 0.01)	Cober ED, Malani PN. (2009)[34]

[a] Management studies of CDI in adults published 2011 or later where outcomes were clearly reported by age in study results and a significant number of participants were 65 years of age or older.

[b] Studies of management of CDI in adults, published 2011 or later, where management outcomes were clearly stratified by age in study results and a significant number of study participants were 65 years of age or older.

Abbreviations: AE = Adverse event(s), CDI = *Clostridium difficile* infection, CCDI = Complicated CDI, FMT = Fecal microbiota transplant, mITT = Modified intention-to-treat, RCDI = Recurrent CDI, SCDI = Severe CDI.

Source: References 34-43.

Table 2. Management Studies of CDI in Adults Where Participants Were 65 Years of Age or Older[a] (continued)

Type of CDI Management	Description of Study	Setting of Study	Type of Study	Outcomes of Study	Study Citation
FMT per center protocol, including esophagogastroduodenoscopy, enteroscopy, colonoscopy, sigmoidoscopy, & enema	Multi-center follow-up outcomes study for long-term efficacy of FMT for recurrent (RCDI), severe (SCDI), and complicated CDI (CCDI) in geriatric patients aged 65-97[a]	9 different medical centers in US, Canada, and Australia for the FMT	Follow-up survey questionnaire (47 items) study to determine primary and secondary outcomes, early (< 12 weeks) and late recurrence rates and any AEs	FMT performed on 89 patients with RCDI, 45 with SCDI, & 12 with CCDI; primary and secondary long-term cure rates were 82.9% and 95.9%, respectively; serious AE reported – 6 hospitalizations for CDI diarrhea including 1 death	Agrawal M, Aroniadis OC, Brandt LJ et al. (2016)[35]
FMT by frozen FMT capsules	Single-center, open-label feasibility outcomes study of efficacy & safety of FMT by 1 or 2 treatments of 15 frozen capsules on 2 consecutive days for recurrent or refractory CDI where 50% of participants were ≥ 65[b]	Hospital, US	Prospective feasibility study with follow-up questionnaire; clinical efficacy measured by diarrhea resolution, defined as no symptoms and no further CDI treatment at 8 weeks after 1 or 2 FMT treatments	10/20 (50%) patients were aged ≥ 65; of these 10, 8 (80%) had diarrhea resolution after 1 (n = 6)-2 (n = 2) FMT treatments; 2/10 (20%) did not have diarrhea resolution; no patients vomited within 24 hours of FMT	Youngster I, Russell GH, Pindar C et al. (2014)[40]
FMT	Single-center outcomes study of cure or failure rates of FMT for older hospitalized adults with severe CDI refractory to antibiotic therapy of at least 7 days of vancomycin ± metronidazole[b]	Tertiary care hospital, 900 beds, US	Retrospective review of 25 months to determine clinical cure rates with FMT for patients with severe CDI refractory to antibiotic therapy	14/49 patients who received FMT met inclusion criteria of severe refractory CDI; 10/14 (71%) were aged 66-92; outcome for 10 patients aged 66+: 70% had clinical cure and 30% experienced treatment failure with FMT	Zainah H, Hassan M, Shiekh-Sroujief L et al. (2015)[41]
FMT by colonoscopy	Single-center outcomes study of efficacy & safety of FMT by colonoscopy in preventing CDI recurrence in patients who had had at least 3 CDI recurrences[b]	Hospital, US, outpatient procedure	Retrospective review over 28 months of safety and efficacy of FMT delivered through the colonoscope in 26 total patients, 12 aged ≥ 65	24/26 (92%) of total patients and 10/12 (83.3%) of patients aged ≥ 65 did not experience further significant diarrhea nor developed a CDI relapse requiring further therapy; mean duration of follow-up, 10.7 months	Kelly CR, de Leon L, Jasutkar N. (2012)[42]
FMT by colonoscopy after a pretreatment with vancomycin or metronidazole until diarrhea symptoms were reduced	Multi-center outcomes study of efficacy of FMT by colonoscopy in patients with RCDI despite antibiotic therapy, total n = 70, n = 56 aged ≥ 65	Five hospitals, Finland; patients treated primarily as outpatients with a few inpatients	Retrospective review of patients treated with FMT by colonoscopy for RCDI 11/2007-2/2010	At 12 weeks post-treatment, 66/70 (94%) of patients, all ages, & 51/56 (91%) of patients ≥ 65 maintained resolution of symptoms; 4/56 (7%) ≥ 65 experienced relapse and death and 1/56 died of unrelated causes	Matilla E, Uusitalo-Seppala R, Wuorela M et al. (2012)[43]

[a] Management studies of CDI in adults published 2011 or later where outcomes were clearly reported by age in study results and a significant number of participants were 65 years of age or older.

[b] Studies of management of CDI in adults, published 2011 or later, where management outcomes were clearly stratified by age in study results and a significant number of study participants were 65 years of age or older.

Abbreviations: AE = Adverse event(s), CDI = *Clostridium difficile* infection, CCDI = Complicated CDI, FMT = Fecal microbiota transplant, mITT = Modified intention-to-treat, RCDI = Recurrent CDI, SCDI = Severe CDI.

Source: References 34-43.

Table 3. Recommendations to Prevent, Reduce Occurrence, or Control CDI in Adults per Current Guidelines

- Institution-based IC program
- CDI surveillance system with data review
- Antibiotic stewardship program[a]
- Appropriate treatment of confirmed CDI to reduce recurrence[b]
- Laboratory alert/report system to HCPs of positive CDI results
- Hand hygiene for all HCPs and visitors to rooms of patients with confirmed or suspected CDI[c]
- Contact precautions (gloves, gowns) for all HCPs & visitors to rooms of patients with confirmed or suspected CDI until diarrhea resolves, or per institution protocol; remove gloves/gowns prior to leaving patient room[d]
- Accommodate patient with confirmed CDI in a private room if possible or in a room with another patient with confirmed CDI
- Cleaning and disinfection of equipment and the environment with EPA-registered disinfectant with CD sporicidal labeling or with 5,000 p.p.m. chlorine-containing agent
- Use single-use disposable equipment or dedicated equipment
- Education of all facility personnel: HCP, administrators, environmental service, laboratory
- Education of CDI patients, family members, and other visitors
- Review compliance with institution-based IC program and CDI surveillance system; revise program as necessary

[a] All antibiotics increase CDI risk, with amoxicillin, cephalosporins, clindamycin, and fluoroquinolones resulting in the most increased risk.
[b] Asymptomatic carriers should not be treated; routine screening of patients without diarrhea is not recommended.
[c] Soap and water, instead of alcohol-based antiseptics, is recommended.
[d] Some institutions continue contact precautions for longer periods, as CD spores are excreted by patients even after CDI symptoms have resolved.

Abbreviations: CDI = *Clostridium difficile* infection, EPA = Environmental Protection Agency, HCP = Health care professional, IC = Infection control, p.p.m. = Parts per million.
Source: References 3, 5, 11, 14.

for the management of CDI are summarized in Table 5, Discussion section.

Primary literature on efforts to prevent, reduce occurrence, or control CDI in older adults

Our findings in the primary literature on interventions studied to prevent, reduce occurrence, or control CDI in adults aged 65 and older are documented in Table 1.[21-33] Studies are grouped by type of intervention, which included antibiotic policy changes, educational approaches, procedure changes, infection control practices, multi-intervention approaches, and probiotic use. Of the possible study settings, community, assisted living, nursing facility, subacute care, or hospital, the database search yielded no studies in the community or assisted living settings. Ten of 13 studies were set either in an acute care or long-term acute care hospital setting.[21-24,27-32] Of the remaining 3 studies, 1 was set in a nursing facility ventilator rehabilitation unit, 1 in a Veteran's Administration (VA) nursing facility, and the final study in both a hospital and a nursing facility.[25,26,33] Seven of the 13 studies were set in the United States and 6 were set in the United Kingdom or Ireland. Only 2 of the 13 studies were RCTs.[32,33] Both RCTs compared CDI rates in patients on antibiotic(s) for a non-CDI infection between those randomized to receive a probiotic or an antimicrobial protein versus placebo in addition to their non-CDI antibiotic.[32,33] The multi-center RCT in the hospital setting resulted in an insignificant reduction in CDI rates between the probiotic (n = 1,470) and placebo (n = 1,471) groups.[32] The very limited RCT, conducted in one nursing facility ventilator rehabilitation unit with tube-fed patients, resulted in a significant reduction in rates of CDI between the antimicrobial protein (n = 9) and placebo (n = 13) groups.[33]

The remainder of the studies from the literature (n = 11) were before and after intervention studies with retrospective analyses to measure the effectiveness of an intervention or interventions to reduce rates of CDI in adults 65 years of age and older (Table 1). The studied interventions resulted in modest to significant reductions in CDI occurrence rates.[21-31] Of these studies, one was set in both a 538-bed skilled nursing facility (SNF) and a 343-

Table 4. Special Considerations for Nursing Facilities with a Resident with CDI[a]

1. **Review facility IC policies and procedures and employ usual prevention strategies per guidelines for all institutions[a]**
2. **Nursing facility transmission-based precautions:**
   - Contact precautions (gloves, gowns) only for the length of time needed to prevent infection transmission
   - Use approach that protects the resident and other residents
   - Maintain resident's dignity, independence, without compromising rehabilitation, if possible
3. **Nursing facility ambulation and socialization of resident while contact precautions are in place:**
   - Assess resident's ability to contain body fluids
   - Assess resident's personal hygiene
   - If feasible, assist resident to perform hand hygiene and gown over clothes so that resident may ambulate outside the room
   - Disinfect any assistive devices (canes, walkers, wheelchair) before it leaves the room with the resident
   - If resident cannot comply with required hygiene or contain bodily fluids because of cognitive impairment or illness, consider 1:1 caregiver
4. **Nursing facility living arrangements:**
   - Private room and bathroom, if possible
   - If shared room necessary, depending on the condition of the two residents, have either the resident with CDI or the other resident use a bed-side commode
5. **Equipment and environment:**
   - Equipment and medical devices should be used only by the resident with CDI and disinfected thoroughly before future use; use disposable equipment and devices when feasible
   - Resident's clothing, towels, linens laundered as usual per facility IC protocol
   - Resident's dishes, cups, utensils cleaned and sanitized as usual per facility IC protocol

[a] Usual strategies for prevention of CDI per current guidelines should be in place and continued and appear in Table 3.

Abbreviations: CDI = *Clostridium difficile* infection, IC = Infection control.
Source: References 3, 5, 11, 14, 62.

bed acute care hospital and compared the CDI diarrhea rates by patient days, pre- versus postintervention.[26] Replacement of electronic thermometers with single-use disposable thermometers resulted in a reduction in CDI diarrhea from 0.41 to 0.11/1,000 patient days in the SNF and from 2.71 to 1.76/1,000 patient days in the hospital.[26] The one other before-and-after study in a nursing facility was conducted in a VA facility and compared antibiotic use and rates of change for CDI positive tests before and after institution of an infectious disease (ID) consultation service for the VA medical residents.[25] After implementation of the ID consultation service, antibiotic use rates (for non-CDI infections) decreased by 30% ($P < 0.0001$) and rates of change for positive CDI tests declined as well ($P = 0.04$). The remainder of the studies conducted in patients 65 years of age and older were set in acute or long-term acute hospital settings, most often in wards or units for geriatric patients.[21-24,27-31] Of these, the two most recent were published in 2015 and involved interventions of note.[28,29] Hooker et al. compared the relative incidence of CDI 16 months before and 14 months after instituting the use of a launderable mattress and bed deck cover in two long-term acute care hospitals designated A (74 beds) and B (30 beds).[28] They found a reduction in the rate of CDI by 47.8% (95% confidence interval [CI] 47.1-48.6) in hospital A and 50% (95% CI 47.5-52.7) in hospital B after initiating the routine use of the launderable mattress and bed deck covers. In the second before-and-after study published in 2015, Miller et al. investigated the effectiveness of implementing multidisciplinary infection control (IC) practices for 11 months and then added the use of a pulsed-xenon ultraviolet (PX-UV) device room disinfection

Table 5. Recommendations to Manage CDI in Adults Per Current Guidelines

Definition	Supporting Clinical Information	Recommended Treatment[a]
Mild or moderate, initial episode	Diarrhea, WBC count ≤ 15,000 cells/mm^3, SrCr < 1.5 times patient baseline	Metronidazole, oral, 500 mg three times daily x10 days[b]
Severe, initial episode	Diarrhea, WBC ≥ 15,000 cells/mm^3, SrCr > 1.5 times patient baseline, albumin < 3 g/dL, abdominal tenderness	Vancomycin, oral, 125 mg four times daily x 10 days[c]
Complicated severe, initial episode	Diarrhea; any of the following from the CDI: hypotension, temperature > 38.5 C, ileus, megacolon, mental status change, WBC ≥ 35,000 cells/mm^3, shock	Vancomycin, oral or nasogastric tube, 125-500 mg four times daily plus metronidazole, IV, 500 mg every 8 hours; add vancomycin, per rectum as enema, 500 mg in saline, every 4 hours with ileus or toxic colon; supportive care: IV fluids and electrolytes, thromboembolic prophylaxis; surgery consultation as needed
1st recurrence	Recurrent CDI within 8 weeks of initial episode[e]	Mild recurrent case – metronidazole if successful in initial episode; if metronidazole not effective or with severe recurrent case – vancomycin, oral, 125 mg four times daily x 10 days[f]
2nd recurrence		Vancomycin[c,f]
3rd recurrence		Fecal microbiota transplant[c,d]

[a] Additional treatment other than antibiotic for CDI: 1) discontinue any existing antibiotic therapy, 2) avoid beginning any other antibiotic therapy other than regimen to treat CDI if at all possible, 3) replace fluid and electrolytes as needed, 4) continue oral or enteral feeding unless patient has ileus or significant abdominal distention, 5) avoid antimotility medications, 6) review any existing proton-pump inhibitor therapy for possible discontinuation.
[b] Vancomycin, oral, 125 mg four times daily x 10 days as alternative treatment to be used in case of allergy or intolerance to metronidazole or if patient does not improve after 5-7 days of metronidazole treatment.
[c] May consider fidaxomicin, oral, 200 mg two times daily x 10 days.
[d] Fecal microbiotal transplant may be combined with oral antibiotic therapy.
[e] There is only limited evidence for using adjunctive probiotics with CDI antibiotic therapy to decrease recurrence rates.
[f] Following vancomycin, oral, 125 mg four times daily x 10 days with a pulsed dose of 125 mg daily every 3 days for 10 doses has been proposed.

Abbreviations: CDI = *Clostridium difficile* infection, IV = Intravenous, SrCr = Serum creatinine, WBC = White blood cell.
Source: References 3, 5, 15.

system as an adjunct to standard cleaning in all patient rooms and communal living areas in a long-term acute care hospital.[29] Infection rates decreased by 56.9% over 15 months of IC plus the PX-UV device compared with the preintervention baseline.

Primary Literature on Efforts to Improve Outcomes of CDI with Different Management Strategies

The few articles in the primary literature of RCTs or retrospective reviews designed for adults 65 years of age and older investigating management strategies for CDI, as well as studies published 2011 or later where results were stratified by age, are presented in Table 2.[34-43] There were two primary literature articles of management strategies for CDI in studies designed specifically to include only adults 65 years of age and older, both retrospective reviews.[34,35] Cober and Malani conducted a retrospective review of clinical outcomes of adults 80 years of age and older (n = 70) who received oral metronidazole (n = 65), oral vancomycin (n = 2), or no antibiotic therapy (n = 3) for an initial episode of CDI.[34] The study was based

at one tertiary care hospital; 15 patients were treated as outpatients and the remainder in the hospital for presentation with or development of initial CDI while hospitalized. The mean age of the 70 patients was 84.0 ± 4.1 years, mean peak WBC was 14.8 ± 8.6 mm^3, and 81.4% and 58.5% of patients, respectively, had received antibiotic therapy or a PPI in the 30 days prior to CDI symptom development. Eighteen of the 70 patients (25.7%) did not respond to therapy, all of whom were initially treated with metronidazole (median of 7 days of therapy) for a metronidazole success rate of 72.3% (47/65). The 18 patients required further treatment with vancomycin. Univariate analysis of risk factors for treatment failure identified an association between higher peak WBC and treatment failure ($P = 0.01$). Though the odds of treatment failure for patients with prior PPI use was twice those who had not used a PPI, it was not significantly significant ($P = 0.34$). Ninety days after CDI treatment, 12/70 patients (17.1%) had a CDI relapse.[34] In the more recent CDI study in older adults, published in 2016, Agrawal et al. investigated clinical outcomes of fecal microbiota transplant (FMT) for RCDI, SCDI, and complicated CDI (CCDI) in patients 65 to 97 years of age (n = 146; 100 females) at nine medical centers in the United States, Canada, and Australia.[35] The FMT was delivered by colonoscopy (80.8% of patients), esophagogastroduodenoscopy (9%), and several other routes (remaining patients). Primary cure, defined per protocol as resolution of symptoms after one FMT treatment with no recurrence in 12 weeks, was 82.9% overall, with primary cure rates of 82%, 91%, and 66%, respectively, for RCDI, SCDI, and CCDI. Secondary cure, defined per protocol as resolution of symptoms after repeat treatment with either vancomycin, FMT, or both after failure of initial FMT, was achieved in 95.9% of patients (140/146). No patient had complications from FMT but 11 patients experienced either non-CDI diarrhea or constipation and 6 patients were hospitalized for recurrent diarrhea, either from recurrent CDI or FMT. In this study, FMT was effective and safe in adults 65 to 97 years of age, mean age of 78.6, 68.5% of whom were females.[35]

The remaining management outcomes studies, Table 2, were randomized controlled trials or retrospective reviews designed for adults 18 years of age and older that included a number of participants 65 years of age and older and also reported the study outcomes by age.[36-43] Four evaluated the efficacy of an antibiotic regimen or compared antibiotic regimens for CDI.[36-39] Of these, the most recent antibiotic study, published in 2015, was a retrospective analysis of metronidazole effectiveness for hospitalized patients with CDI.[36] CDI refractory to metronidazole was defined as persistent diarrhea after seven days of oral metronidazole 500 mg three times a day. Refractory CDI rates were 37%, 28%, and 22%, respectively, for older than 70 years of age, 50 to 70 years, and younger than 50 years. Though refractory rates were higher in the patients older than 70 years of age, age was not identified as an independent risk factor for CDI refractory to metronidazole. Instead, severe CDI, severity of other illnesses, and continued use of non-CDI antibiotics were predictors of CDI refractory to metronidazole.[36] The other studies for adults 18 years of age and older that included a number of adults 65 years of age and older and reported results by age were investigations of outcomes of FMT, one prospective feasibility study, and three retrospective reviews.[40-43] The prospective feasibility study investigated the effectiveness of FMT delivered by frozen capsules in a regimen of one to two treatments of 15 capsules taken on two consecutive days to produce diarrhea resolution, defined as not requiring further therapy and being symptom-free for 8 weeks.[40] Ten of the 20 patients were 65 years of age or older. Eight of 10 had diarrhea resolution after one (n = 6) or two (n = 2) FMT treatments of 15 capsules taken on two consecutive days; no patients vomited within 24 hours of FMT treatment.[40] The most recent retrospective review conducted in the United States was a single center outcomes study of FMT success or failure in older hospitalized patients with SCDI refractory to antibiotic therapy of vancomycin with or without metronidazole.[41] Of the 49 patients who received FMT at this hospital, 14 met the criteria for severe refractory CDI; 10 were 66 to 92 years of age. To meet the criteria for SCDI a patient had to have two or more or the following factors: older than 60 years of age, serum

albumin < 2.5 mg/dL, temperature > 38.3 C, or WBCs > 15,000 cells/mL within 24 hours of diagnosis. A patient also met the criteria for SCDI if he or she received treatment in intensive care for CDI or if he or she had pseudomembranous colitis. All patients received FMT by nasogastric tube or colonoscopy and FMT was repeated, if needed, at 48-72 hours. Seven of the 10 older adults experienced clinical cure with the FMT, defined as less than three bowel movements per day by day seven after FMT plus no further CDI therapy at day seven. The results at the 100-day follow-up were reported for the patients as a group, rather than by age. Of the 11 patients who responded to FMT (7 older and 4 younger) and were available for follow-up, n = 7, none had developed CDI recurrence. However, 3 of the 11 had died from other illnesses.[41]

Discussion

Exposure to the CD organism and systemic antimicrobial therapy are the two most important risk factors for development of CDI.[1,3] Older adults are at increased risk for developing CDI and have a higher CDI, RCDI, and SCDI incidence than the general population because of their increased exposure to antibiotics; increased exposure to health care settings, including hospitals, subacute care, nursing facilities, and clinics; altered intestinal microbiota; multiple comorbid conditions; and decline in renal and immune function.[1,6-9]

Primary Literature on Efforts to Prevent, Reduce Occurrence, or Control CDI in Older Adults

Published studies investigating interventions to reduce CDI rates in adults 65 years of age and older were set in acute hospital or long-term acute hospital settings, most often in geriatric wards or units, or in the nursing facility setting. Interventions that were successful in reducing CDI diarrhea rates in older adults in these settings, per the limited number of published studies, included restrictions on broad-spectrum antibiotic use for infections other than CDI, implementing IC practices and surveillance systems to control and limit patient and health care professional exposure to the CD organism, feedback audit programs, and educating prescribers.[21-25,30,31] Using disposable thermometers, launderable mattress and bed-deck covers, and a dedicated disinfection device also successfully reduced CDI rates by killing spores and reducing exposure to CD.[26-29] A probiotic combination of lactobacilli and bifidobacteria, versus placebo, begun at the onset of antibiotic therapy, was not effective in preventing antibiotic-associated diarrhea or CDI.[32] The results of these limited prevention studies confirm the prevention recommendations per the guidelines and the special prevention considerations for nursing facilities, included in Tables 3, 4 and discussed below. Nursing facility administrators, IC teams, medical directors, nurses, or facility consultant pharmacists may want to consider some of the interventions studied in adults 65 years of age and older that actually reduced CDI rates by limiting exposure to antibiotics and the CD organism.

Primary Literature on Efforts to Improve Outcomes of CDI with Different Management Strategies in Older Adults

Unfortunately, there were few RCTs or retrospective reviews designed specifically for adults 65 years of age or older that investigated or compared management or treatment strategies for existing CDI to improve outcomes, i.e., one antibiotic versus another for initial or recurrent infection, fecal microbiota transplantation versus an antibiotic for recurrent infection, etc., published in the English language. A few articles were found in the literature, published 2011 to present, that stratified study outcomes by age for studies inclusive of adults older than 18 years of age; these were included in this systematic literature review in order to augment both the limited findings of studies exclusive to those 65 years of age and older and to augment the references of the current guidelines.[36-43] Although the prevalence and severity of CDI are higher in older adults than in the younger population, the limited number of studies designed for adults 65 years of age and older could be partially because current and prior guidelines for the management of CDI are considered applicable to all adults 18 years of age and older and management recommendations are based

on disease severity, initial versus recurrent infection, and prior patient response to treatment, rather than age.[1,3,5-9,15] In the limited number of studies of outcomes of CDI management in adults 65 years of age and older, or outcomes studies with results reported by age, FMT was safe, and also effective, at varying success rates, in resolving CDI and preventing CDI recurrence in those 65 years of age and older.[35,40-43] Fidaxomicin, metronidazole, and vancomycin treatment studies resulted in different success and failure rates, depending on the study and severity of the CDI, initial or RCDI, and severity of other patient illnesses.[36-39] The management studies in adults 65 years of age and older and those in all adults with results reported by age confirm the current guideline management recommendations.

Recommendations for Prevention, Occurrence Reduction, or Control of CDI per the Guidelines

To augment the study findings in adults 65 years of age and older, summaries of the recommendations in the current guidelines for the prevention, occurrence reduction, or control of CDI in adults 18 years of age and older are included in Table 3 and recommendations for the management of CDI in Table 5.[3,5,11,14,15] The strategies for prevention, occurrence reduction, or control of CDI per current guidelines, hereafter referred to as prevention measures as in the guidelines, are applicable to all ages and most settings, though they were written primarily for the hospital setting.[3,5,11,14] The prevention measures that proved beneficial in older adults per the research studies (Results, Table 1) are among those recommended in the guidelines, Table 3. These prevention strategies would be beneficial and feasible for adoption in the nursing facility setting if a facility does not already have clearly defined CDI prevention policies and procedures. Measures to decrease personal and environmental contamination are especially important to decrease health care provider, resident, and visitor exposure to the CD organism. In a nursing facility, one must also consider the preservation of residents' rights, dignity, and independence, as discussed below and summarized in Table 4.[14] Some strategies would be more difficult to implement in the assisted-living setting with reduced health care provider presence and IC teams, but the private rooms, bathrooms, and level of patient independence and autonomy in assisted living could make some suggested prevention measures easier to implement. Among the prevention strategies, antibiotic stewardship programs and measures to decrease health care provider, visitors, and other patient (resident) exposure to the CD organism have significantly decreased CDI occurrence rates.[1,3,5] Antibiotic stewardship programs include initiatives to decrease prescribing of antibiotics that are associated with a higher risk of causing CDI, i.e., clindamycin, fluoroquinolones, amoxicillin, cephalosporins, and initiatives to decrease the prescribing of unnecessary antibiotics.[3,5,11,14]

According to the current guidelines, CDI prevention measures with conflicting or unresolved efficacy include the use of probiotics as prophylaxis, restricting the use of gastric acid suppressants, standing orders to test patients with diarrhea for CDI, systems to notify health care providers when patients are admitted with a history of CDI, and no-touch disinfection systems.[3,5,11,14] The efficacy of different and specific probiotics to prevent initial CDI diarrhea has been studied in RCTs and retrospective reviews, and probiotics as a group analyzed via meta-analysis and systematic reviews, with conflicting results.[1,3,5,11,58-60] At present, the guidelines indicate that there is insufficient evidence that probiotics prevent CDI-associated diarrhea (CDAD), but stronger evidence that probiotics prevent antibiotic-associated diarrhea.[3,11] The authors of several systematic reviews and meta-analyses of probiotics for the prevention of CDI for individuals on antibiotics come to slightly more favorable conclusions. A 2013 Cochrane pooled review of 23 RCTs of diverse probiotics taken while adult or pediatric participants were taking antibiotics concluded that there is moderate quality evidence that probiotics are effective in preventing CDAD while individuals are on antibiotics (relative risk [RR] = 0.36, 95% CI 0.26-0.51; random effects), but that probiotics do not reduce the incidence of CDI significantly (RR = 0.89, 95% CI 0.64=1.24).[58] They judged probiotic use, while an individual is on an antibiotic for infection, as safe, as long as the individual is not immunocompromised or severely debilitated, but stated that future research trials need to

adopt standardized adverse event reporting.[58] The authors postulated that probiotics may prevent symptoms of CDI or limit CDI extent instead of preventing colonization or infection.[58] A systematic review and meta-analysis of 20 of the same 23 RCTs analyzed in the Cochrane review was published in *Annals of Internal Medicine* in 2012.[60] Based on their analyses, the authors, several of whom also participated in the Cochrane review, concluded that there is moderate quality evidence both that probiotics are protective in preventing CDAD and also that they cause few adverse events. They encouraged the use of probiotics in individuals taking antibiotics who are at increased risk for CDI.[60] Finally, a third recent meta-analysis of sixteen RCTs investigating probiotic effectiveness in preventing antibiotic-associated diarrhea and CDAD in inpatients concluded that probiotics reduced the incidence of antibiotic-associated diarrhea and CDAD both in the pooled analysis and also in the subgroup analysis of four good quality RCTs.[59] Dubberke et al., authors of the 2014 SHEA/IDSA CDI practice recommendations, point out, as do the authors of the meta-analyses, that a limitation of the existing probiotics studies and meta-analyses of these studies is the high incidence of CDI in the placebo groups, which could bias the results.[11] Gastric acid suppressant use, especially the use of PPIs, is often listed as a risk factor for CDI.[11,13,15] Per the current guidelines, there are insufficient data to indicate that restricting gastric acid suppressant use reduces CDI occurrence.[11,15] Gastric acid suppressant use may be an indicator or prognostic marker of patients at increased risk rather than an independent risk factor.[1,11,15,61] Of note, CD spores are resistant to acid and are not killed by normal gastric pH.[1]

Special Considerations for Prevention, Occurrence Reduction, or Control of CDI in Nursing Facilities

Effective antibiotic stewardship and infection control are imperative in nursing facilities, as in hospitals, in preventing, reducing the incidence of, or controlling CDI.[13] The Association for Professionals in Infection Control and Epidemiology (APIC) CDI prevention guidelines includes a section addressing special considerations in nursing facilities when a resident has confirmed CDI.[14] It includes recommendations for transmission-based precautions, living arrangements, equipment, supplies and the environment, and ambulation and socialization while the resident is in contact precautions, summarized in Table 4.[14] A private room and bathroom, if at all possible, are recommended. The APIC nursing facility considerations cited the 2009 Centers for Medicare & Medicaid Services (CMS) State Operations Manual concerning transmission-based precautions and urged promoting a balance between resident dignity, independence, rehabilitation, and infection prevention.[14] The current CMS State Operations Manual, F441 Interpretive guideline, revision #127, issued 2014, Appendix PP-Guidance to Surveyors for Long Term Care Facilities, contains sections 483.65-Infection Control, 483-65(a)-Infection Control Program, and 483-65(b)-Preventing Spread of Infection.[62] In the section Transmission-based Precautions, the CMS manual indicates that consideration should be given to balancing infection risks with the potential adverse psychologic impact on the infected resident and includes the statement, "Transmission-based precautions are maintained as long as necessary to prevent the transmission of infection. It is appropriate to use the least restrictive approach possible that adequately protects the resident and others. Maintaining isolation longer than necessary may adversely affect the psychosocial well-being. The facility should document in the medical record the rationale for the selected transmission-based precautions." [62] If a resident is not able to comply with good hand hygiene or contain bodily fluids because of cognitive impairment or illness, consideration could be given to one-on-one caregiving.[14] The Centers for Disease Control and Prevention has an established infection surveillance system under their National Health Care Safety network, with a specific section, resources, and data for long-term care facilities available at http://www.cdc.gov/nhsn/LTC/index.html.[63]

Recommendations for Management of CDI per the Guidelines

Table 5 includes a summary of the recommendations for the management of CDI in adults 18 years of age and

older per current guidelines.[3,5,15] Management strategies are recommended based on severity of disease, initial versus recurrent infection, number of recurrences, and patient's prior response to antibiotic therapy. The results of the limited management studies in older adults and the recent studies with results reported by age, Results, Table 2, confirm the guideline recommendations. For an initial CDI episode, oral metronidazole remains first line for mild or moderate cases; vancomycin is recommended for severe cases; and a combination of metronidazole and vancomycin is recommended for complicated, severe cases (Table 5).[3,5,15] Fidaxomicin is considered an effective and safe alternative for severe cases; the cost of fidaxomicin compared with metronidazole and vancomycin has limited its use.[3] Recurrent CDI treatment is guided by disease severity, response to prior therapy, and number of recurrences.[3,5,15] Per the current guidelines, there is not sufficient evidence of efficacy to recommend the use of probiotics, toxin-binding resins and polymers, or monoclonal antibodies for existing CDI.[15] Antiperistaltic agents for diarrhea should normally not be used, as their use could complicate the CDI, but additional studies are needed investigating the use of these agents in mild to moderate CDI once individuals have received several days of antibiotic therapy.[3] The efficacy and safety of FMT in treating recurrent CDI has been established over the past decade.[3,15] Altered colonic microbiota are considered the underlying cause of RCDI and FMT, for RCDI has had a success rate as high as 90%.[64] The FMT workgroup published a helpful summary of FMT indications, donor selection, recipient exclusion criteria, stool preparation, and administration and evaluation of results.[64] The results of additional FMT RCTs are needed, particularly in older or immunocompromised adults, using various treatment delivery methods.[3]

Treatments Under Development

Vaccines to prevent CDI in adults are under development. The goal is to develop a vaccine that could elicit and provide a long-term immune-based response to prevent CDI, not only in healthy younger patients, but in patients at increased risk of CDI, including older patients, patients with underlying chronic illness, and patients with planned hospitalizations or admission to nursing facilities.[65,66] CD produces toxins A and B, an enterotoxin and a cytotoxin, that cause the problematic symptoms in CDI. Individuals that are older in age, have multiple comorbid conditions, or who are immunocompromised may have a decreased antibody response to CD toxins, increasing their risk of symptomatic CDI.[4] Several pharmaceutical companies are developing a vaccine of toxoids A and B with the goal of provoking a sustained immune response to neutralize the effects of toxins A and B to prevent symptomatic CD disease.[65] The government's clinical trials Web site, https://clinicaltrials.gov, a service of the National Institutes of Health, currently lists 14 CDI vaccine trials: 10 completed, 1 terminated, 1 active but not recruiting, and 2 recruiting.[67] Sanofi or Sanofi Pasteur is listed as the sponsor for 7 of the trials, Pfizer for 4, Valneva Austria GmBH for 1, and University of Massachusetts for 2.[67] Sanofi Pasteur, Pfizer, and Valneva Austria have completed Phase I and II trials.[67] Of the 2 trials listed on the Clinical Trials Web site as active and recruiting, 1 is sponsored by Sanofi Pasteur and the other by Pfizer. Sanofi Pasteur is conducting a Phase III trial studying the efficacy of a vaccine for prevention of CDI in subjects at risk of CDI, NCT01887912, with 296 study locations in the United States and around the world.[67,68] Pfizer is conducting a Phase I trial to study the safety, tolerability, and immunogenicity in Japanese adults, NCT02725437, at two locations in Japan, and per their Web site, Pfizer is also conducting a Phase II vaccine trial.[67,69] Valneva has completed a Phase II trial, conducted in two age groups, 50-64 and ± 65, for primary prevention of CDI, and is planning a Phase III trial.[70] The development and FDA approval of a vaccine effective and safe in preventing CDI in adults at risk, including those 65 years of age and older, could greatly decrease the morbidity and mortality from CDI.

Conclusion

There are a limited number of research studies that investigated measures to prevent, reduce occurrence, or control CDI, specifically designed for older adults. Results of these studies confirm the published guidelines'

recommendations for the prevention of CDI, which emphasize antibiotic stewardship and infection-control measures to decrease exposure to and development of CDI. The limited studies on CDI management in older adults, and those in all adults with results by age, confirm the management of CDI per guidelines where CDI severity, initial versus recurrent infection, and success or failure of previous treatment(s) for each patient determine the appropriate management strategy. As recurrent and severe CDI is more prevalent in older adults, including those living in nursing facilities, than in younger and community-dwelling adults, senior care pharmacists and other health care professionals working with nursing facilities and assisted living facilities are encouraged to work with facility personnel to adopt or revise prevention measures, particularly antibiotic stewardship and infection-control programs as highlighted in this systematic review, in an effort to reduce CDI occurrence in their residents.

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