AARHUS UNIVERSITY

Improvement in treatment and care of older patients with *Clostridioides difficile* infection by structured assessment and management

PhD dissertation

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2025

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FINANCIAL SUPPORT

Financial support was obtained from Helsefonden (grant number 22-B-0239). The faecal microbiota transplantation framework was supported by Innovation Fund Denmark (8056-00006B).

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PhD dissertation, Aarhus University, 2025

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Preface

In the world of older adults, there is a quiet strength, a richness of experience, and a complexity that often escapes the narrow gaze of clinical routines.

In Astrid Lindgren's universe, older characters are never mere background figures. They are wise, stubborn and tender. Most importantly; they matter. Perhaps this is what we must carry with us into geriatric medicine and health systems design: the deep belief that older people are not just passive recipients of care, but individuals with needs that go beyond what clinical guidelines alone can prescribe. There is room – and need – for imagination, for new pathways, and for organisational solutions that reflect the complexity. Let us explore how we might do better – not by inventing new tools, but by rethinking how we use the ones we have.

This thesis explores how frailty can inform the organisation of care for older patients with *Clostridioides difficile* infection, and whether structured, team-based approaches offer added value beyond existing clinical guidelines.

Acknowledgements

This PhD has been a journey both personally and professionally. I have been fortunate to have two exceptional primary supervisors, each offering valuable and distinct insights. Christian, your role has been indispensable. You've taught me to embrace the process and shown me the importance of research rooted in real-world practice. You have a unique ability to bring together people from diverse backgrounds and create an environment where different perspectives can be met, nuanced and developed. This ability to foster dialogue and collaboration is something I deeply value. Else Marie, you opened my eyes to the fact that not everything needs to be overthought – sometimes, action is what matters most. Your energy and unwavering belief in the process have been an inspiration, taking both me and the project to new places. A special thanks to the advisory group: Merete, Simon and Jeppe, thank you for invaluable support and discussions throughout the PhD.

I am deeply grateful to the Department of Geriatrics at Aarhus University Hospital and especially to Catherine H. Foss and Kirsten Rahbek for making this project possible.

This project could not have been achieved without the great and invaluable collaborators in the specialty of geriatrics. My heartfelt thanks to Hanne Veilbæk for your unwavering support and commitment throughout this project. Dear Malene and Liselotte, Ishay and Thai-Hong, Mikael, Louise and Cecilie, Joanna and Ying, Marianne, Kirsten B and Christina, Emma and Renée; thank you for your willingness to help and for always being kind and supportive. Troels, thank you for your wonderfully quirky mind, your big listening ears and your unfailing ability to make me smile – I look forward to more winter dips at Odden and the adventures of future projects. Lene, we have sailed many seas during this PhD – through storms and rare calm waters alike; I look forward to new shared horizons. A special thanks to my wonderful colleagues from the office: Anne, Laura, Lone, Mikkel, Bodil, Rikke, Maria, Maike, Ingelise, Hanne and Marie – thank you for cozy morning coffees and many good conversations.

I am genuinely grateful for the collaboration with so many great people at the Centre for faecal microbiota transplantation: Sara, Katrine, Line, Nina, Mette and Pia. I look forward to follow your work and hopefully future collaborations in the daily clinical work as well as in research.

I would like to sincerely thank the two representatives from the Danish Council of Senior Citizens, Rita Stokholm Vinding and Carl Aksel Kragh Sørensen, for their time and valuable insights and contributions throughout this project.

My PhD was enriched by a change of environment at King's College and Guy's and St Thomas' Hospital in London; Claire J. Steves, thank you for great discussions, hopefully this is just the beginning of something more.

To my dearest friends, Kasper, Naja, Lea, Søren, Ellen and Kristian – thank you for always being there for me and providing me with energy, care and support.

Finally and most importantly, a huge thank you to my family. Thanks to my parents and my brother for your unwavering support and positive minds. Dear Ole, thank you for always standing by my side through external and internal battles. Our parallel journey into folk music has carried me through the weight of difficult days. I could not have done this without you by my side. Bror, Birk and Alva, thank you for always bringing light into the darkest days and forever putting my life and work in perspective.

Manuscripts

This thesis is based on the following four manuscripts:

I. **Frailty level at discharge predicts mortality in older patients with *Clostridioides difficile* infection more accurately than age or disease severity**[1]
Rubak T, Baunwall SMD, Gregersen M, Hansen TK, Rosenbæk JB, Erikstrup LT, Hvas CL, Damsgaard EM. Eur Geriatr Med 2023; 14(3): 583-93. doi: 10.1007/s41999-023-00772-3

II. ***Clostridioides difficile* infection in frail older patients, quality in treatment and care: the CLODIFrail study protocol for a multicentre randomized controlled trial**[2]
Rubak T, Veilbæk H, Gregersen M, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Ørum M, Vinding RS, Sørensen CAK, Steves CJ, Baunwall SMD, Hvas CL, Damsgaard EM. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648 (Published as Supplementary file no 1) (Preprint March 2023: doi:10.21203/rs.3.rs-2687093/v1)

III. **Early geriatric assessment and management in older patients with *Clostridioides difficile* infection (CLODIfrail) – a randomised trial**[2]
Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Hansen TK, Ørum M, Steves CJ, Veilbæk H, Hvas CL, Damsgaard EM. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648

IV. **Development of a geriatric checklist to support management of older patients with *Clostridioides difficile* infection**[3]
Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Ørum M, Kongensgaard R, Hansen TK, Gregersen M, Hvas CL. Submitted manuscript, 2025.

Additional publications

The listed publications were published in connection with and during the PhD program. These publications are not included as part of the thesis.

Faecal microbiota transplantation as a home therapy to frail older people
Jørgensen SMD, Rubak T, Damsgaard EMS, Dahlerup JF, Hvas CL. Age Ageing. 2020 Oct 23;49(6):1093-1096. doi: 10.1093/ageing/afaa073

Faecal microbiota transplantation for first or second *Clostridioides difficile* infection (EarlyFMT): a randomized, double-blind, placebo-controlled trial
Baunwall SMD, Andreasen SE, Hansen MM, Kelsen J, Høyer KL, Rågård N, Eriksen LL, Støy S, Rubak T, Damsgaard EMS, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. Lancet Gastroenterol Hepatol. 2022 Dec;7(12):1083-1091. doi: 10.1016/S2468-1253(22)00276-X

Faecal microbiota transplantation for first and second episodes of *Clostridioides difficile* infection - Authors' reply.
Baunwall SMD, Andreasen SE, Hansen MM, Kelsen J, Høyer KL, Rågård N, Eriksen LL, Støy S, Rubak T, Damsgaard EMS, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL.Lancet Gastroenterol Hepatol. 2023 Feb;8(2):112-113. doi: 10.1016/S2468-1253(22)00424-1

Real-world Effectiveness of Fecal Microbiota Transplantation for First or Second *Clostridioides difficile* Infection
Paaske SE, Baunwall SMD, Rubak T, Birn FH, Rågård N, Kelsen J, Hansen MM, Svenningsen L, Krarup AL, Fernis CMC, Neumann A, Lødrup AB, Glerup H, Vinter-Jensen L, Helms M, Erikstrup LT, Grosen AK, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. Clin Gastroenterol Hepatol. 2025 Mar;23(4):602-611.e8. doi: 10.1016/j.cgh.2024.05.038

Cost-Effectiveness of Hospital-at-Home and Fecal Microbiota Transplantation in Treating Older Patients With *Clostridioides difficile*
Olesen RH, Larsen EB, Rubak T, Baunwall SMD , Paaske SE, Gregersen M, Foss CH, Erikstrup C, Krogh CB, Ehlers LH, Hvas CL. Clin Infect Dis. 2025 Apr 17:ciaf104. doi: 10.1093/cid/ciaf104

Clinical management of *Clostridioides difficile* infection with faecal microbiota transplantation: a real-world cohort study
Paaske SE, Baunwall SMD, Rubak T, Rågård N, Kelsen J, Hansen MM, Lødrup AB, Erikstrup LT, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. EClinicalMedicine. 2025 Jun 19:85:103302.

doi: 10.1016/j.eclinm.2025.103302. eCollection 2025 Jul

Improving clinical outcomes of encapsulated faecal microbiota transplantation for *Clostridioides difficile* infection through empirical donor selection and optimized dosing: a quality improvement study

Paaske SE, Baunwall SMD, Rubak T, Rågård N, Kelsen J, Hansen MM, Lødrup AB, Erikstrup LT, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL (Submitted manuscript 2025).

List of figures and tables

Figures

Tables

Abbreviations

ADL	Activities of Daily living
AUC	Area Under the Curve
CDI	*Clostridioides difficile* infection
C. difficile	*Clostridioides difficile*
CDR	Central Denmark Region
CEFTA	Centre for Faecal Microbiota Transplantation
CGA	Comprehensive geriatric assessment
CI	Confidence Interval
ED-HaH	Early discharge hospital-at-home (ED-HaH)
FMT	Faecal microbiota transplantation
HaH	Hospital-at-home
IADL	Instrumental Activities of Daily Living
IGCT	Inpatient geriatric consultation teams
IQR	Interquartile Range
LOS	Length Of Stay
MPI	Multidimensional Prognostic Index
OR	Odds ratio
PCR	Polymerase Chain Reaction
PPI	Patient and Public Involvement group
PROM	Patient-reported outcome measures
QI	Quality Improvement
RCT	Randomised controlled trial
ROC	Receiver Operating Characteristic

English abstract

Background: *Clostridioides difficile* infection (CDI) disproportionately affects older adults, and the frequent occurrence of severe CDI and high mortality rates imposes a substantial burden on patients and healthcare systems. Current clinical guidelines primarily emphasise infection management, potentially overlooking the concurrent progression of frailty and comorbidities and the complex demands these factors place on the organisation of treatment and care for older patients with CDI. The role of frailty as a predictor of mortality in older patients with CDI is not well studied. The clinical effects of comprehensive geriatric assessment (CGA) and frailty evaluation, including the possibility for home-based faecal microbiota transplantation, remain unexplored.

Methods: This thesis is based on four studies involving older patients with CDI. Study I compares frailty measured by the record-based multidimensional prognostic index (MPI), CDI severity and age as predictors of mortality in a population-based cohort study. Study II is a protocol study describing the rationale, objectives and methodological framework for Study III. Study III compares the clinical effects on mortality of the CGA organisational pathway when compared to standard care in a randomised trial with a pragmatic design. Study IV describes the development of a CDI checklist for older patients to support structured management.

Results: In a cohort of older patients beyond 60 years old, the 90-day mortality was 28% and frailty was a better predictor of mortality than age and CDI severity. In a real-world clinical setting, patients who received CGA organisational care had a 90-day mortality rate similar to that of patients who received standard care, but marked reductions in CDI recurrence, acute readmission, and days in hospital. The checklist for CDI treatment planning emphasised medication review, rehydration, nutritional support, and thorough patient information as core components.

Conclusion: Frailty measured by the record-based MPI outperforms age and CDI severity in predicting mortality in older patients with CDI. The CGA organisational pathway did not improve mortality rates in older patients with CDI but suggests an improvement of the overall patient care continuum by reducing CDI recurrence, readmission rate and days in hospital. The CDI checklist offers a holistic approach to CDI management and care planning in older patients.

Dansk resumé

Baggrund: *Clostridioides difficile* infection (CDI) er en af de hyppigste årsager til diarre og rammer særligt ældre svækkede individer. CDI hos ældre udvikler sig ofte til en svær infektion med høj dødelighed til følge hvilket belaster både patient og sundhedssystem. Gældende retningslinjer fokuserer ensidigt på behandling af infektionen men overser den samtidige progression af skrøbelighed hvilket stiller krav til håndtering og organisering af behandling og pleje af ældre patienter med CDI. Betydningen af skrøbelighed som en prognostisk faktor for død hos ældre patienter er endnu underbelyst. Effekten af en tværfaglig geriatrisk vurdering med mulighed for hjemmebehandling med fækal mikrobiota transplantation er endnu ikke undersøgt.

Metode: Denne afhandling er baseret på fire studier med ældre patienter med CDI. Studie I sammenligner skrøbelighed målt ved det journalbaserede skrøbelighedsindex "Multidimensional Prognostic Index" (MPI), CDI sværhedsgrad og alder som prædiktorer for død i en populationsbaseret kohorte. Studie II er et protokol studie, der beskriver det metodiske grundlag og design for studie III. Studie III sammenligner de kliniske effekter på død af et geriatrisk forankret forløb mod standardbehandling i et randomiseret studie med et pragmatisk design. Studie IV beskriver udviklingen af en tjekliste til ældre patienter med CDI, der har til sigte at fremme en struktureret tilgang til behandling og pleje.

Resultater: I en kohorte af ældre patienter over 60 år var 90-dages dødeligheden 28%, og skrøbelighed var en bedre prædiktor for død end både alder og CDI sværhedsgrad. Patienter, der modtog et geriatrisk forankret behandlingsforløb havde en uændret 90-dages dødelighed sammenlignet med patienter i standard care gruppen, men havde reduktioner i recidiv af CDI, akutte genindlæggelser og antal dage på hospital.

Konklusion: Sammenfattende understreger resultaterne vigtigheden af at inkludere skrøbelighed i vurderingen af ældre patienter med CDI. En CGA-baseret organisering af behandling og pleje for ældre patienter med CDI forbedrer ikke overlevelsen, men kan muligvis optimere det samlede patientforløb. CDI tjeklisten bidrager til en helhedsorienteret og struktureret tilgang til behandling og pleje af ældre patienter med CDI.

1. Introduction

Clostridioides difficile infection (CDI) is the leading cause of healthcare-associated diarrhoea[4] and approximately 650,000 patients develop *C. difficile* infection in Europe and the United States each year[5-7]. CDI disproportionately affects older patients[4]. In Europe in 2016–2017, 72.0% of the CDI cases with case-based data were above 64 years old[8]. Considering the demographic shift towards an increasingly ageing population, knowledge of CDI in older adults becomes pivotal[9,10].

CDI represents a significant health threat with 90-day mortality rates reported between 23% and 36%[11,12]. Older age is a well-established risk factor for CDI complications[13]. CDI imposes a considerable burden on the continuum of patient care and contributes to substantial healthcare costs[14,15].

Older patients with severe CDI are characterised by malnutrition, high comorbidity burden, low functional status and a need for support in everyday life[16-18]. These are all factors indicating frailty, a common condition among older adults that results in an increased vulnerability to stressors[19]. However, the literature on the distribution and impact of frailty among older patients with CDI is limited.

The current clinical guidelines[20] for CDI are based on evidence that overlooks outcomes relevant to older adults, such as mortality and hospitalisation. Severity classifications are central to treatment decisions but lack validation in predicting poor outcomes among older patients with CDI. This issue raises concern about the applicability of standard treatment recommendations to older patients with CDI.

The organisation of care for older patients with CDI may play an important role in improving clinical outcomes and ensuring that treatment strategies address the complex needs of this vulnerable population. Current treatment approaches primarily target the CDI itself using CDI-related antibiotics and faecal microbiota transplantation (FMT) while offering limited attention to the broader context, including potential frailty and underlying chronic conditions. Moreover, logistical challenges associated with hospital-based care may limit access to optimal treatment, particularly among the frailest individuals.

In 2020, clinical experience with four older patients with CDI illustrated the rapid and progressive functional deterioration that may follow the infection[21]. These four cases highlighted the potential benefits of a structured pathway of care: a coordinated, multidisciplinary approach involving systematic assessment and follow-up by a specialised geriatric team, coupled with home-based FMT in collaboration with the Centre for faecal microbiota transplantation. This pathway enabled a comprehensive and patient-centred strategy, addressing both the infection and the complex interplay of frailty and comorbidities. Delivering FMT in the home setting further allowed treatment to reach those most in need.

Previous research at the Department of Geriatrics, Aarhus University Hospital, has demonstrated that early, geriatric team-based transitional care interventions can reduce mortality and readmission

risk among older patients with various medical conditions[22-25]. However, the integration of a specialised geriatric team with FMT in a geriatric organisational pathway for older patients with CDI remains unexplored. Whether such an approach provides added value compared to standard care, which may perform equally well, is currently unknown. Given the growing demand for feasible and effective strategies to improve outcomes in this vulnerable patient group, further investigation is warranted.

Closing the gaps addressed above requires addressing key questions such as:

- What is the mortality rate in the Central Denmark Region?
- What is the role of frailty in predicting mortality among older patients with CDI compared to age and disease severity as defined by the clinical guidelines?
- Are the current clinical guidelines sufficient for the assessment and management of CDI in older adults?
- Does a team-based geriatric care intervention provide added value over standard care in the treatment of CDI among older adults?
- How do we support a structured management of CDI in older patients?

The present thesis aims to investigate the potential benefits of a holistic, patient-centred approach to the management of older patients with CDI, with particular emphasis on the organisation of care pathways and structured management. The project explores the role of frailty in both clinical assessment and subsequent planning of treatment and care for older adults with CDI.

2. Background

The background has seven overall sections: 1) *Clostridiodies difficile* infection in older patients 2) Frailty 3) Comprehensive Geriatric Assessment and 4) Hospital at home and transitional care 5) Assessment and treatment of *Clostridioides difficile* infection 6) Study design options 7) Patient and public involvement

2.1 *Clostridioides difficile* infection in older patients

2.1.1. *Clostridioides difficile* infection

Clostridioides difficile (*C. difficile*) is an anaerobic, spore-forming, toxin-producing gram-positive bacterium capable of causing disease through the faecal-oral transmission of spores. The symptoms of *Clostridioides difficile* infection (CDI) correlate with the presence of toxins generated within the colon[26]. The toxins disrupt intestinal epithelial integrity by triggering an inflammatory cascade characterised by massive neutrophil and mastocyte infiltration and release of pro-inflammatory cytokines and chemokines[27,28]. This cascade leads to inflammation and tissue damage, contributing to the clinical manifestations of CDI, such as diarrhoea, colitis and in severe cases, pseudomembranous colitis.

2.1.2 Epidemiology

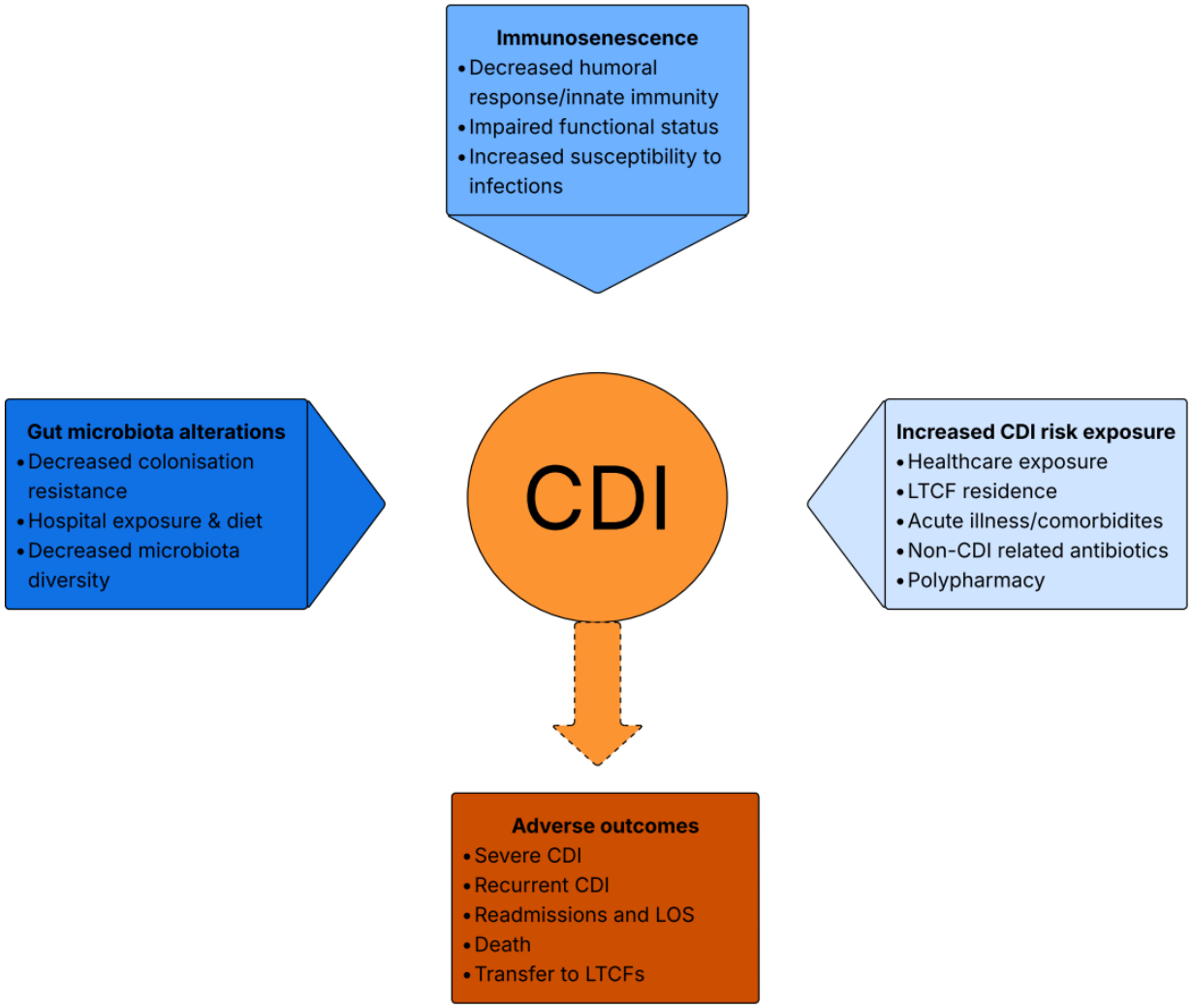
Globally, CDI is prevalent, particularly among patients in healthcare settings[29]. The incidence of CDI increased in the early 2000s following outbreaks of epidemic strain ribotype and the introduction of more sensitive *C. difficile* assays[30,31]. Consequently, the European Centre for Disease Control and Prevention issued recommendations for CDI surveillance[8]. This led to increased awareness of CDI and the implementation of antibiotic stewardship programmes aimed at reducing infections[32,33]. The incidence of CDI among hospitalised patients has generally been increasing[34]. On a global scale, the United States demonstrates the highest incidence rate, whereas within Europe, Poland exhibits the highest incidence, with the United Kingdom reporting the lowest[29]. In Denmark, approximately 4500 patients contract CDI annually[35].

Globally, CDI puts a substantial economic burden on the health care system[14,36,37]. The increased costs are driven by hospitalisation, additional medical complications and medication use[14]. Furthermore, the increased mortality rates observed in older patients with CDI place additional demands on the healthcare system, as those who succumb to the illness typically require longer and more expensive care compared to survivors[38].

2.1.3 *Clostridioides difficile* infection in the ageing host

Age above 65 years is one of the most important risk factors associated with developing CDI[4,39,40]. However, research indicates that while age by itself has limited influence on the risk of CDI, comorbidity has been shown to correlate with CDI risk in older patients independently[41,42]. Advanced age creates a complex interplay of factors that elevate the risk of developing CDI and result in poor outcomes among older adults (Figure 1). The composition of the gut microbiota alters as individuals age, resulting in a decline in the diversity of protective microbes and a decreased resistance to colonisation by *C. difficile*[43-46]. Gradual weakening of the innate defences that comes with ageing, as well as increased exposure to antibiotics, proton-pump-inhibitors, healthcare settings, and the presence of multiple comorbid conditions, all contribute to the risk of developing CDI[4,34,39,47,48].

Figure 1. Factors leading to *Clostridioides difficile* infection and poor outcomes after *Clostridioides difficile* infection in the ageing host. Adapted from Rauseo et al, Exp Rev Anti Inf Ther, 18:3, 203-217[49].



Abbreviations: CDI: *Clostridioides difficile* infection; LTCF: Long Term Care Facility; LOS: Length Of Stay

2.1.4 Mortality and risk factors for mortality among older patients with *Clostridioides difficile* infection

CDI is a life-threatening infection associated with significant mortality rates and attributable mortality, particularly in the older population[12,14,50,51]. The 90-day mortality rates and factors associated with mortality among older patients with CDI are illustrated in Tables 1 and 2, respectively. The literature review of mortality and risk factors for mortality among older patients with CDI is based on systematic searches described in Appendix 1.

Although several studies have examined mortality rates among patients with CDI, fewer studies specifically address the 90-day mortality among older patients with a minimum median/mean age beyond 60 years (Table 1). Reported 90-day mortality rates vary substantially across countries, ranging from 15%-36% following CDI. The divergence may be attributed to differences in median/mean ages among the studies, as well as to small sample sizes in some of the studies[52,53]. Most studies reported mortality throughout the entire 90-day follow-up period from CDI diagnosis, except for Olsen et al.[54] and Reveles[55], who reported only post-discharge mortality. The studies primarily focused on mortality among hospitalised patients. There is a lack of Danish population-based mortality data that includes all patients in primary and secondary healthcare with a positive *C. difficile* toxin test.

Table 1. Cohort study estimates of 90-day mortality in older patients with *Clostridioides difficile* infection

First author, country, year	Sample size (N), median age (IQR)	Observation period	90-day mortality
Reveles et al., US, 2024[55]	11451, 65 years (58-75)	2003-2018	17%
Yu et al., US 2023[51]	14.928, mean age 77.9 years (SD: 6.9)	2012-2019	15%
Atamna et al, Israel, 2022[56]	853 (≥ 65 years: n=571), 79 years	2013-2020	17% (20% for patients aged ≥ 65 years)
Enoch et al., UK, 2020[11]	6862, 81 years (71-87)	2002-2013	36%
Lauda Maillen et al,France, 2018[52]	101, mean age 68 years (SD 19.2)	2014-2015	33% (patients ≥75 years: 53%)
Olsen et al., US 2015[54]	3958, 67 years (18-102)	2014-2015	18% (recurrent CDI: 24%)
Abou Chakra, Canada, 2015[13]	1380, 71 years (58-80)	2005-2008	22%
Hensgen et al,Netherlands, 2013[12]	1366, mean age 63 years (SD: 21.6)	2006-2009	24%
Mitchell et al, Australia, 2013[53]	158, 67 years	2007-2010	15%
Bauer et al., Europe, 2011[57]	455, 71 years (56-81)	2008	22%

Abbreviations: SD: standard deviation; IQR: interquartile range

Recent literature regarding risk factors for mortality is depicted in Table 2. The studies conducted across various regions provide insight into the multifaceted nature of factors associated with mortality among older patients. Few studies included only the oldest group of patients with CDI[15,16,58,59]. Most included studies measured mortality within a 30-day interval after CDI diagnosis, but ranged between in-hospital mortality[60,61] , 60[62], 90[52] and 180 days[54] and one-year mortality[15]. The studies encompass a wide range of factors, including demographic characteristics, comorbidities, clinical parameters and healthcare utilisation patterns.

Advanced age is consistently associated with increased mortality risk, underlining the importance of age as a fundamental determinant of health outcomes in patients with CDI. Several of the clinical characteristics found to be associated with mortality among older patients with CDI, such as comorbidity burden, impaired functional status, frequent healthcare contact and malnutrition are also indicators of frailty[19]. This overlap suggests that frailty may be a relevant descriptive concept but also a potentially valuable prognostic tool in this patient group. Rather than examining individual risk factors in isolation, assessing frailty as a multidimensional construct may offer a more clinically meaningful approach to identify patients at high risk of poor outcomes. Few studies using frailty indices have demonstrated associations between frailty and poor outcomes in patients with CDI[55,63,64]. However, the studies primarily relied on diagnostic ICD codes to calculate frailty with less emphasis on incorporating clinical details. There is a lack of clinically grounded multidimensional frailty assessments to explore the prognostic value in older patients with CDI.

Table 2. Risk factors and factors associated with mortality in older patients with *Clostridioides difficile* infection

First author, country	Design, observation period	Sample size (N=), mean age (SD)	Exposure	Study outcome	Mortality	Risk factors for mortality (OR/HR (95% confidence interval) if available[a])
Jaan et al. 2025[64], US	Cohort study, 2016-2020	144611, frail: 72 years (95% CI 71-72); non-frail; 64 years (95% CI 64-65)	Frailty (Hospital Frailty Risk Score (HFRS ≥ 5))	All-cause in-hospital mortality	In-hospital mortality: 0.36% (non-frail), 2.27 (frail)	HFRS ≥ 5 (OR 4.9 (3.79-6.25))
Chaar et al. 2024[63], US	Cohort study, 2017	93810, 66 years (16.8)	Frailty (Hospital Frailty Risk Score (HFRS ≥ 5))	All-cause in-hospital mortality	In-hospital mortality total 1.3 % (frail: 2.1, non-frail. 0.3)	HFRS ≥ 5 (OR 4.5 (2.8-7.1))
Reveles et al. 2024[55], US	Cohort study, 2003-2018	11451, median age 65 years (IQR: 58-75)	Frailty (Veterans Affairs frailty index (VA-FI >0.2)	All-cause 30 and 90-day mortality	30-day mortality: 11.3 %. 90-day mortality:16.9%	VA-FI>2 associated with increased 30-day mortality ($p < 0.05$)
Stewart et al. 2023[62], Australia	Cohort study, 2016	578, median age 65 years (IQR: 51-79)	Age>65 years, severe CDI[b], previous antibiotic use, S-albumin<25 g/L	All-cause 60-day mortality	60-day: 8%	S-albumin<25 g/L (OR 3.07 (1.62-5.81))
Covino et al. 2022[60], Italy	Cohort study, 2016-2020	450, median age 78 years (IQR: 68-84)	Age, gender, CCI, BP, HR, T, RF, clinical symptoms (abdominal pain, vomit, dyspnea, syncope, malaise, gastrointestinal bleeding, qSOFA score) laboratory parameters (WBC, S-creatinine, S-albumin)	In-hospital mortality	In-hospital mortality: 14% (patients aged ≥ 65 years: 16%)	Age>81 years (HR 3.02 (1.64-5.53)), dyspnea (HR 1.79 (1.01-3.17)), creatinine >2.5 mg/dL (HR 1.88 (1.07-3.29))), WBC > 13 cells x 10^9/L (HR 1.74 (1.03-2.94)), albumin ≤ 30 µmol/L (HR 2.95 (1.25-6.93)), CCI > 3 (HR 2.95 (1.25-6.93))
Feuerstadt et al. 2022[15], US	Cohort study, 2013-2020	497489, 79.5 (8.22)	Age, gender, CCI, indicators of frailty, medical procedures	One-year mortality	One-year mortality: 32% (primary CDI), 10.8% (recurrent CDI)	*Primary CDI*: Age (mean): 78.4 (survivors) vs. 81.5 years (decedents); Δ +3.1, $p < 0.001$. CCI (mean): 5.03 vs. 7.16; Δ +2.1, $p < 0.001$ *Recurrent CDI*: Age (mean): 78.0 vs. 80.4 years; Δ +2.4, $p < 0.001$. CCI (mean): 5.20 vs. 7.19; Δ +2.0, $p < 0.001$
Czepiel et al, 2021[50], Europe	Case-control study, 2011-2019	624 Cases; n=415, median age 89 years (IQR 70-86) Controls; n=209, median age 72 years (IQR 59-82)	Age (mean), gender, BMI, CI, previous hospitalisation, LTFC, malignancy, cachexia, cognitive impairment, surgery, parenteral nutrition, CDI treatment, PPI, antibiotics, CRP, WBC, lactate, albumin	90-day mortality	-	Age (OR 1.57 (1.31- 1.89); inadequate CDI therapy (OR 3.70 (1.08 - 12.69); Cachexia (OR 5.00 (1.34 - 18.57)); Malignancy (OR 2.62 (1.43 - 4.81); Charlson Index (OR 1.24 (1.11 - 1.39); LTCF (OR 2.42 (1.05 - 5.58); WBC (1000/µL increase) (OR 1.03 (1.01 - 1.06); CRP (100 mg/l increase) (OR 1.80 (1.34 - 2.43)); Bacteremia (OR 3.35 (1.06 - 9.93); Cognitive impairment (OR 7.50 (2.73 - 20.66))
Caupenne et al. 2020[16], France	Cohort study, 2016-2017	247, 87 years (5.4)	Age, gender, CDI severity markers[c], organ failure[c], CIRS-G, previous antibiotic therapy, no of medications, CDI-related antibiotic therapy	All-cause 30-day mortality	30-day mortality: 13%	CIRS-G (HR 1.06 (1.00 - 1.12)); Organ failure (HR: 3.04 (1.40-6.59))
Banks et al. 2018[65], Scotland	Cohort study, 2010-2016	11571, 76 years (6.9)	Age, gender, CI, epidemiological category[d], PCR ribotype, ICU stay	All-cause 30-day mortality	18%	Age > 85 (OR 9.28 (7.00-12.54)); Healthcare ass. CDI (OR 1.51 (1.28-1.79)); ICU stay (OR: 1.76 (1.41-2.19)); CI > 3 (OR 1.44 (1.21-1.71))
Lauda Maillen et al, 2018[52], France	Cohort study, 2014-2015	101, 68 years (19.2)	Age	90-day mortality	33% (patients ≥75 years: 53%)	Age ≥ 75 years (53%), aged < 75% (16%), p<0.001

Leibovici et al. 2017[59], Israel	Cohort study, 2009-2014	184, 87 years (4.8)	Age, gender, CI, ADL status, medications and albumin, sepsis, haemoglobin,	30-day and 1-year mortality	30-day mortality: 33.2%; 1-year mortality: 65%	ADL status, dependent (HR[e] 0.46 (0.236–0.897); sepsis (HR 0.597(0.408–0.873); Albumin ≤2.5 (g/dL) (HR 0.580 (0.395–0.850)); CI (HR 0.867 (0.801–0.938))
Chintanaboina et al. 2017[66], US	Cohort study, 2011-2014	893, 62 years (18.5)	Age, gender, length of hospital stay, CDI treatment, non-CDI antibiotics, CCI, ICU admission	All-cause 30-day mortality	30-day mortality: 11%	Advanced age (OR 1.35(1.17-1.56)); CCI (OR 1.09 (1.01-1.18)); ICU (OR 2.67 (1.72-4.14))
Kassam et al. 2016[61], US	Cohort study, 2011	77 776, 69 years (17)	Age, gender, race, CCI, acute renal failure, inflammatory bowel disease, cardiopulmonary/hepatic/rheumatic disease, diabetes, malignancy, hemiplegia/paraplegia, peptic ulcer, ICU admission	In-hospital mortality	In-hospital mortality: 8%	Age 61-80 years (OR 2.51 (2.06-3.06); ICU (OR 5.29 (4.85–5.77)); renal failure (OR 2.93 (2.76-3.13)), liver disease (OR 2.00 (1.78-2.25)); malignancy (OR 1.89 (1.74-2.05)); inflammatory bowel disease (OR 1.72 (1.49-1.99))
Bielakova et al. 2016[58], Czech Republic	Cohort study, 2008-2013	235, 82 years (SD: 7.24)	Age, gender, CCI, fever, abdominal pain, pressure ulcers, non-CDI antibiotic treatment, PPI, cytostatics, corticosteroids, MNA-SF status	All-cause 30-day mortality	30-day mortality: 27%	Number of non-CDI antibiotics (OR 1.55 (1.08-2.21)); MNA-SF status[f] (OR 0.88 (0.78-0.99)), pressure ulcers (OR 2.2 (1.15-4.21)), fever (OR 1.88 (1.01-3.5))
Olsen et al. 2015[54], US	Cohort study, 2014-2015	3958, median age 67 years (IQR: 18-102)	Age, gender, comorbidity, recurrent CDI, S-albumin, cancer, dialysis	30, 60, 90, 180-day mortality	30-day: 9%;, 60-day: 15%; 90-day: 18%; 180-day: 27%	Age (HR 1.48 (1.32-1.67)); recurrent CDI (HR 1.33 (1.12-1.58)); cancer (HR 1.33 (1.10-1.60)); dialysis (HR 1.53 (1.24-1.88))
Takahashi et al. 2014[67], Japan	Cohort study, 2010-2011	924, 76 years	Age, comorbidities, parenteral nutrition or enteral feeding, S- albumin, probiotics, CDI antibiotics	All-cause 30-day mortality	30-day mortality: 11%	Age > 74 years (OR 2.08 (1.19-3.62)); heart failure (OR 2.12 (1.26-3.55)); respiratory failure (OR 1.98 (1.19-3.32));, S-albumin level ≤2.6 g/dL (OR 3.5 (1.33-9.22))
Bloomfield et al. 2013[68], UK	Cohort study, 2010	131, median age 74 years (IQR: 56-86)	Age, Charlson score, WBC, S-albumin, creatinine, CRP	All-cause 30-day mortality	30- day: 10%	WBC >15 x 10^9/l (HR 5.3 (1.7-16.8)); S- albumin level <25 g/l (9.5 (1.2-74.5))
Bauer et al. 2011[57], Netherlands	Cohort study, 2008	455, median age 71 (IQR: 56-81)	Age, APACHE II comorbidity score, use of non-CDI antibiotics, CDI characteristics, microbiological characteristics	All-cause 90-day mortality	90-day mortality: 22%	Age ≥65 years (OR 3.26 (1.08-9.78)); PCR ribotype 018 (OR 6.19 (1.28-29.8)); ribotype 056 (OR 13 (1.14-148))

[a] OR, HR, only multivariate adjusted ratios. Only statistically significant results. [b]Stewart et al[62]. Definition of severe CDI: presence of at least 1 of 5 factors (requirement for ICU admission; presence of pseudomembranes on colonoscopy (if performed); ileus or megacolon on abdominal radiograph or pancolitis on computed tomography scan; surgery (eg, colectomy); and clinical and laboratory criteria including fever of >38.5°C and white blood cell (WBC) > 20x10^9 cells/L). [c]Caupenne et al[16]. Severity risk markers definition: age ≥ 65 years, leukocyte count>15,000/mm^3, rise in creatinine level ≥ 1,5 times the premorbid level, blood albumin < 30 g/L, severe comorbidity. Organ failure defined as intravenous use of diuretics and/or rise in serum creatinine level ≥ 1.5 times the premorbid level and/or need for oxygen during the course of CDI. [d]Banks et al[65]. Epidemiological category: community-associated (CA), healthcare-associated (HA) and unknown CDI. [e]Leibovici et al[59]. Hazard ratio < 1 represents higher risk for long-term mortality. [f]A higher MNA-SF score (indicating better nutritional status) is protective against mortality (OR < 1).
Abbreviations: SD: standard deviation; IQR: interquartile range; OR: odds ratio; HR: hazard ratio; BP: blood pressure; HR: heart rate; T: temperature; RF: respiratory frequence; qSOFA score: the quick sequential organ failure assessment; WBC: white blood cells; CRP: C-reactive protein; CCI: Charlson comorbidity index; CI: Charlson index; CIRS-G: Cumulative Illness Rating Scale-Geriatrics; BMI: body mass index; LTFC: long-term-facility care; PCR: polymerase chain reaction; PPI: proton pump inhibitor; ICU: intensive care unit; ADL: activities of daily living: MNA-SF: Mini nutritional assessment short form; Δ: difference; CDI: *Clostridioides difficile* infection

2.2 Frailty

Frailty is a clinical state that can emerge with ageing, characterised by a progressive decline in physiological resilience[19]. As the ability of the human body to maintain homeostasis diminishes, stressors such as acute illness further challenge systemic stability. Therefore, frailty is a dynamic condition, allowing individuals to move between different levels of severity[69]. This impaired compensatory capacity increases the risk of adverse outcomes, including falls, disability and death[19]. Frailty models have been developed to allow treating physicians to identify frailty and act on the clinical issues identified objectively.

2.2.1. Frailty assessment models

Frailty models are commonly described in the literature according to two overarching frameworks: the phenotype models and the cumulative deficit model, as outlined by Clegg et al[19]. Phenotype-based models, such as Fried's Frailty Phenotype, define frailty based on physical characteristics such as unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity[70]. Cumulative deficit models, exemplified by Frailty index[71] quantify frailty by assessing the accumulation of health deficits across multiple domains, based on the premise that a higher number of deficits reflects a higher degree of frailty. In clinical and research practice, however, additional approaches have emerged. The clinical assessment model, such as the Clinical Frailty Scale, focuses on the functional capacity and physical performance as indicators of frailty [72]. Finally, the multidimensional models such as the Multidimensional Prognostic Index (MPI) [73,74] and the Edmonton Frail Scale[75] integrate physical, psychological and social factors to provide a more comprehensive evaluation of frailty.

2.2.2 The Multidimensional Prognostic Index

The bedside MPI was developed by Pilotto et al. to predict mortality in hospitalised older patients[73,74,76]. The tool operationalises the Comprehensive Geriatric Assessment (CGA) by incorporating key domains such as comorbidity, functional and cognitive status, nutritional state, polypharmacy and social support into an aggregated score. Based on this score, patients are divided into three categories: low frailty (MPI score 0.0–0.33; MPI-1), moderate frailty (MPI score 0.34–0.66; MPI-2), and severe frailty (MPI score 0.67–1.0; MPI-3)[74]. Compared to other frailty measures, the MPI demonstrates superior predictive ability for adverse outcomes, including mortality, in older hospitalised patients[77]. The tool has demonstrated notable flexibility, allowing individual components to be substituted with equivalent measures, for example, MNA-SF[78] instead of the MNA[79,80] and the MMSE[81] instead of SPMSQ[82]. Modified MPI versions have been developed, and among these, the record-based MPI performed in older medical inpatiens[73,83]. The record-based MPI rating method exhibits acceptable inter-rater reliability, strong inter-method reliability and high agreement

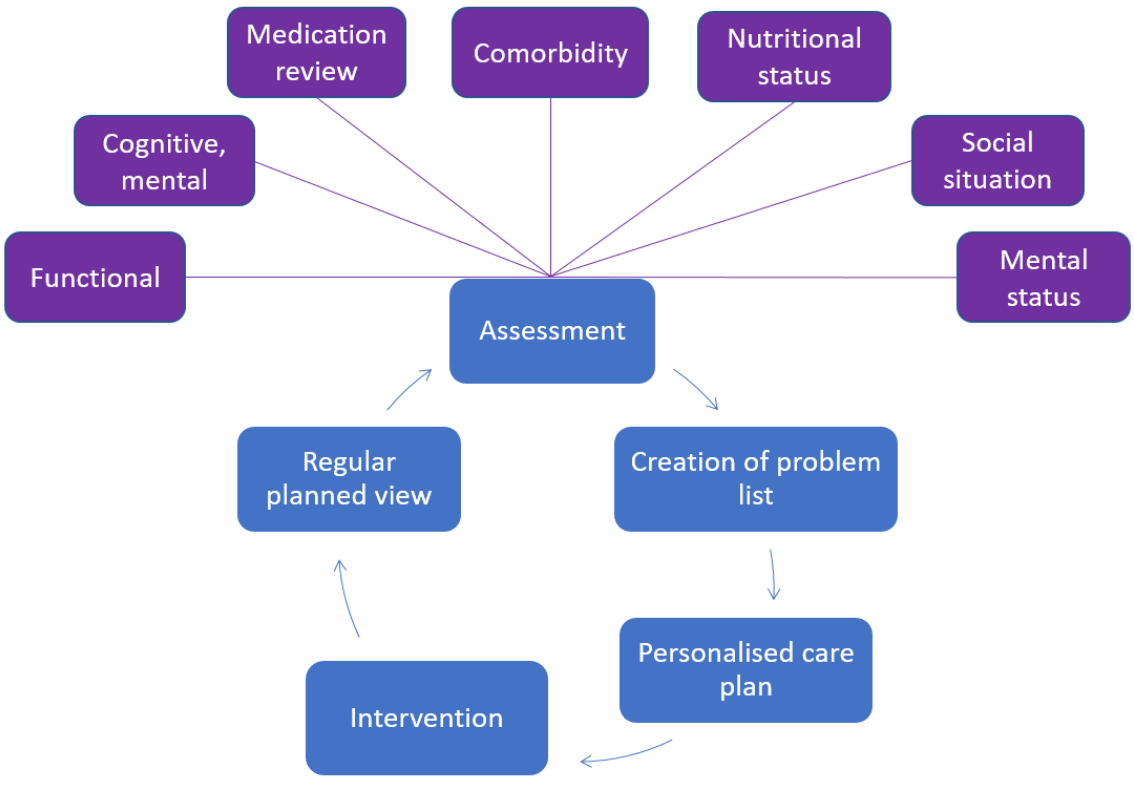
when compared to bedside-rated MPI[83]. Likewise, the ability to predict mortality in Danish medical inpatients is acceptable[84].

In older patients with CDI, a study in a geriatric care unit reported high MPI scores and poor outcomes, however, it did not specifically assess the prognostic accuracy of the MPI[85]. While the prognostic accuracy of MPI has been reported in older patients with infections and gastroenterological disorders, its performance in the context of CDI remains unknown[86,87].

2.3 Comprehensive Geriatric Assessment

CGA is the internationally established method to assess older people in clinical practice and the gold standard to detect frailty[19,88]. CGA is "a multidimensional, multidisciplinary process which identifies medical, social and functional needs, and develops an integrated/co-ordinated care plan to meet those needs"[89]. The CGA involves a variety of interdependent components that function collectively and provide the geriatrician with a holistic perspective on the health status of the older patient[90]. Dimensions of CGA reported consistently include medical, psychological, socioeconomic, functional, and nutritional assessments, but there are variations in the field when it comes to CGA definition, description, and components[89].

Figure 2. Components of Comprehensive Geriatric Assessment



CGA has been adapted across a wide range of healthcare settings, including geriatric wards, inpatient geriatric consultation teams and community-based models[88,91,92] and has been applied to various clinical populations, such as patients in pre- and postoperative service[93,94], oncology[95,96] and emergency departments[97] with variable outcomes depending on context and implementation.

2.3.1 Inpatient geriatric consultation teams

The effect of a geriatric team-based intervention using the components of a CGA for older patients with CDI has not been previously investigated (search described in Appendix 2). As older patients with CDI in the Central Denmark Region are more often admitted to non-geriatric medical wards[2], this thesis focuses on randomised controlled trials (RCT) involving older adults with acute internal medical conditions where CGA is delivered by inpatient geriatric consultation teams (IGCT) rather than through admission to dedicated geriatric wards (search described in Appendix 3). The IGCT involves a mobile multidisciplinary geriatric team that assesses patients and provides tailored recommendations to the primary care team in non-geriatric wards. While IGCTs are widely used as an organisational approach to geriatric care in hospitals, their effectiveness remains debated[88,92]. Few RCTs comparing IGCT to standard medical care have evaluated mortality outcomes, and besides Reuben et al, only as secondary outcomes (Table 3). Most of the studies find no significant differences in mortality at specific timepoints[98-101] besides the studies by Hogan and Thomas, who reported significant reductions in six-month mortality following IGCT intervention[102,103] (Table 3). The considerable heterogeneity in how IGCT services are structured and implemented poses challenges for generalisability and comparisons across studies.

Specialised settings outside geriatric wards have also adopted CGA, including perioperative care for older surgical patients (POPS) and geriatric oncology. The perioperative model has demonstrated reduced length of hospital stay and postoperative complications in older adults undergoing surgery[94,104] and a tendency towards reducing mortality in older patients with hip fracture[93]. Similarly, CGA in oncology has been shown to support treatment decision-making and reduce chemotherapy-related toxicity, although evidence for improved survival remains limited [95,105]. However, perioperative and oncologic applications of CGA were excluded from this literature overview. These models address distinct patient populations and clinical pathways that differ substantially from those of older adults with CDI, who are acutely infected, rarely surgical candidates, and present with rapidly evolving illness trajectories.

Table 3. Overview of randomised trials testing the inpatient geriatric consultation team (ICGT) service against standard care

Author, year, Country	Participants: Age criteria Inclusion Exclusion N(total) I:(number of participants allocated to intervention) C:(number of participants allocated to the control group)	Age (mean age (SD) I C	I: Inpatient geriatric consultation team (IGCT) service C: control group	Overall mortality[a] and other relevant outcome measures	Conclusion and main findings. Comments
Edmans et al., 2013, UK[98]	≥70 years Discharged from an acute medical unit with a score of at least 2/6 on the Identification of Seniors at Risk tool Excluded if lack of mental capacity to give consent, an exceptional reason cited by medical staff or participation in other studies N=433 I: n=216 C: n=217	I: 83 (6.7) C: 83 (7.0)	I: Assessment and management by geriatrician (specialist), no other staff. Follow-up home visits and phone calls per need. C: assessment and treatment by consultant physician and medical team	90 days: days spent at home, death, institutionalisation, secondary care contacts.	No statistically significant difference in 90-day mortality (I: 14(7%); C: 12 (6%); HR=1.22 (95%CI: 0.57-2.65), p=0.61) No statistically significant differences in days spent at home or secondary care contacts.
Kircher et al., 2007 Germany[99]	≥ 65 years Included has expected length of stay ≥ 8 days of functional impairment Excluded if admitted from nursing home, terminal, severe dementia, previously hospitalised in a geriatric evaluation unit N=345 I: n=175[b] C: n=170[b]	I: 79.0 (6.9) C: 78.4 (6.9)	I: geriatric consultant team (comprised a geriatrician, nurse and social worker) summarised problems and recommendations in a structured treatment note during admission. Two weeks post- discharge follow-up phone call. C: usual inpatient care	12 months: nursing home placement rehospitalisation, survival	No statistically significant difference in survival (I:122(81%); C: 109 (85%)), relative risk of death =1.16 (95% CI: 0.69-1.98, p=0.56) No statistically difference in rehospitalisation rate, nursing home placement
Reuben et al, 1995, US[100]	≥ 65 years Admitted to medical centres of the Southern California Kaiser permanente health maintenance organisation (HMO) Inclusion criteria: ≥1/13 frailty screening criteria present Excluded if terminal or admitted from nursing home. N=2353	I: 77.6 C: 76.7	Assessment and management by MDT (geriatrician, nurse, social worker) using a standardised multidimensional assessment instrument. Recommendations were summarised in a structured consultation note and sent to the physician and the primary care physician. Team conferences held daily. Patients were followed until discharge. C: usual care	3 months functional status. 12 months survival and functional status	No statistically significant difference in survival rate (I: 74% (95% CI: 72-76); C:75%(95% CI: 72-77))[c] No statistically difference in functional status at 12 months. Patients in I group had higher scores than the C group at 3 months on mental health index and at 12 months on the current-health-perceptions cale.

	I: n=1337 C: n=1016				
Thomas et al, 1993, US[103]	≥ 70 years Patients admitted to community hospital Excluded if admission to intensive care unit, terminal, renal hemodialysis, living >50 miles from hospital N=120 I: n=68 (62*) C: n=64 (58*))	I: 77 (5.4) C: 76 (5.4)	I: multidimensional geriatric assessment from an MDT (geriatrician, nurse, social worker, dietician, physical therapist), structured recommendations. Follow up on recommendations during admission C: no recommendations or follow-up	6 and 12 months: Mortality, length of stay (days), readmission	At 6 months: Mortality: I: 3/62[d](6%); C: 12/58[d] (21%) (p=0.01) Length of stay (days): I: 9.0; C:10.1 (p=0.20) Readmission: I: 0.3 per patient; C: 0.6 per patient (p=0.02) At 12 months: Mortality: I:7/68 (10%); C:13/64(20%) (p=0.08) No formal power calculation for mortality was reported.
Winograd et al, 1993, US[101]	≥ 65 years Patients admitted to the acute medical service at the Veterans affair medical center. Included is anticipated length of stay > 96 hours, one proxy criterion for frailty Excluded: independent in all activities, nursing home resident, terminal N=197 I: n=99 C: n=98	I: 75.7 (9.0) C: 76.6 (9.7)	I: multidimensional assessment by interdisciplinary team (geriatrician, nurse, social worker. Dietician and physical therapist available as needed). Recommendations was delivered in a structured note. note (a) medical issues, b) rehabilitation c) geriatric syndromes d) psychosocial status. Follow-up contact during admission. C: usual care	12 months: mortality , length of stay of index hospitalization, rehospitalisation	Mortality: I: 41 (41%), C: 35 (36%), (p=0.43) No statistically significant difference in length of stay of index hospitalization and rehospitalisations
Hogan et al, 1987, Canada[102]	≥ 75 years Admitted acute to department of medicine. Inclusion criteria: confusional state, impaired mobility, falls, urinary incontinence, living in nursing home, admission to acute care hospital within the previous 3 months Excluded: intensive care unit, acute cerebrovascular event, lack of consent N=113 I: n=57 C: n= 56	I: 82.2 (6.2) C: 83.3 (6.0)	I: MDT (geriatrician, nurse and physiotherapist) providing recommendations and discharge planning. Patients were seen daily and a full-team round once a week. C: usual hospital care	4-,8- and 12 months Survival, length of hospital stay, use of hospital service	The difference in survival was statistical significant in favour of the intervention group at 4 months (p<0.05), nearly significant at 8 months (p=0.06) and not significant at 12 months. No statistically significant difference in length of hospital stay. Significant differences between the two groups in the use of hospital services (physiotherapy, occupational therapy)

[a]Mortality was secondary or exploratory outcomes in all studies except for Reuben et al (1995)[100] and Thomas[103]. [b]Follow-up was available on n=150 (I) and n=129 (C) because of withdrawal of consent. [c]Survival and functional data only available in n=808 (I) and n=619 (C) at 12 months. [d]5 patients refused assessment (I: n=3;C=2); 7 patients were lost to follow-up (I: n=3; C: n=4).
Abbreviations: SD: standard deviation; MDT: multidisciplinary team; HR: hazard ratio; CI: confidence interval

2.4 Hospital at home and transitional care

Hospital at home (HaH) is a service care provided by healthcare professionals in the patient's home for patients who would otherwise be admitted to hospital[106]. Patients can be affiliated with HaH services either upon discharge from the hospital (early discharge hospital at home) or through direct referral from the primary health care sector (admission avoidance hospital at home)[106,107]. Besides the case study from 2020[21], no prior studies have investigated the aspects of treating older patients with CDI at home (search described in Appendix 4). Given that 80% of older patients with CDI are diagnosed during hospital admission[1,2], literature investigating early discharge hospital-at-home care for older patients was prioritised (search described in Appendix 5).

2.4.1 Early discharge hospital-at-home

Early discharge hospital-at-home (ED-HaH) services represent an alternative to continued inpatient care by providing hospital-level treatment in the patient's home following early discharge and aiming to prevent readmission and mortality and reduce days in hospital. Overall ED-HaH makes no statistically significant difference in mortality to older people with a mix of conditions[107] yet may improve other patient-related outcomes, such as living-at-home status and days in hospital (Table 4). However, the organisation and implementation of early discharge HaH services vary considerably across studies and healthcare systems, both in terms of patient selection, intensity of care and the composition of clinical teams, and the evidence is further limited by the fact that mortality was reported as a secondary outcome in most studies (Table 4).

2.4.2 Transitional care in the Central Denmark Region

Transitional care aims to ensure safe transitions from hospital to home. In the Central Denmark Region, treatment at home for older patients is provided by outgoing geriatric teams anchored in the geriatric specialty in Aarhus, Horsens, and Silkeborg and provide treatment and care of a broad range of medical conditions[23]. The team includes physicians, nurses, physiotherapists and occupational therapists working together to assess patient needs, develop individual treatment plans, and provide continuous monitoring and support for patients at home. Previously, it has been documented by colleagues in Aarhus University Hospital that a geriatric team-based transitional care intervention reduces readmission rates, mortality (in a subgroup of patients living in their own home) and length of stay in older medical inpatients when compared to usual care[22-25] (Table 4). The outgoing geriatric teams can provide the framework for a home-based CDI treatment, bypassing the requirement to go to the hospital for treatment. Building on the established efficacy of faecal microbiota transplantation (FMT) and the existing organisational framework supporting access to home-based treatment, the next step is to investigate the impact of integrating these elements into a cohesive organisational pathway, with the overarching aim of optimising care for older patients with CDI.

Table 4. Overview of randomised controlled trials testing early discharge hospital-at-home, and transitional care interventions to standard hospital discharge care

Early discharge hospital at home interventions					
Author, year, Country	**Participants:** Age criteria, if available Inclusion Exclusion N(total) I:(number of participants allocated to intervention) C:(no of participants allocated to control group)	**Age (mean age (SD)** I C	**I: Hospital at home (HaH) intervention or transitional care intervention** **C: control group**	**Overall mortality[a] and other relevant outcome measures**	**Conclusion and main findings. Comments**
Martin et al. 1994. UK[108]	≥ 75 years Excluded if need for assistance N=54 I: n=29 C: n=25	I: 80.4 (8.2) C: 82.9 (7.4)	I: Hospital based nurse practitioner made a discharge plan. Contact to hospital elderly care unit if necessary. Support up to 6 weeks from discharge C: conventional community service	6 weeks, 12 weeks and 12 months: mortality, readmission, living at home	No significant difference in mortality (deceased) at 6 weeks (I: 2(7%); C: 0(0%), 12 weeks (I: 3(10%); C: 3 (12%)), 12 months (I: 7(24%); C: 5(20%)). Difference in "living at home" status in favour of intervention group at 6 and 12 weeks and 12 months and readmission status at 6 weeks. Small groups, no sample size calculation. Mortality was an exploratory outcome.
Donald et al. 1995. UK.[109]	Patients admitted acutely under the care of the Elderly Care Physicians N=60 I: n=30 C: n=30	I: 81.6 (5.4) C: 84 (6.0)	I: Hospital based nurse-led hospital at home scheme including physiotherapist and occupational therapist and delivering home support and rehabilitation. Support up to 6 weeks from discharge C: conventional hospital discharge	6 months: mortality, living at home, readmission	No significant difference in mortality risk (RR[b]: 1.80 (95% CI: 0.68-4.74). No difference in living at home or readmission Small groups, no sample size calculation. Mortality was an exploratory outcome.
Richards et al. 1998. UK[110]	Patients identified by ward staff from general medical, care of elderly and surgical specialties. N = 241 I: n=160 & C: n=81	Median age (IQR): I:79(74-84) C:79(72-84	I: Health care service at home, incl discharge plan. Care provided between 8.30 AM and 11 PM C: usual hospital care	4 weeks and 3 months; mortality, length of stay[c], functional ability (Barthel index)	No significant difference in mortality at 3 months: (I: 12(7%); C: 6(7%)) Length of stay (mean days): (I: 17; C: 12) No difference in functional ability.
Cunliffe et al. 2004. UK.[111]	≥ 65 years Included were fit for discharge, rehabilitation needs that could be met at home Excluded: patients in need of constant care or receiving institutional care N=370 I: n=185 C: n=185	Median age (IQR): I: 80 (73.85) C: 79 (72-86)	I: The early discharge and rehabilitation service consisted on nurses, occupational therapists and physiotherapists. Medical care was given by hospital team while in hospital and general practitioner when at home. Support up to 4 weeks. C: standard hospital aftercare	3 and 12 months: mortality, readmission, length of stay in hospital, place of residence	No difference in mortality risk (3 months: RR[b]: 0.82 (95% CI: 0.42-1.62); 12 months, RR[b]: 1.06 (95%CI: 0.69-1.65)) Reduced length of stay from randomisation to discharge in I group-. No difference in readmission or place of residence
Caplan et al. 2006. Australia[112]	All inpatients with a length of stay (LOS) exceeding 6 days, who were referred for geriatric rehabilitation, were eligible for inclusion.	I: 83.8 (7.80) C: 84 (7.02)	I: hospital-based multidisciplinary outreach service including nurses, physiotherapists, occupational therapists and doctors.	3 months: incidence of delirium measured by the confusion assessment method	No statistical significant difference in mortality risk ((I: 15(23%); C: 7(21%). RR**: 1.04 (95%CI: 0.47-2.31))

	Excluded: not suitable for rehabilitation; not expected to return home and live independently after rehabilitation; nursing home resident N=104 I: n=70 C: n=34		C: hospital rehabilitation group	(CAM), length-of-stay (days), hospital bed days 6 months: mortality	Difference in mean (SD) hospital bed days (I: 20.31(12.4); C: 40 (23.2) (p<0.0001)) No overall statistical significant difference in CAM or length-of-stay. Mortality was an exploratory outcome.
Transitional care interventions delivered by multidisciplinary geriatric teams					
Pedersen et al. 2016. DK[23]	≥ 75 years Admitted to emergency department and assigned to geriatric care Excluded if terminal at admission, already included in geriatric follow-up or living outside Aarhus municipality N=1330 I: n=693 C: n=637	I: 86.4(6.6) C: 86.4 (5.9)	I: early home visit by outgoing geriatric team (nurse and doctor) Support ≥ 1 week Individualised intervention according to the need of the patient. C: usual care including potential referral to GP-led follow-up	30-day: readmission, length of hospitalisation, mortality	No statistical significant difference in mortality (I: 84(12%); C: 90 (14%), adjusted HR 0.96 (95% CI 0.78-1.19)) Reduced readmission (I: 86 (12%); C: 148 (23%) (adjusted HR 0.49 (95%CI 0.37-0.64), p<0.001) Hospitalisation length was shorter in the intervention group.
Pedersen et al. 2017. DK[22]	Same inclusion/exclusion criteria as Pedersen et al, 2016 (above) N=2076 I: n=1060 C: n=1016	I: 86.4 (6-3) C: 86.4 (5.8)	Same intervention and control as Pedersen et al, 2016 (above).	30- and 90- day: mortality	No statistical significant difference in 30 day-mortality (I: 12%; C: 14%; p=0.08) or 90-day mortality (I: 23%; C:26%; HR 0.87 (95%CI 0.73-1.03). However a small reduction of 90-day mortality among patients discharged to their own home in the intervention group: HR=0.79 (95%CI: 0.63-0.99), p=0.04
Pedersen et al. 2018. DK[24]	Same inclusion/exclusion criteria as Pedersen et al, 2016 (above). Living in nursing homes. N=648 I: n=330 C: n=318	I: 86.5 (6.1) C: 87.0 (5.9)	Same intervention and control as Pedersen et al, 2016 (above).	30- and 90-day: readmission, mortality	No statistical significant difference in 30-day mortality (I: 72(23%); C: 73(23%); HR 0.95(95%CI 0.69-1.33) or 90-day mortality (I: 125(38%); C: 119(38%); p=0.88) Reduced readmission among nursing home residents, adjusted HR =0.63 (95% CI: 0.63-0.99)
Hansen et al. 2021. DK[25]	≥ 75 years Admitted to emergency department and assigned to geriatric care. Moderately or severely frail Excluded if terminal at admission, admitted with stroke or hip fracture, already included in geriatric follow-up, discharged to rehabilitation, living outside Aarhus municipality N=3103 I: n=1558 C: n=1545	Median age I: 85 (80-90) C: 85 (80-90)	I: hospital-based intervention. Responsible: MDT geriatric team C: municipality based intervention. Responsible: general practitioner Both consisting of post-discharge transitional care visits in the patient's place of residence	30-day readmission 90-day post-admission mortality and length of stay (days)	No statistical significant difference in 90-day mortality (I: 330 (21%); C: 340 (22%); crude OR 1.05 (95% CI 0.89-1.25) Reduced readmission (18% in the intervention and 22% in the control group) (OR=1.27 (95%CI: 1.06-1.52), p=0.008) No statistical significant difference in length of stay.

[a]Mortality was a secondary or exploratory outcome in all studies except Pedersen et al (2017)[22]. [b]Crude RR calculated as risk in the hospital-at-home (HAH) group divided by risk in the standard care group. [c]Length of stay was defined as the period for which a patient was supervised by a service (i.e. hospital or hospital at home)[110].
Abbreviations: HR: hazard ratio; IQR: Interquartile range; MDT: multidisciplinary team; OR: odds ratio; RR: relative risk; SD: standard deviation

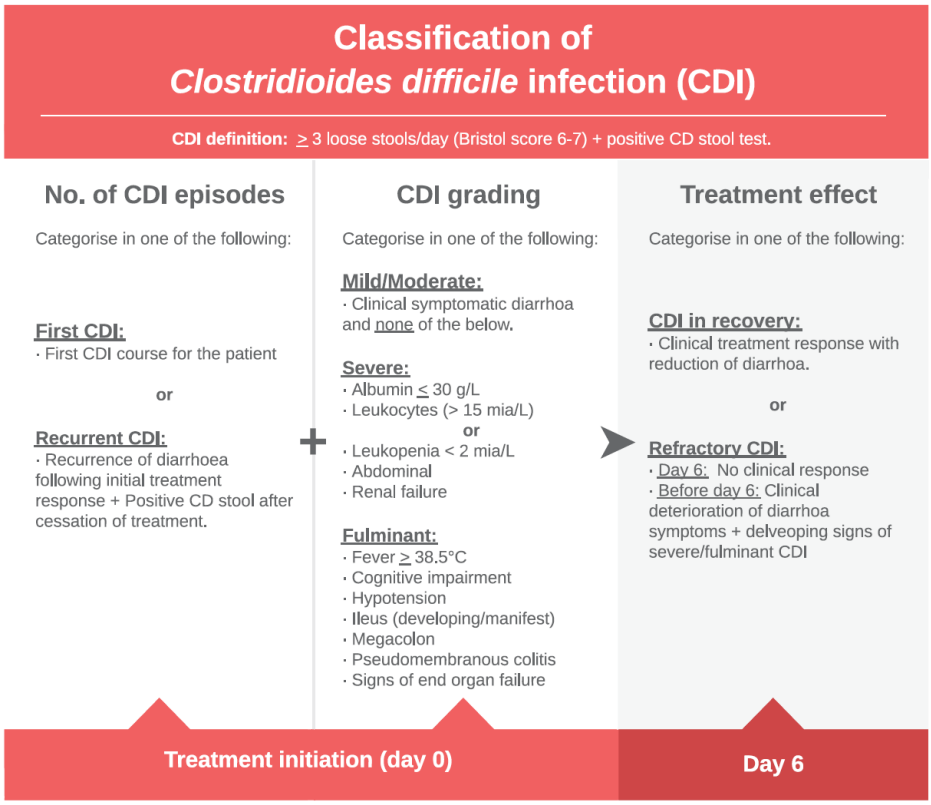
2.5 Assessment and treatment of *Clostridioides difficile* infection

2.5.1 Diagnosis, severity grading and treatment strategies for *C. difficile* infection

In the Danish, European and American clinical guidelines, CDI is defined by the presence of symptoms (diarrhoea) and either a stool test positive for *C. difficile* toxins or detection of toxigenic *C. difficile* or colonoscopic or histopathologic findings revealing pseudomembranous colitis[20,33,40].

The severity of CDI is graded as either mild/moderate, severe, or fulminant[20] based on a combination of clinical manifestations and laboratory parameters (Figure 3) according to the Danish national guideline[113].

Figure 3. Classification of *Clostridioides difficile* infection (CDI) according to the Danish national guideline[113]. Adapted from Baunwall et al, Scan. Scand J Gastroenterol. 2021;56(9):1056-77[20].



Management guidelines for CDI are written for adults of all ages and base management recommendations on CDI severity and number of infections, rather than age, comorbidity and underlying deterioration in chronic conditions[20,33,40]. The treatment algorithm in patients with CDI in Denmark is described in the Danish national clinical guideline[20,113] and elaborated in Table 5.

Table 5. Treatment algorithm in patients with *Clostridioides difficile* infection (CDI) according to the Danish national clinical guidelines[113]. Adapted from Baunwall et al, Scan. Scand J Gastroenterol. 2021;56(9):1056-77[20].

CDI classification	Recommended treatment
All cases of CDI	Revise ongoing antibiotics and proton pump inhibitors
First CDI	Mild/moderate: First choice: Oral vancomycin 125 mg × 4 for ten days Second choice: If vancomycin is not available (non-hospitalised): Oral metronidazole 500 mg × 3 for ten days Severe and/or inpatient: First choice: Oral vancomycin 125 mg × 4 for ten days Second choice: Oral fidaxomicin 200 mg × 2 for ten days Consider faecal microbiota transplantation (FMT)
Recurrent CDI: First recurrence	Mild/moderate (not requiring hospitalisation): First choice: Oral vancomycin 125 mg × 4 for ten days FMT may be considered Severe and/or inpatient: First choice: Oral vancomycin p.o. 125 mg × 4 for ten days Second choice: Oral fidaxomicin 200 mg × 2 for ten days FMT should be offered as an extension of antibiotic treatment*
Recurrent CDI: Second recurrence and above	All degrees of disease: First choice: FMT should be offered in continuation of antibiotic treatment* If FMT cannot be completed: First choice: Oral vancomycin. A tapering regimen may. Be applied, e.g.: 125 mg × 4 daily for two weeks, 125 mg × 2 daily for one week, 125 mg × 1 daily for one week, 125 mg × 1 every two days for one week 125 mg × 1 every three days for two weeks
Fulminant CDI (regardless of number of episodes)	All: Multidisciplinary** assessment should be made with regard to treatment plan. First choice: FMT (possibly repeated at 3-day intervals) Antibiotics: Intravenous metronidazole 1,000 mg × 1 or 500 mg × 3 daily in addition to oral/rectal vancomycin Surgery considered: Colonoscopic desuffling with vancomycin flushing/FMT, loop ileostomy with vancomycin flushing/FMT – or colectomy.
Refractory CDI (regardless of number of episodes)	Revision of antibiotic treatment, both CDI-related and non-CDI-related First choice: FMT (possibly repeated at 3-day intervals) Consider multidisciplinary assessment**

*FMT is preceded by 4–10 days of oral vancomycin (/fidaxomycin) with discontinuation 1–2 days before FMT. With a longer waiting time for FMT, vancomycin/fidaxomycin is continued, possibly with tapering to the lowest possible dose that provides symptom relief. Thus, when referring to FMT, no end date is set for antibiotic treatment.

**Multidisciplinary assessment: gastroenterology, possibly infectious disease medicine, colorectal surgery, clinical microbiology.

The clinical treatment guidelines for CDI[33,40] are developed using the GRADE framework[114], which systematically rates the quality of evidence underlying treatment recommendations. Within this framework, mortality is considered the most critical patient-centred outcome for clinical decision-making. However, the evidence base informing current CDI guidelines emphasises recurrence rather than outcomes such as mortality, which may more accurately reflect disease severity. The severity classification used to guide treatment decisions has not yet been adequately validated for its

prognostic ability to predict such outcomes. In addition, guidelines definitions of severity are based on parameters that may not reflect the clinical complexity of older adults. The clinical guidelines do not consider multimorbidity and frailty and may therefore be less useful for clinicians facing dilemmas on how to treat older patients in real life[115].

2.5.2 Faecal microbiota transplantation

FMT is a therapeutic approach that involves the transfer of minimally manipulated intestinal microbiota from a healthy, screened donor to a recipient with a disrupted gut microbiome. In patients with CDI, FMT facilitates a healthier microbial composition by introducing transplanted microbial communities into the recipient's gut, where they compete with and displace pathogenic or dysbiotic organisms, operating through a complex interplay of microbial, immune, and metabolic mechanisms[116].

FMT has been supported by high-quality evidence to be effective for recurrent CDI[117]. In RCTs assessing the efficacy of FMT versus antibiotics monotherapy in patients with primary or recurrent CDI, a substantial cure rate ranging from 71% to 90% is observed (Table 6). In all the trials, FMT was preceded by treatment with vancomycin. The mean or median age of the patients treated with FMT ranged from 59 to 75 years. The study by Hota et al[118] is a negative trial demonstrating a lower effect of standard care antibiotics alone. Rodes et al[119] identified a 6% 180-day mortality rate in the FMT group in contrast to a 23% 180-day mortality rate in the vancomycin group.

RCTs are considered the highest standard of evidence within the hierarchy of clinical research in their ability to minimise bias and establish the causal relations[120-122]. Meta-analyses of RCTs further consolidate this evidence by synthesising results across multiple studies, thereby enhancing statistical power and generalisability. However, these trials often exclude older adults and focus on single disease entities, frequently neglecting the presence of multimorbidity common in older populations. Consequently, their findings may be less useful for clinicians facing dilemmas on how to treat older patients in real life. The studies do not adequately address how FMT is actually delivered to patients in real-world clinical settings. Issues such as access to treatment and logistical challenges are rarely captured in the controlled environment of clinical trials. There remains a need to investigate how FMT treatment for older adults can be effectively organised to overcome existing barriers to its use.

Table 6. Overview of randomised controlled trials testing FMT to vancomycin for first or recurrent *Clostridioides difficile* infection

First author	Sample size (N=), median age (IQR)	Intervention and comparator	Primary outcome	Results, n (%)	Mortality
Van Nood et al, 2013, Netherlands[123]	42, mean age 73 (SD: 13)	Vancomycin + FMT, nasojejunal tube Vancomycin + bowel lavage Vancomycin	Cure without relapse Follow-up: 10 weeks after initiation of treatment	15/16 (94%)*[b] 3/13 (23%) 4/13 (31%)	0 0 1 (4%)
Cammarota et al, 2015, Italy[124]	39, 71 years (29-89)	Vancomycin + FMT, colonoscopy Vancomycin, pulsed tapered	Cure without relapse Follow-up: 10 weeks after initiation of treatment	18/20 (90%)* 5/19 (26%)	Not reported
Hota et al, 2017, Canada[118]	30, mean age 75.7 (SD 14.5)	Vancomycin + FMT Vancomycin, tapered	Recurrence of infection Follow-up: 120 days	9/16 (56%) 5/12 (42%)[a]	0 0
Hvas et al, 2019, Denmark[125]	64, 68 years (22-90)	Vancomycin + FMT (colonoscopy or nasojejunal tube) Vancomycin Fidaxomicin	Clinical cure and negative C. difficile test Follow-up: 8 weeks after treatment	17/24 (71%)* 3/16 (19%) 8/24 (33%)	0 0 0
Rode et al, 2020, Denmark[119]	98, 75 (66-81)	Vancomycin + FMT (enema multiple infusion) Vancomycin + Rectal bacteriotherapy Vancomyin	Clinical cure Follow-up: 90 days after ended treatment (Mortality: 180 days)	26/34 (76%)* 16/31 (52%) 14/31 (45%)	2/34 (6%) 4/31 (13%) 7/31 (23%)
Baunwall et al, 2022, Denmark [126]	42, 59 years (40-73)	Vancomycin + FMT Vancomycin + Placebo	Clinical cure or a negative C. difficile PCR test Follow-up: 8 weeks after last treatment	19/21 (90%)* 7/21 (33%)	0 0

Footnote, table 4: the randomised studies included are English language studies using faecal microbiota transplantation (FMT) to treat first or recurrent CDI with vancomycin comparator in an adult population (≥ 18 years). FMT was defined as the transfer of processed faeces from healthy, allogenic donors. Excluded: autologous FMT and microbial treatments sourced from cultured microbial consortiums[117]. *Denotes that the result reached statistical significance. [a]13/16 (81%) were cured after the first infusion of donor faeces, 2 remaining patients were cured after a second infusion with faeces from a different donor. [b]2 patients did not receive the allocated intervention (vancomycin).

2.5.3 Barriers to the use of FMT: access to treatment

On a European level, there is an unmet potential for the use of FMT[127]. One barrier to the use of FMT may relate to access to treatment for both patients and clinicians. For clinicians, the use of FMT depends on accessibility[128]. For some patients, the opportunity to receive FMT outside the hospital may reduce barriers to treatment. In general, treatment in familiar surroundings and avoiding exhausting hospital visits may influence patient satisfaction[106]. By convention, FMT requires hospital attendance. Older patients who are too weak or unwilling to tolerate transportation for treatment may therefore be withheld treatment if the treatment does not come to the patient[21]. Furthermore, frailty and comorbidity may represent a barrier to the use of FMT unless these aspects are taken into consideration in the treatment and care planning for older patients with CDI[21]. To bridge the gap between routine treatment and real-life implementation of FMT for older patients with CDI, ways to organise FMT treatment within the existing healthcare system need to be explored. CDI treatment in older patients may improve from a collaboration between the Centre for faecal microbiota transplantation[129,130] and experts in geriatric care, expanding the treatment setting beyond the walls of the hospital. To support such cross-sectoral implementation efforts, careful consideration of study design is essential as it determines the capacity to examine the organisational pathways involved in CDI treatment for older patients.

2.6 Study design options

2.6.1 From research to real-world impact: pragmatic and implementation science

The pragmatic trial is designed to evaluate the effectiveness of an intervention in the context of routine clinical care, with a focus on generalisability and real-world applicability as opposed to an explanatory trial (table 7)[131]. Implementation science explores methods for effectively integrating evidence-based interventions into clinical practice[132] and factors that facilitate or hinder implementation, such as workflow, organisation and attitudes in a real-world setting (table 7). The pragmatic and the implementation approach can be combined into a hybrid design that takes a dual focus in assessing clinical effectiveness and implementation[133]. To better understand and explore approaches to the care of older patients with CDI, it may be necessary to draw on elements from both pragmatic and implementation methodologies.

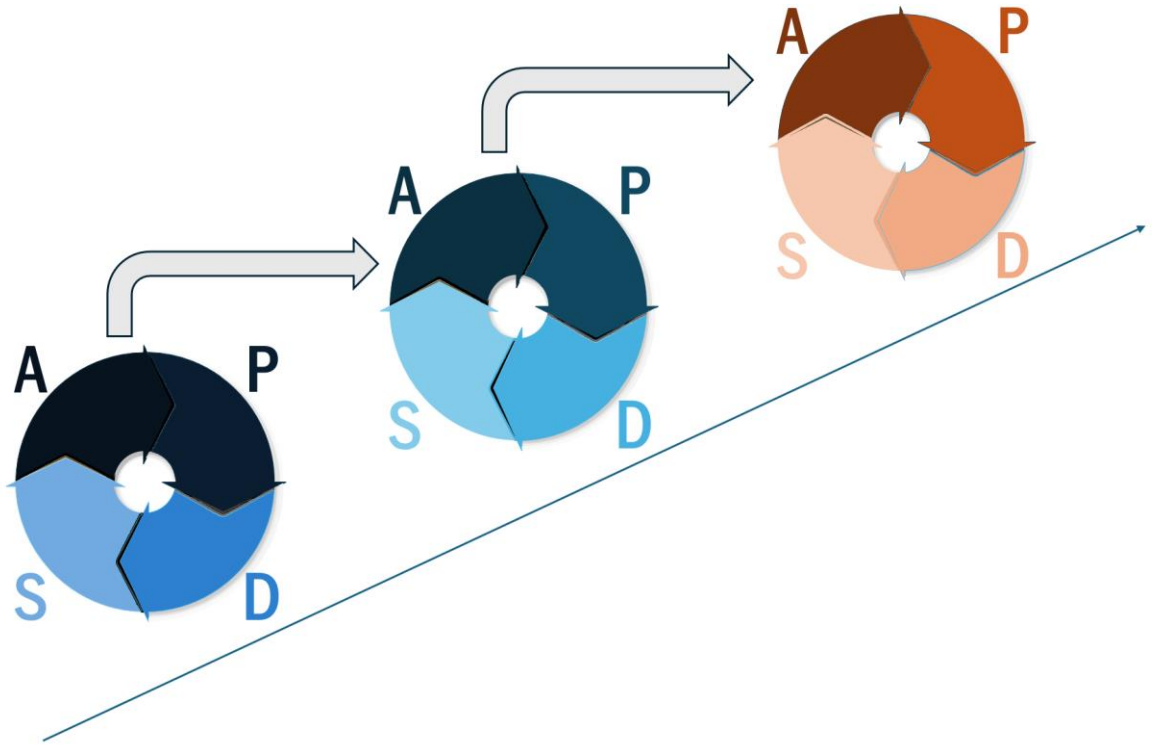
Table 7. Comparison of explanatory, pragmatic and implementation trials[131,132]

Feature	Explanatory trials	Pragmatic trials	Implementation trials
Primary focus	Does the intervention work under ideal conditions?	Does the intervention work in real-world settings?	Understanding how to integrate interventions into routine practice
Context	Controlled research environment	Routine clinical practice	System-level, organisational or clinical workflow focus
Population	Homogenous, highly selected patients	Broad representative groups	Focus on staff, settings and organisational stakeholders
Intervention delivery	By trained experts under strict protocol	By routine providers under usual care conditions	Focus on delivery strategies (e.g. tools, workflow, checklists)
Comparator	Placebo or gold-standard treatment	Standard care	Often not needed: focus may be on strategy comparisons
Outcome measures	Clinical or surrogate outcomes	Patient centred outcome (e.g. mortality, readmission, hospitalisation, quality of life)	Implementation outcomes (e.g. sustainability, fidelity, adoption)

2.6.2 Quality improvement

Quality improvement (QI) refers to systematic, data-driven efforts to enhance patient care and healthcare processes. One of the most widely adopted frameworks for operationalising QI initiatives is the Model for improvement, developed by the Institute for Healthcare Improvement[134]. The Model for improvement provides a structured approach that combines three fundamental questions focused on aim, measurement and change strategies. The Plan-Do-Study-Act (PDSA) cycle (Figure 4) constitutes the operational core of the model and is a method for iterative testing and learning. The PDSA cycle enables healthcare teams to test changes in practice, evaluate the outcomes and refine the approach. Successful QI initiatives rely on multidisciplinary collaboration, continuous measurement and a culture of learning. In clinical settings, QI plays a vital role in aligning practice with evidence-based standards and improving outcomes at both patient and system levels.

Figure 4. The Plan (P) -Do (D) -Study (S) -Act (A) cycle



QI initiatives are essential in the management and prevention of CDI due to the significant mortality in healthcare settings as described above. Key QI interventions in CDI management until now include antimicrobial stewardship programs to minimise unnecessary antibiotic use, enhanced infection control measures to prevent transmission and education programs for healthcare providers on the latest guidelines and best practices[135,136]. Furthermore, previous studies have investigated the effect of the implementation of critical pathways, focusing on in-hospital management of patients with CDI[137,138]. This suggests that a structured approach to patient management with clear pathways for assessment and treatment planning may have a positive impact on clinical outcomes. However, no studies have specifically addressed how to optimise treatment and care trajectories for older patients with CDI. Further research should clarify key elements in treatment care planning for older patients with CDI in a real-world clinical setting.

2.7 Patient and public involvement

Patient involvement in health research refers to the active inclusion of patients, not merely as study participants, but as partners who contribute to the planning, design and dissemination of research. The British National Institute for Health Research defines patient and public involvement (PPI) as research conducted *with* or *by* members of the public, rather than *to*, *about*, or *for* them[139]. A range of platforms have been established to promote PPI[139-141].

Patients may contribute at various stages, including the prioritisation of research questions, development of study materials, or participation in steering committees and advisory groups, with levels of involvement ranging from consultation to co-production[139]. PPI helps to secure shared outcomes for research projects and to enhance the relevance of study findings[142].

Involving frail older patients in research can be challenging. While shared decision-making with older patients has been described across various healthcare settings[143-146], engaging frail older patients as partners throughout a research process can be difficult due to health status and vulnerability[147]. Meaningful involvement requires careful coordination and attention to context-specific barriers. For older patients with CDI, where frailty and acute illness are common, direct participation in research groups may be difficult. In such cases, surrogate representatives, such as senior citizens' council members, can play an important role in ensuring that patient perspectives are reflected in the research process.

2.8 Summary and problem statement

CDI is a frequent and severe condition among older adults, associated with high mortality and considerable healthcare costs. Current clinical guidelines are primarily informed by evidence that insufficiently reflects the complex health profiles of older patients. In particular, the role of frailty remains underexplored. The organisation of care - including the integration of multidisciplinary geriatric assessment and home-based FMT - has received limited attention. These gaps highlight the need to examine whether a geriatric care pathway can better address the interplay between infection and frailty. This thesis aims to investigate mortality and prognostic factors of CDI among older adults and the role of frailty compared with age and guideline-defined severity. Finally, this thesis will assess whether CGA organisational care, including the option for home-based FMT, provides added value over standard care.

3. Aims and hypotheses

The main objective of this PhD project was to improve the understanding and management of CDI in older adults by integrating the concept of frailty into prognostic assessment, organisational care models and structured clinical tools, thereby informing future strategies to improve outcomes in this vulnerable population. To achieve this overarching goal, the project addressed four specific aims.

3.1 Aims

I. Compare multidimensional frailty level at discharge, defined by record-based MPI, CDI severity, and age, as predictors of mortality

II. Develop a protocol for a pragmatic randomised trial comparing CGA organisational care to standard care in older patients with CDI.

III. Investigate the clinical effects of CGA organisational care, including home visits and assessment for FMT in older patients with CDI when compared with the current standard of care

IV. Describe the development of a structured checklist for CDI management to support systematic care planning for older patients with CDI

3.2 Hypotheses

Based on these aims, the following hypotheses were formulated:

I. Multidimensional frailty level is a stronger predictor of mortality in older patients with CDI than age and CDI severity.

II. A structured, frailty-informed trial protocol comparing CGA organisational care and standard care can be systematically developed.

III. Older patients with CDI who receive CGA organisational care, including the option for home-based FMT, will have improved clinical outcomes compared to those who receive standard care.

IV. A CDI checklist addressing the broader care needs of older patients with CDI can be systematically developed to support structured management

Classical hypothesis formulation, rooted in Karl Popper's philosophy of science, emphasises falsifiability as a key criterion for scientific progress[148]. In a context of clinical and quality improvement research, such strict falsification criteria do not always apply because interventions are often implemented based on the best available evidence and expert judgment rather than on immediately testable hypotheses. While falsifiability remains a valuable conceptual tool for evaluating new clinical ideas, its application must be adjusted by the complexity of patient care. Recent critiques of dichotomous statistical testing highlight the need for richer evidential summaries and more flexible approaches to hypothesis evaluation in complex clinical settings[149]. In this thesis, hypotheses II and IV are considered working hypotheses or guiding assumptions rather than classical testable hypotheses. Hypothesis II reflects the expectation that CGA organisational care can improve outcomes for older patients with CDI, providing the rationale for developing a pragmatic randomised trial protocol. Hypothesis IV expresses the assumption that a structured geriatric checklist can systematise CDI management, guiding its development to ensure conceptual grounding and clinical relevance. Formulating such working hypotheses ensures that the two developmental studies are systematic, goal-directed, and embedded in a scientific logic, rather than ad hoc. This approach aligns with a quality improvement perspective, where the primary objective is to create clinically applicable tools and frameworks that may later form the basis for classical hypothesis-testing studies.

4. Materials and methods

The four manuscripts included in this thesis use different methodologies and study designs. Detailed methods are provided in each of the manuscripts I-IV. This section outlines additional methodological considerations.

4.1 Patient population

All patients included in all the studies are older patients with CDI with a varying number of infection episodes and living in the Central Denmark Region. CDI was defined as a positive polymerase chain reaction (PCR) test result for *C. difficile* toxin A, toxin B or binary toxin. The patients were consecutively identified and included based on a complete list from the Danish Microbiology Database comprising all individuals with a positive PCR test for *C. difficile* across primary and secondary health care.

4.2 Study I

The mortality rate following CDI in older adults in Denmark remains undescribed, and the role of frailty, CDI severity and age as predictors of mortality is unknown.

4.2.1 Study design

We designed a population-based cohort study to examine mortality rates among older patients with CDI in the Central Denmark Region and compare frailty, CDI severity and age as predictors of mortality[1]. The study ran for 12 months, from 1 January to 31 December 2018 and included all patients ≥60 years with an index CDI.

4.2.2 Included variables and outcome measures

Patient characteristics were extracted exclusively from electronic medical records and reviewed from the date of index diagnosis.

The level of frailty was assessed retrospectively by performing the record-based MPI at discharge in patients diagnosed with CDI during hospital admission, based solely on information available in the electronic medical records. Patients diagnosed in the outpatient setting and primary healthcare were not assessed for frailty due to insufficient or incomplete documentation in the electronic medical records. The rater was a medical doctor. The MPI sum score is expressed as a number between 0 and 1 by aggregating the total scores of all eight domains and categorised into three groups: MPI-1 (MPI score 0.0-0.33) as low, MPI-2 (MPI score 0.34-0.66) as moderate and MPI-3 (MPI score 0.67-1.0) as severe frailty[1]. The items of the record-based MPI have been described in detail in previous publications[1,83,84].

CDI severity was classified according to the established clinical guidelines into three categories: mild-to-moderate, severe and fulminant/complicated CDI[20]. Classification of severity was based on a range of clinical domains, including laboratory indicators of systemic inflammation or organ dysfunction, presence of gastrointestinal symptoms, systemic compromise reflected by fever, altered mental status, need for intensive care or endoscopic findings such as pseudomembranous colitis.

The primary outcome was 90-day all-cause mortality from the date of the positive PCR test for index CDI.

4.2.3 Statistics

No formal power calculation was performed prior to study initiation. Based on a 90-day mortality rate of 28% during the study period and the inclusion of all eligible older patients diagnosed with CDI, the sample was considered sufficient for exploratory analysis. Analyses were adjusted for age and sex. Given the number of events and covariates, the sample size was considered sufficient to support a multivariable model. Survival was analysed using Kaplan-Meier curves to visualise differences in mortality across age, frailty and CDI severity groups. Hazard ratios were estimated using a Cox proportional hazards model, adjusting for age and gender. The proportional hazard assumptions were tested using 'log–log' plots. Due to the small number of mild severity cases, the three-level severity model was not accepted, and therefore, mild and severe CDI patients were combined and compared with those having fulminant CDI.

Receiver operating characteristic (ROC) curves were used to assess how well age, CDI severity and MPI could distinguish between individuals who survived and those who died within 90 days. The overall accuracy of each measure was evaluated using the area under the curve (AUC).

4.3 Study II

To investigate the role of a CGA organisational pathway on clinical outcomes in older patients with CDI, we designed a multicentre, randomised trial. The following section outlines the rationale behind the development of the protocol and the steps taken prior to its formulation.

4.3.1 Roles and responsibilities

The organisation of the study reflected a collaborative, multicentre effort to ensure a coordinated approach across hospitals and specialties in the Central Denmark Region. Expertise in frailty, CDI and FMT was integrated through a collaborative effort between the Geriatric Research unit in Aarhus and the Centre for Faecal Microbiota Transplantation (CEFTA). This interdisciplinary collaboration facilitated a synergistic exchange of knowledge where clinical insights into the management of frail older patients complemented advanced expertise in FMT and CDI treatment. Geriatricians and geriatric nurses at Aarhus University Hospital and in the regional hospitals were responsible for

patient contact and treatment, ensuring the integration of the pathway into routine practice across sites.

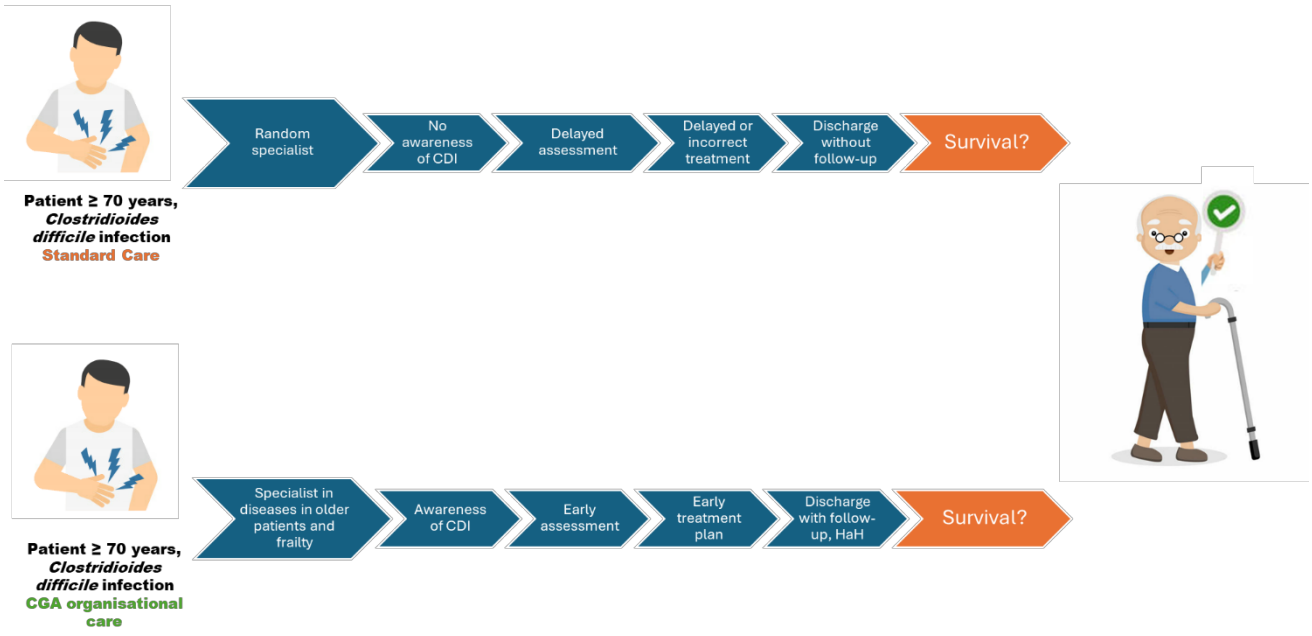
Based on previous experience, involvement of frail, older patients posed practical and ethical challenges[147]. As an alternative to frail older patients with CDI, we engaged two representatives from the Danish Council of Senior Citizens who were able to contribute valuable insights into the needs, preferences and concerns regarding treatment care planning. Their input regarding study planning, choice of outcome and development of patient materials helped inform the design of the pathway. It ensured that patient-centred considerations were integrated into the study framework.

Representatives from the geriatric research unit, local geriatricians, CEFTA and the Danish council of senior citizens formed the steering group.

4.3.2 Preparatory work and implementation considerations prior to Study III

The steering group engaged in critical reflections on the challenges inherent in the existing organisational pathway for this patient group. The review of patient medical records (Study I) suggested that timing of treatment and lack of follow-up may have influenced the course of treatment and outcomes for older patients with CDI (Figure 5). We expected that elements of the existing geriatric care pathway may offer solutions to some of these issues by providing an integrated and patient-centred approach.

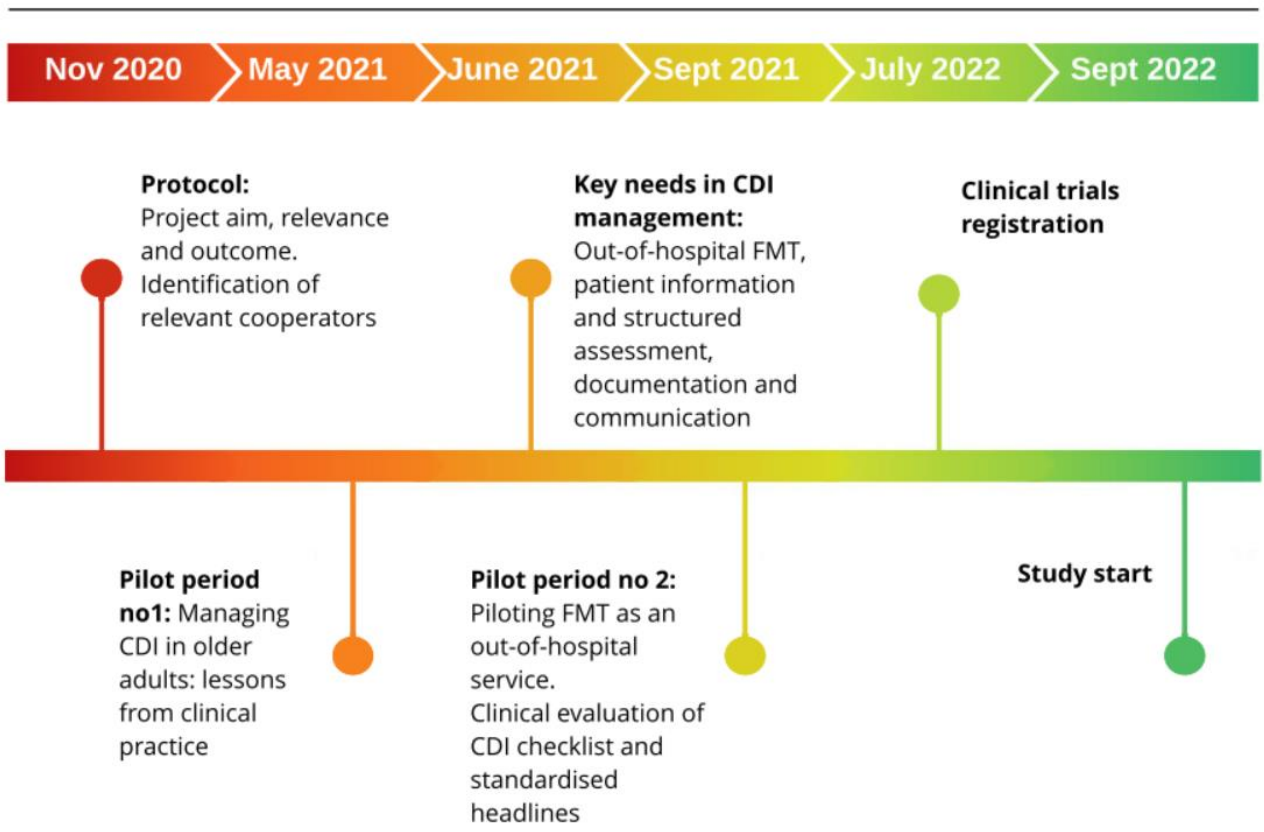
Figure 5. Organisational pathways for management of older patients with *Clostridioides difficile* infection



Abbreviations: CGA: Comprehensive Geriatric Assessment; CDI: *Clostridioides difficile* infection; HaH: Hospital at home

The protocol evolved gradually over two years with quarterly meetings in the steering group (Figure 6). These regular meetings facilitated the integration of diverse clinical insights, ensuring that the protocol remained aligned with current best practices and addressed the specific needs of the older population affected by CDI.

Figure 6. Timeline of key activities in the protocol development



Abbreviations: CDI: *Clostridioides difficile* infection; FMT: faecal microbiota transplantation

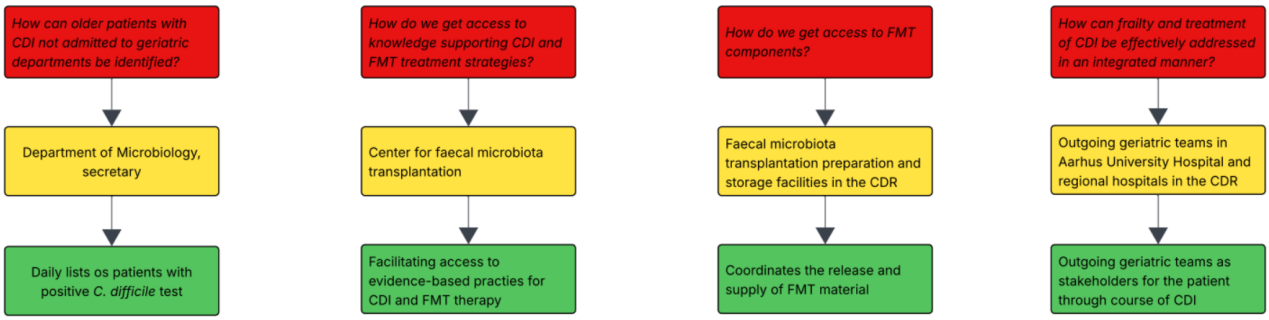
In the development of the Study III protocol, a series of implementation-focused activities were conducted to support the integration of CDI treatment into clinical practice for older patients with CDI. Although not formally designed as an implementation study, this preparatory phase served to inform practical aspects of delivering CDI care, including the feasibility of home-based FMT, potential organisational challenges and adaptations needed to align the protocol with real-world conditions. An overview of the preparatory implementation activities and phases is depicted in Figure 6. During the initial pilot phases of the project, no predefined framework was applied to the management of older patients with CDI. Patients were followed prospectively, and challenges and barriers in treatment and care were documented in real time. Key efforts included: 1) identifying organisational barriers through collaboration with CEFTA, Department of Microbiology and regional geriatricians; 2) establishing home-based FMT through out-going geriatric teams; 3) the

development of a CDI checklist to structure management of older patients with CDI (Study IV). Through this collaborative approach, the protocol was refined and adapted to ensure optimal care strategies and support its pragmatic implementation in the subsequent phase.

4.3.2.1 Identifying organisational barriers and relevant cooperators

To gain an overview of potential barriers and thereby identify key cooperators involved in older patients with CDI in the Central Denmark Region, we formulated a set of key questions (Figure 7). These questions served to guide the systematic identification of clinical and organisational challenges, aiming to inform the development of a coordinated approach.

Figure 7. Key questions and relevant cooperators in the protocol development



Abbreviations: CDI: *Clostridioides difficile* infection; FMT: faecal microbiota transplantation; CDR: Central Denmark Region

4.3.2.2 Establishing home-based FMT through outgoing geriatric teams

To establish a home-based FMT service, close collaboration between the FMT laboratory and the mobile geriatric team was essential. A series of interdisciplinary evening meetings was arranged to facilitate cooperation and knowledge exchange between relevant stakeholders from geriatrics and gastroenterology (physicians, nurses, therapists) and the FMT laboratory staff. During the pilot period phase, practical procedures were trained, including handling and transport of FMT components, the FMT procedure and completing necessary FMT documentation. The FMT laboratory was responsible for developing the FMT components and transport medium to ensure stability and viability during extended distance transportation. The geriatric team was responsible for patient communication, including providing pre-treatment information and instructions on diet and fasting requirements.

Figure 8. Home-based faecal microbiota transplantation through outgoing geriatric teams

Foto by Jens Hjalte Madsen Løgstrup

4.3.2.3 Development of the CDI checklist

The development of the CDI checklist to structure the management of older patients with CDI is described in Study IV.

4.4 Study III

To evaluate the clinical impact of an early CGA organisational care versus standard care in older patients with CDI, we conducted a randomised trial with a 90-day follow-up period (the CLODIfrail study).

4.4.1 Study design

The study was a quality improvement study, designed as a pragmatic randomised trial to improve the quality of care in the routine daily clinic through randomised interventions. The study was approved as a quality improvement study, which allowed for patient randomisation without prior consent. Patients aged ≥ 70 years were randomised to two already established care pathways, thereby

examining the organisational pathways in the management of older patients with CDI. The exclusion criteria were as follows: patients already receiving geriatric assessment (Appendix 6), FMT within 8 weeks before the date of the positive PCR test for CDI, ≥ 5 CDIs or end-of-life care[2].

The study was designed to include 216 patients based on an a priori power calculation with 80% power and a 5% significance level. The sample size was calculated assuming a 90-day mortality rate of 32% in the standard care group and 15% in the CGA group. The anticipated mortality rate in the standard care group was calculated for patients ≥70 years based on data from Study I. Due to the wide variation in 90-day mortality rates reported in previous studies, ranging from 15%-36% and largely influenced by contextual factors (Table 1), mortality data from our own Danish, population-based cohort was chosen. To determine the anticipated impact of the intervention on mortality, existing evidence from two relevant sources was combined: a 12% 90-day mortality rate following FMT[150] and a 21% mortality rate among geriatric patients receiving CGA[25]. No drop-outs due to the design of the study was expected. For ethical reasons, an interim analysis was scheduled after the inclusion of 108 patients, applying the Haybittle-Peto stopping rule to detect between-group significance at a threshold of $p < 0.001$.

4.4.2 Randomisation and blinding

Randomisation was performed electronically in REDCap using a 1:1 allocation stratified by age (≥85 years) and hospitalisation status at CDI diagnosis. The allocation list was concealed from the study personnel, though clinician blinding was not feasible due to documentation in the medical records.

4.4.2 Interventions

Patients in the CGA group received CGA organisational care delivered by geriatric teams embedded in routine clinical practice. The geriatric departments were responsible for patient treatment and clinical follow-up.

The organisational pathways for managing older patients with CDI differ in several key aspects, as outlined in Table 8. The CGA organisational care pathway includes a CGA-based assessment and follow-up, ensuring continuity through contact with the same healthcare personnel throughout the course of care. The pathway allows for home visits, including home-based treatment with FMT.

Table 8. Organisational pathways for older patients with *Clostridioides difficile* infection

	Standard care	CGA organisational care
Assessment of CDI	Danish national guideline for treatment of CDI[20]. Single disease assessment	CGA-based assessment. Multidimensional assessment
Plan of care	Standard care based on pre-discharge or GP assessment and ongoing adjustments after discharge	Individualised, CGA-based tailored treatment and care plan
Involved healthcare professionals	Depends on pre-discharge planning and individual needs assessment	Multidisciplinary geriatric team: geriatric doctor and geriatric nurse/physiotherapists or occupational therapists
Relatives	Sometimes involved	Routinely and repeatedly involved if patient give consent
Responsibility of post-discharge treatment of CDI	Outpatient gastroenterology GP	Geriatric team
FMT treatment	Outpatient treatment or during hospital admission	Home-based FMT, during admission or outpatient treatment
Exacerbation or recurrent CDI	Consult GP Consult physician in the FMT outpatient clinic	Acute follow-up visits including FMT if necessary

Abbreviations: CGA: Comprehensive geriatric assessment; CDI: *Clostridioides difficile* infection; GP: general practitioner; FMT: faecal microbiota transplantation

The CGA organisational care was tailormade and included a multidimensional assessment - covering medical status, frailty status, CDI symptoms and early evaluation for FMT – delivered by a geriatric team operating both within and beyond the hospital setting. The CGA encompassed the following four main parts: a frailty assessment via the bedside MPI; a CDI-specific checklist for older patients with CDI, FMT if indicated and clinical follow-up.

4.4.2.1 GGA and frailty rating with the Multidimensional Prognostic Index

CGA entailed a review of the patient's clinical condition and CDI-related symptoms with early assessment for FMT. The CGA was carried out by a geriatric team with access to consultation with physiotherapists and occupational therapists. The bedside MPI[74] was applied to ensure a structured and standardised approach to the domains of the CGA in older patients with CDI.

The bedside MPI facilitated evaluation across relevant key domains such as comorbidity, sociohousing conditions, medication use, functional status, cognitive function, pressure ulcer risk and nutritional status. To reflect real-world practice as accurately as possible, the bedside MPI tool that was already integrated into the electronic medical records was used. In the bedside MPI used in Study III the Cumulative Illness Rating Scale (CIRS)[151] was replaced with the geriatric version, the CIRS-G[152] and the Katz index (Activities of Daily Living (ADL))[153] and the Lawton scale (Instrumental Activities of Daily living (IADL=)[154] were replaced by the Functional Recovery Score (FRS)[155] which combines both ADL and IADL domains. Additionally, the Braden scale[156] replaced the Exton Smith scale[157] in evaluating the risk of pressure sores, and the Nutritional Risk Score (NRS)[158,159] replaced the Mini Nutritional Assessment (MNA)[160]. Cognitive status was assessed by the Short Portable Mental Status Questionnaire (SPMSQ)[161], and medication use was recorded by

the number of drugs using the Anatomical Therapeutic Chemical Classification system. Calculation of bedside MPI score and the tripartite MPI grade is further displayed in Appendix 7.

Based on the findings from the clinical assessment and the issues identified via the MPI, individualised treatment plans were formulated. The geriatricians made a clinical assessment to determine if the patient should undergo FMT. The assessment was qualified by the issues identified in the MPI, the severity of the CDI according to the national guidelines[20] and the geriatrician-led clinical judgement.

4.4.2.2 Geriatric CDI checklist

The geriatric CDI checklist (Appendix 8) was used to ensure a structured early assessment of CDI and to guide the treatment strategy with CDI-related antibiotics and FMT. The checklist was designed to support the clinician in systematically addressing relevant clinical domains commonly encountered in this population, such as frailty, review of indications for medication (antibiotics and proton pump inhibitors), and optimisation of nutritional and hydration status. The checklist also served to prompt clinicians to initiate timely communication with patients and relevant partners in primary healthcare. This included the use of standardised correspondence letters and discharge summaries to facilitate coordination across sectors.

4.4.2.3 FMT procedure and preparation

FMT was administered via glycerol-based capsules (15-25 capsules) or applied by nasojejunal tube in case of dysphagia. Before the FMT, the patients fasted for at least 6 hours. Metoclopramide 10 mg was administered 10 minutes before the FMT procedure to facilitate peristalsis. The encapsulated FMT was ingested with beverages with low pH, e.g. apple juice, to prevent capsule disintegration. All patients were observed for 30 minutes after the FMT procedure.

The capsules contained 50 g of donor faeces sourced from a single donor. Donor recruitment and processing are based in the public blood bank, ensuring safe, standardised FMT[162,163].

4.4.2.4 Clinical contacts

Follow-up clinical contacts were performed by the local geriatric team. The team provided hospital-at-home care when relevant and continued to monitor CDI treatment for a minimum of 8 weeks following FMT or initiation of CDI-related antibiotic treatment, ensuring continuity of care until clinical resolution.

4.4.3 Standard care

Patients were not contacted by the geriatric team. They received usual treatment at the treating physician's discretion. Standard care of CDI in Denmark is described in the National clinical guideline[20].

4.4.4 Patient characteristics and outcome measures

4.4.4.1 Patient characteristics

Before randomisation sociodemographic and clinical data were collected as previously described[2]. The record-based MPI[83,84] was extracted exclusively from data available in the patient electronic medical records. The clinician doing the ratings was a medical doctor. The items of the record-based MPI have been described in detail in previous publications[83,84].

4.4.4.2 Outcome measures

The primary outcome was all-cause mortality at day 90, counted from the date of the positive PCR test for *C. difficile*.

Secondary quality-related outcomes comprised CDI recurrence, resolution of *C. difficile*-associated diarrhoea, time to initiation of vancomycin and FMT, number of days in hospital and 30-day readmission[164], defined as any unplanned, acute rehospitalisation at any hospital within the Central Denmark Region. Secondary patient-related outcome measures included quality of life measured by the European Quality of Life-5 Domain version (EQ-5D)[165] and the Overall Quality of Life Depression List (OQoL-DL)[166], and functional status measured by the Functional Recovery Score (FRS)[155].

The primary dichotomous outcome according to intention-to-treat, including all patients randomly assigned, was analysed. Logistic regression models with results presented as odds ratios (OR) were used. Kaplan-Meier curves were used to visualise differences in mortality across the CGA and standard care group. Sensitivity analyses were performed adjusting for imbalances in patient characteristics. Interaction between variables with uneven distribution was tested, and stratified analyses for patient characteristics of the primary outcome were done.

Secondary outcomes, including recurrence and readmission, were analysed using logistic regression and presented as OR. Time-to-event outcomes (recurrence and readmission) with death as a competing risk factor were analysed using the Aalen-Johansen estimator and Cox regression to estimate cumulative incidence and hazard ratios, respectively. Time-to-treatment and number of days in hospital were assessed via log-transformed linear regression. All analyses were adjusted for age ≥85 years and hospitalisation status at diagnosis to align with the stratified randomisation design.

4.4.4.3 Collection of data

All data collected at the time of randomisation and during follow-up were obtained from the electronic medical records, which cover all Central Denmark Region public hospitals.

4.5 Study IV

Older patients with CDI present with complex healthcare needs that extend beyond infection management. To address these broader needs and support structured management of older patients with CDI, a CDI checklist was developed. This section outlines the evidence-informed process used to design the checklist.

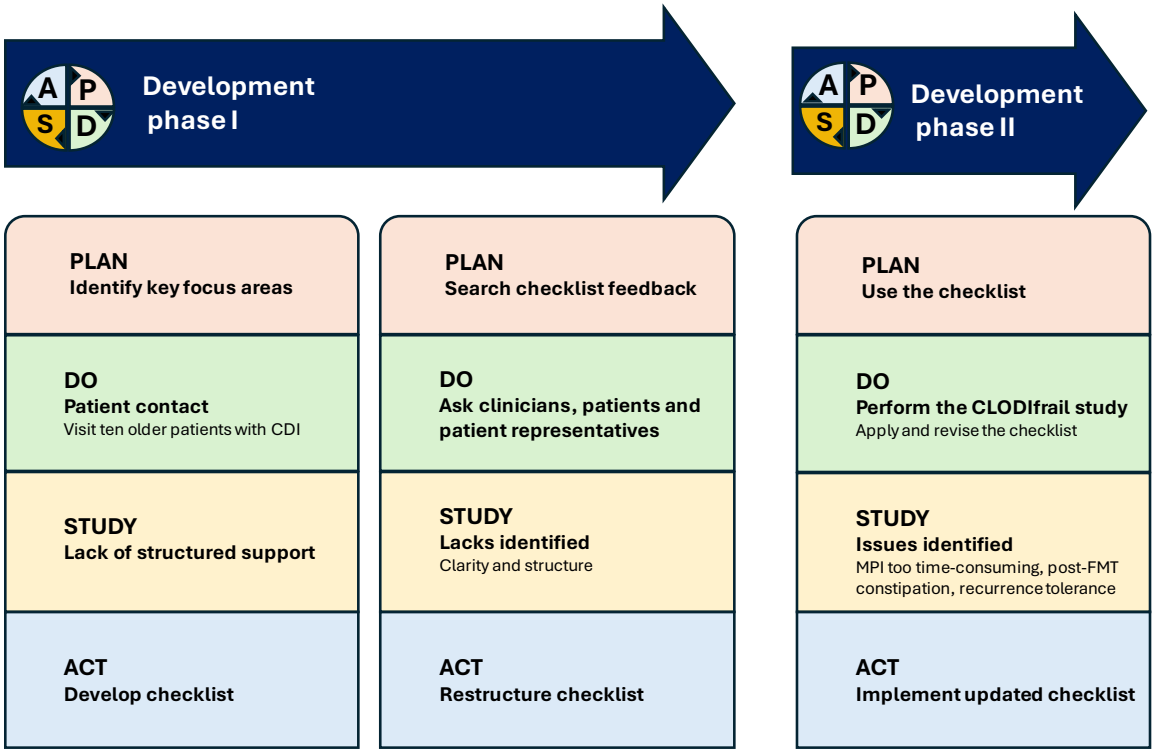
4.5.1 Study design

We designed a model development study conducted in the Central Denmark Region from April 2021 to January 2024.

4.5.2 Methodology

The development of the checklist was guided by the Model for improvement framework[134] using driver diagram and PDSA cycles (Figure 8) to structure the process. The multidisciplinary steering group - including geriatricians, geriatric nurses, one physiotherapist and one occupational therapist, one gastroenterologist, researchers from the CEFTA, and patient representatives - identified core drivers related to the care complexity in older CDI patients. The group developed and refined the checklist iteratively based on clinical experiences and patient feedback, aiming to support comprehensive and systematic treatment planning.

Figure 9. Plan-Do-Study-Act cycles for development of the CDI checklist. The figure is reproduced from Rubak et al 2025[3].



Abbreviations: CDI: *Clostridioides difficile* infection; FMT: faecal microbiota transplantation; MPI: Multidimensional Prognostic Index

4.5.3 Patients

Patients included in the development and evaluation phases were ≥70 years old, had a positive PCR test for CDI, and received treatment within the Central Denmark Region. Clinical data were collected from diagnosis until 90 days after completion of CDI treatment.

4.5.4 Development

4.5.4.1 Development phase I

In development phase I, geriatric teams (physician and nurse) provided weekly home visits to deliver CDI treatment and manage comorbidities in ten older patients with CDI. Patient cases were discussed in the steering group, and feedback from teams, patients, relatives, and primary care collaborators was collected. Medical records were retrospectively reviewed to identify focus areas for intervention. The checklist was iteratively revised, and the steering group reached consensus on the final checklist draft.

4.5.4.2 Development phase II

In development phase II, the checklist was used in Study III as part of the CGA organisational pathway. It was applied within five weekdays of CDI diagnosis and used to guide and structure treatment and care planning. Clinical use was documented in medical records and managed in REDCap. Following the trial, the checklist was reviewed and revised by specialists to ensure clinical relevance and usability.

4.6 Ethics and approvals

The studies were performed according to the Declaration of Helsinki[167]. The studies were classified as quality improvement initiatives, requiring only hospital board approval under Danish law. Access to patient electronic medical records was granted by the hospital boards of all hospitals in the Central Denmark Region.

Study III was approved as a quality improvement project by the Central Denmark Research Ethics Committee (j.no. 1-10-72-1-21). Access to patient electronic medical records was granted by the hospital boards of Aarhus University Hospital and all regional hospitals in the Central Denmark Region (12-11-20). The study protocol and medical record access of Study III were approved by the hospital board of directors at all participating hospitals on March 14, 2021.

5. Results

Main results from Study I, III and IV are summarised below. Additional results can be found in the individual manuscripts.

5.1 Study I

Study I investigated the mortality rate and the predictive value of age, CDI severity and frailty level. Over a 12-month period, 457 patients with index CDI in the Central Denmark region were included with a median age of 77 years (interquartile range: 69-84 years) and primarily diagnosed with CDI during hospital admission (n = 387(85%))[1]. A total of 127 (28%) died within 90 days of the initial CDI diagnosis.

5.1.1 Age

Advanced age was associated with increased 90-day mortality following CDI. Patients aged 80 years or older had a significantly higher risk of death compared to those under 70 years, with an adjusted HR of 2.71 (95% CI 1.64-4.47). Day-to-day survival declined progressively with increasing age, particularly among the oldest patients (Figure 10)[1].

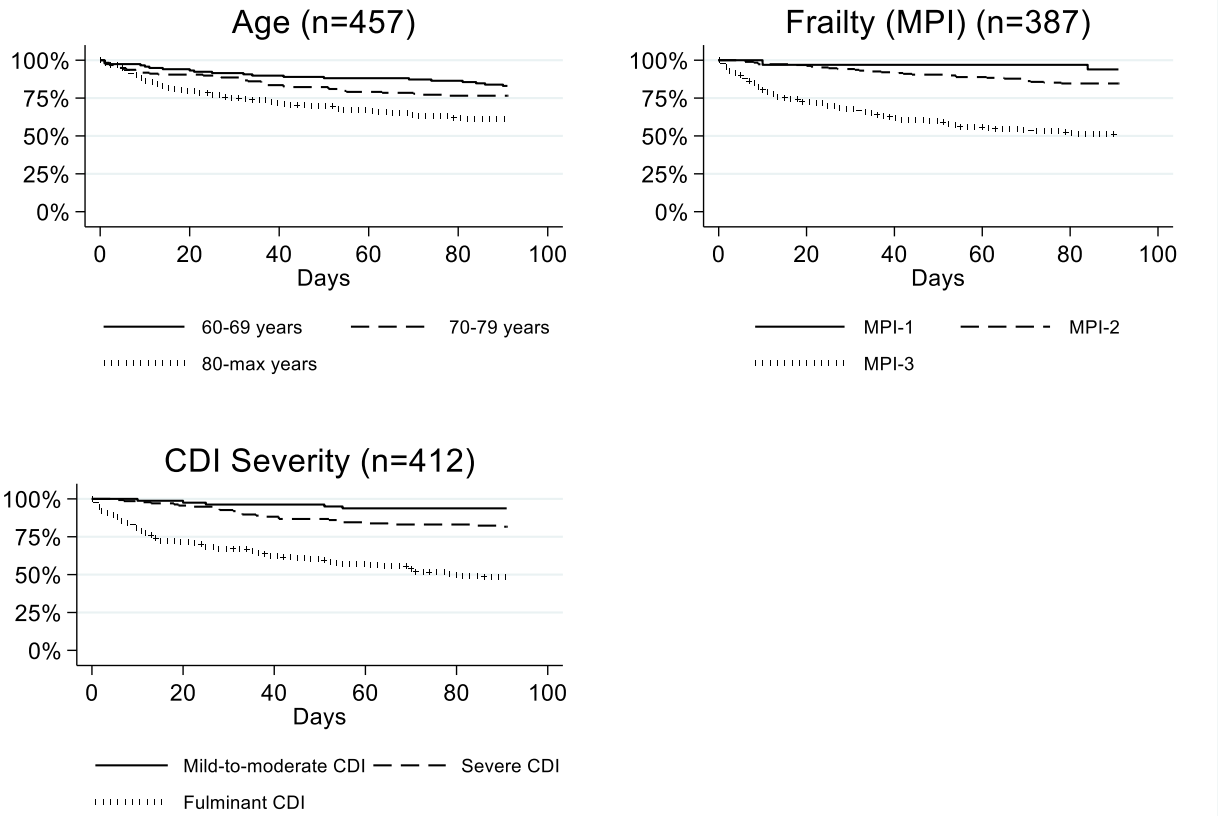
5.1.2 CDI severity

Estimation of CDI severity was possible in 412 patients, and the majority were classified as having severe (n = 189; 41%) or fulminant CDI (n=190; 42%). As shown in Figure 10, most patients with mild CDI survived the 90 days, whereas those with fulminant disease faced a significantly higher daily risk of death, with an adjusted HR of 4.58 (95% CI 3.04-6.88) compared to patients with severe CDI[1].

5.1.3 Frailty

Assessment of frailty by the record-based MPI was possible in 387 patients, and the majority were classified as moderately (n=136; 30%) or severely frail (n=171; 37%). Within 90 days, 88 (51%) of the patients classified with severe frailty died. We found that the frailer the patients were, the lower their chances of survival day by day after diagnosis (Figure 10). The risk of death was nearly ten times higher in the most frail group (HR: 10.15 (95% CI 4.06-25.36) compared to those with low frailty.

Figure 10. Kaplan-Meier survival curves for age, severity and frailty. The figure is reproduced from Rubak et al 2023[1]

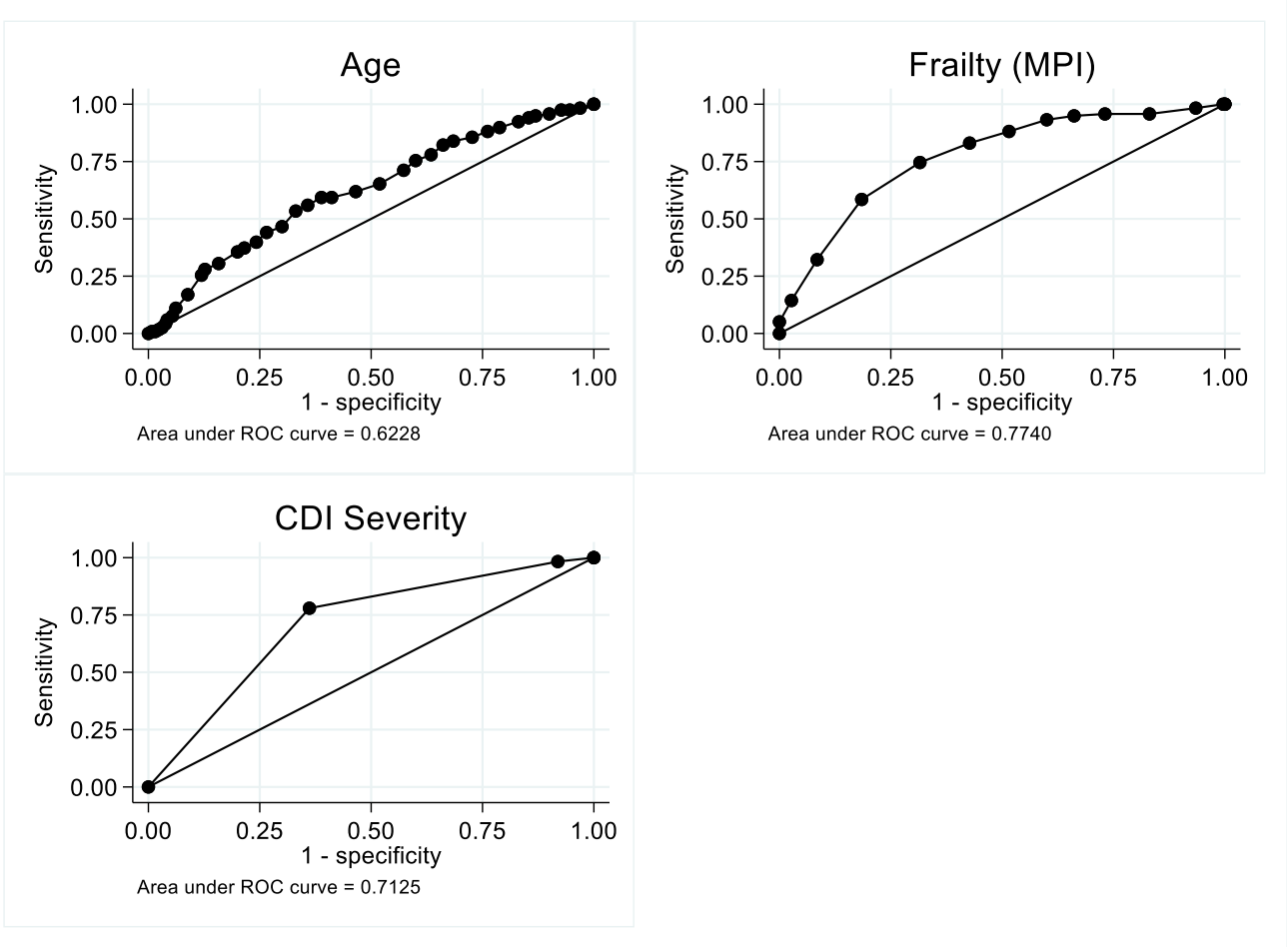


Abbreviations: CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index; MPI-1: low frailty; MPI-2: moderate frailty; MPI-3: severe frailty.

5.1.4 Comparison of predictors of 90-day mortality

Frailty, as assessed by the record-based MPI, was the strongest predictor of 90-day mortality, yielding an AUC of 0.77 (77%, Figure 11). This discriminatory ability was significantly higher than that of age ($p < 0.001$) and CDI severity ($p=0.04$) (Figure 11). CDI severity achieved an AUC of 0.71, also outperforming age.

Figure 11. Receiving operating characteristic curve estimates for 90-day mortality for age, *Clostridioides difficile* infection severity and frailty measured by the record-based Multidimensional Prognostic Index. *Only patients with a known severity and frailty level (n=378) were included in the analysis. The figure is reproduced from Rubak et al[1].



Abbreviations: CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index; ROC: Receiver operating characteristic

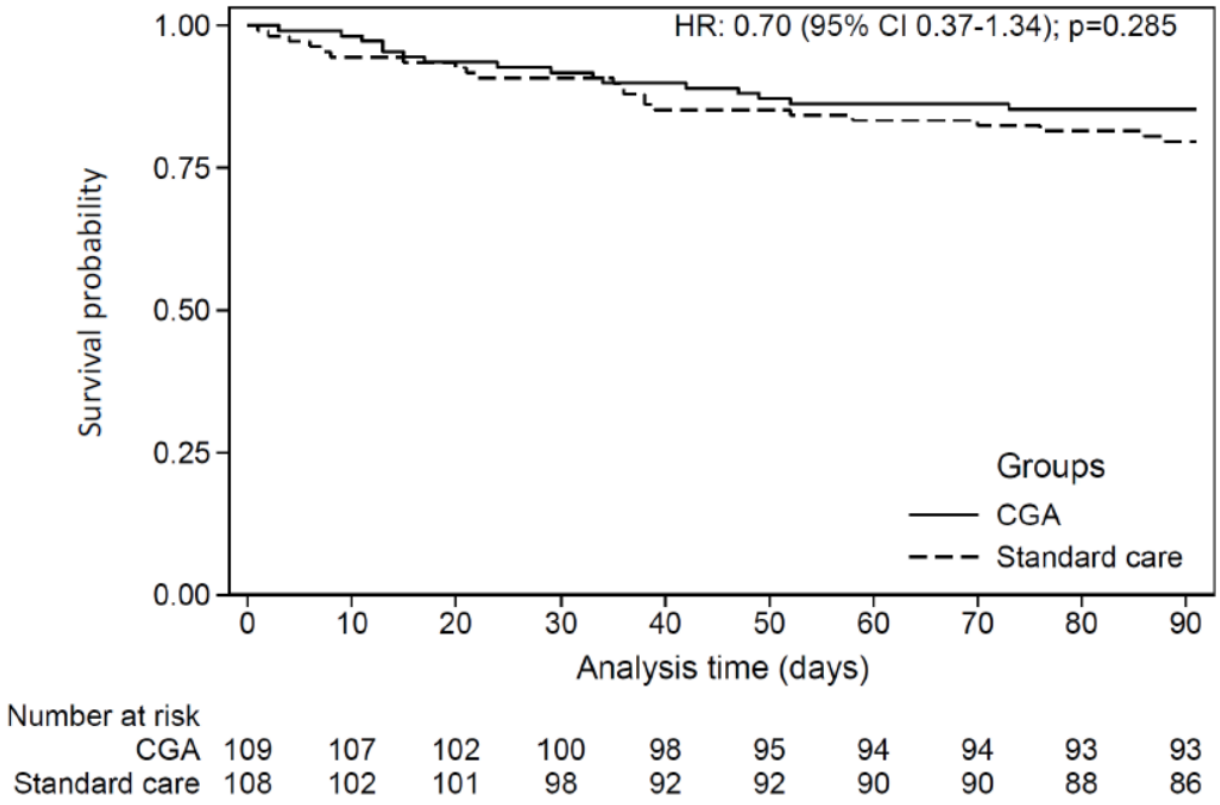
5.2 Study III

Study III compared the clinical impact of CGA organisational care and standard care in older patients with CDI. 217 patients were included from September 2022 until May 2023, with a median age of 79 (IQR: 74-84) in the CGA group and 78 (IQR: 74-84) in the standard care group.

5.2.1 Mortality

Within 90 days of follow-up, 16 out of 109 patients (15%; 95% CI 9-23) who received CGA organisational care had died compared to 22 out of 108 patients (20%; 95% CI 14-29) in the standard care group (figure 12). Although the observed mortality appeared lower in the CGA organisational care group, the difference did not reach statistical significance with an odds ratio of 0.66 (95% CI 0.32-1.38).

Figure 12. Kaplan-Meier survival curve for the CGA group and the standard care group

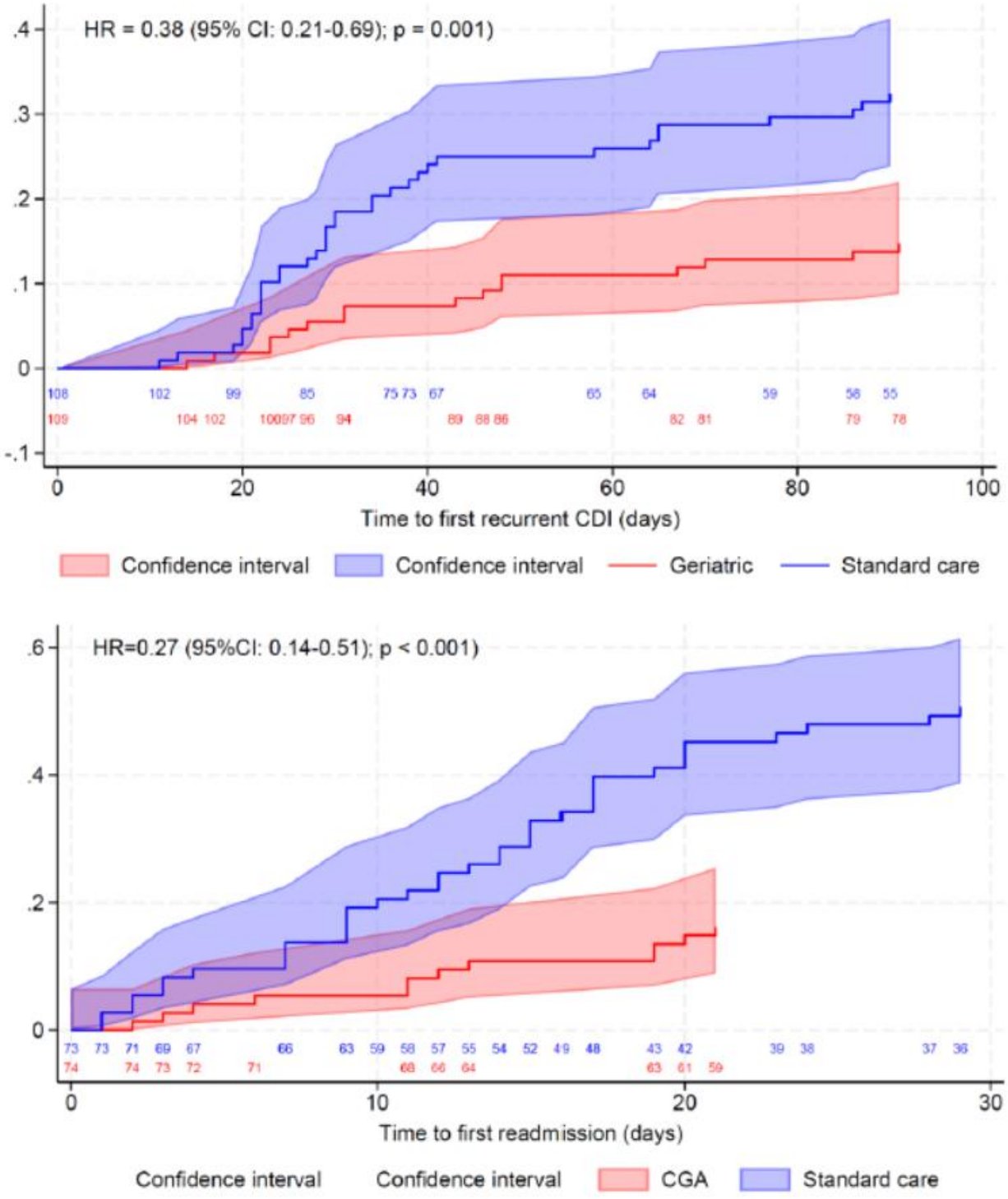


Abbreviations: CGA: Comprehensive geriatric assessment; HR: hazard ratio

5.2.2 CDI recurrence, readmission and hospitalisation

Patients who received CGA organisational care experienced fewer recurrences of CDI within 90 days compared to those receiving standard care, with an OR of 0.35 (95% CI 0.18-0.69) (figure 13). The median number of days in hospital was less for CGA patients than standard care patients, 3 days (95% CI 2-4) versus 5 days (95% CI 3-8) (median ratio 1.88 (95% CI 1.41-2.51). Among patients diagnosed with CDI during hospitalisation who survived the initial admission, readmissions were markedly less frequent in the CGA group (OR 0.18 (95% CI 0.09-0.40)) as depicted in the cumulative incidence curves (Figure 13).

Figure 13. Aalen-Johansen plot (cumulative incidence plot) showing mortality adjusted cumulative incidence of first recurrent *Clostridioides difficile* infection and all-cause 30-day readmission by randomisation group. The figure is reproduced from supplementary of Rubak et al[2].



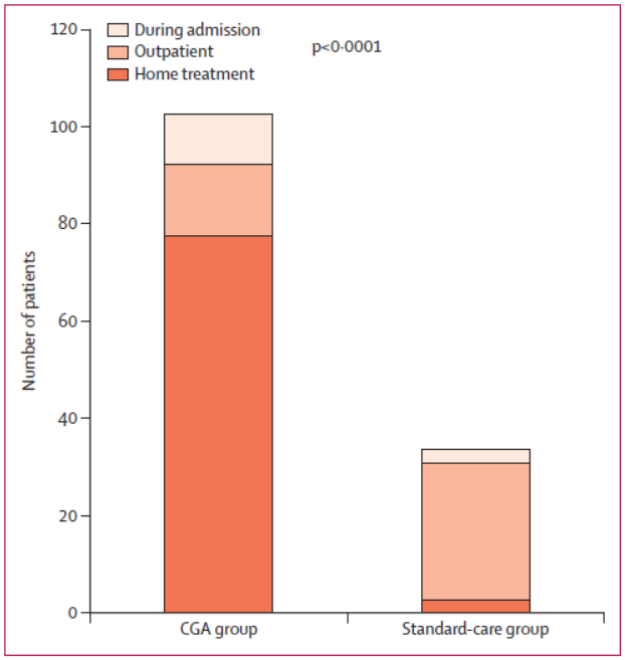
Abbreviations: CGA: Comprehensive geriatric assessment; HR: hazard ratio

5.2.3 Time-to-treatment and use of vancomycin and FMT

Vancomycin and FMT were used more frequently and initiated earlier in the CGA group when compared to standard care. Vancomycin was used in all patients in the CGA group with a median

initiation of one day, compared to 84% in the standard care group, with a median of two days (median ratio 1.54 (95% CI 1.17-2.04; $p < 0.0001$)). FMT was administered to 94% of patients in the CGA group compared to 31% in the standard care group, and the majority as home treatment (Figure 14). Among those treated, FMT was initiated earlier in the CGA group (median 10 days (95% CI 8-12)) than in the standard-care group (median 20 days (95% CI 16-25)), yielding a median ratio of 1.99 (95% CI 1.61-2.47). The use of FMT was associated with a lower 90-day mortality compared to CDI-related antibiotics alone (OR 0.28, 95% CI 0.13-0.61). Baseline characteristics did not differ significantly between FMT-treated and not FMT-treated patients within both the CGA and standard care group (Appendix 9 and 10).

Figure 14. Use of faecal microbiota transplantation in the CGA group and the standard care group. The figure is reproduced from Rubak et al[2].



Abbreviations: CGA: Comprehensive geriatric assessment

5.2.4 CGA-related activities

The bedside MPI provided a structured evaluation of elements of the CGA and was performed in 108 patients, excluding one patient who died before the first visit. The evaluation encompassed an assessment of comorbidity, functional status, medication, cognition, nutrition and social issues, resulting in targeted interventions within each respective domain (Table 9). Among the 108 patients assessed, the most frequently addressed issues were medication-related problems and nutritional status, addressed in 68% and 59% of cases, respectively (Table 9), indicating a clinical emphasis on managing polypharmacy and nutritional concerns within this population.

Table 9. Interventions in the CGA-related domains in the Multidimensional Prognostic Index in the CGA group

Domains in the MPI, activity	**N = 108** **n (%)**
Comorbidity[a]	26 (24)
Functional status[b]	22 (20)
Social support[c]	38 (35)
Medications and polypharmacy[d]	73 (68)
Cognition[e]	7 (6)
Nutrition[f]	64 (59)

[a]Comorbidity-related interventions included referral to further examinations, including imaging diagnostics, optimising treatments, biochemical or microbiology tests
[b]Functional status: referral to physiotherapy and/or referral to occupational therapist
[c]Social support: initiation or adjustment of community-based health care services
[d]Change in medications: deprescribing, initiating or optimising medications
[e]Referral to additional imaging (CT or MR cerebrum), additional Mini Mental Status Examination and/or referral to dementia clinic
[f]Providing oral nutritional advice, prescription of nutritional supplements and/or referral to a dietician
Abbreviations: CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index; CGA: Comprehensive Geriatric Assessment

5.3 Study IV

Study IV reports the results of a two-phase development process of a structured checklist to support clinical management of older patients with CDI.

Development Phase I

Between April and October 2021, ten older patients with CDI were treated at Aarhus University Hospital and Silkeborg Regional Hospital (median age 84 years; 60% female). Half had recurrent infection, and 80% were diagnosed during hospitalisation. Based on clinical experiences and case discussions, the steering group recommended incorporating frailty assessment into CDI management along with evaluation of hydration, nutrition and medication revision. Patient representatives highlighted the need for tailored patient information and structured communication with primary care. These elements informed the initial draft of the CDI checklist.

Development Phase II

From September 2022 to August 2023, 108 patients (median age 79 years; 56% female), allocated to the CGA organisational pathway in the CLODIfrail trial[2], received treatment guided by the structured CDI checklist. All patients were assessed for frailty using the bedside MPI and evaluated to determine whether FMT was indicated. Information materials and communication with primary care were delivered consistently. Nutritional and rehydration needs were addressed in 59% and 56% of patients, respectively. Antibiotic discontinuation was implemented in 52% of relevant cases. Clinical feedback prompted further refinements. Post-FMT constipation was incorporated as a clinical focus area, and the MPI was replaced by a more flexible CGA-based approach to accommodate the practical constraints associated with the time demands of the MPI. The CDI checklist was reorganised to prioritise differential diagnosis and avoid over-reliance on automated treatment patterns.

Clinicians highlighted the importance of coordinated CDI management across specialties to ensure continuity of care. As part of the geriatric assessment, the checklist incorporated an assessment of the patient resilience to recurrent CDI to inform clinical decision-making regarding FMT. These insights informed the final version of the CDI checklist used in clinical practice (Figure 15).

Figure 15. The CDI checklist for older patients. The figure is reproduced from Rubak et al[3]

Patient label_____

midt
regionmidtjylland

***Clostridioides difficile* infection – check list for older patients**

***Clostridium difficile* infection (CDI), definition** ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.	Done	Not relevant
1) Care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin oral tablets or suspension (probe) 125 mg x 4 Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT) Evaluate clinical response on day 5-6. If no clinical response, consider other reasons for diarrhoea (e.g. inflammatory bowel disease, cancer, microscopic colitis) Consider shift of treatment to Fidaxomicin or rescue FMT	☐	☐
Perform Comprehensive geriatric assessment as part of clinical evaluation	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning. Consider whether the patient can tolerate recurrent CDI? Consider the need for coordination of CDI treatment across specialties.	☐	☐
Hand out patient leaflet about C. difficile infection and FMT, including information on risk of post-FMT obstipation	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent catheterization in case of significant post void residual etc.)	☐	☐
Laxative: discontinue if possible	☐	☐
Proton pump inhibitor: discontinue if possible. If discontinuation is not possible at time of assessment, reduced dose may be first step towards this ultimate goal	☐	☐
Diuretics: consider reduction during active diarrhea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
All patients have clinical contact to geriatric department once weekly or more frequently if clinical indication during 8 weeks from date of last FMT or completed vancomycin treatment		

All activities are registered in the electronic medical journal.

6. Discussion

The four studies presented in this thesis investigate mortality among older patients with CDI and the role of frailty and a CGA-based approach in patient assessment and treatment care planning.

The 90-day mortality among older patients with CDI was high in the Danish population-based cohort. Frailty emerged as a key predictor of mortality, challenging existing clinical guidelines that inadequately address this factor. Management of older patients with CDI within a CGA-based organisational framework, designed to provide a structured approach to treatment planning and care, failed in reducing mortality when compared to standard care. However, the CGA organisational pathway positively influenced the patient trajectory by reducing readmission rates, days in hospital and CDI recurrence.

This chapter discusses the implications of these results in relation to current literature, highlights methodological and organisational challenges, and considers directions for future research and clinical practice.

6.1 CDI diagnostics

The diagnostic accuracy of CDI, particularly the distinction between true infection and colonisation in studies I and III, represents a key methodological concern. This is relevant in older adults, where asymptomatic carriage and multifactorial causes of diarrhoea are prevalent. This section addresses the diagnostic uncertainty.

6.1.1 CDI diagnosis

In Denmark, the diagnosis of CDI adheres to American guidelines and requires both clinical evidence of diarrhoea and laboratory confirmation of toxigenic *C. difficile*[33,168]. The PCR-based diagnostics used for diagnosing *C. difficile* do not distinguish between colonisation and active infection[169]. In studies I and III, patients were included based solely on a positive PCR result. Retrospective extraction of diarrhoeal symptoms from the electronic medical records introduces a risk of misclassification due to incomplete documentation. As a result, asymptomatic carriers may have been classified as having active infection in Study I, potentially underestimating the association between frailty and mortality. In Study III, six per cent of the patients had no documented CDI-consistent symptoms. Although this aligns with known rates of asymptomatic carriage[33], it could also indicate incomplete clinical documentation, which limits the certainty of symptom status. The presence of asymptomatic individuals may have diluted the intervention effect, potentially obscuring the benefit of the CGA organisational pathway. Nevertheless, in routine Danish clinical practice, stool samples are typically only collected from patients with suspected CDI based on clinical presentation[168], and non-liquid faecal specimens are rejected by the laboratory following visual inspection. This practice may mitigate the risk of including asymptomatic carriers in clinical care.

6.1.2 Atypical clinical presentation of CDI in older adults

CDI diagnosis remains a challenge, and no rapid, universally accepted gold standard exists[33,40]. Current clinical guidelines assume a uniform clinical presentation across age groups. However, in older adults, the clinical presentation may be absent or atypical and CDI may instead manifest as general weakness, immobility or falls – features commonly associated with the "geriatric syndrome"[170-172]. Such an atypical presentation may lead to underdiagnosis or delayed recognition of CDI in this population. However, in Study III, 94% of the patients presented with diarrhoea, suggesting that most older adults with CDI adhere to the conventional clinical picture outlined in the guidelines. Future studies should further characterise the clinical presentation of CDI in older adults, including potential prodromal symptoms, to improve timely diagnosis and treatment in this vulnerable population.

6.1.3 Distinguishing CDI from other causes of diarrhoea

The possibility of alternative causes of diarrhoea or coincidental colonisation must be considered when interpreting the study outcomes. In older patients with multiple comorbidities, overlapping conditions often obscure the clinical picture, making diagnostic certainty difficult or even unattainable. However, the key question is whether such diagnostic ambiguity should alter clinical management. Evidence of a mortality of 28% in Study I underscores the potential consequences of delayed or withheld treatment. The proactive treatment strategy in Study III seems to improve the overall patient care continuum by mitigating the clinical impact of CDI on chronic morbidity and thereby reduce readmission rates and days in hospital[2]. Therefore, the CDI diagnosis should be interpreted within the broader clinical context, where timely treatment decisions must balance diagnostic uncertainty against the high risk of adverse outcomes in vulnerable older patients.

6.2 The role of frailty in the prognosis and management of *Clostridioides difficile* infection in older adults

Frailty measured by the record-based MPI was a better predictor of mortality in older patients with CDI when compared to CDI severity and age[1]. Following this, frailty assessed by the bedside MPI was used in a CGA organisational pathway, which conferred marked reductions in CDI recurrence and readmissions[2]. In the following, different aspects of using frailty in the assessment and treatment care planning of older patients with CDI will be discussed across Study I-IV. This includes consideration of CDI as a potential expression of gut-related frailty.

6.2.1 Association between frailty and mortality in CDI

Study I found that frailty predicted long-term mortality in older patients with CDI. This finding expands the relevance of frailty assessment beyond the acute hospital setting and highlights its value

for post-discharge care and long-term management. Few previous studies have examined frailty as a prognostic factor in CDI, and none focused on long-term outcomes. Chaar et al., Reveles et al. and Jaan et al all found associations between frailty and short-term mortality, using the Hospital Frailty Risk Score and the Veterans Affairs Frailty Index, respectively[55,63,64]. Despite differences in methods and settings, their findings align with Study I and support a general link between frailty and mortality in patients with CDI. However, whereas Chaar and Jaan emphasise frailty as a marker of acute vulnerability, Study I extends the prognostic utility of frailty across the continuum of care. The distinction between short- and long-term prognostic value underscores the importance of assessing frailty at multiple time points along the care continuum. Study I expands the clinical relevance of frailty assessment beyond the acute phase, offering guidance for post-discharge care planning and long-term management strategies.

6.2.2 Integrating frailty into clinical decision making: limitations of current CDI guidelines

The association between frailty and mortality is not surprising, as frailty inherently implies vulnerability to adverse outcomes. The important question is: how do we apply this knowledge into daily clinical practice? Since treatment decisions are guided by clinical guidelines, these play a central role in bridging evidence and practice. Current national CDI guidelines prioritise disease severity in treatment decisions[20]. The results of Study I indicate that both frailty (the record-based MPI) and the CDI severity classification demonstrated acceptable predictive ability for 90-day mortality[1]. However, current clinical treatment guidelines are based on studies that primarily use recurrent CDI as the outcome rather than mortality and no measure of frailty is included in the severity classification[20,33,40]. This limits the clinical applicability of the guidelines for older, vulnerable patients who may not even survive to experience recurrent CDI, with 28% dying within 90 days[1]. As older patients are more likely than younger to develop severe CDI, it may be too late for treatment by the time the patient has reached the fulminant state of the disease[13,173]. Moreover, the existing CDI severity classification primarily focuses on factors that may be absent or inadequate to fully capture the risk profile of this population. Previous studies have demonstrated that other frailty-related factors, such as cognitive impairment, comorbidity, and poor functional status, are associated with severe CDI outcomes[17,18,56,59]. Study I supports that both frailty and CDI severity should guide treatment decisions in older patients with CDI. There is a need for timely and perhaps more aggressive intervention in patients with increasing degrees of severity and frailty, an area where current clinical guidelines may fall short.

6.2.3 Multidimensional frailty assessment as a clinical framework

Frailty limit the utility of the standard CDI severity score in older patients, as it fails to capture the broader spectrum of health care challenges. As highlighted in Table 2, patients who die with CDI present with multiple comorbidities and clinical vulnerabilities. This underscores the need for a

multidimensional frailty assessment which integrates physical, functional, and biological vulnerabilities to guide clinical decision-making. Deficit accumulation models such as the Hospital Frailty Risk Index and the Veterans Affairs Frailty Index applied in previous CDI studies[55,63] may be useful for mortality risk stratification but offer limited guidance for comprehensive care planning. Study III applied the bedside MPI to support a CGA-based care approach, facilitating identification of clinical issues and targeted interventions across multiple domains (Table 9). This proactive, multidimensional strategy may explain reductions in CDI recurrence, readmissions, and death from CDI by addressing coexisting conditions systematically. However, the MPI is time-consuming; Study IV's post-hoc CDI checklist revision revealed that clinicians found the bedside MPI impractical for routine use. Balancing thoroughness with feasibility remains a critical challenge, warranting exploration of less time-intensive frailty tools for older CDI patients in future research.

6.2.4 Timing of frailty assessment in older patients with CDI

The record-based MPI measured at discharge in Study I may reflect a temporary decline in health capacity related to acute illness and CDI, rather than sustained frailty. This distinction is important, as transient deconditioning may improve with recovery, whereas sustained frailty indicates chronic vulnerability to adverse outcomes. Consequently, this may limit the interpretation of frailty scores obtained at discharge in study I[1]. However, it is plausible that frailty and CDI are intertwined. Previous research demonstrated that patients with CDI are significantly more likely to receive new frailty-associated diagnoses within one year of the CDI diagnosis, suggesting that CDI may accelerate frailty progression[55]. These findings support the need for repeated frailty screening post-acute phase to identify at-risk patients and guide interventions. Importantly, studies I and III explore how frailty can be assessed in real-world clinical practice. When facing an acutely ill patient with CDI, a pre-existing frailty score is often unavailable. Clinicians are left to assess the patient's degree of frailty in the presence of active infection. While this may not reflect the sustained frailty, it could still hold prognostic value as it may help indicate how well the patient might tolerate recurrent CDI and inform the choice and timing of treatment.

6.2.5 Gut microbiota-related frailty

Frailty emerged as a central theme in both Study I and III, functioning not only as a clinical characteristic but also as the framework guiding care and treatment organisation. In this context, it is worth considering whether CDI itself should be conceptualised as a geriatric syndrome - similar to, e.g. falls - representing a physiological expression of frailty specific to the gut. CDI may serve as a marker of gut-related frailty, stemming from age-related changes such as microbial dysbiosis, impaired mucosal integrity, and chronic low-grade inflammation[27,174,175]. Emerging evidence links frailty to reduced gut microbial alpha diversity, underscoring microbial dysbiosis as a potential con-

tributor to the frailty phenotype[176]. López-Otín et al. expanded the characteristics of ageing to include microbial dysbiosis, emphasising the cumulative impact in age-related decline[175]. Notably, CDI may not only result from age-related microbial dysbiosis but also act as a driver of further decline, exacerbating inflammation, disrupting the microbiome, and accelerating nutritional and functional deterioration. From this perspective, interventions that target gut-related frailty, such as FMT, may not only treat infection but also help restore microbiome resilience and potentially modify one of the physiological substrates of frailty. Future studies should explore how gut-related frailty in older patients can be prevented, both by strengthening the microbiome through approaches such as FMT and by developing targeted strategies, including *C. difficile* vaccines, to prevent the damaging effects of the CDI itself.

6.3 Mortality

6.3.1 Variability and challenges in interpreting CDI-related mortality

The ninety-day mortality rates in Study I and III were 28% and 20%, aligning with international variability (15–36%) (table 1)[1,2]. Cross-country comparisons are challenging due to differences in population demographics, diagnostic practices, antibiotic use, and evolving factors such as CDI virulence and stewardship policies. Unlike earlier studies limited to hospitalised patients, studies I and III include both hospitalised and non-hospitalised cases, which is important given the lower mortality associated with community-associated CDI[6].

Within this thesis, mortality declined by eight percentage points from 2018 (Study I) to 2023 (study III). This decline likely reflects improved management, demonstrated by greater use of vancomycin (32% in Study I vs. 100%/84% in CGA/standard care in Study III, 2023) and increased FMT use (1% in 2018 vs. 94%/31% in CGA/standard care in Study III, 2023)[1,2]. These therapeutic advances likely contributed to the improved mortality rates.

Distinguishing CDI-attributable deaths from all-cause mortality remains a key challenge in CDI research. In Study III, 25 of 457 patients died with active diarrhoea and a positive PCR test. However, attributing mortality directly to CDI is complicated by comorbidities, competing causes, and limitations in electronic medical records. CDI may also worsen underlying conditions, further obscuring causality. Evidence suggests CDI contributes independently to mortality, but variation in study design and classification hinders comparison[177]. Standardised, prospective studies are needed to clarify CDI's role in mortality and guide clinical decisions.

6.3.2 Mortality outcomes in Study III

Mortality at 90 days did not differ significantly between patients receiving the CGA organisational pathway and those receiving standard care. This finding raises a critical question: why did the CGA organisational pathway fail to improve survival in this context? The following section discusses

methodological considerations, including sample size adequacy and power, potential dilution of effect related to CDI treatment and CGA fidelity, and finally, the choice of primary outcome.

6.3.2.1 Sample size calculation

The sample size calculation assumed a large absolute risk reduction in 90-day mortality - from 32% to 15% - based on combined estimates from studies on FMT and CGA. However, the estimates may not be directly transferable to the population in Study III. The 12% mortality rate observed in the FMT study likely underestimated true mortality since the frailest patients (n=13) were excluded due to instability, potentially biasing the apparent benefit[150]. Next, assuming a combined effect of 15% of the CGA intervention may have been overly optimistic when considering the 90-day mortality rate of 21% in medical inpatients receiving CGA in a public hospital in the Central Denmark Region[178]. Since most patients in Study III were diagnosed during hospital admission[2] and therefore likely more comorbid, a more accurate baseline mortality estimate closer to 21%, as seen in regional inpatients receiving CGA[25,178], should have been applied. If this conservative and clinically plausible effect size - e.g., an absolute reduction of 10% (from 32% to 21%) - had been assumed, the required sample size would have increased substantially. The lack of a significant effect on the primary outcome in Study III raises the possibility of a type 2 error, whereby a true effect of the intervention remains undetected due to insufficient statistical power.

6.3.2.2 Evolvement of CDI treatment in standard care

CDI treatment evolved during the study period, complicating mortality interpretation. Compared to Study I, 90-day mortality was significantly lower in both groups, likely due to improved CDI management, including more widespread use of vancomycin and FMT[1,2]. Notably, 31% of patients in the standard care group also received FMT - a treatment potentially associated with reduced mortality compared to vancomycin alone[119]. This advanced treatment in the standard care group likely improved their outcomes, diminishing the therapeutic contrast with the CGA group and potentially attenuating the observed effect of the CGA organisational pathway.

6.3.2.3 CGA fidelity

CGA fidelity remains a key challenge in CGA-based care models[179]. Without systematic implementation of recommendations, particularly those targeting rehabilitation, the potential benefit from the CGA may be substantially undermined as described in a previous IGCT trial[101]. In Study III, the CDI checklist (Study IV) facilitated action on the CDI-specific domains (e.g. deprescribing antibiotics and initiating fluid therapy), but the extent of the actual delivery of the MPI-tailored recommendations, such as mobilisation, remains unknown. Much of the treatment occurred in patients'

homes, where resources such as physiotherapy or occupational therapy were not consistently available, limiting the reach of the intervention. Additionally, acute illness often impaired the capacity for intensive assessment and rehabilitation, further constraining full CGA implementation.

6.3.2.4 Beyond mortality: meaningful outcomes in frail older adults

Mortality was selected as the primary outcome in Study III based on input from the patient and public involvement group (PPI). The PPI group expressed concerns regarding older patients potentially declining CDI treatment due to the burden associated with hospital visits, highlighting the ethical imperative to ensure access to treatment with potential survival benefits. It is important to acknowledge that the PPI representatives may have held a different life perspective compared to the frail CDI patient population, which may have influenced the prioritisation of mortality as the most salient and meaningful outcome measure.

Mortality may fail to capture the broader and multidimensional impact of CGA-based care in older patients with CDI. By the time CDI is diagnosed, many older, comorbid patients may already be on an irreversible trajectory of physiological decline, thereby limiting the potential for CGA to alter mortality rates meaningfully[16,50]. The secondary outcomes suggest that embedding CGA within pathways including FMT, reduces CDI recurrence, readmissions, and hospitalisations, indicating a role for coordinated home-based care[2]. These secondary outcome findings underscore the importance of considering healthcare utilisation as an alternative primary outcome measure in future trials. In addition to clinical outcomes, the use of home care services should be included. Persistent diarrhoea and functional decline following untreated or recurrent CDI may lead to increased dependence on municipal healthcare, including support with hygiene, incontinence care and medication management. Such outcomes are not only relevant from a health economics perspective but also reflect key aspects of patient dignity and autonomy.

6.3.3 Faecal microbiota transplantation and mortality

Overall, the use of FMT was associated with a reduction in 90-day mortality, suggesting a potential survival benefit in this patient population.

Few studies have addressed the long-term mortality outcomes following FMT (Table 6). Rode et al observed a trend towards reduced mortality in the FMT group when compared to vancomycin alone, however, this was seen in a relatively younger and less comorbid patient population[119]. The association between FMT and reduced mortality in Study III must be interpreted with caution, as pooling randomised groups may introduce confounding, limiting causal inference. Within Study III, baseline characteristics between FMT recipients and non-recipients in both CGA and standard care groups showed a non-significant trend towards fewer comorbidities and a lower prevalence of cancer in FMT recipients, which could suggest potential selection bias favouring healthier patients.

Thus, observed mortality benefits may partly reflect underlying patient differences rather than FMT alone.

Given the association between FMT and reduced mortality, it is somewhat surprising that the CGA group, which received FMT more frequently, did not exhibit a more pronounced reduction in mortality. One possible explanation is that the beneficial effects of FMT in this context are primarily mediated through a reduction in recurrence rates, which was indeed observed in the CGA group. This mechanism may influence prognosis more gradually, and its full impact may only become apparent over a longer follow-up period. Consequently, future studies should aim to evaluate long-term outcomes to determine the extent to which FMT contributes to improved survival.

6.4 Use of FMT in older adults: overtreatment or preventive strategy?

In study III, all patients in the CGA group received vancomycin, and 94% received FMT, raising concerns about possible overtreatment given the diagnostic uncertainty of CDI in older adults as described previously in section 6.1. Administering FMT without definitive clinical confirmation may present ethical and economic challenges, especially in a frail, multimorbid population. Overuse of vancomycin and FMT may subject patients to unnecessary procedures and reflect a suboptimal allocation of healthcare resources. Nevertheless, the pathway with increased FMT use was associated with reduced readmissions and fewer days in hospital without increased mortality. In Study III no serious adverse events related to FMT were recorded in either groups, which aligns with prior research which report no significant difference in adverse events between FMT and placebo[126] (table 6). Importantly, the greatest safety concern in CDI management is not related to FMT itself, but to the risk of recurrence, which is associated with increased mortality[54]. Restricting FMT due to liability concerns may therefore reflect a defensive strategy that could deny patients a clinically effective and cost-efficient treatment[117,150,180]. Furthermore, hospital-at-home care combined with FMT has demonstrated superior cost-effectiveness compared to standard treatment, mainly through reduced hospitalisation[181]. These results indicate a potential role for FMT as a preventive strategy in older adults with CDI, aimed at reducing recurrence and mitigating downstream healthcare burdens.

6.5 Organising FMT treatment

In Study III, the CGA organisational pathway led to increased use of FMT and reduced time to FMT compared to the standard care group. This section discusses how the organisation of FMT service influence access, uptake and outcomes within different care delivery frameworks.

6.5.1 The role of organisational structure in FMT delivery

The blood bank ensures safe, standardised FMT provision, crucial for regulatory compliance, but operates largely independently from clinical decision-making[163]. In Aarhus CEFTA is a facility collaborating closely with clinical teams in routine care to enhance accessibility and effectiveness of

FMT for patients in the Central Denmark Region[129]. Despite this, Study III demonstrated that patients managed under standard care were less likely to receive FMT and experienced longer delays, highlighting the pivotal role of organisational structure beyond mere availability of treatment[2]. Standard care delivered FMT mainly via outpatient gastroenterology clinics[2], which may impose barriers related to formal referral processes and fragmented care pathways. Moreover, frail patients may be unwilling or unable to attend outpatient appointments, which likely contributes to the reduced utilisation of FMT in this group[2,21].

Integrating FMT delivery within geriatric teams allowed early initiation of coordinated care and home-based treatment, facilitating timely administration and reducing delays. The organisational structure for FMT delivery directly shaped not only access and timing of FMT but also clinical outcomes. The reduced CDI recurrence and readmission rates observed in the CGA group suggest an overall improvement of the patient care continuum. It is not possible to isolate the effect of FMT from the other components of the CGA organisational pathway, which likely worked synergistically. However, given the evidence of the benefits of early FMT on CDI recurrence[126], the timely administration of FMT may have contributed to improve secondary outcomes by rapidly controlling symptoms and limiting the impact of CDI on older patients chronic morbidity.

6.5.2 Clinical reasoning and FMT utilisation in geriatric care

The integration of care within geriatric teams introduced a distinct clinical perspective that influenced FMT utilisation. In the CGA group in study III, most patients received FMT irrespective of frailty level, and a higher proportion of the patients received FMT during their index CDI episode when compared to patients in the standard care group[2]. This pattern likely reflects a shift in clinical reasoning. As emphasised in the revised CDI checklist (Study IV), the patient's capacity to tolerate a potential recurrence became central to treatment decisions. Geriatricians incorporated this consideration into their evaluations, moving beyond a purely guideline-based indication framework. This proactive approach, partly guided by frailty assessment, may explain the earlier and more frequent use of FMT. However, the increased use of FMT in the CGA group may also simply reflect heightened clinical awareness fostered through structured interdisciplinary collaboration and expert input via CEFTA.

6.5.3 Organisational sustainability and clinical pathways

Sustaining FMT delivery through outgoing geriatric teams faces resource and workforce challenges, limiting scalability. Post-trial data indicate a decline in regional FMT use, revealing sustainability issues and the need for strategic solutions[182,183]. Rather than restricting responsibility to geriatric care, structured clinical pathways that ensure continuity across care sectors may be more effective. In this context, de Belvis et al employed a pre-post observational study and reported a positive impact of implementing a critical pathway on CDI management with a non-significant trend towards

reduced mortality and improved care continuity[138]. Although methodological approaches differed in addressing in-hospital standardisation of CDI treatment compared to long-term follow-up treatment in study III, both studies underscore the importance of structured, system-level interventions in enhancing the overall management of CDI, whether this be through clinical pathways or CGA-based organisational care. This aspect aligns with broader evidence suggesting that clinical pathways may enhance care processes[184]. Future implementation should map organisational pathways for FMT delivery and explore partnerships with primary care and community services, such as home nursing services.

6.6 Organising CGA for broader reach in older patients with CDI

The organisational CGA delivery is critical for extending its reach to older patients with CDI. In Study III, 62/301 patients (21%) were excluded because they were already receiving geriatric care[2], highlighting a key challenge: most older adults with CDI are managed outside geriatric departments. This raises the question of how CGA can be made more accessible in routine care. A major barrier is the limited capacity of geriatric teams, and therefore, alternative models are required. Home-based CGA, delivered through primary care, represents one potential solution, offering more integrated and accessible care for community-dwelling older adults[91]. Similarly, efforts to embed geriatric expertise in non-geriatric wards, such as the Geriatric Task Force at Aarhus University Hospital[185], aim to disseminate CGA principles through interdisciplinary, workplace-based learning. In line with these initiatives, the CDI checklist (Study IV) represents a targeted attempt to operationalise CGA principles in the context of CDI management. In future studies, the CDI checklist may serve as a useful tool to explore how optimised care for older patients with CDI might be implemented in clinical environments beyond geriatric inwards by non-geriatric personnel.

6.7 Methodological considerations in record-based and bedside MPI assessments

6.7.1 Study I: methodological limitations of the record-based MPI

A key methodological limitation of the retrospective and record-based frailty assessment in Study I was the risk for observer bias, as the medical doctor performing the ratings was not blinded to outcomes. To mitigate subjectivity and enhance reproducibility, a structured tool as the MPI was applied at a predefined time point in the electronic medical record. The rater was familiar with the rating method, however, precise and comprehensive clinical information was not always available. Similar to reporting bias, clinical documentation may focus on abnormal or positive findings, while normal features - often crucial for a comprehensive frailty assessment - remain unrecorded. This can result in an incomplete representation of the patient's condition when relying solely on electronic medical records. Retrospective frailty assessment therefore lacks the nuance and contextual

detail that direct patient contact provides, potentially increasing the risk of interpretation bias. Future studies should consider prospective, standardised frailty assessments involving multiple independent raters to enhance internal validity.

The record-based MPI predicted mortality in older patients with CDI, but findings were limited to hospitalised patients, as the MPI assessments could not be calculated for those diagnosed outside the hospital. Since hospital-acquired CDI is associated with more severe infection and higher comorbidity, these results underline frailty as a strong independent predictor of mortality even in severely ill patients[6,33]. However, this context limits the generalisability of the findings to patients diagnosed in primary or outpatient care.

6.7.2 Study III: methodological limitations of the bedside MPI

The modifications made to the bedside MPI in Study III (as described in section 4.4.2.1) reflect efforts to align the tool with real-world clinical practice and leverage instruments already integrated into the electronic medical record system. While these changes enhanced feasibility, they may raise concerns about content validity and the potential impact on the predictive accuracy of the bedside MPI. Although the replacement of the Katz Index and the Lawton Scale with other ADL and IADL assessment scales was previously validated[186] and the adjusted bedside MPI using FRS and CIRS-G was comparable to the original MPI in predicting mortality[187], the cumulative effect of the changes may alter the tool's performance. Furthermore, the lack of full validation in accordance with TRIPOD guidelines[188] limits the ability to generalise findings beyond the study setting. However, the MPI is a flexible tool with considerable plasticity, as described in section 2.2.2. Several studies have successfully made adjustments to the MPI[79,82,186,189]. In the bedside MPI applied in Study III, no new domains were introduced into the MPI, rather existing instruments were substituted with equivalent, validated alternatives. Given that content validity had previously been evaluated by Pilotto et al[74], the modifications can be justified. Additionally, the bedside MPI primarily served to structure CGA. Frailty assessment helped nuance the clinical assessment of the patient, however, were not the sole determining factor in clinical decision-making. Finally, to quantify the modified bedside MPI's ability to discriminate between 90-day survivors and non-survivors, post-hoc ROC curve analysis was performed, showing an area under the curve of 75% (Appendix 11), indicating reasonable discriminatory ability despite methodological adaptations.

6.8 Study design

The design of a study evaluating a complex, multidisciplinary care model in older patients with CDI needs to balance scientific rigour with clinical relevance. Given the substantial mortality associated with CDI in older adults[1,12,15,16] and the high FMT effectiveness[119,123-125] ethical concerns become

particularly salient when designing clinical studies in this population. This section outlines key design elements, including the rationale for employing a pragmatic randomised trial in Study III, the limitations of this approach and the implementation elements that emerged during the study.

6.8.1 The rationale for a pragmatic design

Study III aimed to assess the benefits of a CGA organisational pathway in older adults with CDI using a pragmatic randomised trial with post-randomisation consent. The pragmatic design enabled the evaluation of two different care models under routine healthcare conditions without prior patient consent. The rationale is supported by similar pragmatic studies, such as Bretthauer et al[190] in which the pragmatic design enabled the inclusion of a population-representative sample and facilitated the assessment of effectiveness under real-world conditions. The study design aligns with the pragmatic principles outlined in the PRECIS-2 framework[131], particularly in its emphasis on real-world applicability, broad consecutive participant inclusion with virtually no attrition and minimal deviation from routine clinical care, which all enhance the external validity. The design allowed for the inclusion of older and vulnerable patients with CDI, who are often underrepresented in controlled trials. However, external validity was somewhat limited by the exclusion of patients already receiving geriatric care (22%), a group likely to be older and more frail. Consequently, the impact of the CGA organisational pathway on this subgroup remains uncertain.

The pragmatic design includes trade-offs, including reduced control over intervention fidelity and the inability to blind staff in Study III, which may compromise the internal validity by introducing performance bias. However, the robust randomisation procedure supported internal validity by reducing the risk of selection bias and ensured a balanced distribution of known and unknown confounders in Study III. Moreover, the use of routinely documented, objective outcomes such as mortality, readmission and number of days in hospital reduced observer bias, which represents a key methodological strength.

6.8.2 Implementation aspects

Although not formally designed as an implementation study, Study III incorporated key implementation strategies during the preparatory phase (Study II). These included addressing system-level barriers such as identifying older patients with CDI in routine care, facilitating home-based FMT through collaboration between geriatric teams and CEFTA, and developing a clinical checklist to support consistent decision-making. Coordination across these actors was essential to operationalise the intervention. In light of these features, Study III could be considered a hybrid type I effectiveness–implementation trial[132], prioritising effectiveness while supporting early implementation insights. However, no formal process evaluation was conducted, limiting understanding of fidelity, contextual adaptations, and stakeholder perspectives necessary for future scaling and sustainability.

The trial also introduced a regional model in which the geriatric teams assisted across hospital sites. While this facilitated recruitment and delivery, it does not fully reflect the organisational conditions to which the intervention must return post-trial. FMT use has declined following the study[182,183], suggesting challenges to sustainability and highlighting the need to explore dimensions such as acceptability and adaptation in future research.

6.9 Unreported secondary outcomes

The study protocol for Study III included patient-reported outcome measures (PROM) such as EQ-5D, OQoL-DL, and the FRS, but these were not reported in Study III. Collecting reliable PROM data proved infeasible due to the patients' advanced frailty. Moreover, baseline patient-reported outcome measures were unavailable for the standard care group, as patient interaction risked influencing clinical decisions or prompting ethical obligations to intervene, thereby compromising the integrity of the comparison between the two organisational pathways. Follow-up data were subject to selection bias, as deceased patients could not complete questionnaires, biasing results toward those with better outcomes. Future research should consider embedded observational approaches or stepped-wedge designs to enable valid evaluation of quality of life and functional outcomes.

6.10 Ethical considerations

Study III was conducted as a QI initiative embedded in two routine care pathways differing in organisation and clinical approach. No experimental procedures or additional biological sampling were involved. By embedding the study in routine practice, all eligible older patients could be included without prior individual consent, thereby overcoming a key barrier to involve frail and underrepresented populations[191]. This enhanced inclusivity strengthened generalisability and aligned with the ethical imperative to improve existing care rather than test isolated interventions. Autonomy was respected by offering all patients in the CGA group the organisational pathway with the option to decline, although none did. The main ethical consideration concerned withholding the CGA pathway from controls. This was defensible since all controls received guideline-based standard care, representing best practice. The comparison was thus between standard and enhanced care—protecting patient welfare while enabling rigorous evaluation of added benefit.

Although both groups had equal access to FMT, the CGA model - with structured frailty assessment, interdisciplinary collaboration, and staff training and access to FMT - may have facilitated more consistent identification of FMT candidates and uptake. This does not constitute an ethical problem, as all patients remained under the care of treating clinicians with full access to FMT. The key consideration was acknowledging that the organisation itself could shape how systematically treatments were delivered. To safeguard against unintended harm, a pre-planned interim analysis assessed whether allocation to the CGA pathway substantially affected mortality. Conducted by an independent reviewer using Pearson's chi-squared test with Haybittle–Peto stopping boundaries (p

< 0.001), the analysis showed no excess mortality in the control group. Based on these findings, and in consultation with the supervisory team, the study was continued as designed, ensuring both patient safety and robust evaluation under real-world conditions.

6.11 A proposed concept of assessment and management of CDI-related disease

The knowledge generated through this work calls for a reconceptualisation of CDI in older adults - not merely as an acute infectious disease, but as a syndrome closely linked to frailty. The proposed frailty-informed CDI management model integrates three interrelated components: 1) Patient-level interventions, ensuring key treatments - such as FMT, revision of antibiotic and proton-pump inhibitor use, nutrition, and rehydration - are adapted to the patient's overall vulnerability; 2) Organisational processes, promoting cross-sector communication, standardised patient information, and continuity within care teams; and 3) System-level strategies, implementing frailty-informed guidelines and structured care pathways. The model positions frailty-informed care as both a conceptual and practical strategy.

To ensure that the model achieves its intended impact in practice, the CGA organisational pathway should be systematically evaluated. Drawing on the UK Medical Research Council framework for complex interventions, mixed-methods process evaluations can complement effectiveness data by examining mechanisms of action, contextual fit, and adaptation[192,193]. In the context of Study III, such an evaluation could explore questions like: Which elements of CGA mattered most to patients? How did sustained contact with geriatric teams shape care experiences? What delivery model for FMT was most acceptable and practical? And what obstacles emerge in implementing home-based FMT in other specialties? Incorporating interviews with patients and staff, alongside comparative case studies of different sites, could provide rich insights into real-world implementation. By embedding reflective evaluation within the model, the framework may not only guide coordinated care but also ensure continuous learning and sustainability across clinical contexts.

7. Conclusions

This thesis integrates findings from a cohort study, a randomised trial and a checklist development study to explore the impact of frailty and the organisational requirements in the management of older patients with CDI.

The results of this thesis conclude that frailty, as assessed by the record-based MPI at discharge, is a strong predictor of mortality compared to age or CDI severity markers in older patients diagnosed with CDI.

This work did not demonstrate a significant effect on 90-day mortality following CGA organisational care in older patients with CDI. Nevertheless, it provided evidence that a geriatric-led model of care, incorporating home-based FMT, is both feasible and effective for improving the patient trajectory by reducing readmissions, CDI recurrence, and days in hospital.

Finally, the CDI checklist offers a framework to support structured care planning in older patients with CDI. By emphasising critical areas such as CDI treatment planning, indications for FMT, frailty assessment, medication review, and supportive interventions, the checklist facilitates a holistic approach tailored to the complex needs of this vulnerable population.

8. Perspectives

Looking forward, several critical questions remain regarding the long-term implementation and optimisation of CGA pathways and FMT in older patients with CDI. Sustaining and scaling geriatric-led care is challenging due to patient distribution across multiple departments and limited geriatric capacity. Understanding how these interventions can be adapted across specialties, and how they interact with patient-specific factors is essential for sustainable and patient-centred care.

The long-term impact of the CGA pathway may become evident over time, highlighting the need for real-world observational cohorts to complement the randomised trial findings. A one-year follow-up of the CGA cohort from Study III is warranted to assess sustained survival outcomes, and new cohorts are needed to evaluate FMT use, mortality, and healthcare utilisation across geriatric and other specialties.

Innovative strategies are required to embed geriatric principles more broadly. Future quality improvement projects should determine whether improved outcomes are driven primarily by geriatric-led FMT or by services in other specialties, such as gastroenterology, which may provide alternative, effective, and potentially less costly care models. The comprehensive assessment informing clinical decisions should also be evaluated outside geriatrics; the CDI checklist may offer a scalable tool for structured treatment planning and warrants further testing. Future studies must address not only whether interventions work, but also how, for whom, and under what conditions - questions central to sustainable implementation in dynamic healthcare systems.

Several questions remain regarding FMT itself. The potential of FMT to reduce readmissions, hospitalisation, and healthcare utilisation represents a critical, patient-relevant avenue for older patients with CDI. Beyond its established role in CDI management, FMT may influence age-related vulnerabilities through interactions with nutrition and gut physiology. Study III highlighted the prevalence of nutritional deficits, underscoring the need to test whether combining FMT with targeted nutritional support can enhance engraftment, restore microbial diversity, and counteract anorexia or malabsorption. Future research should identify which specific dietary interventions (e.g., protein or fibre supplementation, micronutrient support) best sustain FMT benefits. Conversely, FMT may improve nutrient absorption and metabolic efficiency, suggesting a reciprocal link between microbiota modulation and nutritional status. Finally, the concept of gut-related frailty remains to be explored and discussed. It has yet to be clarified whether gut-related frailty is a subsystem within the broader concept of frailty or whether the status of the gut is an indicator of overall frailty. In this sense, interventions targeting the gut, such as FMT may have the potential to modulate physical resilience in older adults.

9. References

1. Rubak T, Baunwall SMD, Gregersen M, et al. Frailty level at discharge predicts mortality in older patients with Clostridioides difficile more accurately than age or disease severity. *Eur Geriatr Med* 2023; 14(3): 583-93.
2. Rubak T, Baunwall SMD, Gregersen M, et al. Early geriatric assessment and management in older patients with Clostridioides difficile infection in Denmark (CLODIfrail): a randomised trial. *Lancet Healthy Longev* 2024; 5(12): 100648.
3. Rubak T BS, Gregersen M, Paaske SE, Ørum M, Kongensgaard R, Hansen TK, Gregersen M, Hvas CL. . Development of a geriatric checklist to support management of older patients with Clostridioides difficile infection. Unpublished, submitted. 2025.
4. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; 372(9): 825-34.
5. European Centre for Disease Prevention and Control. Strategies and guideines for Clostridioides difficile infections. Avaialbe at: https://www.ecdc.europa.eu/en/clostridium-difficile-infections/facts. Accessed August 13.
6. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of Clostridioides difficile Infection and Outcomes. *N Engl J Med* 2020; 382(14): 1320-30.
7. European Centre for disease prevention and control. Surveillance report. Clostridioides difficile infections, Annual Epidemiological Report for 2018-2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/AER-Clostridium-difficile-2018-2020.pdf Accessed August 29, 2025.
8. European Centre for Disease Prevention and Control. Clostridioides (Clostridium) difficile infections. Annual epidemiological report for 2016–2017. Stockholm: ECDC; 2022. Available at: https://www.ecdc.europa.eu/en/publications-data/clostridiodes-difficile-infections-annual-epidemiological-report-2016-2017. Accessed August 29, 2025.
9. Danmarks Statistik. Population pyramid 2050. Available at: https://extranet.dst.dk/pyramide/pyramide.htm#!y=20502024. Accessed August, 29, 2025.
10. Oksuzyan A, Höhn A, Krabbe Pedersen J, Rau R, Lindahl-Jacobsen R, Christensen K. Preparing for the future: The changing demographic composition of hospital patients in Denmark between 2013 and 2050. *PLoS One* 2020; 15(9): e0238912.
11. Enoch DA, Murray-Thomas T, Adomakoh N, et al. Risk of complications and mortality following recurrent and non-recurrent Clostridioides difficile infection: a retrospective observational database study in England. *J Hosp Infect* 2020; 106(4): 793-803.
12. Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with Clostridium difficile infection: a multicenter cohort study. *Clin Infect Dis* 2013; 56(8): 1108-16.
13. Abou Chakra CN, McGeer A, Labbé AC, et al. Factors Associated With Complications of Clostridium difficile Infection in a Multicenter Prospective Cohort. *Clin Infect Dis* 2015; 61(12): 1781-8.
14. Braae UC, Møller FT, Ibsen R, Ethelberg S, Kjellberg J, Mølbak K. The Economic Burden of Clostridioides difficile in Denmark: A Retrospective Cohort Study. *Front Public Health* 2020; 8: 562957.
15. Feuerstadt P, Nelson WW, Drozd EM, et al. Mortality, Health Care Use, and Costs of Clostridioides difficile Infections in Older Adults. *J Am Med Dir Assoc* 2022; 23(10): 1721-8.e19.
16. Caupenne A, Ingrand P, Ingrand I, et al. Acute Clostridioides difficile Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality. *J Am Med Dir Assoc* 2020; 21(1): 110-4.
17. Rao K, Micic D, Chenoweth E, et al. Poor functional status as a risk factor for severe Clostridium difficile infection in hospitalized older adults. *J Am Geriatr Soc* 2013; 61(10): 1738-42.
18. Kyne L, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. *Age Ageing* 1999; 28(2): 107-13.

19. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013; 381(9868): 752-62.
20. Baunwall SMD, Dahlerup JF, Engberg JH, et al. Danish national guideline for the treatment of Clostridioides difficile infection and use of faecal microbiota transplantation (FMT). *Scand J Gastroenterol* 2021; 56(9): 1056-77.
21. Dahl Jørgensen SM, Mørck Rubak TM, Damsgaard EM, Dahlerup JF, Hvas CL. Faecal microbiota transplantation as a home therapy to frail older people. *Age Ageing* 2020; 49(6): 1093-6.
22. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces mortality among patients living in their own home. A randomised controlled trial. *European Geriatric Medicine* 2017; 8(4): 330-6.
23. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces readmissions – A quasi-randomised controlled trial. *Eur Geriatr Med* 2016; 7(5): 443-8.
24. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up visits to nursing home residents reduce the number of readmissions: a quasi-randomised controlled trial. *European Geriatric Medicine* 2018; 9(3): 329-37.
25. Hansen TK, Pedersen LH, Shahla S, Damsgaard EM, Bruun JM, Gregersen M. Effects of a new early municipality-based versus a geriatric team-based transitional care intervention on readmission and mortality among frail older patients - a randomised controlled trial. *Arch Gerontol Geriatr* 2021; 97: 104511.
26. Smits WK, Lyras D, Lacy DB, Wilcox MH, Kuijper EJ. Clostridium difficile infection. *Nat Rev Dis Primers* 2016; 2: 16020.
27. Fletcher JR, Pike CM, Parsons RJ, et al. Clostridioides difficile exploits toxin-mediated inflammation to alter the host nutritional landscape and exclude competitors from the gut microbiota. *Nat Commun* 2021; 12(1): 462.
28. Kuehne SA, Cartman ST, Heap JT, Kelly ML, Cockayne A, Minton NP. The role of toxin A and toxin B in Clostridium difficile infection. *Nature* 2010; 467(7316): 711-3.
29. Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) - a systematic review of the epidemiology of primary and recurrent CDI. *BMC Infect Dis* 2021; 21(1): 456.
30. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; 353(23): 2442-9.
31. Gould CV, Edwards JR, Cohen J, et al. Effect of nucleic acid amplification testing on population-based incidence rates of Clostridium difficile infection. *Clin Infect Dis* 2013; 57(9): 1304-7.
32. Dingle KE, Didelot X, Quan TP, et al. Effects of control interventions on Clostridium difficile infection in England: an observational study. *Lancet Infect Dis* 2017; 17(4): 411-21.
33. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66(7): 987-94.
34. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med* 2015; 372(16): 1539-48.
35. Statens Serum Institut. Clostridioides difficile infektion (CDI). Available at: https://www.ssi.dk/sygdomme-beredskab-og-forskning/sygdomsleksikon/c/clostridium-difficile-infektion Accessed August 19, 2025.
36. Dubberke ER, Olsen MA. Burden of Clostridium difficile on the healthcare system. *Clin Infect Dis* 2012; 55 Suppl 2(Suppl 2): S88-92.
37. Kuijper EJ, Coignard B, Tüll P. Emergence of Clostridium difficile-associated disease in North America and Europe. *Clin Microbiol Infect* 2006; 12 Suppl 6: 2-18.
38. Amin A, Nelson WW, Dreyfus J, et al. Mortality, healthcare resource utilization, and cost among Medicare beneficiaries with Clostridioides difficile infection with and without sepsis. *Therapeutic Advances in Infectious Disease* 2022; 9.

39. Loo VG, Bourgault AM, Poirier L, et al. Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med* 2011; 365(18): 1693-703.
40. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. *Clin Microbiol Infect* 2021; 27 Suppl 2: S1-s21.
41. Olsen MA, Stwalley D, Demont C, Dubberke ER. Increasing Age Has Limited Impact on Risk of Clostridium difficile Infection in an Elderly Population. *Open Forum Infect Dis* 2018; 5(7): ofy160.
42. Ticinesi A, Nouvenne A, Folesani G, et al. Multimorbidity in elderly hospitalised patients and risk of Clostridium difficile infection: a retrospective study with the Cumulative Illness Rating Scale (CIRS). *BMJ Open* 2015; 5(10): e009316.
43. Biagi E, Candela M, Turroni S, Garagnani P, Franceschi C, Brigidi P. Ageing and gut microbes: perspectives for health maintenance and longevity. *Pharmacol Res* 2013; 69(1): 11-20.
44. Rea MC, O'Sullivan O, Shanahan F, et al. Clostridium difficile carriage in elderly subjects and associated changes in the intestinal microbiota. *J Clin Microbiol* 2012; 50(3): 867-75.
45. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* 2019; 7(1).
46. Fernandez-Cotarelo MJ, Jackson-Akers JY, Nagy-Agren SE, Warren CA. Interaction of Clostridioides difficile infection with frailty and cognition in the elderly: a narrative review. *Eur J Med Res* 2023; 28(1): 439.
47. Mizusawa M, Doron S, Gorbach S. Clostridium difficile Diarrhea in the Elderly: Current Issues and Management Options. *Drugs Aging* 2015; 32(8): 639-47.
48. Kee VR. Clostridium difficile infection in older adults: a review and update on its management. *Am J Geriatr Pharmacother* 2012; 10(1): 14-24.
49. Rauseo AM, Olsen MA, Reske KA, Dubberke ER. Strategies to prevent adverse outcomes following Clostridioides difficile infection in the elderly. *Expert Rev Anti Infect Ther* 2020; 18(3): 203-17.
50. Czepiel J, Krutova M, Mizrahi A, et al. Mortality Following Clostridioides difficile Infection in Europe: A Retrospective Multicenter Case-Control Study. *Antibiotics (Basel)* 2021; 10(3).
51. Yu H, Alfred T, Nguyen JL, Zhou J, Olsen MA. Incidence, Attributable Mortality, and Healthcare and Out-of-Pocket Costs of Clostridioides difficile Infection in US Medicare Advantage Enrollees. *Clin Infect Dis* 2023; 76(3): e1476-e83.
52. Lauda-Maillen M, Liuu E, Catroux M, et al. Treatment compliance with European guidelines and prognosis of Clostridium difficile infection according to age. *Med Mal Infect* 2019; 49(3): 173-9.
53. Mitchell BG, Gardner A, Hiller JE. Mortality and Clostridium difficile infection in an Australian setting. *J Adv Nurs* 2013; 69(10): 2162-70.
54. Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent Clostridium difficile infection is associated with increased mortality. *Clin Microbiol Infect* 2015; 21(2): 164-70.
55. Reveles KR, Strey KA, Albuquerque EL, Jacota D, Jones X, Carreno JJ. Retrospective, propensity score--matched study examining the relationship between frailty and Clostridioides difficile infection in a national cohort of US veterans. *Am J Infect Control* 2024; 52(12): 1412-8.
56. Atamna A, Babich T, Margalit I, et al. Does accepted definition of Clostridioides difficile infection (CDI) severity predict poor outcomes in older adults? *Aging Clin Exp Res* 2022; 34(3): 583-9.
57. Bauer MP, Notermans DW, Van Benthem BH, et al. Clostridium difficile infection in Europe: A hospital-based survey. *The Lancet* 2011; 377(9759): 63-73.
58. Bielakova K, Fernandova E, Matejovska-Kubesova H, Weber P, Prudius D, Bednar J. Can we improve the therapy of Clostridium difficile infection in elderly patients? *Wien Klin Wochenschr* 2016; 128(15-16): 592-8.
59. Leibovici-Weissman Y, Atamna A, Schlesinger A, Eliakim-Raz N, Bishara J, Yahav D. Risk factors for short- and long-term mortality in very old patients with Clostridium difficile infection: A retrospective study. *Geriatr Gerontol Int* 2017; 17(10): 1378-83.
60. Covino M, Gallo A, Pero E, et al. Early Prognostic Stratification of Clostridioides difficile Infection in the Emergency Department: The Role of Age and Comorbidities. *J Pers Med* 2022; 12(10).

61. Kassam Z, Cribb Fabersunne C, Smith MB, et al. Clostridium difficile associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with C. difficile infection. *Aliment Pharmacol Ther* 2016; 43(6): 725-33.
62. Stewart AG, Chen SCA, Hamilton K, et al. Clostridioides difficile Infection: Clinical Practice and Health Outcomes in 6 Large Tertiary Hospitals in Eastern Australia. *Open Forum Infectious Diseases* 2023; 10(6).
63. Chaar A, Yoo JW, Nawaz A, Rizwan R, Agha OQ, Feuerstadt P. Frailty is a predictor for worse outcomes in patients hospitalized with Clostridioides difficile infection. *Ann Gastroenterol* 2024; 37(4): 442-8.
64. Jaan A, Farooq U, Alayoub AA, et al. Superiority of frailty over age in predicting outcomes among clostridium difficile patients: Evidence from national data. *Clin Res Hepatol Gastroenterol* 2025; 49(1): 102499.
65. Banks A, Moore EK, Bishop J, et al. Trends in mortality following Clostridium difficile infection in Scotland, 2010-2016: a retrospective cohort and case-control study. *J Hosp Infect* 2018; 100(2): 133-41.
66. Chintanaboina J, Navabi S, Suchniak-Mussari K, et al. Predictors of 30-Day Mortality in Hospitalized Patients with Clostridium difficile Infection. *South Med J* 2017; 110(8): 546-9.
67. Takahashi M, Mori N, Bito S. Multi-institution case-control and cohort study of risk factors for the development and mortality of Clostridium difficile infections in Japan. *BMJ Open* 2014; 4(9): e005665.
68. Bloomfield MG, Carmichael AJ, Gkrania-Klotsas E. Mortality in Clostridium difficile infection: a prospective analysis of risk predictors. *Eur J Gastroenterol Hepatol* 2013; 25(6): 700-5.
69. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet* 2019; 394(10206): 1365-75.
70. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M146-56.
71. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001; 1: 323-36.
72. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Cmaj* 2005; 173(5): 489-95.
73. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. *Ageing Res Rev* 2020; 60: 101047.
74. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008; 11(1): 151-61.
75. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. *Age Ageing* 2006; 35(5): 526-9.
76. Volpato S, Bazzano S, Fontana A, Ferrucci L, Pilotto A. Multidimensional Prognostic Index predicts mortality and length of stay during hospitalization in the older patients: a multicenter prospective study. *J Gerontol A Biol Sci Med Sci* 2015; 70(3): 325-31.
77. Pilotto A, Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. *PLoS One* 2012; 7(1): e29090.
78. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001; 56(6): M366-72.
79. Sancarlo D, D'Onofrio G, Franceschi M, et al. Validation of a Modified-Multidimensional Prognostic Index (m-MPI) including the Mini Nutritional Assessment Short-Form (MNA-SF) for the prediction of one-year mortality in hospitalized elderly patients. *J Nutr Health Aging* 2011; 15(3): 169-73.
80. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 1999; 15(2): 116-22.

81. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12(3): 189-98.
82. Angleman SB, Santoni G, Pilotto A, Fratiglioni L, Welmer AK, Investigators MAP. Multidimensional Prognostic Index in Association with Future Mortality and Number of Hospital Days in a Population-Based Sample of Older Adults: Results of the EU Funded MPI_AGE Project. *PLoS One* 2015; 10(7): e0133789.
83. Hansen TK, Damsgaard EM, Shahla S, Bruun JM, Gregersen M. A reliable and record-based frailty assessment method for older medical inpatients. *Eur Geriatr Med* 2020; 11(5): 803-12.
84. Hansen TK, Shahla S, Damsgaard EM, Bossen SRL, Bruun JM, Gregersen M. Mortality and readmission risk can be predicted by the record-based Multidimensional Prognostic Index: a cohort study of medical inpatients older than 75 years. *Eur Geriatr Med* 2021; 12(2): 253-61.
85. Govoni B, Zurlo A, De Giorgio R, Cultrera R, Volpato S. Clostridium difficile infection in a geriatric care unit: Clinical characteristics and prognosis. *Journal of Gerontology and Geriatrics* 2021; 69(1): 1-5.
86. Pilotto A, Addante F, Ferrucci L, et al. The multidimensional prognostic index predicts short- and long-term mortality in hospitalized geriatric patients with pneumonia. *J Gerontol A Biol Sci Med Sci* 2009; 64(8): 880-7.
87. Pilotto A, Addante F, D'Onofrio G, Sancarlo D, Ferrucci L. The Comprehensive Geriatric Assessment and the multidimensional approach. A new look at the older patient with gastroenterological disorders. *Best Pract Res Clin Gastroenterol* 2009; 23(6): 829-37.
88. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017; 9: Cd006211.
89. Parker SG, McCue P, Phelps K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* 2018; 47(1): 149-55.
90. Pilotto A, Cella A, Pilotto A, et al. Three Decades of Comprehensive Geriatric Assessment: Evidence Coming From Different Healthcare Settings and Specific Clinical Conditions. *J Am Med Dir Assoc* 2017; 18(2): 192.e1-.e11.
91. Hayes C, Yigezu A, Dillon S, et al. Home-Based Comprehensive Geriatric Assessment for Community-Dwelling, At-Risk, Frail Older Adults: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc* 2025.
92. Deschodt M, Flamaing J, Haentjens P, Boonen S, Milisen K. Impact of geriatric consultation teams on clinical outcome in acute hospitals: a systematic review and meta-analysis. *BMC Med* 2013; 11: 48.
93. Eamer G, Taheri A, Chen SS, et al. Comprehensive geriatric assessment for older people admitted to a surgical service. *Cochrane Database Syst Rev* 2018; 1(1): Cd012485.
94. Partridge JS, Harari D, Martin FC, Dhesi JK. The impact of pre-operative comprehensive geriatric assessment on postoperative outcomes in older patients undergoing scheduled surgery: a systematic review. *Anaesthesia* 2014; 69 Suppl 1: 8-16.
95. Hamaker M, Lund C, Te Molder M, et al. Geriatric assessment in the management of older patients with cancer - A systematic review (update). *J Geriatr Oncol* 2022; 13(6): 761-77.
96. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007; 25(14): 1824-31.
97. Conroy SP, Ansari K, Williams M, et al. A controlled evaluation of comprehensive geriatric assessment in the emergency department: the 'Emergency Frailty Unit'. *Age Ageing* 2014; 43(1): 109-14.
98. Edmans J, Bradshaw L, Franklin M, Gladman J, Conroy S. Specialist geriatric medical assessment for patients discharged from hospital acute assessment units: randomised controlled trial. *BMJ* 2013; 347: f5874.
99. Kircher TT, Wormstall H, Müller PH, et al. A randomised trial of a geriatric evaluation and management consultation services in frail hospitalised patients. *Age Ageing* 2007; 36(1): 36-42.
100. Reuben DB, Borok GM, Wolde-Tsadik G, et al. A randomized trial of comprehensive geriatric assessment in the care of hospitalized patients. *N Engl J Med* 1995; 332(20): 1345-50.
101. Winograd CH, Gerety MB, Lai NA. A negative trial of inpatient geriatric consultation. Lessons learned and recommendations for future research. *Arch Intern Med* 1993; 153(17): 2017-23.

102. Hogan DB, Fox RA, Badley BW, Mann OE. Effect of a geriatric consultation service on management of patients in an acute care hospital. *Cmaj* 1987; 136(7): 713-7.
103. Thomas DR, Brahan R, Haywood BP. Inpatient community-based geriatric assessment reduces subsequent mortality. *J Am Geriatr Soc* 1993; 41(2): 101-4.
104. Partridge JS, Harari D, Martin FC, et al. Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery. *Br J Surg* 2017; 104(6): 679-87.
105. Lund CM, Vistisen KK, Dehlendorff C, Rønholt F, Johansen JS, Nielsen DL. The effect of geriatric intervention in frail elderly patients receiving chemotherapy for colorectal cancer: a randomized trial (GERICO). *BMC Cancer* 2017; 17(1): 448.
106. Shepperd S, Iliffe S, Doll HA, et al. Admission avoidance hospital at home. *Cochrane Database Syst Rev* 2016; 9(9): Cd007491.
107. Gonçalves-Bradley DC, Iliffe S, Doll HA, et al. Early discharge hospital at home. *Cochrane Database of Systematic Reviews* 2017; (6).
108. Martin F, Oyewole A, Moloney A. A randomized controlled trial of a high support hospital discharge team for elderly people. *Age Ageing* 1994; 23(3): 228-34.
109. Donald IP, Baldwin RN, Bannerjee M. Gloucester hospital-at-home: a randomized controlled trial. *Age Ageing* 1995; 24(5): 434-9.
110. Richards SH, Coast J, Gunnell DJ, Peters TJ, Pounsford J, Darlow MA. Randomised controlled trial comparing effectiveness and acceptability of an early discharge, hospital at home scheme with acute hospital care. *BMJ* 1998; 316(7147): 1796-801.
111. Cunliffe AL, Gladman JR, Husbands SL, Miller P, Dewey ME, Harwood RH. Sooner and healthier: a randomised controlled trial and interview study of an early discharge rehabilitation service for older people. *Age Ageing* 2004; 33(3): 246-52.
112. Caplan GA, Coconis J, Board N, Sayers A, Woods J. Does home treatment affect delirium? A randomised controlled trial of rehabilitation of elderly and care at home or usual treatment (The REACH-OUT trial). *Age Ageing* 2006; 35(1): 53-60.
113. Danish Society for Gastroenterology and Hepatology. National clinical guideline for Clostridoides difficile infection og faecal microbiota transplantation (FMT), updated 2024. Avaliable at: https://dsgh.dk/wp-content/uploads/2022/06/CDIFF_FMT.pdf. Accessed August 10, 2025.
114. Schünemann H BJ GG, Oxman A, editor(s) Handbook for grading quality of evidence and the strength of recommendations using the GRADE approach (Updated October 2013). GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html.
115. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. *Age Ageing* 2013; 42(1): 62-9.
116. Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol* 2016; 13(9): 508-16.
117. Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. *EClinicalMedicine* 2020; 29.
118. Hota SS, Sales V, Tomlinson G, et al. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent Clostridium difficile Infection: An Open-Label, Randomized Controlled Trial. *Clin Infect Dis* 2017; 64(3): 265-71.
119. Rode AA, Chehri M, Krogsgaard LR, et al. Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent Clostridioides difficile infections. *Aliment Pharmacol Ther* 2021; 53(9): 999-1009.
120. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312(7023): 71-2.
121. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008; 336(7651): 995-8.
122. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336(7650): 924-6.
123. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013; 368(5): 407-15.

124. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. *Aliment Pharmacol Ther* 2015; 41(9): 835-43.
125. Hvas CL, Dahl Jorgensen SM, Jorgensen SP, et al. Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection. *Gastroenterology* 2019; 156(5): 1324-32 e3.
126. Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2022; 7(12): 1083-91.
127. Baunwall SMD, Terveer EM, Dahlerup JF, et al. The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. *Lancet Reg Health Eur* 2021; 9: 100181.
128. Porter RJ, Fogg C. Faecal microbiota transplantation for Clostridium difficile infection in the United Kingdom. *Clin Microbiol Infect* 2015; 21(6): 578-82.
129. Centre for Faecal Microbiota Transplantation - CEFTA. Available at: https://cefta.au.dk/. Accessed August 19, 2025.
130. Jorgensen SMD, Hansen MM, Erikstrup C, Dahlerup JF, Hvas CL. Faecal microbiota transplantation: establishment of a clinical application framework. *Eur J Gastroenterol Hepatol* 2017; 29(11): e36-e45.
131. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ* 2015; 350: h2147.
132. Wolfenden L, Foy R, Presseau J, et al. Designing and undertaking randomised implementation trials: guide for researchers. *BMJ* 2021; 372: m3721.
133. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* 2012; 50(3): 217-26.
134. Langley G MR, Nolan K et al. The Improvement guide, 2nd edn. San Fransisco: Jossey-Bass A Wiley Imprint; 2009.
135. Dohrendorf CM, Unkel S, Scheithauer S, et al. Reduced Clostridioides difficile infections in hospitalised older people through multiple quality improvement strategies. *Age and ageing* 2021; 50(6): 2123-32.
136. Power M, Wigglesworth N, Donaldson E, Chadwick P, Gillibrand S, Goldmann D. Reducing Clostridium difficile infection in acute care by using an improvement collaborative. *BMJ* 2010; 341: c3359.
137. Cheng YW, Phelps E, Nemes S, et al. Fecal Microbiota Transplant Decreases Mortality in Patients with Refractory Severe or Fulminant Clostridioides difficile Infection. *Clin Gastroenterol Hepatol* 2020; 18(10): 2234-43.e1.
138. de Belvis AG, Barbara A, Giubbini G, et al. Impact evaluation of a Critical Pathway for patients with Clostridium difficile infection: A pre-post analysis in a Third Level Referral Center. *Int J Infect Dis* 2019; 80: 105-10.
139. NHS Health Research Authority. Planning and improving research, public involvement. Available at: https://www.hra.nhs.uk/planning-and-improving-research/best-practice/public-involvement/. Accessed June 27, 2025.
140. Canadian Institutes of Health Research. CIHR's Framework for Citizen Engagement. Available at: https://cihr-irsc.gc.ca/e/41270.html. Accessed June 27, 2025.
141. Danske patienter. Knowledge Center for User Involvement (ViBIS). Available at: https://danskepatienter.dk/about-danish-patients. Accessed June 27, 2025.
142. Young B, Bagley H. Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates. *Res Involv Engagem* 2016; 2: 25.
143. Backman WD, Levine SA, Wenger NK, Harold JG. Shared decision-making for older adults with cardiovascular disease. *Clin Cardiol* 2020; 43(2): 196-204.
144. Cranley LA, Slaughter SE, Caspar S, et al. Strategies to facilitate shared decision-making in long-term care. *Int J Older People Nurs* 2020; 15(3): e12314.

145. Dyrstad DN, Laugaland KA, Storm M. An observational study of older patients' participation in hospital admission and discharge--exploring patient and next of kin perspectives. *J Clin Nurs* 2015; 24(11-12): 1693-706.
146. Fried TR, Street RL, Jr., Cohen AB. Chronic Disease Decision Making and "What Matters Most". *J Am Geriatr Soc* 2020; 68(3): 474-7.
147. Hansen TK, Jensen AL, Damsgaard EM, Rubak TMM, Jensen MEJ, Gregersen M. Involving frail older patients in identifying outcome measures for transitional care-a feasibility study. *Res Involv Engagem* 2021; 7(1): 36.
148. Taran S, Adhikari NKJ, Fan E. Falsifiability in medicine: what clinicians can learn from Karl Popper. *Intensive Care Med* 2021; 47(9): 1054-6.
149. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019; 567(7748): 305-7.
150. Hocquart M, Lagier JC, Cassir N, et al. Early Fecal Microbiota Transplantation Improves Survival in Severe Clostridium difficile Infections. *Clin Infect Dis* 2018; 66(5): 645-50.
151. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968; 16(5): 622-6.
152. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res* 1992; 41(3): 237-48.
153. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; 10(1): 20-30.
154. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969; 9(3): 179-86.
155. Zuckerman JD, Koval KJ, Aharonoff GB, Skovron ML. A functional recovery score for elderly hip fracture patients: II. Validity and reliability. *J Orthop Trauma* 2000; 14(1): 26-30.
156. Halfens RJ, Van Achterberg T, Bal RM. Validity and reliability of the braden scale and the influence of other risk factors: a multi-centre prospective study. *Int J Nurs Stud* 2000; 37(4): 313-9.
157. Bliss MR, McLaren R, Exton-Smith AN. Mattresses for preventing pressure sores in geriatric patients. *Mon Bull Minist Health Public Health Lab Serv* 1966; 25: 238-68.
158. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr* 2003; 22(3): 321-36.
159. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003; 22(4): 415-21.
160. Guigoz Y, Vellas B. The Mini Nutritional Assessment (MNA) for grading the nutritional state of elderly patients: presentation of the MNA, history and validation. *Nestle Nutr Workshop Ser Clin Perform Programme* 1999; 1: 3-11; discussion -2.
161. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975; 23(10): 433-41.
162. Jørgensen SMD, Hvas CL, Dahlerup JF, et al. Banking feces: a new frontier for public blood banks? *Transfusion* 2019; 59(9): 2776-82.
163. Keller JJ, Ooijevaar RE, Hvas CL, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. *United European Gastroenterol J* 2021; 9(2): 229-47.
164. Heggestad T, Lilleeng SE. Measuring readmissions: focus on the time factor. *Int J Qual Health Care* 2003; 15(2): 147-54.
165. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16(3): 199-208.
166. Gregersen M, Jordansen MM, Gerritsen DL. Overall Quality of Life (OQoL) questionnaire in frail elderly: a study of reproducibility and responsiveness of the Depression List (DL). *Arch Gerontol Geriatr* 2015; 60(1): 22-7.
167. World Medical Association. WMA Declaration of Helsinki - ethical principles for medical research involving human subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects. Accessed August 19, 2025.

168. Persson S, Nielsen HL, Coia JE, et al. Sentinel surveillance and epidemiology of Clostridioides difficile in Denmark, 2016 to 2019. *Eurosurveillance* 2022; 27(49): 2200244.
169. Guery B, Galperine T, Barbut F. Clostridioides difficile: diagnosis and treatments. *BMJ* 2019; 366: l4609.
170. Fried LP, Storer DJ, King DE, Lodder F. Diagnosis of illness presentation in the elderly. *J Am Geriatr Soc* 1991; 39(2): 117-23.
171. Potts FEt, Vukov LF. Utility of fever and leukocytosis in acute surgical abdomens in octogenarians and beyond. *J Gerontol A Biol Sci Med Sci* 1999; 54(2): M55-8.
172. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc* 2007; 55(5): 780-91.
173. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *Am J Gastroenterol* 2012; 107(1): 89-95.
174. Martinez E, Taminiau B, Rodriguez C, Daube G. Gut Microbiota Composition Associated with Clostridioides difficile Colonization and Infection. *Pathogens* 2022; 11(7).
175. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell* 2023; 186(2): 243-78.
176. Jackson MA, Jeffery IB, Beaumont M, et al. Signatures of early frailty in the gut microbiota. *Genome Med* 2016; 8(1): 8.
177. Boven A, Vlieghe E, Engstrand L, et al. Clostridioides difficile infection-associated cause-specific and all-cause mortality: a population-based cohort study. *Clin Microbiol Infect* 2023; 29(11): 1424-30.
178. Heath A, Shahla S, Bossen SRL, Løfgren B, Gregersen M, Hansen TK. Geriatric assessment may prevent readmission in frail medical inpatients. *Dan Med J* 2023; 70(6).
179. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993; 342(8878): 1032-6.
180. Hammeken LH, Baunwall SMD, Hvas CL, Ehlers LH. Health economic evaluations comparing faecal microbiota transplantation with antibiotics for treatment of recurrent Clostridioides difficile infection: a systematic review. *Health Econ Rev* 2021; 11(1): 3.
181. Olesen RH, Larsen EB, Rubak T, et al. Cost-Effectiveness of Hospital-at-Home and Fecal Microbiota Transplantation in Treating Older Patients With Clostridioides difficile. *Clin Infect Dis* 2025.
182. Paaske SE, Baunwall SMD, Rubak T, et al. Clinical management of Clostridioides difficile infection with faecal microbiota transplantation: a real-world cohort study. *EClinicalMedicine* 2025; 85: 103302.
183. Paaske SE BS, Rubak T, Rågård N, Kelsen J, Hansen MM, Lødrup AB, Lyhne S, Glavind E, Fernis CMC, Hald S, Erikstrup LT, Vinter-Jensen L, Lal S, Mikkelsen S, Erikstrup C, Dahlerup JF, Hvas CL. Improving clinical outcomes of encapsulated faecal microbiota transplantation for Clostridioides difficile infection through empirical donor selection and optimised dosing: a quality improvement study. Unmpublished, submitted, under review. 2025.
184. Rotter T, Kinsman L, James E, et al. Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. *Cochrane Database Syst Rev* 2010; (3): Cd006632.
185. AB Verholt CF, LM Hinrichsen, LH Madsen, CSN Odderskov, LH Andersen, LW Lietzen. Advancing a Patient-Centred and Holistic Approach for Older Patients with Frailty in a Vascular Surgical Department; A Quality Improvement initiative. Unpublished data. Under review. . 2025.
186. Pilotto A, Veronese N, Quispe Guerrero KL, et al. Development and Validation of a Self-Administered Multidimensional Prognostic Index to Predict Negative Health Outcomes in Community-Dwelling Persons. *Rejuvenation Res* 2019; 22(4): 299-305.
187. Gregersen M, Hansen TK, Jørgensen BB, Damsgaard EM. Frailty is associated with hospital readmission in geriatric patients: a prognostic study. *European Geriatric Medicine* 2020; 11(5): 783-92.
188. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015; 350: g7594.

189. Veronese N, Custodero C, Cella A, et al. Prevalence of multidimensional frailty and pre-frailty in older people in different settings: A systematic review and meta-analysis. *Ageing Res Rev* 2021; 72: 101498.
190. Bretthauer M, Løberg M, Wieszczy P, et al. Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death. *N Engl J Med* 2022; 387(17): 1547-56.
191. Habicht DW, Witham MD, McMurdo ME. The under-representation of older people in clinical trials: barriers and potential solutions. *J Nutr Health Aging* 2008; 12(3): 194-6.
192. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *Int J Nurs Stud* 2024; 154: 104705.
193. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015; 350: h1258.
194. Gardner M, Shepperd S, Godfrey M, et al. Health Services and Delivery Research. Comprehensive Geriatric Assessment in hospital and hospital-at-home settings: a mixed-methods study. Southampton (UK); 2019. doi:10.3310/hsdr07100.
195. Lin L, Cheng M, Guo Y, et al. Early discharge hospital at home as alternative to routine hospital care for older people: a systematic review and meta-analysis. *BMC Med* 2024; 22(1): 250.

10. Appendices

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Appendix 1.

The literature review of mortality and risk factors for mortality among older patients with *Clostridioides difficile* infection is based on a systematic search made in PubMed. Pilot studies, protocols, abstracts, editorials and reviews were excluded. Limitation on publication year was set to 2013 and language limited to English and Danish. The search was updated on July 2025.

The search focused on studies with:

1. original, peer-reviewed research
2. All-cause mortality as an outcome (primary or secondary)
3. Inclusion of older patients (median or mean age > 60 years) with *Clostridioides difficile* infection (CDI)

Subgroups of older patients with CDI were excluded (e.g. CDI in older patients with chronic liver disease, CDI patients elected for colectomy, CDI in patients with malignant disease).

Details of the literature search strategy:

1) Population + Outcome

Search: (("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[Title/Abstract] AND "difficile"[Title/Abstract]) OR "Clostridioides difficile"[Title/Abstract] OR ("clostridium"[Title/Abstract] AND "difficile"[Title/Abstract]) OR "clostridium difficile"[Title/Abstract]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[Title/Abstract] AND "difficile"[Title/Abstract]) OR "Clostridioides difficile"[Title/Abstract])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[Title/Abstract]) OR ("Aged"[MeSH Terms] OR "Aged"[Title/Abstract] OR "elderly"[Title/Abstract] OR "elderlies"[Title/Abstract] OR "elderly s"[Title/Abstract] OR "elderlys"[Title/Abstract]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[Title/Abstract] AND "elderly"[Title/Abstract]) OR "Frail Elderly"[Title/Abstract]) OR "Frail Elderly"[MeSH Terms])) AND ("Mortality"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Mortality"[Title/Abstract] OR "mortalities"[Title/Abstract] OR "Mortality"[MeSH Subheading] OR "death"[MeSH Terms] OR "death"[Title/Abstract] OR "deaths"[Title/Abstract]) Filters: Danish, English, from 2013 - 2023

2) Population + Outcomes + "Risk factors"

Search: (("Clostridioides"[Mesh] OR "clostridioide*"[Title/Abstract] OR "Clostridioides difficil*"[Title/Abstract]) AND ("Aged"[Mesh] OR "Aged"[Title/Abstract] OR "old age*"[Title/Abstract] OR "elderl*"[Title/Abstract])) AND (("Mortality"[Mesh] OR "mortality"[Subheading]) AND "Risk Factors"[Mesh] OR "mortal*"[Title/Abstract] OR "risk factor*"[Title/Abstract]) Filters: Danish, English, from 2013 – 2023

3) Population + Outcome (mortality) + Frailty

Search: (((((("Patient Acuity"[Mesh]) OR "Mortality"[Mesh]) OR "mortality" [Subheading]) AND (("Aged"[Mesh]) OR "Geriatrics"[Mesh])) AND (("Frailty"[Mesh]) OR "Frail Elderly"[Mesh])) AND (((((("Patient Acuity"[Mesh]) OR "Mortality"[Mesh]) OR "mortality" [Subheading]) AND (("Aged"[Mesh]) OR "Geriatrics"[Mesh])) AND (("Frailty"[Mesh]) OR "Frail Elderly"[Mesh]))) AND (("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]))) AND (("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]))

Appendix 2

Systematic search for Comprehensive geriatric assessment for older patients with *Clostridioides difficile* infection. The literature review is based on a systematic search made in PubMed and Embase. Preferred: randomised controlled trials. Pilot studies, protocols, abstracts and editorials were excluded. Language limited to English and Danish. The search was updated on: July 2025.

Population:
- *Clostridioides difficile* infection in medical inpatients
- median/mean age ≥ 60 years
Intervention:
-Comprehensive geriatric assessment/geriatric assessment

PubMed

#Search 1: Population (older patients with CDI) + Intervention (Comprehensive geriatric assessment) + Outcome (Mortality)

("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]) AND ("Geriatric Assessment"[MeSH Terms] OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields]) OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields] OR ("comprehensive"[All Fields] AND "geriatric"[All Fields] AND "assessment"[All Fields]) OR "comprehensive geriatric assessment"[All Fields]) OR ("geriatric"[All Fields] OR "Geriatrics"[MeSH Terms] OR "Geriatrics"[All Fields]) OR "Geriatrics"[MeSH Terms]) AND ("Mortality"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Mortality"[All Fields] OR "mortalities"[All Fields] OR "Mortality"[MeSH Subheading] OR "death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields])

#Search 2: Population (olde patients with *C. difficile infection*) + Intervention (Comprehensive geriatric assessment)

((("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]) AND ("Geriatric Assessment"[MeSH Terms] OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields]) OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields] OR ("comprehensive"[All Fields] AND "geriatric"[All Fields] AND "assessment"[All Fields]) OR "comprehensive geriatric assessment"[All Fields]) OR ("geriatric"[All Fields] OR "Geriatrics"[MeSH Terms] OR "Geriatrics"[All Fields]) OR "Geriatrics"[MeSH Terms])) AND (1983:2024[pdat])

Embase

#1: "Clostridium difficile infection"/exp [MESH]
#2: "Clostridium difficile infection"
#3: "aged"/exp [MESH]
#4: "aged"
#5: "frail elderly"/exp [MESH]
#6: "frail elderly"

#7: "geriatric assessment"/exp [MESH]
#8: "geriatric assessment"
#9: "comprehensive geriatric assessment"/exp [MESH]
#10: "geriatrics"
#11: "geriatrics"/exp [MESH]

#12: "mortality"/exp [MESH]
#13: "mortality"
#14: "death"/exp [MESH]
#15: "death"
#16: (#1OR#2)AND(#3OR#4OR#5OR#6)AND(#7OR#8OR#9OR#10)
#17: (#1OR#2) AND (#3OR#4OR#5OR#6) AND (#7OR#8OR#9OR#10)

Appendix 3

The literature search for inpatient geriatric consultation teams interventions was initially based on systematic reviews by Ellis[88], Gardner[192] and Deschodt[92] which provided a comprehensive overview of randomised controlled trials evaluating comprehensive geriatric assessment for older adults admitted to hospital. Literature review focused on RCT investigating team-based CGA with mortality as primary, secondary or exploratory outcome in medical inpatients. To identify more recent evidence, the review was supplemented by a targeted search for RCTs published from 2017 onwards. The search was updated on July 2025.

PubMed

(("Geriatric Assessment"[MeSH Terms] OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields]) OR ("Geriatric Assessment"[MeSH Terms] OR ("geriatric"[All Fields] AND "assessment"[All Fields]) OR "Geriatric Assessment"[All Fields] OR ("comprehensive"[All Fields] AND "geriatric"[All Fields] AND "assessment"[All Fields]) OR "comprehensive geriatric assessment"[All Fields]) OR ("geriatric"[All Fields] OR "Geriatrics"[MeSH Terms] OR "Geriatrics"[All Fields]) OR "Geriatrics"[MeSH Terms]) AND ("Mortality"[MeSH Terms] OR "death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields] OR "Mortality"[MeSH Terms] OR "Mortality"[All Fields] OR "mortalities"[All Fields] OR "Mortality"[MeSH Subheading])) AND (geriatric consultation team) Filters: Randomized Controlled Trial, from 2017 - 2025

Appendix 4.

Systematic search for hospital-at-home for older patients with *Clostridioides difficile* infection and faecal microbiota transplantation provided as home treatment. The literature review is based on a systematic search made in PubMed, Embase and Cochrane. Pilot studies, protocols, abstracts, editorials and reviews were excluded. Language limited to English and Danish. The search was updated on July 2025.

PubMed:

#Search 1: Population (Clostridioides difficile infection, older patients) + intervention (hospital-at-home)

("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]) AND ("home hospitalization"[Title/Abstract] OR "Admission Avoidance"[Title/Abstract] OR "HaH program"[Title/Abstract] OR "Home Treatment"[Title/Abstract] OR "Acute Care at Home"[Title/Abstract] OR "Home-based hospitalization"[Title/Abstract] OR "Hospital at Home"[Title/Abstract] OR "Hospital in the Home"[Title/Abstract] OR "Hospital in Home"[Title/Abstract] OR "Hospital care at Home"[Title/Abstract] OR "geriatric home hospitalization"[Title/Abstract] OR ("Home Care Services"[MeSH Terms] AND "Hospitalization"[MeSH Terms]) OR "home care services, hospital based"[MeSH Terms])

#Search 2: Population + Intervention (fecal microbiota transplantation + hospital-at-home)

("Clostridioides difficile"[MeSH Terms] OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields] OR ("clostridium"[All Fields] AND "difficile"[All Fields]) OR "clostridium difficile"[All Fields]) OR ("Clostridioides difficile"[MeSH Terms] OR ("clostridioides"[All Fields] AND "difficile"[All Fields]) OR "Clostridioides difficile"[All Fields])) AND ("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR

"Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]) AND ("Fecal Microbiota Transplantation"[MeSH Terms] OR ("Fecal Microbiota Transplantation"[MeSH Terms] OR ("fecal"[All Fields] AND "microbiota"[All Fields] AND "transplantation"[All Fields]) OR "Fecal Microbiota Transplantation"[All Fields])) AND ("home hospitalization"[Title/Abstract] OR "Admission Avoidance"[Title/Abstract] OR "HaH program"[Title/Abstract] OR "Home Treatment"[Title/Abstract] OR "Acute Care at Home"[Title/Abstract] OR "Home-based hospitalization"[Title/Abstract] OR "Hospital at Home"[Title/Abstract] OR "Hospital in the Home"[Title/Abstract] OR "Hospital in Home"[Title/Abstract] OR "Hospital care at Home"[Title/Abstract] OR "geriatric home hospitalization"[Title/Abstract] OR ("Home Care Services"[MeSH Terms] AND "Hospitalization"[MeSH Terms]) OR "home care services, hospital based"[MeSH Terms])

Embase
#1: "fecal microbiota transplantation"/exp
#2: "hospital at home"
#3: "home hospitalization"
#4: "home care"
#5: "Clostridioides difficile infection"
#6: #1AND#2OR#3OR#4
#7: #5AND#2OR#3OR#4

Cochrane library
#1: fecal microbiota transplantation
#2: fecal microbiota transplantation [MESH explode all trees]
#3: hospital at home
#4: home care [MESH explode all trees]
#5: Clostridioides difficile infection
#6: Clostridium difficile infection
#7: Clostridium infections [MESH explode all trees]
#8: (#1OR#2) AND (#3OR#4OR)
#9: (#5OR#6OR#7) AND (#3OR#4OR)

Appendix 5

The literature search for early discharge hospital-at-home (HaH) interventions was initially based on the Cochrane systematic review by Gonçalves-Bradley et al. (2017)[107], which provided a comprehensive overview of randomised controlled trials (RCTs) evaluating early discharge HaH as an alternative to inpatient care. To identify more recent evidence, the review was supplemented by a targeted search for RCTs published from 2017 onwards. The search focused on RCT studies with: older patients (median/mean age > 70 years) with mixed medical conditions, early discharge hospital-at-home, mortality as an outcome, medical inpatients (not specific disease populations such as e.g. COPD, hip replacement)
The search was updated on July 2025.

PubMed
("Aged"[MeSH Terms] OR ("Aged"[MeSH Terms] OR "Aged"[All Fields]) OR ("Aged"[MeSH Terms] OR "Aged"[All Fields] OR "elderly"[All Fields] OR "elderlies"[All Fields] OR "elderly s"[All Fields] OR "elderlys"[All Fields]) OR ("Frail Elderly"[MeSH Terms] OR ("frail"[All Fields] AND "elderly"[All Fields]) OR "Frail Elderly"[All Fields]) OR "Frail Elderly"[MeSH Terms]) AND ("home hospitalization"[Title/Abstract] OR "Admission Avoidance"[Title/Abstract] OR "HaH program"[Title/Abstract] OR "Home Treatment"[Title/Abstract] OR "Acute Care at Home"[Title/Abstract] OR "Home-based hospitalization"[Title/Abstract] OR "Hospital at Home"[Title/Abstract] OR "Hospital in the Home"[Title/Abstract] OR "Hospital in Home"[Title/Abstract] OR "Hospital care at Home"[Title/Abstract] OR "geriatric home hospitalization"[Title/Abstract] OR ("Home Care Services"[MeSH Terms] AND "Hospitalization"[MeSH Terms]) OR "home care services, hospital based"[MeSH Terms]) AND ((randomizedcontrolledtrial[Filter]) AND (2017:2025[pdat]))

Appendix 6.

Patients already receiving geriatric assessment were defined as follows: when diagnosed with CDI affiliated with the department of Geriatrics (in- or outpatient activity) or performed CGA during CDI-related hospital admission.

Hospital:	**Receiving geriatric intervention defined as:**
Aarhus University Hospital	Patients affiliated with the Department of Geriatrics (in- or outpatient activity)
Silkeborg Regional Hospital	Patients affiliated to Clinic of Geriatrics, code ZZ0150D ("Optagelse af geriatrisk anamnese")
Gødstrup Hospital	Patients admitted to Geriatric inpatient ward ("Sengeafsnit for Ældresygdomme", "Standardplan for geriatric") or performed geriatric examination (standardplan "Geriatrisk indlagt patient")
Horsens Regional Hospital	Patients affiliated with the Department of Geriatrics (in- or outpatient activity). Department code: 6006040M1-GERI. Department MS2. Patients not admitted to geriatric ward but performed geriatric examination in another department or medical inpatient ward ((code: BWTT11F "Tilsyn ved geriater").
Viborg Regional Hospital	Patients affiliated with "Medicinsk afsnit 2" and performed "Målsamtale".
Randers Regional Hospital	Patients affiliated with the Department of Geriatrics (MS-A)

Appendix 7

The subcategories and the calculation of the bedside Multidimensional Prognostic Index.

SCORE ASSIGNED TO EACH DOMAIN			
	LOW (SCORE=0)	MODERATE (SCORE = 0.5)	HIGH (SCORE = 1)
Social support network	Living with family	Institutionalised	Living alone
No of medications	0-3	4-7	≥8
FRS (ADL)	60-67	37-59	0-36
FRS (I-ADL)	17-23	13-16	0-12
SPMSQ (no. of correct answers)	7-10	4-6	0-3
Braden Scale	15-23	10-14	6-9
CIRS-G	0	1-2	≥3
NRS	0-2	3-4	5-7
SUM EACH SCORE AND DIVIDE THE TOTAL FOR 8 = FINAL SCORE			
FRAILTY LEVEL	LOW (MPI-1)	MODERATE (MPI-2)	SEVERE (MPI-3)
RANGE	0-0.33	0.34-0.66	0.67-1.0

Abbrevations: FRS; Functional Recovery Score: ADL; Activities of daily living (ADL): I-ADL; Instrumental Activities of daily living: SPMSQ; Short Portable Mental Status Questionnaire: CIRS-G; Cumulative Illness Rating Scale - Geriatrics: NRS; Nutrition Risk Screening.

Appendix 8

The *Clostridioides difficile* infection check list

The checklist for older patients ≥ 70 years with *Clostridioides difficile* infection (CDI) during hospital admission or at home. The figure is reproduced from supplementary of Rubak et al[2].

Patient label_____

Clostridioides difficile infection – check list for older patients

Patients with Clostridioides difficile infection (CDI) during hospital admission or at home.

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.		
	Done	Not relevant
1) CDI treatment care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin peroral or bactocin oral suspension (probe) 125 mg x 4. Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT).	☐	☐
Perform the Multidimensional Prognostic Index	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning.	☐	☐
Deliver information material to the patient	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent cathetherization etc.)	☐	☐
Laxative: discontinue	☐	☐
Proton pump inhibitor: discontinue if possible	☐	☐
Diuretics: consider reduction during active diarrhoea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
Consider other reasons for diarrhoea! (e.g. inflammatory bowel disease, cancer, microscopic colitis)	☐	☐
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT or completed vancomycin treatment.		

All activities are registered in the electronic medical journal.

Appendix 9.

Subgroup analysis of patients in the CGA organisational care group (N=109) treated with and without faecal microbiota transplantation. Patients aged ≥ 70 years with *Clostridioides difficile* infection in the Central Denmark Region in the period from 1 September 2022 to 4 May 2023.

Baseline characteristics	**Total (N= 109)**	**Treated with FMT within 90 days (n=102)**	**Not treated with FMT within 90 days (n = 7)**	**P value**
Age (median, IQR)	79 (74-84)	79 (74-85)	76 (71-81)	0.142
Gender (female)	61 (56)	57 (56)	4 (57)	0.948
Charlson Comorbidity Index score (median (IQR))	3 (2-6)	3 (2-6)	5 (3-7)	0.265
Terminal disease registration before date of positive PCR test for CDI, n (%)	5 (5)	3 (3)	2 (29)	0.032
Cancer before positive PCR test for CDI, n (%)	45 (41)	41 (40)	4 (57)	0.444
Frailty level[d], n (%) **Low (MPI-1)** **Moderate (MPI-2)** **Severe (MPI-3)** **N = 79**	11 (14) 36 (46) 32 (40)	10 (14) 32 (44) 30 (42)	1 (14) 4 (57) 2 (29)	0.780
Habitation status, n (%) **Living in own home** **Nursing home resident**	101 (93) 8 (7)	94 (92) 8 (8)	7 (100) 0 (0)	1.00
***C. difficile* diagnose site, n (%)** **Outpatient** **Primary healthcare** **Inpatients**	13 (12) 17 (16) 79 (72)	13 (13) 17 (17) 72 (71)	0 (0) 0 (0) 7 (0)	0.242
Renal disease, n (%)	14 (13)	13 (13)	1 (14)	1.00
Haematological cancer, n (%)	10 (9)	10 (10)	0 (0)	1.00

Abbreviations: IQR: interquartile range; PCR: polymerase chain reaction; FMT: faecal microbiota transplantation; CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index

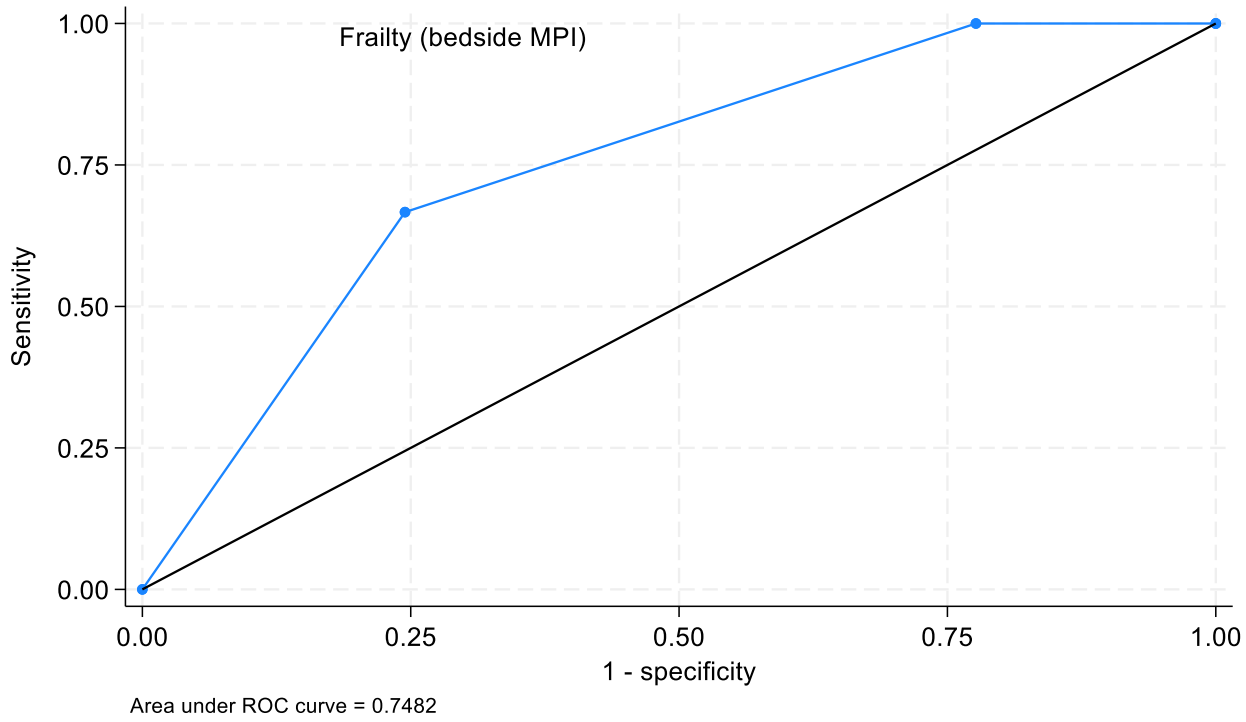
Appendix 10

Subgroup analysis of patients in the standard care group (N=108) treated with and without faecal microbiota transplantation. Patients aged ≥ 70 years with *Clostridioides difficile* infection in the Central Denmark Region in the period from 1 September 2022 to 4 May 2023.

Baseline characteristics	**Total (N = 108)**	**Treated with FMT within 90 days (n = 33)**	**Not treated with FMT within 90 days (n = 75)**	**P value**
Age (median, IQR)	78 (74-84)	77 (73-83)	78 (74-84)	0.348
Gender (female)	55 (51)	17 (52)	38 (51)	0.935
Charlson Comorbidity Index Score (median (IQR))	3 (1-6)	2 (0-6)	3 (1-6)	0.269
Terminal disease registration before date of positive PCR test for CDI, n (%)	0 (0)	0 (0)	0 (0)	-
Cancer before positive PCR test for CDI, n (%)	31 (29)	7 (21)	24 (32)	0.356
Frailty level[d], n (%) **Low (MPI-1)** **Moderate (MPI-2)** **Severe (MPI-3)** **N = 79**	 12 (15) 36 (46) 31 (39)	 3 (18) 5 (29) 9 (53)	 9 (15) 31 (50) 22 (35)	0.307
Habitation status, n (%) **Living in own home** **Nursing home resident**	 91 (84) 17 (16)	 27 (82) 6 (18)	 64 (85) 11 (15)	0.775
C difficile diagnose site, n (%) **Outpatient** **Primary healthcare** **Inpatients**	 12 (11) 17 (16) 79 (73)	 8 (24) 8 (24) 17 (52)	 4 (5) 9 (12) 62 (83)	0.002
Renal disease, n (%)	13 (12)	4 (12)	9 (12)	1.00
Haematological cancer, n (%)	9 (8)	1 (3)	8 (11)	0.271

Abbreviations: IQR: interquartile range; PCR: polymerase chain reaction; FMT: faecal microbiota transplantation; CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index

Appendix 11. ROC curve estimates for 90-day mortality for frailty measured by the bedside MPI version used in Study III.



Abbreviations: MPI: Multidimensional Prognostic Index; ROC: receiver operating curve

11. Papers

Paper I Frailty level at discharge predicts mortality in older patients with *Clostridioides difficile* infection more accurately than age or disease severity. Rubak T, Baunwall SMD, Gregersen M, Hansen TK, Rosenbæk JB, Erikstrup LT, Hvas CL, Damsgaard EM. Eur Geriatr Med 2023; 14(3): 583-93. doi: 10.1007/s41999-023-00772-3

Paper II *Clostridioides difficile* infection in frail older patients, quality in treatment and care: the CLODIFrail study protocol for a multicentre randomized controlled trial. Rubak T, Veilbæk H, Gregersen M, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Ørum M, Vinding RS, Sørensen CAK, Steves CJ, Baunwall SMD, Hvas CL, Damsgaard EM. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648 (Published as Supplementary file no 1) (Preprint March 2023: doi:10.21203/rs.3.rs-2687093/v1)

Paper III Early geriatric assessment and management in older patients with *Clostridioides difficile* infection (CLODIfrail) – a randomized trial. Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Hansen TK, Ørum M, Steves CJ, Veilbæk H, Hvas CL, Damsgaard EM. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648

Paper IV Development of a geriatric checklist to support management of older patients with *Clostridioides difficile* infection. Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Ørum M, Kongensgaard R, Hansen TK, Gregersen M, Hvas CL. Submitted manuscript, 2025.

PAPER I

European Geriatric Medicine
https://doi.org/10.1007/s41999-023-00772-3

RESEARCH PAPER

Frailty level at discharge predicts mortality in older patients with *Clostridioides difficile* more accurately than age or disease severity

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Received: 1 November 2022 / Accepted: 22 March 2023

Key summary points

Aim To calculate mortality rates in older patients with *Clostridioides difficile* infection (CDI) and compare multidimensional frailty level, CDI severity and age as predictors of mortality.
Findings Older patients with their first CDI had a high 90-day mortality of 28%. Multidimensional frailty assessment at discharge outperformed CDI severity and age in predicting 90-day mortality among older patients with CDI.
Message Compared with age and CDI severity, the multidimensional frailty assessment is the best predictor of 90-day mortality in older patients with CDI.

Abstract

Purpose *Clostridioides difficile* infection (CDI) has a high mortality among older patients. Identification of older patients with CDI in increased mortality risk is important to target treatment and thereby reduce mortality. The aim of this study was to investigate mortality rates and compare frailty levels at discharge, measured by the record-based Multidimensional Prognostic Index (MPI), with age and severity of CDI as mortality predictors in patients with CDI diagnosed during hospitalisation.
Methods This was a population-based cohort study from Central Denmark Region, Denmark, including all patients ≥60 years with a positive CD toxin test without prior infection and diagnosed from 1 January to 31 December 2018. Frailty level, estimated from the electronic medical record, was defined as low, moderate, or severe frailty. CDI severity was graded according to international guidelines. Primary outcome was 90-day mortality.
Results We included 457 patients with median age 77 years (interquartile range 69–84) and females (49%). Overall, 90-day mortality was 28%, and this was associated with age (hazard ratio (HR): 2.71 (95% confidence interval 1.64–4.47)), CDI severity (HR 4.58 (3.04–6.88)) and frailty (HR 10.15 (4.06–25.36)). Frailty was a better predictor of 90-day mortality than both age ($p < 0.001$) and CDI severity ($p = 0.04$) with a receiver operating characteristic curve area of 77%.
Conclusion The 90-day mortality among older patients with CDI in a Danish region is 28%. Frailty measured by record-based MPI at discharge outperforms age and disease severity markers in predicting mortality in older patients with CDI.

Keywords *Clostridioides difficile* · Frailty · Mortality · Aged

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Published online: 13 April 2023

Introduction

Clostridioides difficile infection (CDI) has a poor prognosis with an average 90-day mortality of 23–46% in selected patient cohorts [1–3]. Mortality rates dramatically increase with age [1, 2, 4]. Population-based mortality rates in older patients with validated CDI are lacking. Preventive strategies and effective therapeutic approaches are warranted to reduce these patients' risk of dying from CDI [1].

Early identification of patients with a high mortality risk followed by targeted interventions may improve prognosis in patients with CDI. A classification of CDI severity has been suggested [5]. This classification uses clinical and laboratory characteristics assumed to correlate positively with the severity of colitis according to the recommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [6]. The classification is in line with the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) [7], and it is supported by multivariate analyses [8–11]. The established definitions of severe disease have not clearly been associated with mortality rates in the oldest patients, implying that current guidelines need to be further qualified with respect to assessment of older patients with CDI on admission [3].

Frailty is a measure that may encompass the overall health status in patients with CDI. Frailty is a common condition among older adults [12] and develops due to age-related decline in physiological systems, collectively resulting in an increased vulnerability to stressors [13]. Older patients with severe CDI are characterised by a high comorbidity burden, low functional status, high degree of polypharmacy, malnutrition and a need for support in everyday life [2, 13–17]. Collectively, these factors indicate frailty. The literature on the predictive value of frailty among CDI patients is scarce [18] and has not yet been compared with severity of CDI in older patients.

The Multidimensional Prognostic Index (MPI) is a frailty assessment tool with a demonstrated predictive value for mortality in older hospitalised patients [19, 20]. The MPI is based on the Comprehensive Geriatric Assessment (CGA), which allows the clinician to intervene on clinical issues related to the overall health status of the patient [19, 21]. The CGA is a multidisciplinary diagnostic and treatment process identifying medical, psychosocial and functional limitations of a frail older patient [22]. Thus, the frailty-related risk factors for severe CDI among older patients are all included in the MPI [3, 15, 16, 23]. Hence, the MPI may be useful for assessing the risk of mortality in older patients with CDI. A record-based MPI has been validated as a retrospective assessment tool based on medical record data [24].

The aim of the present study was to investigate the mortality rate among older patients with CDI in a Danish region and compare multidimensional frailty level at discharge, CDI severity, and age as predictors of mortality.

Methods

Study design and participants

The study was as a population-based cohort study in the Central Denmark Region (CDR), Denmark. Data were collected retrospectively from electronic medical records (EMR). Patients were consecutively included from a complete list of all patients diagnosed with CDI in hospital, outpatient activity and primary health care in the CDR. Patients included in the study were aged ≥ 60 years and had been diagnosed with an index CDI in the period from 1 January to 31 December 2018. We chose the calendar year 2018 to leave the cohort including the follow-up period untouched by the COVID 19 pandemic. Index CDI was defined as a positive polymerase chain reaction (PCR) test result for *Clostridioides difficile* (CD) toxin A, toxin B or binary toxin, and no previous positive PCR test result for CD toxins or CDI treatment within the previous year. All hospitals in the CDR share the same diagnostic methodology for CD and all analyses were conducted in the same laboratory. The CD toxin PCR test was performed with an in-house PCR, or, for urgent diagnosis, with GeneXpert (Xpert C. difficile BT, Cepheid, Sunnyvale, CA, USA). Any combination of toxins was considered a positive test result. Patients were identified from the Danish Microbiology Database via the national identification number-based Civil Registration Register. The primary outcome was 90-day all-cause mortality from the date of the positive PCR test for index CDI.

Data collection

EMRs and discharge summaries were reviewed from the date of the index CDI by a specialty registrar in geriatric medicine.

Level of frailty was assessed retrospectively by performing the record-based MPI at discharge from the CDI-related hospital admission [24]. The electronic medical records in the CDR share interdisciplinary information from doctors, nurse, physiotherapy and occupational therapy and includes information from primary healthcare. Assessment of physical functional capacity and social status as well as home care reports are mandatory for documentation. Information is concomitantly documented in the same system. MPI-featured components are described in older inpatients' EMRs and includes clinical,

cognitive, functional, nutritional, and social parameters. The MPI is an aggregated score based on eight items, cohabitation status, number of prescription drugs, Functional Recovery Score Activities of Daily Living (FRS-ADL), Functional Recovery Score Instrumentalized Activities of Daily Living (FRS-IADL), Short Portable Mental Status Questionnaire, Exton Smith Scale, Cumulative Illness Rating Scale-Geriatrics and Mini Nutritional Assessment- Short Form, and is performed in a record-based manner [19, 24]. The MPI sum score is expressed as a number between 0 and 1 by aggregating the total scores of all eight domains and categorised into three groups: MPI-1 (MPI score 0.0–0.33) as low, MPI-2 (MPI score 0.34–0.66) as moderate and MPI-3 (MPI score 0.67–1.0) as severe frailty. When diagnosed with CDI during admission, the record-based MPI was performed as close to the date of discharge as possible but maximally within one week before discharge. Patients diagnosed during outpatient activity or via primary health care were not assessed for frailty, because their EMR data were considered as lacking or insufficient described. The CDI severity score was based on the data recorded in the EMR at the time of the index CDI diagnosis. Data were registered within the CDI-related hospital contact from date of positive PCR test result for CD toxins and up until discharge. Severity of CDI was categorised as mild-to-moderate disease, severe disease and fulminant/complicated CDI [5, 25]. Factors indicating severe CDI were one of the following: P-albumin < 30 g/L, leucocytes > 15 × 10^9/L or abdominal pain. Severe CDI combined with one of the following indicated fulminant CDI: pseudomembranous colitis diagnosed via colonoscopy or sigmoidoscopy; hypotension (defined as systolic blood pressure < 80 mmHg or a need of vasopressor treatment); fever (temperature > 38.5 °C); ileus; change in mental state; admission to an intensive care unit; leucocytes > 35 × 10^9/L or < 2.2 × 10^9/L; lactate > 2.2 mmol/L. Biochemical parameters were collected within 1 week after the positive CD toxin PCR test result. Disease-related symptoms were registered from the EMRs during hospital contacts related to the CDI from date of positive PCR test and up until discharge. For patients diagnosed during outpatient contact, disease-related symptoms were registered within 1 week from date of positive PCR test. Patients diagnosed via primary health care or lacking information in the EMRs during hospital contact were not assessed for CDI severity, because their EMR data were considered insufficient. Study data were collected and managed using the REDCap electronic data capture tool [26].

Statistical analysis

P-values below 0.05 were considered statistically significant. Patient characteristics were presented as number, mean or median, as appropriate. Mortality rates according to age, CDI severity and frailty were compared in a Cox proportional hazards regression model and displayed using the Kaplan–Meier (KM) survival estimator. The KM analysis assumptions were assessed. The analyses were adjusted for age and sex. Age was adjusted only for sex and stratified into three age groups to compare the hazard ratios (HRs). The proportional hazards assumption was tested with inspection of 'log–log' plots. A model control of analysis of severity in three severity levels could not be accepted due to a very limited number of events in the mild severity group. Therefore, we merged the patients with mild and severe CDI and compared them with those with fulminant CDI.

Receiver operating characteristic (ROC) curves were used to quantify the overall ability of age, CDI severity and MPI to discriminate between dead and surviving individuals within 90 days. For the overall measure of the test accuracy, the area under the curve (AUC) was used. A value of > 0.7 represents a "useful' predictive ability [27]. To be able to compare the ROC curves for age, severity of CDI and MPI, we only included patients with known severity of CDI and frailty level in the analysis.

Every item of the MPI was tested for association with 90-day mortality in a multivariate logistic regression analysis.

Test for association between recurrence rate within 90 days and age, CDI severity and MPI, respectively, was performed by binary regression analysis adjusted for 90-day mortality.

All analyses were made using Stata version 17 (Stata Corp, Texas, USA).

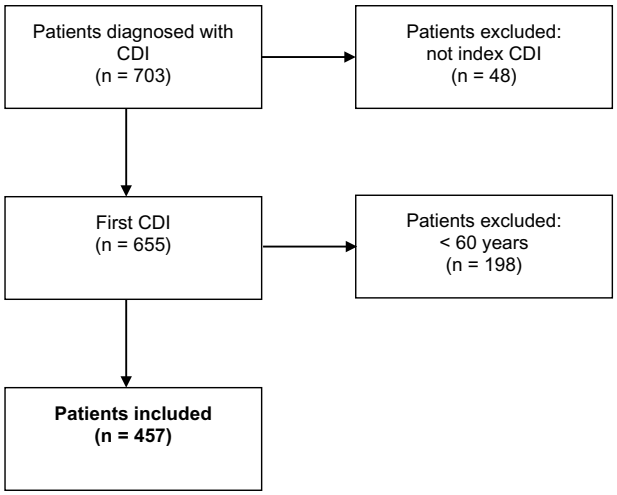
Ethics approval

The study was defined as a quality improvement study which, according to Danish law, solely requires approval from the hospital board. This was confirmed by the Central Denmark Region Ethics Committee (1-10-72-1-21). Permission to assess patient EMRs was obtained by the hospital boards at a University Hospital and all regional hospitals in the CDR (12-11-20).

Results

Patient characteristics

A total of 457 consecutive patients with their first CDI in 2018 were included (Fig. 1). Estimation of CDI severity was possible in 412 patients and assessment of frailty by record-based MPI in 387 (Table 1). Patients diagnosed



Abbreviation: CDI, *Clostridioides difficile* infection.

Fig. 1 Flow diagram. A total of 703 patients with a positive PCR test for *Clostridioides difficile* in the Central Denmark Region, from 1 January through 31 December 2018, were screened. Patients who had experienced a prior CDI less than one year ago and patients younger than 60 years of age were excluded

during outpatient activity ($n=56$) or via primary health care ($n=14$) were not assessed for frailty because their EMR data were missing or insufficient. Median age was 77 years (interquartile range (IQR): 69–84 years), and 49% were females. The majority was classified as having severe ($n=189$; 41%) or fulminant CDI ($n=190$; 42%) and as moderately ($n=136$; 30%) or severely frail ($n=171$; 37%). Fulminant CDI was diagnosed based on pseudomembranous colitis ($n=21$; 11%), hypotension ($n=54$; 28%), fever ($n=36$; 19%), ileus ($n=10$; 5%), change in mental state ($n=106$; 56%), admission to an intensive care unit ($n=32$; 17%), leucocytes > 35 × 10^9/L ($n=18$; 9%), leucocytes < 2.2 × 10^9/L ($n=10$; 5%) and lactate > 2.2 mmol/L ($n=43$; 23%). Patients fulfilling more than one criteria for fulminant CDI was $n=103$; 54%. Patients classified as fulminant CDI only because of change in mental state was ($n=29$; 15%). Most patients ($n=387$; 85%) were diagnosed with CDI during hospital admission. Median duration from positive PCR test (time of CDI severity score) and until date of discharge (time of multidimensional frailty assessment) was 3 days (IQR: 1–6 days) (Fig. 2).

Mortality and recurrence

Within 90 days following the initial diagnosis, 127 (28%) of all 457 patients had died. Among patients with severe frailty (MPI-3), 88 (51%) of 171 had died. The overall 30-day mortality was 16%. Patients aged 80 years or older had a higher 90-mortality than patients younger than 70 years

Table 1 Patient characteristics, patients aged ≥ 60 years with *Clostridioides difficile* infection in the Central Denmark Region in the period from 1 January to 31 December 2018

	n (%)
Total, *N*	457 (100)
Age groups (years)	
60–69	118 (25)
70–79	158 (35)
80–max	181 (40)
Severity	
Mild	33 (7)
Severe	189 (41)
Fulminant	190 (42)
Unknown	45 (10)
Frailty level	
Low (MPI-1)	80 (18)
Moderate (MPI-2)	136 (30)
Severe (MPI-3)	171 (37)
Unknown	70 (15)
Gender, *n* (%)	
Female	223 (49)
Habitation status	
Living in own home	384 (84)
Nursing home resident	73 (16)
CDI diagnose, site	
Primary healthcare	14 (3)
Outpatients	56 (12)
Inpatients	387 (85)
Primary disease requiring admission	
Clostridioides difficile	86 (19)
Other enteral infectious disease	14 (3)
Urinary tract infection	20 (4)
Sepsis	27 (6)
Erysipelas	3 (1)
Viral infectious disease	4 (1)
Pneumonia	51 (11)
Chronic Obstructive Pulmonary disease	20 (4)
Cardiovascular disease	13 (3)
Endocrine disease	6 (1)
Dehydration and electrolyte disturbance	14 (3)
Gastrointestinal disease	31 (7)
Renal disease	9 (2)
Rheumatic disease	12 (3)
Anaemia	3 (1)
Central nervous system disease	5 (1)
Delirium	2 (0,5)
Other skin diseases	2 (0,5)
Lesions and intoxication	20 (4)
Cancer	15 (3)
Other	30 (7)
Unknown	70 (15)
Toxin profile	

Table 1 (continued)

	n (%)
Toxin A/B	455 (99)
Binary toxin	75 (16)
Subtype 027	2 (0.4)
CDI definition[a]	
Healthcare facility-onset (HO)	193 (42)
Community-onset, healthcare facility-associated (COHCFA)	137 (30)
Community-associated (CA)	127 (28)
Treatment at index CDI, *n* (%)	
No treatment	55 (12)
Metronidazole	257 (56)
Vancomycin	69 (15)
Metronidazole + Vancomycin	69 (15)
Vancomycin + Fidaxomicin	3 (0.7)
Vancomycin + Feacal microbiota transplantation	4 (0.9)

CDI Clostridioides difficile infection, *MPI* multidimensional prognostic index

[a]HO: case of CDI collected > 3 days after admission to facility; COHCFA: case of CDI occurring within 28 days after discharge from a healthcare facility; CA: case of CDI occurring more than 28 days after discharge from a healthcare facility

($HR_{adjusted} = 2.71$ (95% CI 1.64–4.47)) (Table 2). Increasing age reduced day-to-day survival, especially for patients aged 80 years or older (Fig. 3).

Ninety-day survival according to CDI severity showed a reduced day-to-day survival, especially in patients with fulminant CDI, whereas nearly all patients with mild CDI survived through 90 days (Fig. 3). Patients with fulminant CDI had a higher day-to-day mortality hazard than patients with severe CDI, as reflected in the adjusted HR 4.58 (95% CI 3.04–6.88).

An increasing frailty level reduced day-to-day survival (Fig. 3). The 90-day mortality risk differed significantly between the MPI groups (Table 2). In patients with severe frailty (MPI-3), the adjusted HR was 10.15 (95% CI 4.06–25.36) compared with patients with low frailty (MPI-1). For patients with moderate frailty (MPI-2), the adjusted HR was 2.70 (95% CI 1.03–7.11) as compared with MPI-1.

All the eight items of the MPI were associated with 90-day mortality except number of prescription drugs.

In addition to mortality, we examined CDI recurrence. Overall, 107 (23%) of all 457 patients had CDI recurrence within 90 days from date of positive PCR toxin test. No patients had a colectomy. There was no statistically significant association between recurrence of CDI and age ($p = 0.776$), CDI severity ($p = 0.906$) or MPI ($p = 0.491$).

Comparison of predictors of 90-day mortality

The areas under the ROC curves were used to quantify the overall ability of age, CDI severity and MPI to predict 90-day mortality (Fig. 4). The discrimination of the MPI according to 90-day mortality was good with a ROC area of 77%, which differed statistically significant from the ROC area for discrimination of age ($p < 0.001$) and CDI severity ($p = 0.04$). The discrimination of CDI severity according to mortality was 71% and differed significantly only when compared with the ROC area for discrimination of age ($p = 0.017$).

Sensitivity analysis

To test the robustness of risk estimates and investigate whether missing data may have had an impact on the adjusted HRs, we performed a sensitivity analysis. Insufficient information in the EMRs to calculate a CDI severity

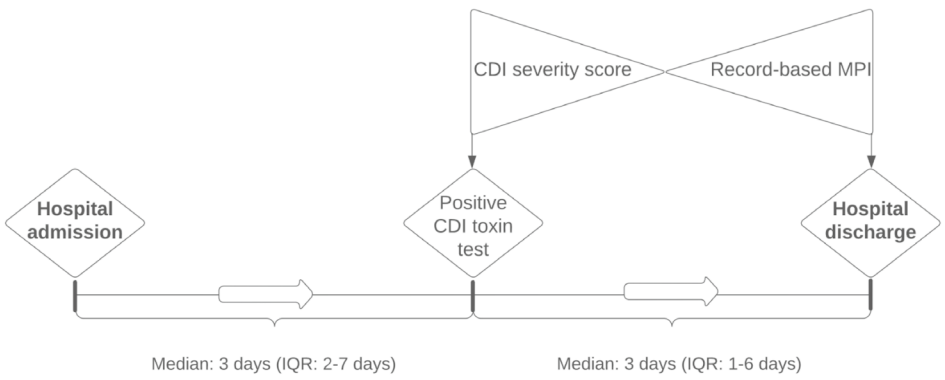


Fig. 2 Collection of data, timeline

Abbreviation: CDI, *Clostridioides difficile* infection; MPI, Multidimensional Prognostic Index; IQR: interquartile range.

Table 2 90-Day mortality and hazard ratio estimates for age, severity and frailty of *Clostridioides difficile* infection

	Total, *n* (%)	Death within 90 days, *n* (%)	Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)[a]	*P*-value
Total	*N* = 457	127 (28)	–	–	–	–
Age groups (years)						
60–69	118 (25)	20/118 (17)	1.00 (reference)	–	1.00 (reference)	–
70–79	158 (35)	37/158 (23)	1.46 (0.85–2.51)	0.175	1.48 (0.86–2.55)	0.162
80-max	181 (40)	70/181 (39)	2.67 (1.62–4.38)	< 0.001	2.71 (1.64–4.47)	< 0.001
Severity (*N* = 412)						
Severe[b]	222 (54)	31/222 (14)	1.00 (reference)	–	1.00 (reference)	–
Fulminant	190 (46)	94/190 (49)	4.69 (3.12–7.05)	< 0.001	4.58 (3.04–6.88)	< 0.001
Frailty level (*N* = 387)						
Low (MPI-1)	80 (18)	5/80 (6)	1.00 (reference)	–	1.00 (reference)	–
Moderate (MPI-2)	136 (30)	25/136 (18)	3.10 (1.19–8.10)	0.021	2.70 (1.03–7.11)	0.044
Severe (MPI-3)	171 (37)	88/171 (51)	11.32 (4.60–27.90)	< 0.001	10.15 (4.06–25.36)	< 0.001
Unknown	70 (15)	9/70 (13)	–	–	–	–

Patients with unknown MPI or CDI severity were not included in the analysis, but separate sensitivity analyses were made

CDI Clostridioides difficile infection, *MPI* multidimensional prognostic index

[a]Adjusted for age and gender. Age groups only adjusted for gender

[b]Mild (*n* = 33) and severe (*n* = 189) CDI were merged

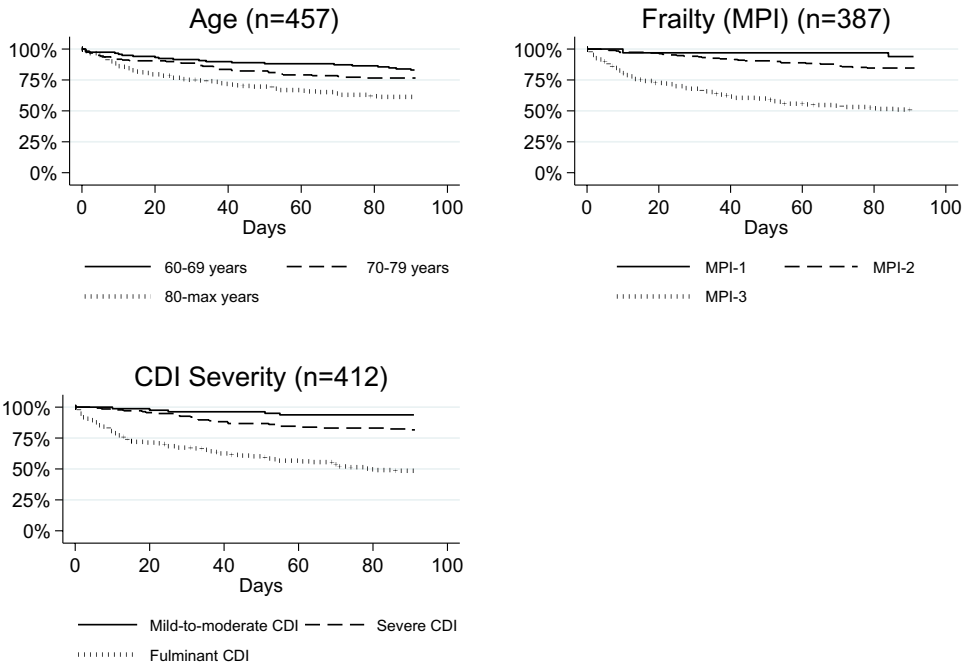


Fig. 3 Kaplan–Meier survival curves for age, severity and frailty

Abbreviations: CDI,*Clostridioides difficile* infection; MPI, Multidimensional Prognostic Index; MPI-1: low frailty; MPI-2: moderate frailty; MPI-3: severe frailty.

score (n = 45 (10%)) and frailty level (*n* = 70 (15%)) was stated as missing values.

When patients with an unknown level of severity were coded as mild CDI and included in the analysis, the adjusted HR was 2.80 (95% CI 0.98–7.99) for severe disease compared with mild CDI. For fulminant disease, the adjusted HR was 11.73 (95% CI 4.29–32.04) compared with mild CDI.

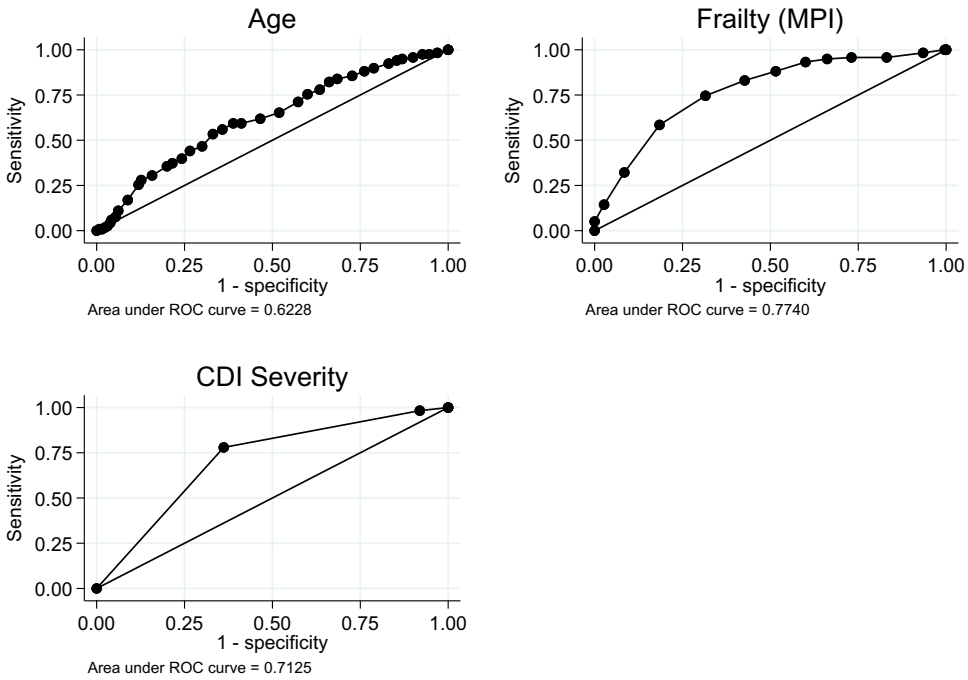


Fig. 4 ROC curve estimates for 90-day mortality for age, CDI severity and frailty measured by MPI. Only patients with a known severity and frailty level ($n = 378$) were included in the analysis

Abbreviations: CDI, *Clostridioides difficile* infection; MPI, Multidimensional Prognostic Index; ROC, Receiver operating characteristic

Thus, including patients with an unknown level of severity in the analyses did not change the results.

When patients with an unknown frailty grade were merged with MPI-1 and included in a sensitivity analysis, the adjusted HRs remained statistically significant only for MPI-3 (adjusted HR = 6.76 (95% CI 3.78–12.10)) when compared with the merged group. When MPI-1 was merged with MPI-2, the adjusted HR for MPI-3 remained significant (adjusted HR = 4.76 (95% CI 3.11–7.30)).

Discussion

The key finding of this population-based study was a 90-day mortality of 28% in patients with CDI and older than 60 years. Among patients with severe frailty 51% died before 90 days. Both patient age, disease severity, and frailty level at discharge predicted mortality. Frailty level outperformed age and severity in predicting mortality at 90 days.

The finding of a high 90-day mortality is in accordance with previous studies [1, 2, 4, 28]. The present study provides population-based mortality data and included all patients with a positive CDI toxin test during hospital admission as well as outpatient treatment and primary healthcare, with a record-based validation of clinical CDI. Our study thus describes the overall mortality in age-specific groups of patients with CDI in a Danish region and not merely in a selected cohort.

Literature on multidimensional assessed frailty in patients with CDI is limited. In a retrospective observational study including 33 patients older than 75 years [18], most of the patients (84%) were severely frail according to the MPI, but no statistically significant difference with respect to mortality was identified. This may be explained by a low number of participants and because only patients admitted to a geriatric care unit were included, whereas we included all patients presenting with a positive CDI test, regardless whether they came from a geriatric or other medical departments or surgical departments. The MPI was performed during the first 48 h after admission whereas we performed the MPI at discharge. The predictive value of MPI for patients with CDI at discharge was in line with its value in other medical inpatients at time of discharge, showing an AUC for 90-day mortality of 0.76 [29]. The patients were older (≥ 75 years) and required daily assistance or had a Charlson Comorbidity Index ≥ 1, whereas patients in our study were included solely if they had a positive CDI test and were aged ≥ 60 years. This indicated that frailty may play a crucial role for patients with CDI. Frailty rating may be performed in several ways. We suggest that the MPI is relevant for the evaluation of patients with CDI because it includes the CGA-based aspect. A concomitant clinical intervention using the CGA approach to issues identified via the MPI may lead to less severe outcomes and ultimately fewer deaths. The role of CGA employed as an intervention in old patients with CDI needs to be further investigated.

Time of frailty assessment can be discussed. In this study we chose to assess frailty measured by the record-based MPI at discharge, as this timing made the retrospective assessment based on information from the EMRs as precise as possible. The aggregate MPI score was a better predictor of mortality than the individual MPI items. Except for number of prescription drugs all the MPI items were associated with 90-day mortality. However, what would also be interesting is to know the baseline frailty status and the outcome of CDI. However, such study design would be very challenging and resource intensive. We chose the record-based MPI as a marker of frailty recognizing that the measurement may be affected by the state of acute illness. Therefore, the MPI at discharge may merely reflect the acute deconditioning due to the disease process and CDI and not the true frailty status as the baseline frailty status is unknown. However, risk assessment is only meaningful at the time of CDI to help the clinician evaluate the patient, including the choice and timing of treatment.

Frailty had a higher predictive value of 90-day mortality than disease severity. Severity classification which is based on clinical and biochemical parameters that may not independently capture the degree of CDI severity in older patients. Studies conducted in similar-aged populations have focused on individual risk factors for severe outcomes such as level of comorbidity, nutritional and functional status [3, 16, 23]. These factors are included in the MPI but not in the classification of CDI severity. Furthermore, in frail old patients, typical illness symptoms are often absent [30] or atypical [31]. Instead, patients may present with symptoms such as general weakness and immobility, commonly known as the "geriatric syndrome" [32], which may be better assessed using a multidimensional frailty approach. The population of this cohort was older and, as frailty increases steadily with age, the prevalence of frailty among our cohort was presumably larger than in a younger patient cohort with CDI [33]. The higher predictive value of 90-day mortality for multidimensional frailty when compared to CDI severity may be because the components of the record-based MPI and CDI severity classification differ.

Disease severity, although outperformed by frailty level, also predicted mortality at 90 days. Our study thus confirms the clinical applicability of the severity classification. Yet, the use of CDI severity markers in older patients has been questioned. In a study of patients older than 65 years, the accepted CDI severity criteria (IDSA) were not significantly associated with poor outcomes [34]. Similarly, a cohort study of patients older than 80 years found no significant difference in 30-day mortality between patients defined as having severe or non-severe CDI according to the IDSA definition of severe CDI [3]. Other studies indicate that comorbidity and not the IDSA severity score is a key driver for mortality [35, 36]. However, in the present study, the CDI severity level [25] was validated and it had a significant predictive ability to predict 90-day mortality. This discrepancy between the results of previous studies and our study may be explained by the fact that previous studies [3, 34] only examined risk of death based on laboratory parameters following the IDSA and did not include clinical symptoms. The adequacy of the European markers of the risk of severity was reported in a meta-analysis [37]. In accordance with our findings, in a cohort study of patients older than 75 years, the European markers were shown to be adequate in predicting mortality in patients $\geq$ 75 years; and the authors concluded that level of severity was a risk factor of mortality [15]. Because of varying definitions of standard severity markers, it is difficult to compare data between studies. Our severity assessment differed from the studies mentioned above as we included abdominal pain and not age above 65 years or a rise in creatinine level in the CDI severity assessment. In the daily clinical work, level of CDI severity heightens the clinician's awareness of the importance of the CDI among older patients. Severe and fulminant CDI should impose on clinicians not to hesitate initiating treatment to prevent death.

High age is a risk factor for severe CDI and complicated CDI outcomes, including death [38, 39]. In accordance with our findings, previous studies of adult CDI patients of all ages reported that age older than 80 years is a significant risk factor for death [40, 41]. In a study including patients aged $\geq$ 18 years [40], age was a better predictor of death during hospitalisation than in our study. The older population in our cohort may explain this difference. Compared with the record-based MPI, the predictive ability of age for mortality was minor. This indicates that age alone is insufficient as a prognostic factor in the older population when assessing the overall severity of CDI.

It is striking that metronidazole was the most frequent initial treatment and vancomycin less frequently prescribed considering the severity of the disease. This implies suboptimal treatment and lack of adherence to guidelines at that time [7, 42]. This may explain the high relapse rates. No colectomy was performed although 42% of the patients had fulminant CDI. This may indicate a misclassification bias or suboptimal management of the very severe cases. In terms of severity classification, it is a limitation to the study that it is not clear whether the hypotension and lactic academia were due to CDI or the primary disease process warranting admission. Emergency colectomy is indicated for a small minority of patients with severe CDI who have the potential to recover from major surgery [43, 44]. However, the mortality rate following surgery remains extremely high and the timing of such surgery is poorly defined [45, 46]. Meta-analysis of high-quality studies revealed that the strongest predictors of postoperative death were those relating to preoperative physiological status [47]. We propose that the patients in

this cohort were too frail to be candidates for colectomy. The clinical treatment practice documented in our data was suboptimal suggesting a delayed implementation of the guidelines. This delay may be pronounced among older patients and is, therefore, an independent learning from our study.

The strengths of our study include a large sample size and a complete description of mortality of all CDI patients with a positive CD test during the period. This is a population-based study which includes all CDI patients with a positive CD test during the period, disregarding if patients are diagnosed in primary health care or in hospital. Patients were included based on age and positive PCR test solely, minimising the risk of selection bias. No patients were lost to follow-up on the primary outcome. Providing the MPI domains allowed us to conduct a multidimensional characterisation of inpatients with CDI. This may be used to design a multidimensional approach to patients with CDI in future studies.

Our study has important limitations. Firstly, data were collected retrospectively and rely on the completeness of the medical records which may induce information bias and underestimate the frailty level. The prognostic ability of the record-based MPI has recently been validated in a Danish cohort study including 1190 older (75 +) medical patients admitted to a general internal medicine unit [29] It is a limitation that the record-based MPI has not been evaluated specifically in surgical departments. However, at admission, all Danish EMRs encompass updated information from primary health care as well as interdisciplinary observations. The municipality delivers data regarding need for assistive remedies and allocation of home care. Medication charts from primary care are linked to the medical records medication list. Therefore, we consider the data from the EMRs sufficient for a record-based MPI measurement.

Diagnosing CD necessitates both clinical evidence of diarrhoea and evidence of toxinogenic CD. A study limitation is the retrospective collection of clinical data from the EMRs. All patients were diagnosed with acute onset diarrhoea and tested for CDI based on clinical suspicion. In standard clinical practice, the laboratory rejects faecal specimens if they are not liquidous (e.g., Bristol stool chart score 6–7), as determined by visual inspection. The use of a standalone PCR test for CDI diagnosis is debated because of the high prevalence of asymptomatic carriers with CD [48]. Although asymptomatic carriage may affect the results of this study, limiting the inclusion criteria to patients with onset and relevant exposure may mitigate its impact, as all patients exhibited new-onset diarrhoea.

Secondly, frailty data were collected only for patients admitted to hospitals where medical records were available. The role of frailty as a predictor of mortality among patients with community-acquired CDI, therefore, remains unknown. The low number of community-acquired CDI may be explained by a low awareness of CDI in the primary healthcare setting. Because the number of community-acquired CDI cases was limited, we believe that the record-based MPI provided a valuable tool to assess frailty in older patients with CDI. Thirdly, the severity definition includes components collected at the time of the positive PCR test whereas the frailty measure is more closely related to the discharge date. Because the median duration from date of positive PCR test and until date of discharge of CDI-related admission was 3 days, any bias resulting from this difference is considered low. It was surprising that more than 40% of the cases were classified as fulminant CDI. Fifteen percent was classified as such solely due to a change in mental status which might have overestimated the prevalence of patients with fulminant CDI. On the other hand, we may consider whether frail older patients may present with atypical symptoms [30, 31] which may challenge the assessment of severity of CDI. Traditional severity indices for CDI are not necessarily present in older patients [3]. A change of mental status may be an important indicator of fulminant CDI in older patients. If not recognized early this may delay initiation of appropriate treatment and thereby increase the risk of an exacerbation of prognosis [49]. Causes of death were not recorded because it is difficult to determine cause-specific deaths from CDI and the degree to which CDI contributes to death.

Finally, current mortality rates might differ from the rates in this study since practice has changed in CDI management the last few years. In a Danish setting, vancomycin is considered first choice and faecal microbiota transplantation (FMT) has emerged as a life-saving treatment in patients with first and recurrent CDI in achieving sustained resolution from CDI [25, 50, 51]. FMT treatment tends to reduce mortality compared with treatment with vancomycin [52]. The 90-day mortality rate may be reduced with current antibiotic approaches combined with faecal microbiota transplantation.

In conclusion, in a population-based, well-defined, and consecutively included cohort of older patients with their first CDI, we found a high 90-day mortality, increasing with age, disease severity and frailty level. Multidimensional frailty measured by the record-based MPI was a superior predictor of mortality in patients with CDI, outperforming both age and CDI severity. An imminent need exists for future studies to investigate the effect of an early frailty assessment with CGA on CDI outcomes to optimise the clinical management of older patients with CDI.

Acknowledgements The authors express their gratitude to the collaborators at the participating medical departments.

Author contribution The authors meet the ICMJE criteria for authorship. Study concept and design: TMMR, EMD, MG, CLH, SMDB, TKH; acquisition of data: TMMR, SMDB. Analysis and interpretation: TMMR, EMD, CLH, MG, TKH, SMDB, JBR, LTE.

Funding Open access funding provided by Royal Danish Library. This work formed part of a PhD project supported by the Health Research Foundation of Central Denmark Region [DKK 100,000]. The Centre for Faecal Microbiota Transplantation is supported by Innovation Fund Denmark (r. no. 8056-00006B).

Data availability Code book for data entry databases and all other project-related raw material are available upon reasonable request to the corresponding author.

Declarations

Conflict of interest None of the authors had any conflicts of interest to declare.

Ethical approval The study was defined as a quality improvement study which, according to Danish law, solely requires approval from the hospital board and not informed consent. This was confirmed by the Central Denmark Region Ethics Committee (1-10-72-1-21).

Informed consent Permission to assess patient EMRs was obtained by the hospital boards at Aarhus University Hospital and all regional hospitals in the CDR (12-11-20). Only anonymised and summarised data are presented.

References

1. Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ (2013) All-cause and disease-specific mortality in hospitalized patients with Clostridium difficile infection: a multicenter cohort study. Clin Infect Dis 56(8):1108–1116
2. McGowan AP, Lalayiannis LC, Sarma JB, Marshall B, Martin KE, Welfare MR (2011) Thirty-day mortality of Clostridium difficile infection in a UK National Health service Foundation Trust between 2002 and 2008. J Hosp Infect 77(1):11–15
3. Leibovici-Weissman Y, Atamna A, Schlesinger A, Eliakim-Raz N, Bishara J, Yahav D (2017) Risk factors for short- and long-term mortality in very old patients with Clostridium difficile infection: a retrospective study. Geriatr Gerontol Int 17(10):1378–1383
4. Feuerstadt P, Nelson WW, Drozd EM, Dreyfus J, Dahdal DN, Wong AC (2022) Mortality, health care use, and costs of Clostridioides difficile infections in older adults. J Am Med Dir Assoc 23(10):1721-1728.e19
5. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH (2013) Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 108(4):478–498 (**quiz 99**)
6. Bauer MP, Kuijper EJ, van Dissel JT (2009) European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clin Microbiol Infect 15(12):1067–1079
7. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE (2018) Clinical Practice Guidelines for Clostridium difficile Infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 66(7):987–994
8. Fujitani S, George WL, Murthy AR (2011) Comparison of clinical severity score indices for Clostridium difficile infection. Infect Control Hosp Epidemiol 32(3):220–228
9. Gujja D, Friedenberg FK (2009) Predictors of serious complications due to Clostridium difficile infection. Aliment Pharmacol Ther 29(6):635–642
10. Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M (2009) Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg 144(5):433–439
11. Dudukgian H, Sie E, Gonzalez-Ruiz C, Etzioni DA, Kaiser AM (2010) C. difficile colitis–predictors of fatal outcome. J Gastrointest Surg 14(2):315–322
12. Cunha AIL, Veronese N, de Melo BS, Ricci NA (2019) Frailty as a predictor of adverse outcomes in hospitalized older adults: a systematic review and meta-analysis. Ageing Res Rev 56:100960
13. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K (2013) Frailty in elderly people. Lancet 381(9868):752–762
14. Cober ED, Malani PN (2009) Clostridium difficile infection in the "oldest" old: clinical outcomes in patients aged 80 and older. J Am Geriatr Soc 57(4):659–662
15. Caupenne A, Ingrand P, Ingrand I, Forestier E, Roubaud-Baudron C, Gavazzi G (2020) Acute Clostridioides difficile infection in Hospitalized persons aged 75 and older: 30-day prognosis and risk factors for mortality. J Am Med Dir Assoc 21(1):110–114
16. Rao K, Micic D, Chenoweth E, Deng L, Galecki AT, Ring C (2013) Poor functional status as a risk factor for severe Clostridium difficile infection in hospitalized older adults. J Am Geriatr Soc 61(10):1738–1742
17. Kyne L, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D (1999) Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. Age Ageing 28(2):107–113
18. Govoni B, Zurlo A, De Giorgio R, Cultrera R, Volpato S (2021) Clostridium difficile infection in a geriatric care unit: clinical characteristics and prognosis. J Gerontol Geriatr 69(1):1–5
19. Pilotto A, Ferrucci L, Franceschi M, D'Ambrosio LP, Scarcelli C, Cascavilla L (2008) Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res 11(1):151–161
20. Volpato S, Bazzano S, Fontana A, Ferrucci L, Pilotto A (2015) Multidimensional prognostic index predicts mortality and length of stay during hospitalization in the older patients: a multicenter prospective study. J Gerontol A Biol Sci Med Sci 70(3):325–331
21. Pilotto A, Addante F, D'Onofrio G, Sancarlo D, Ferrucci L (2009) The comprehensive geriatric assessment and the multidimensional approach. A new look at the older patient with gastroenterological disorders. Best Pract Res Clin Gastroenterol 23(6):829–837
22. Ellis G, Gardner M, Tsiachristas A, Langhorne P, Burke O, Harwood RH (2017) Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev 9:Cd006211

23. Bielakova K, Fernandova E, Matejovska-Kubesova H, Weber P, Prudius D, Bednar J (2016) Can we improve the therapy of Clostridium difficile infection in elderly patients? Wien Klin Wochenschr 128(15–16):592–598
24. Hansen TK, Damsgaard EM, Shahla S, Bruun JM, Gregersen M (2020) A reliable and record-based frailty assessment method for older medical inpatients. Eur Geriatr Med 11(5):803–812
25. Baunwall SMD, Dahlerup JF, Engberg JH, Erikstrup C, Helms M, Juel MA (2021) Danish national guideline for the treatment of Clostridioides difficile infection and use of faecal microbiota transplantation (FMT). Scand J Gastroenterol 56(9):1056–1077
26. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)- a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42(2):377–381
27. Swets JA (1988) Measuring the accuracy of diagnostic systems. Science 240(4857):1285–1293
28. Hocquart M, Lagier JC, Cassir N, Saidani N, Eldin C, Kerbaj J (2018) Early fecal microbiota transplantation improves survival in severe clostridium difficile infections. Clin Infect Dis 66(5):645–650
29. Hansen TK, Shahla S, Damsgaard EM, Bossen SRL, Bruun JM, Gregersen M (2021) Mortality and readmission risk can be predicted by the record-based multidimensional prognostic index: a cohort study of medical inpatients older than 75 years. Eur Geriatr Med 12(2):253–261
30. Fried LP, Storer DJ, King DE, Lodder F (1991) Diagnosis of illness presentation in the elderly. J Am Geriatr Soc 39(2):117–123
31. Cooper GS, Shlaes DM, Salata RA (1994) Intraabdominal infection: differences in presentation and outcome between younger patients and the elderly. Clin Infect Dis 19(1):146–148
32. Inouye SK, Studenski S, Tinetti ME, Kuchel GA (2007) Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc 55(5):780–791
33. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC (2012) Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc 60(8):1487–1492
34. Atamna A, Babich T, Margalit I, Avni T, Ben Zvi H, Raz NE (2022) Does accepted definition of Clostridioides difficile infection (CDI) severity predict poor outcomes in older adults? Aging Clin Exp Res 34(3):583–589
35. Kampouri E, Filippidis P, Wölfle M, Taveira A, Badinski T, Croxatto A (2022) Clostridioides difficile infection (CDI) epidemiology and patient characteristics in Switzerland. Infect Dis Now 52(5):267–272
36. Barbosa-Martins J, Mendonça J, Carvalho C, Sarmento H, Mota P, Coutinho C (2022) Clostridium difficile Severity and outcome at a North of Portugal healthcare facility. Acta Med Port 35(4):279–285
37. Abou Chakra CN, Pepin J, Sirard S, Valiquette L (2014) Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. PLoS One 9(6):e98400
38. Bauer MP, Notermans DW, Van Benthem BH, Brazier JS, Wilcox MH, Rupnik M (2011) Clostridium difficile infection in Europe: a hospital-based survey. Lancet 377(9759):63–73
39. Patel UC, Wieczorkiewicz JT, Tuazon J (2016) Evaluation of advanced age as a risk factor for severe Clostridium difficile infection. J Clin Gerontol Geriatri 7(1):12–16
40. Bednarska A, Bursa D, Podlasin R, Paciorek M, Skrzat-Klapaczyńska A, Porowski D (2020) Advanced age and increased CRP concentration are independent risk factors associated with Clostridioides difficile infection mortality. Sci Rep 10(1):14681
41. Morrison RH, Hall NS, Said M, Rice T, Groff H, Brodine SK (2011) Risk factors associated with complications and mortality in patients with Clostridium difficile infection. Clin Infect Dis 53(12):1173–1178
42. Debast SB, Bauer MP, Kuijper EJ (2014) European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 20(Suppl 2):1–26
43. Al-Abed YA, Gray EA, Rothnie ND (2010) Outcomes of emergency colectomy for fulminant Clostridium difficile colitis. Surgeon 8(6):330–333
44. Perera AD, Akbari RP, Cowher MS, Read TE, McCormick JT, Medich DS (2010) Colectomy for fulminant Clostridium difficile colitis: predictors of mortality. Am Surg 76(4):418–421
45. Pepin J, Vo TT, Boutros M, Marcotte E, Dial S, Dub S (2009) Risk factors for mortality following emergency colectomy for fulminant clostridium difficile infection. Dis Colon Rectum 52(3):400–405
46. Byrn JC, Maun DC, Gingold DS, Baril DT, Ozao JJ, Divino CM (2008) Predictors of mortality after colectomy for fulminant Clostridium difficile colitis. Arch Surg 143(2):150–154
47. Bhangu A, Nepogodiev D, Gupta A, Torrance A, Singh P (2012) Systematic review and meta-analysis of outcomes following emergency surgery for Clostridium difficile colitis. Br J Surg 99(11):1501–1513
48. Van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B (2021) European society of clinical microbiology and infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect 27(Suppl 2):S1-s21
49. Lauda-Maillen M, Liuu E, Catroux M, Caupenne A, Priner M, Cazenave-Roblot F (2019) Treatment compliance with European guidelines and prognosis of Clostridium difficile infection according to age. Med Mal Infect 49(3):173–179
50. Baunwall SMD, Andreasen SE, Hansen MM, Kelsen J, Høyer KL, Rågård N, Rubak T (2022) Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol Hepatol 7(12):1083–1091
51. Baunwall SMD, Lee MM, Eriksen MK, Mullish BH, Marchesi JR, Dahlerup JF (2020) Faecal microbiota transplantation for recurrent Clostridioides difficile infection: an updated systematic review and meta-analysis. EClinicalMedicine 2020:29
52. Rode AA, Chehri M, Krogsgaard LR, Heno KK, Svendsen AT, Ribberholt I (2021) Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent Clostridioides difficile infections. Aliment Pharmacol Ther 53(9):999–1009

PAPER II

THE LANCET
Healthy Longevity

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rubak T, Baunwall SMD, Gregersen M, et al. Early geriatric assessment and management in older patients with *Clostridioides difficile* infection in Denmark (CLODIfrail): a randomised trial. *Lancet Healthy Longev* 2024. https://doi.org/10.1016/j.lanhl.2024.100648

Supplementary file 1. The protocol article entitled "Clostridioides difficile infection in frail older patients, quality in treatment and care: the CLODIFRAIL study protocol for a multicentre randomised controlled trial"

Clostridioides difficile infection in frail older patients, quality in treatment and care: the CLODIFRAIL study protocol for a multicentre randomised controlled trial

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Running title: *Clostridioides difficile* infection and frailty, the CLODIFRAIL study

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Abstract

Background: *Clostridioides difficile* infection (CDI) is complex and associated with adverse clinical outcomes in older patients, including increased mortality rates. Effective transition of care for patients with CDI is critical to improve survival and health outcomes and to reduce recurrence rates. This study aimed to investigate the effect of a geriatric intervention on the survival of older patients with CDI compared with those receiving standard care.

Methods and analysis: This is a quality improvement study comparing two organisational pathways. We plan to include 216 patients aged 70 years or more diagnosed with CDI. Patients with a positive *Clostridioides difficile* toxin polymerase chain reaction (PCR) test are randomised 1:1 to either 1) a geriatric assessment and intervention (the CLODIFRAIL intervention) or 2) standard care at the treating physician's discretion. The intervention has three main parts: 1) a clinical geriatric assessment; 2) a clinical evaluation of indication for and treatment with faecal microbiota transplantation (FMT); 3) weekly clinical assessments during eight weeks. The follow-up period is 90 days. The primary outcome is 90-day survival from the date of positive CDI PCR test.

Ethics and dissemination: The trial is conducted in accordance with the Declaration of Helsinki and poses no project-related risks, experimental treatments, or invasive biological sample collection. The study is conducted as a quality improvement study, embedded in two parallel and fundamentally different routine clinical care pathways. The study design and its categorisation as a quality improvement study is approved by the Central Denmark Region Committees on Health Research Ethics. This study will provide new knowledge on the effects of a geriatric intervention for older patients with CDI, incorporating an early assessment of the indication for FMT on patient survival and clinical outcomes.

Trial registration: The study was pre-registered at ClinicalTrials.gov on 28 June, 2022. Study identifier: NCT05447533.

Keywords: *Clostridioides difficile*; Frailty; Aged; Faecal microbiota transplantation; Gastroenterology

Strengths:

- The project is innovative in aiming to improve care and treatment for all older patients with *Clostridioides difficile* infection in a real-life setting
- All patients with a positive *C. difficile* test are included and therefore, the population is representative of a broad range of older patients with *Clostridioides difficile* infection.

Limitations:

- Standard care may include elements of the intervention during the follow-up period (geriatric care and FMT), making it less likely that the intervention will produce any effects.
- Component disaggregation for geriatric intervention is challenging, hindering replication precision.

Introduction

Clostridioides difficile infection (CDI) has a poor prognosis, and mortality rates increase dramatically with age.[1] Treatment and care are managed across multiple healthcare settings, and this challenges the overall health care management process.[2] Preventive strategies and effective therapeutic approaches are warranted to reduce older patients' risk of dying from CDI.

CDI primarily affects older patients.[3] Older patients with severe CDI are characterised by a high comorbidity burden, low functional status, high degree of polypharmacy, malnutrition and a need for support in everyday life.[4-6] Collectively, these factors indicate frailty. Frailty is a framework used in geriatrics to describe older patients' risk of a poor prognosis. It develops due to age-related decline in physiological functions,[7] collectively increasing vulnerability to stressors.[8] Previous studies indicate that CDI affects frail patients.[9] Frailty indicators, rather than age alone, are therefore important determinants of CDI risk in an older adult population.[10]

Frail older patients present with atypical symptoms[11], and typical symptoms of illness may change or be absent.[12-14] The traditional CDI severity markers are not necessarily present in older patients.[15] This challenges the CDI severity assessment and may delay appropriate treatment initiation.[16]

Geriatricians are trained in the assessment and planning of care for multimorbid older patients. The Comprehensive Geriatric Assessment (CGA) is considered the gold standard of multidisciplinary assessment and care planning for this group.[17] It is a diagnostic process intended to determine an older person's medical, psychosocial, and functional capacities and problems to create an overall treatment plan with short- and long-term follow-up, ultimately guiding intervention.[18] Frailty identification and assessment are important constituent parts of the CGA. The Multidimensional Prognostic Index (MPI) is a systematic CGA-based assessment tool for prediction of short- and long-term mortality in older hospitalised patients.[19,20]

Systematic reviews have affirmed the clinical utility of CGA-guided interventions for older patients compared with standard care, including improved functional ability,[21-23] reduced mortality[22,24] and increased survival at home after discharge.[25] This was documented in the setting of in-hospital medical patients in dedicated ageing and health wards and across different departments and medical conditions.[25,26] In a Danish older adult inpatient population, early geriatric follow-up conducted by outgoing geriatric teams after discharge reduced readmission rates[27-29] and mortality rates in such patients living in their own homes.[30]

The need for transition of care for patients with CDI has been emphasized by others.[2] Older patients with CDI are often diagnosed and managed across multiple health care settings and discharged prior to completion of

CDI therapy without follow-up, which increases their risk of recurrence, readmission and death. There is currently no existing literature regarding CGA and geriatric follow-up treatment at home for older patients with CDI.

Faecal microbiota transplantation (FMT) has emerged as a life-saving treatment in patients with CDI. For first and recurrent CDI, it is effective in achieving sustained resolution,[31,32] and it tends to reduce mortality rates compared with vancomycin treatment alone.[33] Limited data support that FMT has a similar effect and safety profile in patients aged ≥ 65 years.[34-37] Despite its benefits to this population at risk of recurrence and severe disease, [37] access to this treatment remains limited for older patients. In most settings, FMT requires hospital attendance. Older patients who are too frail to tolerate transportation may therefore be withheld treatment. We previously proposed that FMT may be conducted as a hospital-at-home treatment, but this has yet to be confirmed in larger scale.[38]

Aim

The aim of this study is to investigate the effect of a geriatric intervention on the survival of older patients with CDI compared with those receiving standard care.

Methods

Study design

This is a multicentre randomised controlled trial (RCT) named *CLOstridioides Difficile* Infection in FRAIL older patients (CLODIFRAIL). Outcomes are assessed after 90 days of follow-up. The patient flow is illustrated in Figure 1; the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[39] in Figure 2. The SPIRIT checklist is included in Additional file 1.

Roles and responsibilities

The study is conducted at Aarhus University Hospital, Denmark, and at four affiliated regional hospitals in the Central Denmark Region (CDR). The study compares two well-known organisations of care and does not involve experimental treatments or sampling of biological material beyond material obtained as part of routine care. It is therefore classified as a quality improvement project and does not require patient consent before randomisation. The project is anchored in the Geriatric Research Unit, which has experience in conducting clinical research on frailty, and in cooperation with the Centre for Faecal Microbiota Transplantation that holds expertise

on research and development of FMT.[40] The geriatricians in the medical departments in the CDR are responsible for patient treatment and clinical contacts to patients**.** The organisation chart is illustrated in Additional file 2.

Patient and public involvement

Two members of the Danish Council of senior citizens are engaged in the project steering group as patient representatives (Additional file 2). The patient representatives have actively participated in the initial idea phase, study planning, protocol review, development of information materials and offering assistance in securing funding for the study (Additional file 3).

Study population

Eligible patients are consecutively included from a complete list of all patients in the CDR diagnosed with a positive *Clostridioides difficile* (CD) toxin polymerase chain reaction (PCR) test. The list is maintained at the Department of Clinical Microbiology at Aarhus University Hospital and is sent to the project manager every weekday. Patients are identified via the national identification number-based Civil Registration Register, collected and managed using REDCap electronic data capture tools hosted at Aarhus University.[41]

Patient inclusion criteria

- Patients aged ≥ 70 years and living in the CDR
- Positive PCR toxin test for CD
- Not previously included in the study during the study period

Patient exclusion criteria

- Patients already receiving geriatric assessment of CDI within 8 weeks from positive PCR test, defined as follows: affiliated with the ageing and health wards (in- or outpatient activity) at the time of the positive PCR test for CDI
- FMT treatment 8 weeks before date of positive PCR test for CDI
- > 4 episodes of CDI
- End-of-life care defined as follows: end-of-life care treatment has been initiated before positive PCR test for CDI and the patient has a life expectancy less than days/few weeks, based on investigator consensus.

Patients included are patients not already receiving parts of the intervention, including geriatric assessment and/or FMT treatment. Only a few patients survive 4 or more episodes with CDI (unpublished data). Patients

with multiple recurrent CDI are refractory to any treatment and would therefore pose a special challenge. We have chosen to exclude these patients as clinical experience indicates that these patients differ from the rest of the population with CDI.

Randomisation and blinding

Eligible patients are identified consecutively from the reporting system by the project manager and will be randomised within the first weekday from a positive CD test. When the patient is allocated for geriatric intervention, the project manager will contact the regional ageing and health wards who will contact the department that ordered the PCR test and plan a visit to the patient. Randomisation allocation will be performed in REDCap. Allocation lists are generated for the treatment groups at a 1:1 ratio. Proper randomisation concealment was obtained by use of an external randomisation service (Clinical Trial Unit, Department of Clinical Medicine, Aarhus University, Denmark).

The research assistant, who provides all the assessments at follow-up, is blinded with respect to allocation. Given the nature of the intervention, it is not feasible to blind either the patients or the clinicians.

Geriatric intervention

The geriatric intervention is called the CLODIFRAIL intervention. It includes a systematic assessment of both the patient's geriatric problems (CGA) and a systematic assessment of CDI-related symptoms, including an early assessment of indication for FMT. The intervention will be performed at the time of CDI diagnosis and includes an organised set of contacts to ensure close evaluation of clinical status and early intervention in case of exacerbation (Figure 3).

The CLODIFRAIL intervention consists of the following components:

1. CGA, including frailty assessment by the bedside MPI[19]
2. Geriatric CDI check list, including geriatric evaluation of indication for FMT
3. Treatment with FMT if this is indicated
4. Clinical contacts, weekly or more, if necessary during 8 weeks or until cured

1. Comprehensive geriatric assessment and frailty assessment

Within five weekdays from the date of randomisation, the patients receive a visit by a physician trained in geriatric medicine. A CGA with a tailor-made intervention will be conducted at the location where the patient is situated at the time of positive PCR test, i.e., in the allocated ward or at home. Relevant blood analyses are ordered if not already available (electrolytes, renal function, nutritional indicators, infectious parameters and haematological tests). Bedside evaluation of frailty will be conducted, using the MPI[19] and registered in the Electronic Medical Record (EMR). The MPI is a systematic CGA-based aggregate risk score based on comorbidity, habitation status, number of daily prescription drugs used, activities of daily living, cognitive status, wound pressure score and nutritional risk. The MPI provides a tripartite score, categorising patients into groups of non-frail (MPI score 0.0-0.3; MPI=1), moderately frail (MPI score 0.34-0.66; MPI=2) and severely frail (MPI score 0.67-1.0; MPI=3)[19]. An individualised intervention will be performed according to the clinical issues identified.

2. Geriatric CDI checklist and early assessment of FMT indication

The geriatric CDI checklist (Figure 4) will be performed by the geriatrician at the first visit to secure early CDI assessment and prepare a treatment strategy. The checklist will be uploaded to the electronic archive of the EMR. The procedure implies a geriatric evaluation of indication for FMT and treatment planning. CDI-related symptoms are reported in the EMR using standardised headlines (Additional file 4). The checklist recommends to start vancomycin treatment 125 mg x 4 on the same day as the positive PCR test for CDI has been received, if indicated. Next, the checklist recommends to revise the medication list, in particular by discontinuing antibiotics and proton pump inhibitors, if possible, as well as optimising the patient's nutritional and hydration status according to our national guidelines.[42] FMT will be considered if the patient fulfils one of the following criteria:

1) Severe index, recurrent or refractory CDI as defined by national clinical guidelines[43]

or

2) High-risk patient defined as frailty grade MPI-2 (moderate) or MPI-3 (severe).

If FMT is indicated, a date for the FMT procedure will be scheduled. Information material (Additional file 5) targeting CDI and treatment will be delivered to the patient. Targeted CDI information for primary health care will be ensured through corresponding letters, using standardised headlines (Additional file 4).

3. Treatment with faecal microbiota transplantation

When the patient meets the indication for FMT, FMT will be performed at hospital or at home. FMT will be delivered as 15-25 capsules (~ 50 grams of donor faeces from one thoroughly screened healthy donor [44]). If the patient has dysphagia diagnosed by dysphagia screening or carries a nasogastric tube, vancomycin and FMT can be delivered by naso-jejunal tube (Bengmark 10 Fr, Nutricia), requiring referral to the Radiology Department for verification of duodenal/jejunal tube placement. If the patient cannot come to the hospital for control of placement of the naso-jejunal tube, FMT can be delivered by a nasogastric tube under close clinical monitoring. Each FMT component is accompanied by a treatment leaflet and a patient consent form. The treatment leaflet ensures traceability between each unique FMT component and recipient. It contains the recipient's name and national identification number-based Civil Registration Register, FMT information and anonymised donor data. It is completed by the attending physician at each FMT. If the patient is not admitted to hospital, FMT can be delivered as home treatment via a regional geriatric team or the project manager and project nurse (Additional files 6 and 7).

4. Clinical contacts

Physicians arrange weekly telephone contact and schedule the necessary clinical contacts within the project period. Clinical contacts can encompass a clinical evaluation, further drug adjustments, blood tests, etc., and can be conducted by a geriatrician and/or a geriatric nurse or through telephone contacts with the patient, a relative or the home nursing service. To secure clinical symptom feedback on treatment, patients and/or relatives or home nursing service personnel are asked to fill out stool diary, including Bristol scale (Additional file 8) and return the answers in a standardised form (Additional file 4, "Corresponding letter for primary health care"), which is documented in the EMRs. The ageing and health wards remain responsible for CDI treatment for a minimum of 8 weeks from the last FMT or start of antibiotic CDI treatment and until CDI resolution. A control stool PCR test for CDI will be performed upon treatment termination.

Upon FMT treatment termination, we will ensure continued cooperation with the primary sector by incorporating standardised headlines in the discharge summary describing the treatment status and any precautionary principles for future treatment (Additional file 4).

Procedures for monitoring intervention adherence

To secure adherence to the intervention, all activities will be logged in the patient's EMR, including the MPI, the CDI checklist and FMT.

Standard care group

Patients are not contacted by the geriatric team until after 90 days of follow-up but can be admitted and/or referred to ageing and health wards by their patient care team during the entire period. They receive usual treatment at the treating physician's discretion. The Danish healthcare system is tax-financed and available to all Danish residents on a free and equal basis. The general practitioner functions as a gatekeeper to the secondary sector. In the CDR, Aarhus University Hospital and the four main regional hospital units provide secondary care (outpatient, inpatient and intensive care). Standard care includes assessment of CDI and treatment with CDI-related antibiotics and FMT if the physician finds that this is indicated. All patients can be referred to FMT as an outpatient clinic activity or during admission. Standard care for patients with CDI in Denmark is described in the national clinical guideline.[42]

Outcome measures

All outcome measures are predefined and will be registered at 90 days (± 7 days) from the date of positive PCR test for CDI.

The primary outcome is 90-day survival from the date of positive PCR test for CDI.

Secondary outcomes include quality improvement-related and patient-related outcomes:

1. Quality- related outcome measures
    a. Time-to-treatment with FMT. Time frame: from date of positive PCR test for CD to date of FMT.
    b. Time-to-treatment with vancomycin. Time frame: from date of positive PCR test for CD to date of start treatment with vancomycin.
    c. CDI recurrence within a 90-day follow-up period. Recurrent CDI is defined as a new CDI episode after ended CDI treatment with treatment response. New episode of diarrhoea (≥3 loose stools, Bristol 6-7) and a positive CD toxin test.
    d. Readmission defined as any unplanned, acute rehospitalisation (elective or planned admissions and outpatient procedures excluded) at any hospital within the CDR, occurring within four hours and up to 30 days after hospital discharge.[45]
    e. Days in hospital: number of days in hospital from date of first positive PCR/inclusion in study and until 90 days. Both dates are included.
2. Patient related outcomes

a. Quality of life measured by the European Quality of Life (EuroQol) measurement of health-related quality of life[46] (version of the European Quality of Life-5 Domain (EQ-5D-5L) Interviewer Administration and EQ-5D-5L proxy 2) and by the Overall Quality of Life Depression List (OQoL-DL)[47]

b. Functional status is measured by the Functional Recovery Score (FRS)[48]

Mortality is chosen as the primary outcome and quality of life and functional capacity as a secondary outcome by consensus in the project steering group. Overall QoL is assessed by the OQoL-DL because of its acceptable level of agreement and reliability in frail older persons with moderate cognitive impairment [47]. The OQoL-DL is supplemented by the EQ-5D,[46,49] which is intended to complement other QoL measures and to facilitate collection of a common data set for reference purposes. It is a generic health-related QoL instrument that has been used to describe population health and health outcomes in clinical trials. Five dimensions are mapped: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The version EQ-5D-5L paper interviewer administration and the EQ-5D-5L proxy version will be performed.

The FRS[48] consists of a refined Katz Index[50] and Lawton Scale[51] and includes mobility assessment (Activities of Daily Living (ADL)+ I-ADL), resulting in an instrument that has five (ADL) and six (I-ADL) options for assessing each item. ADL and mobility comprise 77% of the FRS score; I-ADL, 23%. It has predictive and discriminant validity and is responsive to changes.

Data collection, management and analysis

Baseline variables

The following descriptive variables are registered at baseline:

- Demographic data
- Charlson Comorbidity Index[52]
- Frailty level measured by record-based MPI[53]
- CDI diagnosis, site (primary healthcare, outpatient, inpatient)
- CD toxin profile
- CDI definition[54] Healthcare facility-onset, Community-onset, Healthcare facility-associated, Community-associated
- Faecal chart consistency and frequency will be registered for the intervention group
- Habitation status (Living in own home, Nursing home resident)

- Use of antibiotics (other than CDI related antibiotics) at time of positive PCR test for CDI and within one month before date of positive PCR test for CDI
- Use of proton-pump inhibitors at time of positive PCR test for CDI

Measuring QoL and functional capacity at baseline is not feasible because this could possibly affect the standard care group, which is intended to receive no interaction from the geriatric team until the follow-up date.

Data collection

Data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University to secure data security and storage.[41] The database includes range checks for data values. To avoid double data entries, the national identification number-based Civil Registration Register is checked before data entrance. Baseline characteristics are obtained from the EMRs only, and will be collected before randomisation. Primary outcome and quality-related outcome measures will be obtained from the EMRs. The project manager will collect all data from the EMRs. Collection of data on primary outcome will also be checked by a specialist in either geriatric or gastrointestinal diseases to avoid errors. The project manager has access to all EMRs in the CDR.

FRS, OQoL-DL and EQ-5D-5L tests will be performed on both groups by a trained project assistant during planned home visits. Additionally, the FRS will be performed retrospectively on both groups, including recording of functional capacity before CDI at the date of positive CDI PCR test.

Sample size calculation

Sample size calculation: 90-day mortality rate in CDI patients aged ≥ 70 years is 32% according to our cohort study (unpublished data) and another European study.[1] Hence, the 90-day mortality rate for the standard care group was set to 32%. The assumed effect of the intervention was calculated on the basis of the 12% 90-day mortality rate among CDI patients receiving FMT[55] and the 20% mortality rate in geriatric patients receiving CGA.[29] However, in Hocquart' s study,[55] a sixth of the patients are below the age of 70 years. Therefore, the 12% mortality rate might be underestimated. Furthermore, Hansen et al.[29] performed CGA only on moderate to severely frail patients. As we will include patients also with mild frailty, the 90-day mortality rate of 20% might be overestimated. Assuming an additive effect of CGA on FMT interventions, a mortality rate between 12% and 20% is considered realistic, with an estimated rate of 15%. Consequently, the expected mortality difference would be 17% (32%-15%). With a power of 80% and an alpha of 5%, 108 patients are needed in each group;

which is the final number of patients, not taking into account drop-outs. We have predetermined an interim analysis to be conducted after enrolling 108 randomised patients, with predefined stopping rules based on the Haybittle-Peto limits, which require statistical significance levels below 0.001.[56] The analysis will be performed by a blinded external reviewer.

Statistical analysis plan

The statistical analysis will be performed by the project manager and members of the team when the last patient has completed the follow-up period and all data have been entered into REDCap. Patients' baseline characteristics will be compared using chi-square test or Fisher's exact tests for categorical variables and Wilcoxon Rank Sum test or Student's t-test for continuous variables, as appropriate.

Primary outcome analyses of 90-day mortality will be performed according to the intention-to-treat and per-protocol principles. The per-protocol analysis will include all patients who have undergone their first visit, which includes assessment of the multidimensional prognostic index and completion of the CDI checklist. The binary primary outcome will be tested for significance in a binary regression model and presented as an odds ratio (OR) estimate with 95% confidence intervals (CIs). Estimates will be provided with 95% exact confidence intervals and medians with interquartile ranges or ranges, as applicable. Precision will be performed by adjusting for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no). Furthermore, subgroup analysis of the two stratified groups (age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no)) will be performed according to binary primary outcome and presented as OR. The OR for patients diagnosed during hospital admission will be compared with the OR of patients diagnosed outside hospital. Likewise, the RR of patients aged ≥ 85 years will be compared with the OR of patients < 85 years. We will conduct an as-treated-analysis of the primary outcome, comparing patients receiving FMT within 90 days from positive PCR test for CDI compared with those who did not. The primary outcome will be tested for significance using chi-square test, and OR will be estimated using the binary regression model.

Secondary outcomes: Recurrent CDI and readmission will be tested for statistical significance in a binary regression model. Functional status (estimated by FRS sum score) and overall QoL (estimated by EQ-5D-5L and OQoL-DL sum scores) in the survivors on day 90 will be compared in a linear regression model. Precision will be assessed by adjusting for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no). Likewise, days in hospital within 90 days from positive PCR test for CDI and time-to-treatment with vancomycin and FMT in all randomised patients will be compared in a linear regression model. Precision will be assessed by adjusting

for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no) by performing linear regression analysis. If data are non-normally distributed, data will be logarithm-transformed in the regression model.

There will be no missing data on the primary outcome as these data are available from the EMRs. The number of missing follow-up data on the secondary outcomes will be presented and we will perform a dropout analysis of the data.

All analyses will be performed in Stata version 17 (Stata Corp, Texas, USA).[57] The data will be monitored by an independent external monitoring institution.

Discussion

CDI constitutes a major health risk for frail older patients. The key challenge lies in conducting a personalised early assessment and treatment approach for CDI. For this purpose, clinical evaluations and close monitoring of the patient's condition are necessary.

In designing the CLODIFRAIL study, we prioritise investigating real-life scenarios. While the treatment will be individualised, our intention is to evaluate the intervention using stringent scientific methods. The project is innovative in aiming to improve care and treatment for all older patients with CDI in a real-life setting disregarding their mental or physical capability. This includes evaluating FMT in older frail patients who would otherwise be ineligible or unwilling to participate in randomised controlled trials of microbe-based therapeutics.[58]

There are important limitations to the study. First, the participants will be old and multi-morbid and therefore prone to experience new illnesses during the study period. This might make the intervention less effective. Second, the standard care may include elements of the intervention during the follow-up period (geriatric care and FMT), making it less likely that the intervention will produce any effects. The patients and their relatives are not blinded. Therefore, there is a risk that the research assistant might be unblinded if the participants reveal their group allocation. Nor are the geriatricians participating in the study blinded, and those administering the intervention to patients may exhibit heightened attention their patients' treatment throughout the study period. Finally, it is possible to validate the CDI diagnosis according to clinical symptoms only from data in the EMR as it is not possible to contact the standard care group.

Because our intervention will address the concurrent frailty and clinical issues of each patient, it is important to note that the intervention is not completely standardised. Interventions for geriatric patients are often complex.[59,60] Describing the intervention with sufficient precision as to facilitate replication is a major challenge.[61] The CLODIFRAIL intervention includes several components. We chose the multi-component intervention as we found it unethical and clinically questionable to assess patients for FMT without also giving them a CGA. For that reason, we do not envisage these components to be disaggregated. It therefore makes sense to evaluate the whole package of intervention. Consequently, pinpointing the specific components of the intervention that are most effective may pose a challenge. To address this, we intend to compensate for this challenge by providing a detailed description of the interventions that were implemented.

The geriatric intervention is extensive. Still, if it is effective, we argue that it can be conducted within the existing framework of an outgoing and multidisciplinary geriatric clinic. Alongside performing the study, we will

gain clinical knowledge on challenges in the treatment of older patients with CDI and implement a clinical framework for home treatment with FMT in the ageing and health wards.

Trial status

The approved protocol with amendment number 4 was issued on 28 June 2022. The first patient was included on 01 September 2022. The study has finished recruiting patients at 3 May 2023.

List of abbreviations

CDI, *Clostridioides difficile* infection; CD, *Clostridioides difficile*; CDR, Central Denmark Region; CGA, Comprehensive Geriatric Assessment; EMR, Electronic medical record; EQ-5D-5L, 5-level EQ-5D version; FMT, Faecal microbiota transplantation; FRS, Functional Recovery Score; MPI, Multidimensional Prognostic Index; OQoL-DL, Overall Quality of Life Depression List; SPIRIT, Standard Protocol Items, Recommendations for Interventional Trials

Declarations

Ethical statement

This study is conducted in accordance with the Helsinki Declaration.[62] All patients receive, as a minimum, established standard medical care according to national clinical guidelines.[42] In the study, we compare two established organisational care pathways, i.e., a geriatric team assessment and the standard care of the attending team. The study is conducted as a quality improvement study, embedded in two parallel and fundamentally different routine clinical care pathways. It does not include experimental procedures or collection of biological specimens other than those needed for clinical diagnostics and care planning. No patients will be exposed to any project-related risk or experimental treatments. Participants may decline parts of or the entire plan or treatment at any time. According to Danish law, the study does therefore not fall under the jurisdiction of the Scientific Ethics Committees. The study protocol was approved by the hospital board of directors at all participating hospitals. Approval was obtained 14 March 2021. The study design and its categorisation as a quality improvement study was approved by the Central Denmark Region Committees on Health Research Ethics (j.no. 1-10-72-1-21, 2 February 2021), following review of the complete study protocol. On publication, only anonymised and summarising data will be presented.

Permission to assess and transmit personal data from the EMRs relevant for quality improvement for patients with CDI was obtained from the hospital boards at Aarhus University Hospital and all attending regional hospitals in the CDR. CD tests, conducted at the Department of Clinical Microbiology, AUH, are a part of the EMRs. Thus, the project manager's permission to access the microbiological lists was granted via the same permission. The CDR is the data protection responsible party. Personal data from the EMRs for quality improvement are transferred to the research project at Aarhus University with a legal basis according to law, viz. the Data Protection Act §10. Data will be managed via REDCap according to a cooperation agreement between Aarhus University and the CDR.

By Danish law, consent to routine clinical treatment is given by oral and not written consent. All examinations and treatments in the study are conducted according to routine clinical practice and following obtaining informed oral consent, as required by the Danish Health Authority, under Danish law. In patients who do not have the capacity to provide oral consent, consent is given on behalf of the patient by a next of kin. All patients in the study are contacted by the geriatric team at 12 weeks of follow-up. Oral consent to perform QoL and functional status assessments is obtained and documented in the EMRs.

FMT treatment is provided following informed written consent, using a standardised FMT consent form (Additional file 9). The patient's consent concerns permission for record access and data storage to allow full traceability according to the Tissue Act. Before FMT, the patient is informed orally and through a written information leaflet about the effect and possible side effects.

Consent for publication

No personal information is published.

Availability of data and materials

No study data are available at the protocol stage of the project process. A code book for data entry databases and all other project-related raw material are available upon reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

All funding embedded in routine care was obtained from the department of geriatrics, gastroenterology, and clinical immunology at Aarhus university Hospital. The expenses related to the project that were not provided by routine hospital funding, such as administrative personnel and PhD students, were covered by grants under the clinical professor and chair at the Department of Geriatrics (EMD) and by the project leader (CH) of Centre for Faecal Microbiota Transplantation (CEFTA), supported by the Health Research Foundation of the Central Denmark Region (grant number A2778) and Helsefonden (grant number 22-B-0239). The clinical safety board at CEFTA approved the study protocol following internal peer review. Furthermore, independent professors at the Aarhus University have peer reviewed the study protocol before acceptance of the protocol as a PhD study. The FMT framework is supported by an investment from Innovation Fund Denmark (j.no. 8056-00006B). Christian Lodberg Hvas has received project funding from the Novo Nordisk Foundation (j.no. NNF22OC0074080). The design, management, analysis and reporting of the study are entirely independent of the funding sources.

Authors' contributions

TR*, HV*, MG*, MA*, IB*, JJ*, MR*, JR*, MØ*, RV*, CK*, CS*, SB*, CH* and ED* contributed to the design and planning of the study and have critically revised the manuscript. HV, RV and CS contributed to developing patient material. MG and CS provided statistical expertise. TR is responsible for the daily running of the study, data collection and wrote the manuscript. All authors have approved the final manuscript. The authors follow the ICMJE authorship guidelines. We made no use of professional writers.

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Acknowledgements

The authors thank all participating centres and patient representatives.

Figures and Tables legends

Figure 1. CONSORT diagram. Patient flow.

Abbreviations: CDI: *Clostridioides difficile* infection; PCR: Polymerase chain reaction

Figure 2. Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) flow diagram figure

* All examinations and treatments in the intervention group are conducted according to routine clinical practice and following obtaining informed oral consent, as required by the Danish Health Authority, in accordance with Danish law.

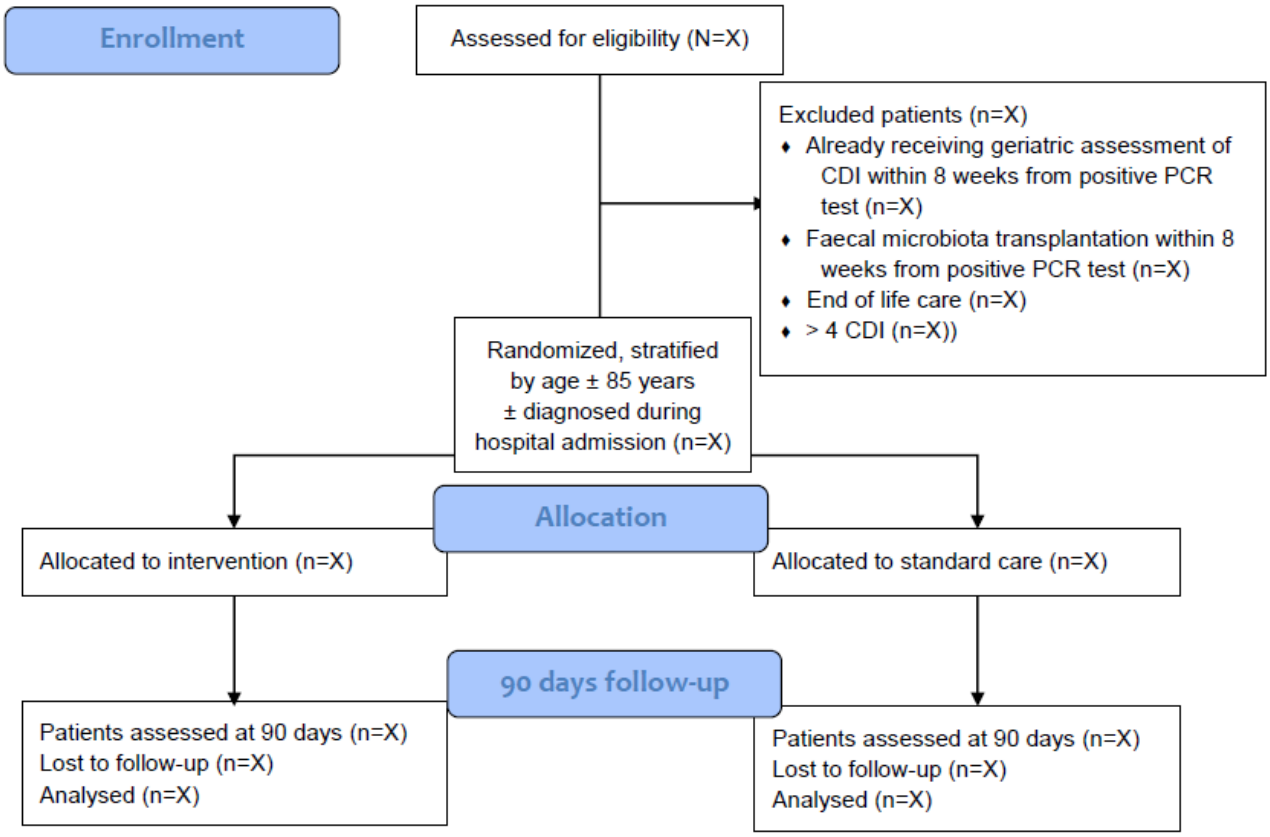
**All patients in the intervention and standard care group are contacted by the geriatric team at 90 days of follow-up, and oral consent to perform overall quality of life and functional status assessment is given and registered in the electronic medical journal.

Figure 3. CLODIFRAIL intervention, flowchart.

Abbreviations: PCR: Polymerase chain reaction; CGA: Comprehensive geriatric assessment; MPI: Multidimensional Prognostic Index; FMT: Faecal microbiota transplantation

Figure 4. *Clostridioides difficile* infection, geriatric checklist

Figure 1



Abbreviations: CDI: Clostridioides difficile infection; PCR: Polymerase Chain Reaction

Figure 2

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT**	***-t_1***	**0**	***Intervention***	***90 days***	***90 days***
ENROLMENT:					
Eligibility screen	X				
Informed consent intervention		X		X	
Informed consent control*				X	
Non blinded randomisation	X				
Allocation		X			
INTERVENTIONS:					
Intervention group (geriatric assessment)		X	X		
Standard care group		X			
ASSESSMENTS:					
Electronic medical records:					
Patient characteristics		X			
90 day survival				X	X
Time to treatment with FMT (FMT date)				X	X
Time to treatment with vancomycin (date of start treatment with vancomycin)				X	X
CDI recurrence				X	X

Readmission				X		X
Days in hospital				X		X
Trained research assistant						
Overall Quality of Life Depression List (OQoL-DL)				X		X
Overall Quality of Life EuroQol measurement (version EQ-5D-5L Interviewer Administration				X		X
Overall Quality of Life EuroQol measurement (version EQ-5D-5L proxy 2)				X		X
Functional status: Functional recovery score (FRS)				X		X

Figure 3

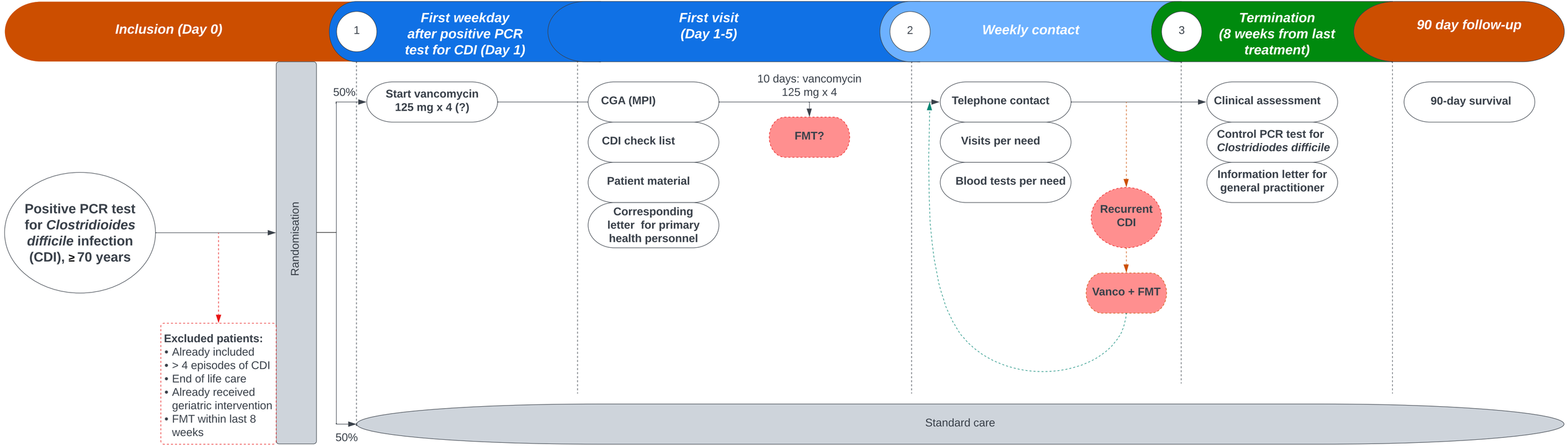

Inclusion (Day 0)
1
First weekday after positive PCR test for CDI (Day 1)
First visit (Day 1-5)
2
Weekly contact
3
Termination (8 weeks from last treatment)
90 day follow-up
Positive PCR test for Clostridioides difficile infection (CDI), ≥ 70 years
Excluded patients:
• Already included
• > 4 episodes of CDI
• End of life care
• Already received geriatric intervention
• FMT within last 8 weeks
Randomisation
50%
Start vancomycin 125 mg x 4 (?)
CGA (MPI)
CDI check list
Patient material
Corresponding letter for primary health personnel
10 days: vancomycin 125 mg x 4
FMT?
Telephone contact
Visits per need
Blood tests per need
Recurrent CDI
Vanco + FMT
Clinical assessment
Control PCR test for Clostridiodes difficile
Information letter for general practitioner
90-day survival
50%
Standard care

Figure 4

Patient label_____

Clostridioides difficile infection – check list for older patients

Patients with Clostridioides difficile infection (CDI) during hospital admission or at home.

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.		
	Done	Not relevant
1) CDI treatment care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin peroral or bactocin oral suspension (probe) 125 mg x 4. Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT).	☐	☐
Perform the Multidimensional Prognostic Index	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning.	☐	☐
Deliver information material to the patient	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent catheterization etc.)	☐	☐
Laxative: discontinue	☐	☐
Proton pump inhibitor: discontinue if possible	☐	☐
Diuretics: consider reduction during active diarrhoea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
Consider other reasons for diarrhoea! (e.g. inflammatory bowel disease, cancer, microscopic colitis)	☐	☐
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT or completed vancomycin treatment.		

All activities are registered in the electronic medical journal.

References

1. Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with Clostridium difficile infection: a multicenter cohort study. *Clin Infect Dis* 2013; **56**(8): 1108-16.
2. Khanna S, Lett J, Lattimer C, Tillotson G. Transitions of care in Clostridioides difficile infection: a need of the hour. *Therap Adv Gastroenterol* 2022; **15**: 17562848221078684.
3. Bauer MP, Notermans DW, van Benthem BH, et al. Clostridium difficile infection in Europe: a hospital-based survey. *Lancet* 2011; **377**(9759): 63-73.
4. McGowan AP, Lalayiannis LC, Sarma JB, Marshall B, Martin KE, Welfare MR. Thirty-day mortality of Clostridium difficile infection in a UK National Health Service Foundation Trust between 2002 and 2008. *J Hosp Infect* 2011; **77**(1): 11-5.
5. Cober ED, Malani PN. Clostridium difficile infection in the "oldest" old: clinical outcomes in patients aged 80 and older. *J Am Geriatr Soc* 2009; **57**(4): 659-62.
6. Caupenne A, Ingrand P, Ingrand I, et al. Acute Clostridioides difficile Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality. *J Am Med Dir Assoc* 2020; **21**(1): 110-4.
7. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013; **381**(9868): 752-62.
8. Cunha AIL, Veronese N, de Melo Borges S, Ricci NA. Frailty as a predictor of adverse outcomes in hospitalized older adults: A systematic review and meta-analysis. *Ageing Res Rev* 2019; **56**: 100960.
9. Govoni B, Zurlo A, De Giorgio R, Cultrera R, Volpato S. Clostridium difficile infection in a geriatric care unit: Clinical characteristics and prognosis. *JGG* 2021; **69**(1): 1-5.
10. Olsen MA, Stwalley D, Demont C, Dubberke ER. Increasing Age Has Limited Impact on Risk of Clostridium difficile Infection in an elderly population. *Open Forum Infect Dis* 2018; **5**(7): ofy160.
11. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc* 2007; **55**(5): 780-91.
12. Cooper GS, Shlaes DM, Salata RA. Intraabdominal infection: differences in presentation and outcome between younger patients and the elderly. *Clin Infect Dis* 1994; **19**(1): 146-8.
13. Fried LP, Storer DJ, King DE, Lodder F. Diagnosis of illness presentation in the elderly. *J Am Geriatr Soc* 1991; **39**(2): 117-23.
14. Potts FEt, Vukov LF. Utility of fever and leukocytosis in acute surgical abdomens in octogenarians and beyond. *J Gerontol A Biol Sci Med Sci* 1999; **54**(2): M55-8.
15. Leibovici-Weissman Y, Atamna A, Schlesinger A, Eliakim-Raz N, Bishara J, Yahav D. Risk factors for short- and long-term mortality in very old patients with Clostridium difficile infection: A retrospective study. *Geriatr Gerontol Int* 2017; **17**(10): 1378-83.
16. Lauda-Maillen M, Liuu E, Catroux M, et al. Treatment compliance with European guidelines and prognosis of Clostridium difficile infection according to age. *Med Mal Infect* 2019; **49**(3): 173-9.
17. Parker SG, McCue P, Phelps K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* 2018; **47**(1): 149-55.
18. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017; **9**: Cd006211.
19. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008; **11**(1): 151-61.
20. Volpato S, Bazzano S, Fontana A, Ferrucci L, Pilotto A. Multidimensional Prognostic Index predicts mortality and length of stay during hospitalization in the older patients: a multicenter prospective study. *J Gerontol A Biol Sci Med Sci* 2015; **70**(3): 325-31.
21. Ellis G, Whitehead MA, Robinson D, O'Neill D, Langhorne P. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. *Bmj* 2011; **343**: d6553.
22. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993; **342**(8878): 1032-6.
23. Baztán JJ, Suárez-García FM, López-Arrieta J, Rodríguez-Mañas L, Rodríguez-Artalejo F. Effectiveness of acute geriatric units on functional decline, living at home, and case fatality among older patients admitted to hospital for acute medical disorders: meta-analysis. *Bmj* 2009; **338**: b50.
24. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. *J Am Geriatr Soc* 1991; **39**(9 Pt 2): 8S-16S; discussion 7S-8S.
25. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017; **9**(9): Cd006211.
26. Veronese N, Custodero C, Demurtas J, et al. Comprehensive geriatric assessment in older people: an umbrella review of health outcomes. *Age Ageing* 2022; **51**(5).

27. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up visits to nursing home residents reduce the number of readmissions: a quasi-randomised controlled trial. *European Geriatric Medicine* 2018; **9**(3): 329-37.
28. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces readmissions – A quasi-randomised controlled trial. *Eur Geriatr Med* 2016; **7**(5): 443-8.
29. Hansen TK, Pedersen LH, Shahla S, Damsgaard EM, Bruun JM, Gregersen M. Effects of a new early municipality-based versus a geriatric team-based transitional care intervention on readmission and mortality among frail older patients - a randomised controlled trial. *Arch Gerontol Geriatr* 2021; **97**: 104511.
30. Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces mortality among patients living in their own home. A randomised controlled trial. *Eur Geriatr Med* 2017; **8**(4): 330-6.
31. Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7**(12): 1083-91.
32. Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: An updated systematic review and meta-analysis. *EClinicalMedicine* 2020; **29-30**:100642.
33. Rode AA, Chehri M, Krogsgaard LR, et al. Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent Clostridioides difficile infections. *Aliment Pharmacol and Ther* 2021; **53**(9): 999-1009.
34. Girotra M, Garg S, Anand R, Song Y, Dutta SK. Fecal microbiota transplantation for recurrent Clostridium difficile infection in the elderly: long-term outcomes and microbiota changes. *Dig Dis Sci* 2016; **61**(10): 3007-15.
35. Agrawal M, Aroniadis OC, Brandt LJ, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated clostridium difficile infection in 146 elderly individuals. *J Clin Gastroenterol* 2016; **50**(5): 403-7.
36. Friedman-Korn T, Livovsky DM, Maharshak N, et al. Fecal transplantation for treatment of Clostridium difficile infection in elderly and debilitated patients. *Dig Dis Sci* 2018; **63**(1): 198-203.
37. Nivet C, Duhalde V, Beaurain M, Delobel P, Quelven I, Alric L. Fecal microbiota transplantation for refractory Clostridioides difficile infection is effective and well tolerated even in very old subjects: a real-life study. *J Nutr Health Aging* 2022.
38. Dahl Jørgensen SM, Mørck Rubak TM, Damsgaard EM, Dahlerup JF, Hvas CL. Faecal microbiota transplantation as a home therapy to frail older people. *Age Ageing* 2020; **49**(6): 1093-6.
39. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *Bmj* 2013; **346**: e7586.
40. Jorgensen SMD, Hansen MM, Erikstrup C, Dahlerup JF, Hvas CL. Faecal microbiota transplantation: establishment of a clinical application framework. *Eur J Gastroenterol Hepatol* 2017; **29**(11): e36-e45.
41. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)- a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**(2): 377-81.
42. Baunwall SMD, Dahlerup JF, Engberg JH, et al. Danish national guideline for the treatment of Clostridioides difficile infection and use of faecal microbiota transplantation (FMT). *Scand J Gastroenterol* 2021; **56**(9): 1056-77.
43. DSGH DsfGoH. Clostridioides Difficile infektion og fækal mikrobiota transplantation (FMT). 12/11/2020 2020. https://www.dsgh.dk/index.php/andre/c-diff-fmt (accessed 23/11/2020.
44. Keller JJ, Ooijevaar RE, Hvas CL, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. *United European Gastroenterol J* 2021; **9**(2): 229-47.
45. Heggestad T, Lilleeng SE. Measuring readmissions: focus on the time factor. *Int J Qual Health Care* 2003; **15**(2): 147-54.
46. EuroQol -a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**(3): 199-208.
47. Gregersen M, Jordansen MM, Gerritsen DL. Overall Quality of Life (OQoL) questionnaire in frail elderly: a study of reproducibility and responsiveness of the Depression List (DL). *Arch Gerontol Geriatr* 2015; **60**(1): 22-7.
48. Zuckerman JD, Koval KJ, Aharonoff GB, Skovron ML. A functional recovery score for elderly hip fracture patients: II. Validity and reliability. *J Orthop Trauma* 2000; **14**(1): 26-30.
49. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy* 2021; **19**(4): 579-91.
50. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; **10**(1): 20-30.

627 51. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily
628 living. *Gerontologist* 1969; **9**(3): 179-86.
629 52. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in
630 longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**(5): 373-83.
631 53. Hansen TK, Damsgaard EM, Shahla S, Bruun JM, Gregersen M. A reliable and record-based frailty
632 assessment method for older medical inpatients. *Eur Geriatr Med* 2020; **11**(5): 803-12.
633 54. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection
634 in adults and children: 2017 update by the Infectious Diseases Dociety of America (IDSA) and Society for
635 Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; **66**(7): 987-94.
636 55. Hocquart M, Lagier JC, Cassir N, et al. Early Fecal Microbiota Transplantation Improves Survival in Severe
637 Clostridium difficile Infections. *Clin Infect Dis* 2018; **66**(5): 645-50.
638 56. Pocock SJ. When to stop a clinical trial. *Bmj* 1992; **305**(6847): 235-40.
639 57. StataCorp. 2021. Stata Statistical Software: Release 17. College Station TSL. Stata Statistical Software:
640 Release 17. College Station, TX: StataCorp LLC; 2021.
641 58. Kelly CR, Fischer M, Grinspan A, Allegretti JR. Patients eligible for trials of microbe-based therapeutics do
642 not represent the population with recurrent Clostridioides difficile infection. *Clin Gastroenterol Hepatol* 2020;
643 **18**(5): 1099-101.
644 59. Saltvedt I, Mo ES, Fayers P, Kaasa S, Sletvold O. Reduced mortality in treating acutely sick, frail older
645 patients in a geriatric evaluation and management unit. A prospective randomized trial. *J Am Geriatr Soc* 2002;
646 **50**(5): 792-8.
647 60. Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. *Br Med Bull* 2004; **71**:
648 45-59.
649 61. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex
650 interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013; **50**(5): 587-92.
651 62. World Medical Association. WMA Declaration of Helsinki - ethical principles for medical research
652 involving human subjects. 2022. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-
653 principles-for-medical-research-involving-human-subjects/2024).

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Additional Files

Manuscript title

***Clostridioides difficile* infection in frail older patients, quality in treatment and care: the CLODIFrail study protocol for a multicentre randomized controlled**

Table of contents

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 5,7,18
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5-6
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5,7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9, Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

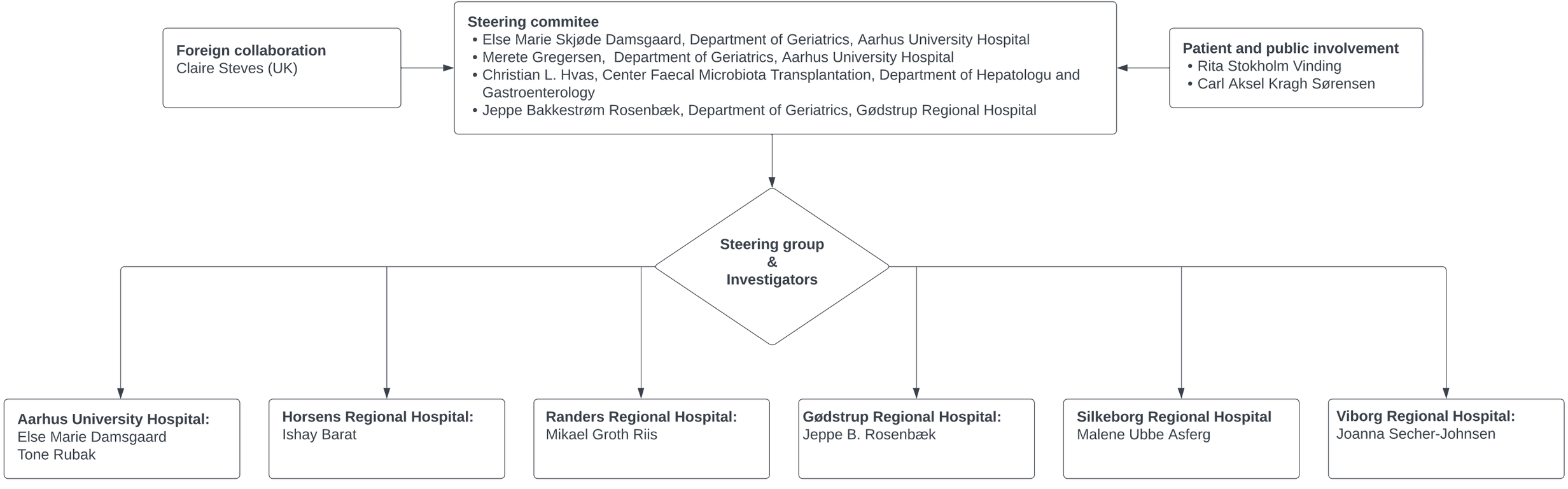
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___17-18_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___17-18_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____18_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____n/a_____ _
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____19_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___17-18_____

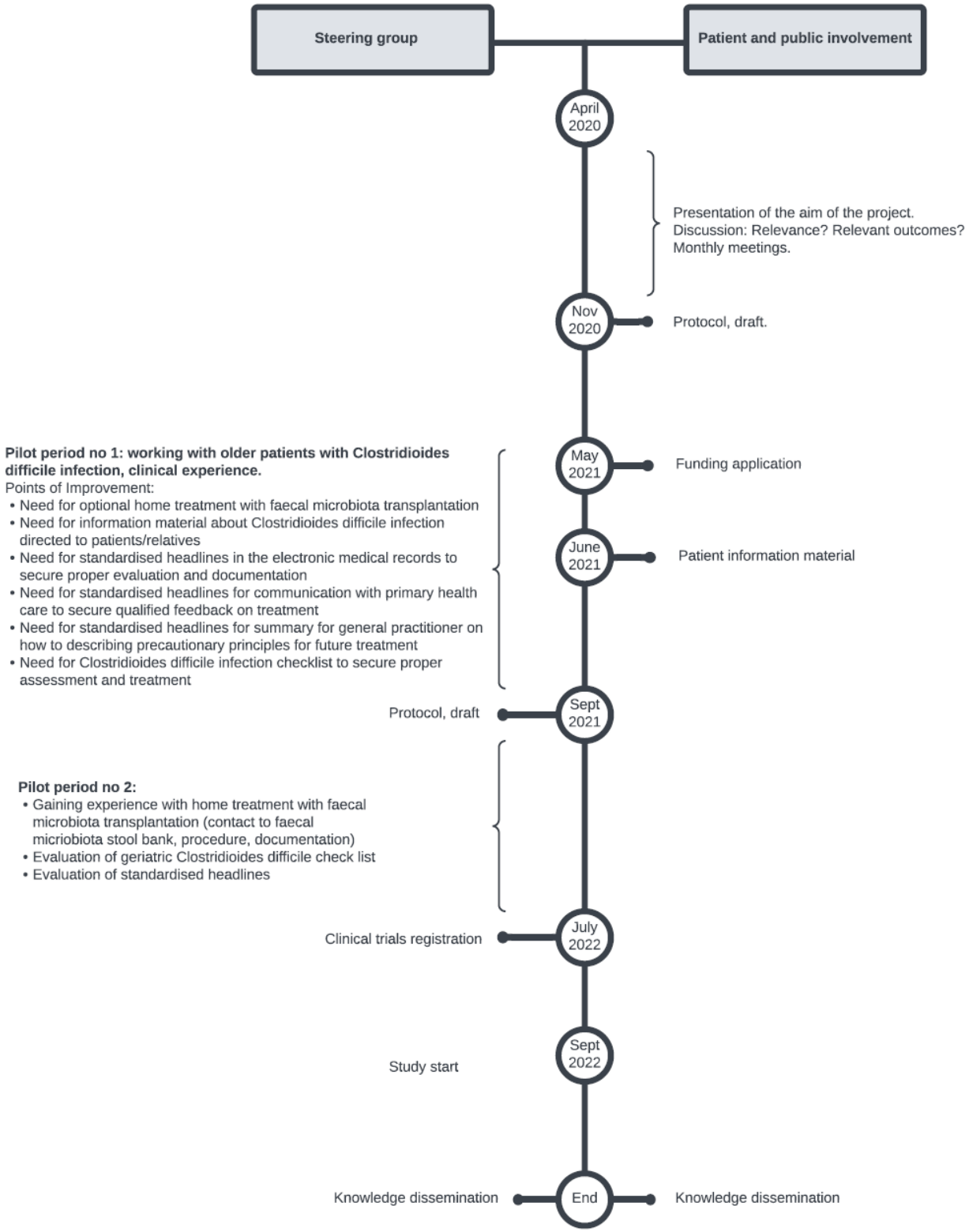
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Additional file 2. Organisation chart for the study



Additional file 3. Study planning, Patient and public involvement



Additional file 4. Standardised headlines for documenting *Clostridioides difficile* infection

Name (code)	Standard headlines
CDI clinical status at first contact (cdi1)	Abdominal pain? Number of stools per day? Bristol type? Faecal incontinence? Loss of appetite? Is the patient candidate for faecal microbiota transplantation according to a geriatric assessment? Plan: The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.* Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of recurrent CDI. Contact information (…)
Correspondence letter for primary health care (cdi2)	The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.* Please send weekly status of the following (correspondence letters/telephone contact): Abdominal pain? yes/no Number of daily stools Bristol type Appetite? Is the patient overall improving, status quo or clinically worsening? Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of increasing diarrhea, abdominal pain or waning general condition. Contact information (…)
Correspondence letter for general practitioner (cdi3)	The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.* Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of increasing diarrhea, abdominal pain or waning general condition. Contact information (…)
Discharge summary for general practitioner (cdi4)	The patient has been affiliated with the Department of Geriatrics because of gastrointestinal infection with *Clostridioides difficile*. The infection has been treated with vancomycin and faecal microbiota transplantation (date). Bowel movement has normalised (?). The patient has an increased risk of recurrent *Clostridioides difficile* infection, especially when treated with antibiotics other than CDI related antibiotics and/or treatment with proton pump inhibitors. In case of unexplained diarrhea, we recommend PCR toxin test for *Clostridioides difficile*. If positive toxin test we recommend to start vancomycin as soon as possible and referral to faecal microbiota transplantation. Feel free to contact us if in doubt. Contact information (…)

Faecal microbiota transplantation procedure (cdi5)	The patient takes (number) of capsules within (minutes). Experiences no discomfort (?) and is observed in 30 minutes without acute complaints (?). Complications to treatment: (?) Clinical contact and follow-up via Department of Geriatrics. The patient and/or relatives and/or healthcare staff are informed of test stool kit which should be delivered as control test 8 weeks from today. Informed to continue to note stool frequency and gastrointestinal symptoms via stool diary. During the day after faecal microbiota transplantation procedure the patient may experience abdominal pain and loose stools. If fever or clinical worsening the patient is informed to contact the Department of Geriatrics (contact information).

Additional file 5. Patient information material regarding *Clostridioides difficile* infection and treatment

Clostridioides Difficile infection and faecal microbiota transplantation

Clostridioides difficile is a bacterium that can cause serious infection of the intestine. In the elderly patient, where other illness has caused weakness, an infection with *Clostridioides difficile* can become serious. The infection tends to come back. What is typically experienced is numerous diarrhoea, nausea, reduced appetite, dehydration, fever, fatigue, weight loss and increased sadness. Some patients lose the will to live because of loss of energy.

We identify the infection using a stool sample supplemented with blood tests. Treatment is started with an antibiotic targeting the *Clostridioides difficile* bacterium following supply of healthy intestinal bacteria.

Faecal microbiota transplantation

Supply of healthy intestinal bacteria is also called faecal microbiota transplantation (FMT). There are no known side effects or late effects of FMT in patients who do not have other bowel disease. The healthy intestinal bacteria come from donors affiliated with the Department of Hepatology and Gastroenterology, Aarhus University Hospital. Strict requirements are placed on the donors equally to the Danish blood donor system. Donors are anonymous.

Faecal microbiota transplantation can take place in three ways:

1. via capsules taken orally over 30-45 minutes
2. via tube to the intestine
3. via endoscopy of the intestine (colonoscopy)

Regardless of which type you are offered, there will be clinical follow up contacts via the Department of Geriatrics.

Clinical follow-up contacts

Many older patients with *Clostridioides difficile* infection are severely weakened and need supportive treatment with fluids and nutrition including close monitoring of gastrointestinal symptoms. We offer clinical follow-up by staff trained in diseases in older patients. The purpose is to ensure an evaluation of the gastrointestinal symptoms and early start of treatment if indication for this.

How does the follow-up take place?

The follow-up involves a visit from the outgoing ageing and health ward team when you have received the diagnosis and a weekly telephone contact regarding evaluation of the gastrointestinal related symptoms. If there is a need for further visits, treatment or supportive therapy this will take place in your own home via the outgoing ageing and health ward teams.

What should I be aware of?

In case of changes in bowel movements, abdominal pain, nausea, reduced fluid intake/nutrition you/your relatives should contact Department of Geriatrics. In need of antibiotics other than the antibiotics used to treat CDI you must contact the Department of Geriatrics regarding treatment strategy because antibiotics can trigger a relapse of the infection. Transmission of the infection occurs with faeces and bacterial spores in the surroundings close to the patient. Handwash followed by hand disinfection must be carried out before leaving the patient. It important to use water/soap or

chloring alcohol. We recommend that health personnel ware plastic aprons and gloves to reduce infection transmission.

What are my responsibilities?

At termination we will ask you to deliver a stool sample to test for *Clostridioides difficile*. We will hand out a faeces kit and ask you to send/deliver it to Department of Microbiology.

Contact information

(…).

Additional file 6. Faecal microbiota transplantation home treatment – check list

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test
1) FMT – treatment planning
Plan date for FMT and hand out patient preparation information material
Patient consent form is to be completed by the patient
Contact Center for Faecal Microbiota transplantation for capsules preparation
2) FMT Procedure
On the day of FMT collect capsules in freezer bag. The capsules must be used within 4 hours from start of thawing.
The patient takes the FMT capsules within one hour with apple juice/ cola. Observe for 30 minutes after last capsule has been taken.
3) FMT documentation
Complete treatment leaflet and send copy to Center for Faecal Microbiota transplantation, auh.cefta@rm.dk
Document FMT procedure in the electronic medical record using standard headline (cdi5)
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT.
4) At termination (8 weeks)
Clinical resolution: number of daily stools + Bristol scale.
Stool PCR test for Clostridioides difficile

All activities are registered in the electronic medical journal.

Additional file 7. Patient information regarding preparation for home-treatment with faecal microbiota transplantation

Dear (patient label) _____

You have been offered and accepted treatment with faecal microbiota transplantation. The treatment consists of 15-25 capsules to be taken with apple juice or cola within one hour.

The treatment is performed by: (name of nurse/doctor) _____

on the (date)_____/_____ time _____

Following preparations are needed:

Fast from (time)_____ on the (date)_____/_____.

You are allowed to take liquids, but not dairy products until (time)_____ on the (date)_____.

Vancomycin is terminated at (time)_____ at (date)_____/_____.

You have received tablet of Metoclopramide 10 mg which you are to take at (time)_____ on the (date) _____/_____.

After the treatment (name of doctor/nurse) _____, we will be there for half an hour. After one hour you are allowed to eat/drink as usual. Some patients find that it takes a few hours before they feel hungry. You may experience loose stools, abdominal pain

within the first day. This is harmless and should resolve spontaneously. In case fever we advise you to contact us.

If you have any questions you are welcome to contact us: (contact info).

Additional file 8. Stool diary

Please write down daily.
We will contact you and ask to your gastrointestinal symptoms to take stock of your clinical status.

Date	Abdominal pain (yes/no)	Number of stools per day	Bristol type	Loss of appetite? (yes/no)	Do you feel better? (yes/no)

Additional file 9. Faecal microbiota transplantation consent form

Information on fecal microbiota transplantation (FMT)
Center for Fecal Microbiota Transplantation (CEFTA)

Consent to quality assurance and research
You have agreed with your doctor to receive treatment with fecal microbiota transplantation (FMT). In order to investigate the quality and effects of the treatment, we need your consent. The aim is to gain a better understanding of how FMT works and to investigate the long-term consequences of treatment. The purpose is fulfilled through quality assurance and research. We ask for your consent to three things:

Consent to disclose health information
Information about your course is passed on to a database at Aarhus University. Only the researchers associated with the treatment have access to the database. All data is kept confidential and complies with the Personal Data Act and the European Personal Data Directive.

Consent to lookup in your patient record
After your treatment has ended, we would like to look up in your patient record to investigate any long-term consequences of the treatment. If we become aware that the treatment may pose a risk to you, we will contact you.

Consent for storage of samples for future research
There is still a lot we do not know about FMT. We therefore perform quality assurance and research to learn. All research projects are approved by the local Ethics Committee.

About the treatment
You will receive separate written patient instructions about the treatment. The written leaflet contains information on how the treatment takes place and the expected effect and any side effects.

About donor
Healthy faecal donors are found among blood donors. In order to be able to donate feces, a donor must undergo a study program
- Personal inquiry about medical history, previous or hereditary diseases, medication consumption
Questionnaire on risk of transmission of contagious diseases: travel abroad, tattoos, risk of infection with sexually transmitted diseases, etc.
- Blood tests with examination for infectious diseases and chronic diseases
- Stool sample with examination for infectious diseases and antibiotic resistance
A physician reviews all test results, and only approved donors provide stool for treatment.

Responsible for the treatment
Chief physician Christian Lodberg Hvas, Department of Hepatology and Gastroenterology, Aarhus University Hospital.
www.levermavetarm.auh.dk

Consent for fecal microbiota transplantation (FMT)
Center for Fecal Microbiota Transplantation (CEFTA)

Name and cpr
1. Consent to transfer gut-related health information to a database
2. Consent to follow-up by posting in your patient record at a later date
3. Consent for storage of samples for future research

"I hereby confirm that, having received the above written information, I know sufficiently about the purpose, advantages and disadvantages of giving this consent.
I know that participation is voluntary and that I can withdraw my commitment to participate at any time, after which my data will be deleted without affecting my current or future treatment options."
You have the right to a reflection period before you sign the consent form
Information about your health conditions is subject to a duty of confidentiality and will only be available to doctors and nurses at the Department of Hepatology and Gastroenterology and the Blood Bank at Aarhus University Hospital. If data are passed on, it only happens in anonymised form.

_____ _____
Date Signature (patient)

Name of responsible doctor:

_____
Name (responsible doctor)

_____ _____
Date Signature (responsible doctor)

PAPER III

Early geriatric assessment and management in older patients with *Clostridioides difficile* infection in Denmark (CLODIfrail): a randomised trial

Tone Rubak, Simon Mark Dahl Baunwall, Merete Gregersen, Sara Ellegaard Paaske, Malene Asferg, Ishay Barat, Joanna Secher-Johnsen, Mikael Groth Riis, Jeppe Bakkestrøm Rosenbæk, Troels Kjærskov Hansen, Marianne Ørum, Claire J Steves, Hanne Veilbæk, Christian Lodberg Hvas, Else Marie Skjøde Damsgaard

Summary

Background ***Clostridioides difficile*** **infection causes diarrhoea and colitis. Older patients with *C difficile* infection are often frail and have comorbidities, leading to high mortality rates. The frailty burden in older people might restrict access to treatments, such as *C difficile* infection-specific antibiotics and faecal microbiota transplantation. We aimed to investigate the clinical effects of early comprehensive geriatric assessment (CGA) and frailty evaluation, including home visits and assessment for faecal microbiota transplantation, in older patients with *C difficile* infection.**

Methods **In this randomised, quality improvement trial with a pragmatic design, patients from the Central Denmark Region aged 70 years or older with a positive PCR test for *C difficile* toxin were randomly assigned (1:1) to CGA or standard care, both with equal access to faecal microbiota transplantation. Patients and investigators were unmasked to treatment. The primary outcome was 90-day mortality, and was compared in the study groups according to the intention-to-treat principle. The study is registered with ClinicalTrials.gov, NCT05447533.**

Findings **Between Sept 1, 2022, and May 3, 2023, we randomly assigned 217 patients to CGA (n=109) or standard care (n=108). The median patient age was 78 years (IQR 74–84). 116 (53%) of 217 patients were female and 101 (47%) were male. 16 (15%; 95% CI 9–23) of 109 patients in the CGA group and 22 (20%; 14–29) of 108 patients in the standard-care group died within 90 days (odds ratio 0·66, 95% CI 0·32–1·38. No serious adverse events or deaths related to patient assessment or faecal microbiota transplantation were recorded in either group. Deaths directly attributable to *C difficile* infection were lower in the CGA group (seven [44%] of 16 deaths *vs* 18 [82%] of 22 deaths in the standard-care group; p=0·020).**

Interpretation **Older patients who received CGA had a 90-day mortality rate similar to that of patients who received standard care, but with fewer deaths directly attributable to *C difficile* infection.**

Funding **Innovation Fund Denmark, Novo Nordisk Foundation, and Helsefonden.**

Introduction

Clostridioides difficile infection poses a substantial health threat to older patients, with 90-day mortality rates of 23–36%.[1–3] *C difficile* infection is characterised by diarrhoea and colitis caused by toxin-producing *C difficile*. In patients aged 70 years or older, the effectiveness of first-line treatments, such as vancomycin or fidaxomicin, is limited, illustrated by high recurrence rates.[4] Frailty is a hallmark characteristic of older patients with *C difficile* infection and is associated with high mortality rates.[2] Managing *C difficile* infection in older patients is complicated by physical decline due to multimorbidity,[2] leading to increased all-cause mortality.[1] Although treatment strategies rely on using anti-*C difficile* antibiotics, any underlying deterioration in chronic conditions might go unaddressed.[5,6] Effective *C difficile* infection management necessitates addressing both the infection and the associated frailty. Multimorbidity and frailty might complicate the assessment of *C difficile* infection severity and thus affect timing of appropriate treatment.

Faecal microbiota transplantation, used in conjunction with anti-*C difficile* antibiotics, is a promising treatment for *C difficile* infection that confers sustained resolution in up to 91% of patients and potentially reduces mortality rates.[7–9] Logistical requirements for hospital attendance might hinder optimal use for older patients with frailty who are unwilling or unable to tolerate transportation and associated waiting times. Therefore, a personalised, home-based treatment approach that facilitates home application of faecal microbiota transplantation is necessitated.

Comprehensive geriatric assessment (CGA) is the gold standard for multidisciplinary assessment and care planning in older patients with multimorbidity.[10] CGA-based tailored treatment and care planning effectively decreases both readmission and mortality rates.[11–13] The CGA process identifies medical, nutritional, psychosocial, and functional

Lancet Healthy Longev 2024

Published Online https://doi.org/10.1016/j.lanhl.2024.100648

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Research in context

Evidence before this study

Older patients with *Clostridioides difficile* infection tend to be frail and have increased mortality risk. Improved care planning for older patients with *C difficile* infection might increase patient survival. Faecal microbiota transplantation can provide sustained resolution of *C difficile* infection but is often withheld from older patients. We searched PubMed, Embase, and Cochrane from database inception until June 28, 2022, with no language restrictions, using the search terms "*Clostridioides/Clostridium difficile* infection" and "Geriatric assessment" and "Home-treatment/Hospital at Home" and "Faecal/Fecal microbiota transplantation". We found no clinical trials on the topic.

Added value of this study

To our knowledge, this randomised quality improvement trial is the first to investigate the effects of early comprehensive geriatric assessment (CGA) in older patients with *C difficile* infection. Geriatric care included assessment for faecal microbiota transplantation and possible home treatment with faecal microbiota transplantation. The study design allowed broad inclusion criteria to reflect real-world patients with *C difficile* infection. Mortality was lower in the CGA group compared with the standard-care group, but the difference was not statistically significant. In the CGA group, the number of deaths attributed to *C difficile* infection was lower, and we observed significantly decreased *C difficile* infection recurrence rates, readmission to hospital, and days in hospital compared with the standard-care group. These findings underscore the efficacy of well-planned treatment strategies and care continuity. Notably, faecal microbiota transplantation in standard care for *C difficile* infection was increased compared with an earlier cohort of older patients with *C difficile* infection.

Implications of all the available evidence

Our study highlights the importance of early assessment and treatment care planning incorporating evaluation for faecal microbiota transplantation. Access to such specialised treatment could improve clinical outcomes for older patients.

capabilities of an older adult, enabling formulation of a personalised treatment plan with tailored follow-up.[14] We previously showed the feasibility of integrating CGA in the management of frailty and making early decisions for home-based faecal microbiota transplantation in older patients with frailty with *C difficile* infection,[8,15] but the effects of this approach on critical parameters, such as mortality, *C difficile* infection recurrence, and days in hospital, remain unknown. We aimed to investigate the effect of personalised CGA and geriatric management, including assessment for faecal microbiota transplantation, either in hospital or at home, in older patients with *C difficile* infection, compared with the current standard of care.

Methods

Study design and participants

CLODIfrail was a multicentre, randomised, quality improvement study, designed as a pragmatic randomised trial, to compare two organisational care pathways, with 90-day follow-up. The study followed CONSORT guidelines. The protocol is available in the appendix (pp 1–24) and online.

See Online for appendix

For the **protocol** see https://cefta.au.dk/about-fmt

All patients in the Central Denmark Region aged 70 years or older and with a positive *C difficile* toxin PCR test during the study period were eligible. Eligible patients were consecutively identified and included from a complete list of all patients with a positive *C difficile* test in primary and secondary health care. The complete list was maintained at the Department of Clinical Microbiology at Aarhus University Hospital (Aarhus, Denmark) and sent to the project manager every working day. The study was conducted at the Department of Geriatrics, Aarhus University Hospital (Aarhus, Denmark).

Exclusion criteria included: patients already receiving geriatric assessment; those who had received faecal microbiota transplantation within 8 weeks; those with a history of five or more *C difficile* infections; and those who had initiated end-of-life care before positive PCR test. End-of-life care was defined as a life expectancy of less than few days or weeks based on information from electronic medical records at the time of inclusion. Data on sex were collected via civil registration number, which is sex-specific.

The Central Denmark Region has 1·32 million inhabitants, encompassing Aarhus University Hospital and five affiliated regional hospitals (Horsens, Randers, Silkeborg, Viborg, and Gødstrup). The Danish health-care system is tax-financed and available to all Danish residents on a free and equal basis. Geriatric assessment and management are done in hospital and at home via geriatric departments. Microbiology diagnostics is centralised to one department of clinical microbiology in Aarhus University Hospital that serves both the primary sector and all public hospitals in the region. Faecal microbiota transplantation is an established routine treatment throughout the region, recommended to prevent antibiotic treatment failure or recurrent *C difficile* infection.

All treatments were done in accordance with the Declaration of Helsinki[16] and all patients had access to standard medical care as per national guidelines.[5] The trial had a pragmatic design. The study design and its categorisation as a quality improvement study was approved by the Central Denmark Region Committees on Health Research Ethics (1-10-72-1-21; Feb 2, 2021). By Danish law, oral consent suffices for routine clinical treatment with a designated next of kin consenting for those with impaired mental capacity. All patients who received faecal microbiota transplantation, regardless of their allocation, gave written informed consent

to the transfer of intestinal health-related information from their medical records to the stool bank at Aarhus University Hospital (appendix pp 59–60). The trial posed no project-related risks and did not include experimental treatments or biological sample collection. Participants could refuse treatment as per Danish Health Authority rules. The study protocol and medical record access were approved by the hospital board of directors at all participating hospitals and on March 14, 2021.

The study is registered with ClinicalTrials.gov, NCT05447533.

Randomisation and masking

All patients consecutively diagnosed with *C difficile* infection were identified from a list of patients with positive *C difficile* tests, provided by the Department of Clinical Microbiology every working day. Those who fulfilled inclusion criteria were randomly allocated (1:1) to either CGA or standard care. Randomisation allocation was done electronically in REDCap[17] on the weekday of each patient's appearance on the list. Allocation lists were generated for treatment groups at a 1:1 ratio, stratified by age 85 years or older (yes *vs* no) and hospitalisation at *C difficile* infection diagnosis (yes *vs* no). The randomisation list was concealed from all study personnel and kept with restricted access. Masking of clinicians was unfeasible due to documentation in the electronic medical records revealing the randomisation allocation.

Procedures

The CGA group received CGA organisational care provided by geriatric teams integrated into the daily routine clinic. CGA included systematic assessment of a patient's medical condition and any *C difficile* infection-related symptoms, including early assessment of indication for faecal microbiota transplantation. CGA and its associated interventions comprised a multidimensional approach, facilitated by geriatric teams that included a physician and a nurse with access to consultation with physiotherapists and occupational therapists. These teams operated either within the allocated ward (internal medicine other than geriatrics or surgical wards) or in the patient's home. CGA encompassed the following components: frailty assessment using the bedside Multidimensional Prognostic Index (MPI);[18] the geriatric *C difficile* infection checklist (appendix p 54); faecal microbiota transplantation if indicated, delivered by the geriatric team; and systematic evaluation at least once weekly with additional clinical evaluation of vital signs and bowel symptoms, after a minimum of 8 weeks or until resolution (appendix pp 55–56).

In initial patient management, a structured evaluation was done using the MPI, which is based on the elements defining a CGA.[18] This evaluation included assessment of comorbidity, socio-housing condition, medication use, functional status, cognition, pressure ulcer score, and nutritional risk. The MPI categorises patients into three groups: non-frail (MPI score 0·0–0·33; MPI-1), moderately frail (MPI score 0·34–0·66; MPI-2), and severely frail (MPI score 0·67–1·0; MPI-3).[18] An individualised treatment plan was devised according to clinical issues identified via the MPI. Record-based MPI was done only in patients diagnosed with *C difficile* infection during hospital admission. Patients diagnosed in primary health care or as outpatients were registered with an unknown MPI because of missing information from electronic medical records.

The geriatric *C difficile* infection checklist (appendix p 54) included a geriatric evaluation of indication for faecal microbiota transplantation, assessment of hydration and nutritional status, and revision of the medication list. All patients with *C difficile* infection initiated vancomycin 125 mg orally four times daily. Collection of targeted *C difficile* infection information for primary health care was ensured through standardised letters (appendix p 58).

Indication for faecal microbiota transplantation was based on clinical assessment by a geriatrician, qualified by the issues identified in the MPI, frailty level, and *C difficile* infection severity as defined by the Danish national guidelines.[5] Faecal microbiota transplantation was considered if the patient had severe, recurrent, or refractory *C difficile* infection, if the patient was at high risk, if the patient was defined as frailty grade MPI-2 (moderate) or MPI-3 (severe), or at the physician's discretion. In case of worsening symptoms, geriatricians had the option to expedite faecal microbiota transplantation or supplement with fidaxomicin as per Danish national guidelines.[5]

Patients with indication for faecal microbiota transplantation received pretreatment with oral vancomycin 125 mg four times daily. Faecal microbiota transplantation was done in hospital or at home by geriatric teams. Upon obtaining informed consent, which involved oral information and a written information leaflet detailing the effects and potential side-effects, alongside a patient consent form for data transfer (appendix pp 59–60), faecal microbiota transplant was delivered as 15–25 capsules containing approximately 50 g of donor faeces sourced from a single donor, recruited and screened for safety parameters according to established guidelines.[19] In patients with dysphagia, faecal microbiota transplant was applied by a nasojejunal tube (Bengmark 10 Fr; Nutricia, Utrecht, Netherlands).

The geriatric nurse and geriatrician conducted weekly telephone calls, providing clinical evaluation, drug adjustments, rehydration and nutrition therapy, and blood tests as needed. The geriatric team offered hospital-at-home care when appropriate and continued to oversee *C difficile* infection treatment for at least 8 weeks after faecal microbiota transplantation or initiation of antibiotic *C difficile* infection treatment, ensuring management until resolution. A control stool PCR test for *C difficile* was done upon completion of the 8-week treatment period. All activities were logged in electronic medical records using standardised headings (appendix p 58) alongside the MPI and the *C difficile* infection checklist.

The standard-care group received standard organisational care from their attending physician. Standard care followed the national clinical guideline[5] and involved *C difficile*

infection assessment, treatment with antibiotics, and faecal microbiota transplantation when deemed necessary by the attending clinician (appendix p 61).

All data were obtained from electronic medical records, which cover all Central Denmark Region public hospitals, and facilitate sharing of interdisciplinary information. Before randomisation, the following data were collected: sociodemographic and clinical data, including Charlson Comorbidity Index,[20] frailty measured by record-based MPI for hospital-admitted patients,[21] *C difficile* diagnosis site and toxin profile, habitation status, and antibiotic and proton-pump inhibitor use 1 month before a positive *C difficile* toxin PCR test. Bristol Stool Chart consistency and frequency at *C difficile* infection diagnosis, *C difficile* infection antibiotic treatment, and faecal microbiota transplantation data were collected retrospectively from the electronic medical record at 90-day follow-up. *C difficile* was classified into the following case definitions: health-care facility onset (*C difficile* infection >3 days after admission to health-care facility), community onset, but health-care facility-associated (*C difficile* infection within 28 days after discharge from a health-care facility), and community-associated (*C difficile* infection >28 days after discharge from a health-care facility).

Resolution of *C difficile*-associated diarrhoea was registered as close to day 90 as possible and defined as either clinical resolution of diarrhoea or persistent diarrhoea with a negative *C difficile* toxin test (indicating diarrhoea from other causes). All patients were asked at 90-day follow-up about their gastrointestinal status (diarrhoea yes *vs* no) and this status was registered. For patients who died before day 90, their status closest to day 90 was recorded. Status was noted as unknown in patients who died within 90 days and for whom no follow-up data were documented in electronic medical records.

Outcomes

The primary outcome was all-cause mortality at day 90, counted from the date of positive PCR test for *C difficile* toxin. Secondary quality-related outcomes included first *C difficile* infection recurrence, resolution of *C difficile*-associated diarrhoea, number of days in hospital, time-to-treatment with vancomycin and faecal microbiota transplantation, and 30-day readmission rate. Recurrent *C difficile* infection was defined as a new episode of diarrhoea (defined as ≥3 stools per day and Bristol stool chart consistency ≥6) and a positive *C difficile* toxin test after the end of treatment with an initial treatment response. Resolution of *C difficile*-associated diarrhoea was defined as either clinical resolution of diarrhoea or persistent diarrhoea with a negative *C difficile* toxin test. 90-day hospitalisation was defined as acute hospitalisation, excluding elective admissions and any outpatient activity. 30-day readmission was defined as any unplanned, acute rehospitalisation (elective or planned admissions and outpatient procedures were excluded) at any hospital within the Central Denmark Region occurring up to 30 days after *C difficile* infection-related hospital discharge.[22] Secondary patient-related outcome measures included quality of life measured by the European Quality of Life-5 Domain version and the Overall Quality of Life Depression List and functional status measured by the Functional Recovery Score. Patients who died during the first *C difficile* infection-related admission were excluded. Refractory *C difficile* infection was defined as persisting or worsening diarrhoea (stool count ≥3 and Bristol chart type ≥6) during antibiotic treatment. The prespecified patient-reported secondary outcomes and quality-of-life indices were not assessed due to an inability to obtain baseline data in the standard-care group.

Cause of death was evaluated by the physician investigator (TR) from medical records in both groups and categorised as follows: positive *C difficile* toxin test and diarrhoea; death from complication of *C difficile* infection (eg, ileus, megacolon, or pseudomembranous colitis); neither positive *C difficile* toxin test nor diarrhoea at time of death; or unknown. These categories were merged into either death from *C difficile* infection or death from other causes.

Faecal microbiota transplantation was done in accordance with international guidelines and the regulatory standards of the National Danish Tissue Act. These standards include the documentation and oversight of potential adverse reactions, conducted within the faecal microbiota transplantation centre, and a 30-year follow-up programme for all patients treated with faecal microbiota transplantation. Because faecal microbiota transplantation was administered as part of routine care and was equally accessible to both groups, adverse reactions were not specifically monitored within this trial.

At the faecal microbiota transplantation centre, a clinical safety board reviews and evaluates all serious adverse reactions, reports them to the relevant authorities within specified timeframes, and submits annual reports. The safety board comprised specialists from gastroenterology, infectious diseases, clinical microbiology, and clinical immunology and serves as a general safety monitoring board. For the present study, we established a study-specific board, comprising geriatric specialists from all participating centres and functioning as a study-specific data safety monitoring board. This board had two scheduled meetings per year and ad-hoc conferences, coordinated by the principal investigator (TR).

Statistical analysis

We calculated the sample size assuming 90-day mortality of 32% in the standard-care group and 15% in the CGA group. The anticipated mortality rate in the standard-care group was calculated for patients aged 70 years or older based on data from a previous cohort study.[2] The anticipated effect of the intervention was determined by considering a 90-day mortality rate of 12% in patients who underwent faecal microbiota transplantation,[23] and combining it with a mortality rate of 21%, which was observed in older patients receiving CGA.[12] Assuming the additive effect of CGA on faecal microbiota transplantation, the combined mortality

rate by intervention was estimated to be 15%, considering potential underestimation and overestimation in previous studies. To achieve 80% power and a 5% α level, 108 patients were required in each group. As this was a quality improvement trial, we expected no dropouts.

The primary outcome was compared in the study groups according to the intention-to-treat principle, tested in a logistic regression model and presented as an odds ratio (OR). In a sensitivity analysis, imbalances in patient characteristics (previous cancer and habitation status) were adjusted for. We tested for interaction between the variables with uneven distributions (previous cancer and habitation status). Stratified analyses for patient characteristics of the primary outcome were done. Estimates were provided with 95% CIs and medians with IQR or ranges, as applicable.

We compared the secondary outcomes, recurrence and readmission, in the two study groups in a logistic regression model, with results presented as ORs. The cumulative incidence of readmission and *C difficile* infection recurrence taking death into account was estimated using the Aalen-Johansen estimator and the hazard ratio was estimated by a Cox regression model. Numbers of days in hospital and differences between time-to-treatment with vancomycin and faecal microbiota transplantation were analysed in a linear regression model after applying a logarithmic transformation yielding a median ratio. Supplementary analyses of faecal microbiota transplantation treatment (yes *vs* no) were done by logistic regression analysis of the primary outcome. All analyses were adjusted for age 85 years or older and hospitalisation at diagnosis to reflect the stratified randomisation technique used.

All analyses were done in Stata version 18.0.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 1, 2022, and May 3, 2023, we consecutively assessed 301 patients, and 217 were randomly assigned to CGA (n=109) or standard care (n=108; figure 1). All patients included in the study were White. All included patients adhered to the study protocol apart from one patient in the CGA group, who died before the first study visit. In the standard-care group, seven patients were treated in geriatric departments during the 90-day follow-up. No patients were lost to follow-up.

Patient characteristics were similar in the CGA and the standard-care group, except for imbalances in the distribution of previous cancer and habitation status (table 1). The median patient age was 78 years (IQR 74–84). 116 (53%) of 217 patients were female and 101 (47%) were male. 187 (86%) of 217 patients had a first *C difficile* infection and 30 (14%) had a recurrent infection. 158 (73%) of 217 patients were hospitalised at the time of diagnosis of *C difficile* infection. 203 (94%) patients had symptoms compatible with *C difficile* infection.

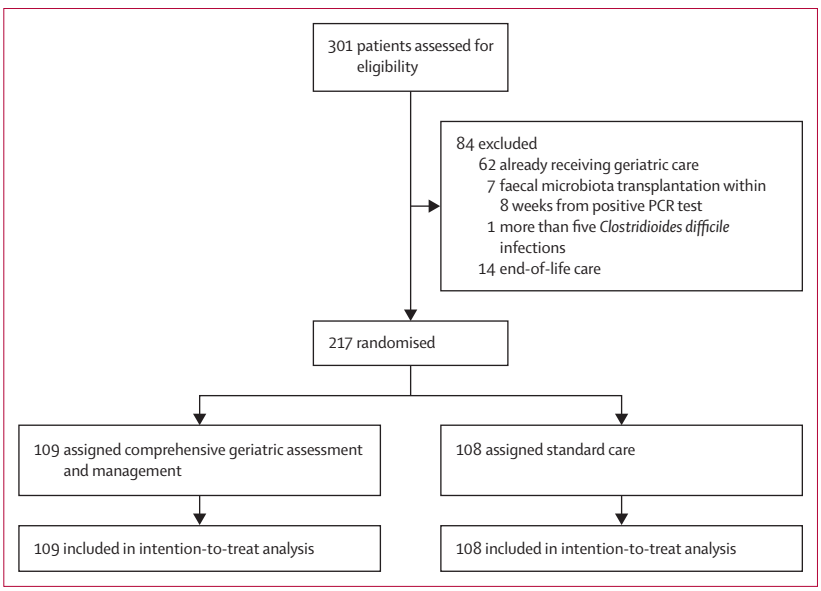

Figure 1: **Trial profile**

16 (15%; 95% CI 9–23) of 109 patients in the CGA group and 22 (20%; 14–29) of 108 patients in the standard-care group died within 90 days (OR 0·66, 95% CI 0·32–1·38; table 2). A sensitivity analysis adjusted for previous cancer status and habitation found similar results (0·65, 0·31–1·35). We found no signs of significant interactions in variables with uneven distributions (previous cancer p=0·15, habitation status p=0·36). Stratification for further patient characteristics yielded strata that were too small to obtain valid estimates (appendix p 62). The number of deaths directly attributed to *C difficile* infection was significantly lower in the intervention group (seven [44%] of 16 deaths *vs* 18 [82%] of 22 deaths in the standard-care group; p=0·020; appendix p 64).

Secondary outcome findings differed between the two groups (table 2). Recurrent *C difficile* infection within 90 days occurred less frequently in the CGA group than in the standard-care group (OR 0·35, 95% CI 0·18–0·69). By day 90, three (3%) patients in the CGA group had not reached *C difficile*-associated diarrhoea resolution compared with ten (11%) patients in the standard-care group (p=0·041). The median number of days in hospital was 3 (95% CI 2–4) in the CGA group and 5 (3–8) in the standard-care group (median ratio 1·88, 95% CI 1·41–2·51). For patients diagnosed with *C difficile* infection during hospital admission who survived the initial admission, fewer readmissions occurred in the CGA group (0·18, 0·09–0·40; table 2). The cumulative incidence of the first recurrent *C difficile* infection and first readmission are shown in the appendix (p 57).

Time to treatment initiation also differed between the study groups. Vancomycin was used to treat all 109 (100%; 95% CI 97–100) patients in the CGA group and 91 (84%; 76–91) patients in the standard-care group (p<0·0001). Time-to-treatment with vancomycin was shorter in the CGA

	Comprehensive geriatric assessment group (n=109)	Standard-care group (n=108)
Age, years	79 (74–84)	78 (74–84)
Sex		
Female	61 (56%)	55 (51%)
Male	48 (44%)	53 (49%)
Symptomatic *Clostridioides difficile* infection	104 (95%)	99 (92%)
Charlson Comorbidity Index score	3 (2–6)	3 (1–6)
Terminal disease registration before date of positive PCR test for *C difficile*	5 (5)	0
Primary disease requiring admission*		
Enteral infectious disease	29/79 (37%)	29/79 (37%)
Gastrointestinal disease	4/79 (5%)	1/79 (1%)
Cardiovascular disease	7/79 (9%)	9/79 (11%)
Pneumonia	6/79 (8%)	5/79 (6%)
Sepsis	5/79 (6%)	6/79 (8%)
Renal disease	11/79 (14%)	8/79 (10%)
Urinary tract infection	1/79 (1%)	3/79 (4%)
Chronic obstructive pulmonary disease	1/79 (1%)	2/79 (3%)
Dehydration and electrolyte disturbance	1/79 (1%)	2/79 (3%)
Rheumatic disease	2/79 (3%)	1/79 (1%)
Lesions and intoxication	2/79 (3%)	1/79 (1%)
Cancer	1/79 (1%)	2/79 (3%)
Malnutrition	1/79 (1%)	1/79 (1%)
Other	0	2/79 (3%)
Erysipelas	1/79 (1%)	0
Viral infectious disease	0	1/79 (1%)
Anaemia	1/79 (1%)	0
Other skin diseases	1/79 (1%)	0
Hip fracture	1/79 (1%)	0
Cancer before positive PCR test for *C difficile*	45 (41%)	31 (29%)
Renal disease requiring dialysis	14 (13%)	13 (12%)
Haematological cancer	10 (9%)	9 (8%)
Frailty level		
Low (MPI-1)	11 (10%)	12 (11%)
Moderate (MPI-2)	36 (33%)	36 (33%)
Severe (MPI-3)	32 (29%)	31 (29%)
Unknown	30 (28%)	29 (27%)
Habitation status		
Living in own home	101 (93%)	91 (84%)
Nursing home resident	8 (7%)	17 (16%)
Use of antibiotics within the previous month from date of positive PCR test for *C difficile*	91 (83%)	89 (82%)
Type of antibiotics†		
Penicillin	79 (72%)	83 (77%)
Cephalosporines	22 (20%)	19 (18%)
Fluoroquinolones	4 (4%)	14 (13%)
Macrolides	11 (10%)	4 (4%)
Aminoglycosides	6 (6%)	6 (6%)
(Continued from previous column)		
Carbapenems	6 (6%)	5 (5%)
Metronidazole	3 (3%)	2 (2%)
Sulphonamides	1 (1%)	3 (3%)
Nitrofurantoin	1 (1%)	0
Clindamycin	0	1 (1%)
Proton-pump inhibitor treatment within the previous month from date of positive PCR test for *C difficile*	57 (52%)	56 (52%)
Number of usual medications		
0–3	4 (4%)	9 (8%)
4–7	29 (27%)	37 (34%)
≥8	76 (70%)	62 (57%)
Number of *C difficile* infections		
First infection	96 (88%)	91 (84%)
Recurrent	13 (12%)	17 (16%)
Site of *C difficile* diagnosis		
Primary health care	17 (16%)	17 (16%)
Outpatient	13 (12%)	12 (11%)
Inpatient	79 (72%)	79 (73%)
C difficile profile‡		
Toxin A	98 (90%)	98 (91%)
Toxin B	107 (98%)	106 (98%)
Binary toxin	9 (8%)	17 (16%)
Ribotype 027	0	1 (1%)
C difficile case definition		
Health-care facility onset	50 (46%)	45 (42%)
Community onset, health-care facility-associated	29 (27%)	30 (28%)
Community-associated	30 (28%)	33 (31%)

Data are median (IQR), n (%), or n/N (%). MPI=Multidimensional Prognostic Index. *Accessible only for patients admitted to hospital. †Patients could receive more than one type of antibiotic, but data on combined therapy were not collected. ‡Patients could have a combined toxin profile, but data on combined toxin profiles were not collected.

Table 1: **Patient characteristics**

group than in the standard-care group (median 1 day, 95% CI 1–2 *vs* 2 days, 2–3; median ratio 1·54, 95% CI 1·17–2·04). More patients in the CGA group (102 [94%] of 109 patients; 95% CI 87–97) than in the standard-care group (33 [31%] of 108 patients; 23–40) received faecal microbiota transplantation (figure 2). Most patients who received faecal microbiota transplantation had capsule-based treatment (99 [97%] of 102 patients in the CGA group; 31 [94%] of 33 patients in the standard-care group), and the remaining patients received faecal microbiota transplantation by naso-jejunal tube. No technical failures were observed. Among patients who received faecal microbiota transplantation, treatment was provided earlier in the CGA group than in the standard-care group (median 10 days, 95% CI 8–12 *vs* 20 days, 16–25; median ratio 1·99, 95% CI 1·61–2·47). Faecal microbiota transplantation was used to treat

refractory disease in 30 (29%) of 102 patients in the CGA group (95% CI 21–36) and 14 (42%) of 33 patients in the standard-care group (26–60). Patients in the CGA group treated with faecal microbiota transplantation did not differ from patients in the standard-care group in terms of their characteristics (appendix p 65). In patients with their first *C difficile* infection, 90 (94%) of 96 patients (95% CI 87–97) in the CGA group were treated with faecal microbiota transplantation compared with 23 (25%) of 91 patients (17–35) in the standard-care group.

Fidaxomicin was more frequently used in the CGA group (17 [16%] of 109 patients; 95% CI 9–24) than in the standard-care group (four [4%] of 108 patients; 1–10). In both groups, fidaxomicin was used to extend treatment after vancomycin due to vancomycin failure and as a primary treatment in one patient in the standard-care group. Metronidazole use did not differ between the groups (one [1%] of 109 patients *vs* five [5%] of 108 patients; p=0·12). 14 patients received no anti-*C difficile* antibiotics, all in the standard-care group. None of these patients died during follow-up, and only one had *C difficile* infection recurrence. Based on medical records, six (43%) of 14 patients had clinical *C difficile* infection and none were severely frail (appendix p 66).

No serious adverse events related to patient assessment or faecal microbiota transplantation, including death, were recorded in either group. No adverse events for all patients were reported through the incident reporting system administered by the Danish Patient Safety Authority.

In a supplementary analysis of the independent effects of faecal microbiota transplantation, regardless of care pathway, we found that the use of faecal microbiota transplantation was associated with reduced 90-day mortality (OR 0·28, 95% CI 0·13–0·61). The patient characteristics in those who received faecal microbiota transplant and those who did not were similar (appendix p 67). Restricting the analysis to patients with their first *C difficile* infection, we found that the use of faecal microbiota transplantation was likewise associated with reduced 90-day mortality (0·38, 0·17–0·84) and *C difficile* infection recurrence rates (0·32, 0·16–0·69) versus patients solely treated with *C difficile* infection-related antibiotics.

Discussion

In this randomised trial, we compared two organisational care pathways for older patients with *C difficile* infection and found similar 90-day mortality rates across both groups. CGA conferred marked reductions in *C difficile* infection recurrence, death from *C difficile* infection, days in hospital, and acute readmissions compared with standard care. These differences could be attributable to increased use of faecal microbiota transplantation after CGA, even when access to faecal microbiota transplantation was unrestricted in both care pathways. Overall, use of faecal microbiota transplantation was associated with decreased 90-day mortality.

	Comprehensive geriatric assessment group (n=109)	Standard-care group (n=108)	Crude OR* (95% CI)	p value
90-day mortality	16 (15%)	22 (20%)	0·66 (0·32–1·38)	0·27
Clostridioides difficile-associated diarrhoea	16 (15%)	35 (32%)	0·35 (0·18–0·69)	0·0020
C difficile-associated diarrhoea resolution by day 90†	100/103 (97%)	82/92 (89%)	..	0·041‡
Readmission	12/74 (16%)	37/73 (51%)	0·18 (0·09–0·40)	<0·0001

Data are n (%) or n/N (%). OR=odds ratio. *Standard care is the reference group. †Status was unknown in six patients in the comprehensive geriatric assessment group and 16 patients in the standard-care group. ‡Fisher`s exact p value.

Table 2: **Clinical outcomes on day 90**

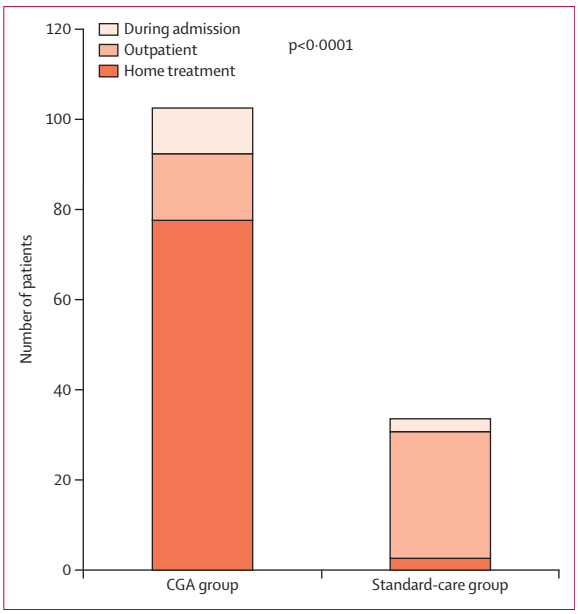

Figure 2: **Use of faecal microbiota transplantation**
CGA=comprehensive geriatric assessment.

The overall 90-day mortality rate observed in this study was markedly lower than in a previous similar cohort.[2] This mortality difference could result from overall optimised treatment, including better use of vancomycin and faecal microbiota transplantation in both study groups than in the previous cohort.[2] Although the mortality rate in the CGA group was lower than in the standard-care group, the difference was not significant. The use of faecal microbiota transplantation was associated with decreased 90-day mortality, aligning with research indicating a decrease in mortality compared with vancomycin treatment alone.[9] 31% of patients randomly assigned to standard care received faecal microbiota transplantation, which might have improved 90-day mortality outcomes in the standard-care group.

Because of the high mortality risk among patients with *C difficile* infection, we hypothesised that CGA as an add-on to current standard care for older patients with *C difficile* infection could independently reduce mortality. Previous research in older patients with concurrent medical

conditions found that obtaining a significant mortality difference with CGA is difficult.[12] Reduced all-cause mortality might be a too optimistic outcome measure in older patients with frailty. Considering this finding, we note that most patients in the standard-care group died from *C difficile* infection or its complications. Because older age and comorbidity are recognised risk factors for severe outcomes in older patients with *C difficile* infection,[24,25] other factors might influence mortality rates. Therefore, we note the positive effects of CGA reflected in the secondary outcomes (ie, reduced recurrence risk, readmission rate, and risk of long-term hospitalisation). Together with a numerical reduction in all-cause mortality risk, our findings might be considered a success in favour of CGA in treatment of older patients with *C difficile* infection. Furthermore, a 90-day follow-up might not capture the full effect of the intervention, considering that mortality caused by recurrent *C difficile* infection often occurs beyond the initial 90-day window.[26]

The reduced *C difficile* infection recurrence, readmission, and in-hospital days associated with CGA suggest improvement of the overall patient care continuum. These reductions could be attributed to both the organisation of care and the treatment strategy, which are interrelated and reinforce each other. Faecal microbiota transplant was administered to most patients in the CGA group after their first *C difficile* infection. Given previous research showing superiority of early faecal microbiota transplantation in achieving sustained resolution,[8] early faecal microbiota transplantation might explain the reduced risk of *C difficile* infection recurrence in the CGA group. Time to faecal microbiota transplantation was shorter in the CGA group compared with the standard-care group. The organisation of care in the CGA group included early faecal microbiota transplantation administered in patients' homes, which might have decreased the risk of *C difficile* infection recurrence by promptly addressing associated diarrhoea. Securing early faecal microbiota transplantation could mitigate the effect of *C difficile* infection on the chronic morbidity of older patients, potentially reducing symptoms and hence readmission and days in hospital. CGA and geriatric management were effective in preventing unplanned readmissions among older patients with *C difficile* infection. This finding is consistent with previous studies in older inpatients with other medical conditions.[11,12] Patients with *C difficile* infection are at increased risk of 30-day readmission compared with medical inpatients without *C difficile* infection.[27] In our study, the main difference between the two treatment pathways was that the CGA group received hospital-at-home care when appropriate, thus preventing rehospitalisation without incurring an elevated risk of later readmission. The geriatric team had thorough knowledge of the patient's *C difficile* infection history, allowing them to tackle the challenge of treating older patients with *C difficile* infection across multiple health-care settings.[28] The efficacy of the geriatric intervention relies on prompt and specialised assessment by a multidisciplinary team and unrestricted access to faecal microbiota transplantation. The option to manage patients in their home offers a unique opportunity to incorporate this treatment in a manner distinct from the standard care framework.

In this study, no patients declined the geriatric intervention, underlining its feasibility. We found that implementing faecal microbiota transplantation as a home treatment on a large scale was feasible, consistent with previous findings.[15] Future studies should evaluate the cost-effectiveness of home treatment with faecal microbiota transplantation and investigate potential clinical outcome disparities between hospital-based and home-based faecal microbiota transplantation treatments.

Our results mainly apply to health-care systems with universal access and similar effectiveness and depend on access to specific teams (eg, travelling geriatric teams). Home faecal microbiota transplantation treatment could be administered by gastroenterology teams, general practitioners, or home nursing care. Our data underscore that the CGA-based intervention was essential for achieving the feasibility of home-based faecal microbiota transplantation and for effectively addressing the myriad health issues encountered in older patients with frailty with *C difficile* infection, including the provision of hospital-at-home treatment as an option in cases of exacerbation of chronic illness.

Our study has some strengths. Because the study was done as a quality improvement project, it successfully included frail older patients with *C difficile* infection who are often excluded from randomised clinical trials. All patients with a positive *C difficile* test in a specified geographical area were consecutively included, representing a broad and unselected range of older patients with *C difficile* infection. No patients were lost to follow-up for the primary and secondary outcomes. Data collection was done impartially and related to clinical care, except for the recording of data required to describe *C difficile* resolution. No technical failures of faecal microbiota transplantation were observed, probably due to experienced geriatric teams. Furthermore, home-based faecal microbiota transplantation enables treatment in a safe and well known environment for the patient (ie, the patient's home) and increase success rates.

Our study has important limitations. We based our sample size calculation on similar, historical cohorts with high mortality rates. The overall lower mortality rate observed in our study might be caused by an improved standard treatment algorithm with increased use of faecal microbiota transplantation in both study groups. This drift in the standard-care group, showing overall improved quality of care, could be regarded as a Hawthorne effect (ie, a drift towards the new treatments).[29] In a clinical real-life setting, such a drift undoubtedly benefits patients. Actively withholding faecal microbiota transplantation from a patient in a clinical trial would in our view conflict with the Declaration of Helsinki.[16] If a future study includes a larger proportion of patients treated with faecal microbiota transplantation, a

similar challenge should be anticipated. The study design prevented us from collecting comparable baseline and mortality data beyond what is routinely documented in medical records. We did not assess the effect of potential socioeconomic factors caused by the Danish welfare system that ensures equal and free access to health care. Also, all patients were White. Both these factors might limit generalisability. We followed the national Danish guideline for treating *C difficile* infection,[5] and future clinical trials could investigate the clinical effectiveness of algorithms suggested in other guidelines, such as sequential or tapered antibiotics or monoclonal antibodies.[6] Finally, the CGA comprised many components tailored to each patient, hindering independent replication of each component. This difficulty mirrors real-world clinical challenges in treating older patients with multimorbidity. The CGA-based intervention worked synergistically with faecal microbiota transplantation because CGA-based assessment and treatment care planning for faecal microbiota transplantation were prerequisites for performing the procedure and included the possibility of home-based faecal microbiota transplantation. Therefore, access to faecal microbiota transplantation components for older people is required.

In conclusion, CGA and home visits for older patients with *C difficile* infection caused significant reductions in *C difficile* infection recurrence, acute readmissions, and days in hospital. However, no difference in all-cause 90-day mortality rates was seen. An intervention tailored for older people, including the option for home-based treatment, might improve clinical outcomes by facilitating earlier and increased access to faecal microbiota transplantation. Clinicians should risk stratify older patients with *C difficile* infection, both index and recurrent, for recurrence risk, and consider early faecal microbiota transplantation for those at high risk. Access to early faecal microbiota transplantation could be the most beneficial component of CGA and might improve clinical outcomes the most, which emphasises that this patient group might benefit from specialised care.

Contributors

Study concept and design: TR, EMSD, CLH, SMDB, MG, HV, TKH, MA, IB, JS-J, MGR, JBR, and MØ. Acquisition of data: TR, EMSD, HV, MA, IB, JS-J, MGR, JBR, and SEP. TR (the project manager) accessed all Central Denmark Region electronic medical records, collecting all data except data on day 90 *C difficile*-associated diarrhoea resolution, which were handled by SEP (a researcher in gastroenterology). MG checked primary outcome data collection to prevent errors. Data verification was done by TR, SEP, and MG. Data analysis: TR, MG, CLH, SMDB, and EMSD. Data interpretation: TR, EMSD, CLH, SMDB, MG, TKH, MA, IB, JS-J, MGR, JBR, MØ, HV, SEP, and CJS. TR drafted the manuscript. All authors revised the manuscript for intellectual content and approved the final review. All authors had full access to all study data and are jointly responsible for the decision to submit for publication.

Declaration of interests

CJS declares funding from Wellcome Trust Medical Research Council and the Chronic Disease Research Foundation. SMDB declares lecture fees from Takeda Pharmaceuticals. CLH received research funding from the Novo Nordisk Foundation. All other authors declare no competing interests.

Data sharing

Data will be made available upon request in an anonymised form compliant with the European General Data Protection Regulation legislation. To gain access to pseudonymised participant data, a formal data access agreement is required and, if necessary, a formal ethics committee approval. Data dictionary forms will be made available following publication. The study protocol and statistical analysis plan are available online. All proposals should be directed to the corresponding author.

Acknowledgments

We express our gratitude to our collaborators at the participating hospital departments. We thank biostatistician Stefan Nygaard Hansen for statistical expertise and assistance. The study was conducted at the Department of Geriatrics, Aarhus University Hospital (Aarhus, Denmark). Administrative personnel costs were covered by the Department of Geriatrics. Financial support was obtained from Helsefonden (grant number 22-B-0239). The faecal microbiota transplantation framework was supported by Innovation Fund Denmark (8056-00006B).

References

1 Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. *Clin Infect Dis* 2013; **56:** 1108–16.

2 Rubak T, Baunwall SMD, Gregersen M, et al. Frailty level at discharge predicts mortality in older patients with *Clostridioides difficile* more accurately than age or disease severity. *Eur Geriatr Med* 2023; **14:** 583–93.

3 Enoch DA, Murray-Thomas T, Adomakoh N, et al. Risk of complications and mortality following recurrent and non-recurrent *Clostridioides difficile* infection: a retrospective observational database study in England. *J Hosp Infect* 2020; **106:** 793–803.

4 Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; **376:** 305–17.

5 Baunwall SMD, Dahlerup JF, Engberg JH, et al. Danish national guideline for the treatment of *Clostridioides difficile* infection and use of faecal microbiota transplantation (FMT). *Scand J Gastroenterol* 2021; **56:** 1056–77.

6 van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. *Clin Microbiol Infect* 2021; **27** (suppl 2)**:** S1–21.

7 Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: an updated systematic review and meta-analysis. *EClinicalMedicine* 2020; **29–30:** 100642.

8 Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second *Clostridioides difficile* infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 1083–91.

9 Rode AA, Chehri M, Krogsgaard LR, et al. Randomised clinical trial: a 12-strain bacterial mixture versus faecal microbiota transplantation versus vancomycin for recurrent *Clostridioides difficile* infections. *Aliment Pharmacol Ther* 2021; **53:** 999–1009.

10 Parker SG, McCue P, Phelps K, et al. What is comprehensive geriatric assessment (CGA)? An umbrella review. *Age Ageing* 2018; **47:** 149–55.

11 Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces readmissions—a quasi-randomised controlled trial. *Eur Geriatr Med* 2016; **7:** 443–48.

12 Hansen TK, Pedersen LH, Shahla S, Damsgaard EM, Bruun JM, Gregersen M. Effects of a new early municipality-based versus a geriatric team-based transitional care intervention on readmission and mortality among frail older patients—a randomised controlled trial. *Arch Gerontol Geriatr* 2021; **97:** 104511.

13 Pedersen LH, Gregersen M, Barat I, Damsgaard EM. Early geriatric follow-up after discharge reduces mortality among patients living in their own home. A randomised controlled trial. *Eur Geriatr Med* 2017; **8:** 330–36.

14 Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017; **9:** CD006211.

15 Jørgensen SMD, Rubak TMM, Damsgaard EM, Dahlerup JF, Hvas CL. Faecal microbiota transplantation as a home therapy to frail older people. *Age Ageing* 2020; **49:** 1093–96.

16 World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. 2022. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ 2024 (accessed Feb 27, 2024).

17 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.

18 Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a Multidimensional Prognostic Index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008; **11:** 151–61.

19 Keller JJ, Ooijevaar RE, Hvas CL, et al. A standardised model for stool banking for faecal microbiota transplantation: a consensus report from a multidisciplinary UEG working group. *United European Gastroenterol J* 2021; **9:** 229–47.

20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40:** 373–83.

21 Hansen TK, Damsgaard EM, Shahla S, Bruun JM, Gregersen M. A reliable and record-based frailty assessment method for older medical inpatients. *Eur Geriatr Med* 2020; **11:** 803–12.

22 Heggestad T, Lilleeng SE. Measuring readmissions: focus on the time factor. *Int J Qual Health Care* 2003; **15:** 147–54.

23 Hocquart M, Lagier JC, Cassir N, et al. Early fecal microbiota transplantation improves survival in severe *Clostridium difficile* infections. *Clin Infect Dis* 2018; **66:** 645–50.

24 Caupenne A, Ingrand P, Ingrand I, et al. Acute *Clostridioides difficile* infection in hospitalized persons aged 75 and older: 30-day prognosis and risk factors for mortality. *J Am Med Dir Assoc* 2020; **21:** 110–14.

25 Czepiel J, Krutova M, Mizrahi A, et al. Mortality following *Clostridioides difficile* infection in Europe: a retrospective multicenter case-control study. *Antibiotics (Basel)* 2021; **10:** 299.

26 Olsen MA, Yan Y, Reske KA, Zilberberg MD, Dubberke ER. Recurrent *Clostridium difficile* infection is associated with increased mortality. *Clin Microbiol Infect* 2015; **21:** 164–70.

27 Drozd EM, Inocencio TJ, Braithwaite S, et al. Mortality, hospital costs, payments, and readmissions associated with *Clostridium difficile* infection among Medicare beneficiaries. *Infect Dis Clin Pract* 2015; **23:** 318–23.

28 Khanna S, Lett J, Lattimer C, Tillotson G. Transitions of care in *Clostridioides difficile* infection: a need of the hour. *Therap Adv Gastroenterol* 2022; **15:** 17562848221078684.

29 McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014; **67:** 267–77.

PAPER IV

Development of a checklist to support management of older patients with *Clostridioides difficile* infection

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Running title: Treatment and care planning in *Clostridioides difficile* infection

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Word counts: Abstract: 287/300; Key points: 207/300; Manuscript: 3081/3500

Number of tables/figures: 2/3

Abbreviations: CCI: Charlson Comorbidity Index; CGA: Comprehensive Geriatric Assessment; *C. difficile*: *Clostridioides difficile*; CDI: *Clostridioides difficile* infection; FMT: fecal microbiota transplantation; IQR: Interquartile Range; PDSA: Plan-Do-Study-Act; PCR, MPI, Multidimensional Prognostic Index; PCR: Polymerase chain reaction.

Key points

- *Clostridioides difficile* infection (CDI) is associated with high morbidity and mortality and remains a major challenge in geriatric care.
- We developed and iteratively refined a clinical CDI checklist to support structured care planning for older patients with CDI, aiming to optimize clinical practices and decrease mortality rates. We used it as part of a randomized quality improvement study.
- The CDI checklist covers five core areas: 1) CDI treatment planning, including frailty and fecal microbiota transplantation (FMT) evaluation, 2) information-sharing with patients, relatives, and primary healthcare, 3) medication review, 4) rehydration, and 5) nutritional support.
- A key consideration is whether the patient can tolerate CDI recurrence, guiding decisions on FMT and care coordination.

Why does this paper matter?

Older patients with *Clostridioides difficile* infection (CDI) have high mortality rates and often receive suboptimal treatment despite having severe infection. This paper presents a geriatric-focused checklist developed and iteratively refined to guide structured care planning for this vulnerable patient group. By supporting standardization of treatment, discontinuation of high-risk medications, and integration of supportive therapies, the checklist offers a pragmatic model that can be implemented across clinical settings. It operationalizes a holistic and evidence-informed management that addresses the complex needs of older adults with CDI and may contribute to improved outcomes.

Abstract

Background: Older patients with *Clostridioides difficile* infection (CDI) are often frail and multimorbid, with reported 90-day mortality rates of 28-36%. Despite this, treatment often fails to align with infection severity, and care coordination remains complex. This study describes the development and iterative refinement of a clinical checklist to support structured treatment and care planning in this high-risk group.

Methods: We conducted a two-phase model development study applying quality improvement methods, to identify key management factors. In phase I, older patients with CDI were followed to identify key treatment and care priorities, informing the initial checklist version. In phase II, the checklist was used in a pragmatic, randomized trial investigating Comprehensive Geriatric Assessment (CGA) in older patients with CDI. The checklist was iteratively revised, based on clinical use and feedback.

Results: In phase I, treatment courses of ten older patients with CDI were reviewed, identifying three key priorities for the initial checklist: (1) CDI treatment planning with frailty assessment, (2) medication review, and (3) attention to rehydration and nutrition. In phase II, the CDI checklist was applied in 108 patients allocated to CGA. Standardized treatment planning was ensured, including assessment of fecal microbiota transplantation (FMT) eligibility. Among those treated with non-CDI related antibiotics or proton-pump inhibitors, 52% (26/50) and 70% (39/56) respectively, had treatment discontinued. Nutritional and rehydration support was provided in 64 (59%) and 61 (56%) patients. The CDI checklist was subsequently

expanded based on clinical use to include new elements, such as post-FMT laxative treatment and cross-specialty coordination.

Conclusion: A clinical checklist can support structured and holistic care planning in older adults with CDI. Core components include CDI treatment planning, assessment of FMT eligibility, frailty evaluation, medication review, and supportive therapies such as nutrition and rehydration.

Key words: *Clostridioides difficile*, Frailty, Fecal Microbiota Transplantation, checklist, Comprehensive Geriatric Assessment

Introduction

Clostridioides difficile infection (CDI) poses a substantial challenge in the care of older adults, given its high prevalence and severity in both hospital and community settings[1]. Older adults are particularly vulnerable due to advanced age, comorbidity, and frailty - factors that heighten the risk of severe disease progression and mortality[2,3]. Multimorbidity and frailty are distinctive features observed in older patients with CDI[4,5]. Still, clinical guidelines remain predominantly focused on infection management, potentially overlooking the concurrent progression of frailty and comorbidities and the complex implications for individualized treatment planning[6].

Treatment planning for CDI in older patients poses a clinical challenge due to patient frailty and a tendency towards undertreatment[5,7]. In a previous cohort study of older patients with CDI, 67% were classified as moderately or severely frail, and 82% presented with severe or fulminant CDI. Despite this, only 32% received vancomycin and 1% underwent fecal microbiota transplantation (FMT), with a 90-day mortality rate of 28%[5]. This mismatch between clinical needs and delivered care highlights a critical gap, raising concerns over potential loss of clinical focus and oversight in care coordination. Frailty complicates treatment decisions as patients may have limited physiological reserve, heightened vulnerability to adverse effects, and reduced tolerance for standard interventions. Clinicians must navigate multiple comorbidities while considering patients' limited capacity to tolerate interventions such as FMT, which necessitates hospital-based care. Effective treatment therefore requires not only antibiotics or FMT but also personalized management aligned with the patient's frailty status[5], demanding a holistic, multidisciplinary approach.

Comprehensive Geriatric Assessment (CGA) is the gold standard for multidisciplinary evaluation and care planning for older patients with frailty[8,9]. In a previous randomized trial (CLODIfrail)[10], which enrolled patients aged 70 years or older with CDI, we observed

marked reductions in acute readmissions, hospital length of stay, and CDI recurrence among those allocated to CGA-based organizational care. While this care included a CDI checklist for older patients, the structured clinical management approach underpinning its use has not yet been described.

The aim of the present study was to describe the development of the CDI checklist model for management of older patients with CDI, as applied in the CLODIfrail study.

Methods

Study design

We conducted a model development study within a quality improvement framework inspired by the Model for Improvement[11], applying driver diagrams and Plan-Do-Study-Act (PDSA) cycles to support iterative development. The study took place in the Central Denmark Region, a publicly funded health system serving approximately 1.32 million residents across Aarhus University Hospital and five affiliated regional hospitals. The study was conducted from April 2021 to January 2024.

Setting and context

In 2021, geriatric and gastroenterology specialists convened to develop a structured approach to the treatment and care of older patients with CDI, prompted by evidence from a previous study indicating that these patients often received care misaligned with disease severity and faced high mortality rates[5]. The study population comprised older patients with CDI managed within the Central Denmark Region, a publicly funded healthcare system with a decentralized hospital structure. Care is provided free of charge for all patients across Aarhus University Hospital and five affiliated regional hospitals.

Diagnosis of CDI is based on polymerase chain reaction (PCR) testing of *Clostridioides difficile* (*C. difficile)* toxins A and B and the binary toxin, performed in one centralized clinical microbiology service across primary and secondary healthcare sectors, including hospital wards, short-stay units, and patients' homes. Treatment is provided in medical and surgical inpatient wards, outpatient gastroenterology clinics, and primary healthcare settings.

The steering group comprised three geriatric specialists and one geriatric nurse from Aarhus University Hospital; five geriatricians, two nurses, one physiotherapist, and one occupational therapist from the affiliated regional hospitals mentioned above; two representatives

140 from a patient and public involvement group; and one gastroenterology specialist and re-
141 searchers from the Centre for Fecal Microbiota Transplantation[12]. The group was led by the
142 same project manager as the CLODIfrail initiative[10] and brought together clinical expertise,
143 research insight, and patient perspectives to discuss how to support a structured and compre-
144 hensive management approach for older patients with CDI. Quarterly meetings were held and
145 decisions were made by consensus. Discussions centered on the complexities of managing
146 older CDI patients, given their numerous comorbidities and diverse treatment needs. A driver
147 diagram was developed to identify key drivers of improvement and structure potential change
148 ideas for a more systematic approach to CDI care (Figure 1). The group identified a gap in ad-
149 dressing broader needs beyond CDI treatment guidelines and recognized the necessity for a
150 standardized checklist to address them effectively in a reproducible manner.
151
152 *Development of the CDI checklist*
153 The CDI checklist for older patients was developed through an iterative process applying
154 PDSA cycles[11] in close collaboration with the steering group, as outlined in Figure 2.
155
156 *Phase I: Identification of key elements and initial CDI checklist design*
157 Patients included in phase I had a positive PCR test for *C. difficile* and were treated in the
158 Central Denmark Region. Following CDI diagnosis, geriatric teams, including a physician
159 and a nurse trained in geriatric medicine, visited patients weekly in their homes to provide
160 treatment for CDI and manage coexisting comorbidities. Patient issues were discussed con-
161 secutively in the steering group, and feedback from geriatric teams, patients, relatives, and
162 primary healthcare collaborators was documented. The project manager retrospectively re-
163 viewed patients' electronic medical records to identify key focus areas warranting interven-
164 tion. Data were collected from the date of a positive CD toxin PCR test until 8 weeks after the

final CDI-related treatment. The checklist design was iteratively revised to enhance structural coherence and improve clinical clarity, and the steering group reached consensus to finalize the CDI checklist draft (Figure 2).

Phase II: Use and refinement of the CDI checklist

In phase II, the CDI checklist was applied to patients randomized for CGA organizational care in a multi-center randomized quality improvement trial (CLODIfrail) (24) comparing two models of care over a 90-day follow-up period (Figure 2). Eligible patients were aged ≥ 70 years, resided in the Central Denmark Region, and had a positive *C. difficile* stool PCR test. They were consecutively identified from a complete list of all patients with a positive *C. difficile* test in primary or secondary healthcare between 1 September 2022 and 3 May 2023.

The CDI checklist constituted an integral component of the geriatric intervention, which entailed a comprehensive evaluation and management of the geriatric issues and symptoms associated with CDI to create an individualized treatment and care plan as described previously[10]. A physician trained in geriatric medicine used the checklist within five weekdays of a positive PCR test for CD. All clinical activities and the completed CDI checklists were documented in patients' electronic medical records and managed using REDcap[13]. As part of the CDI checklist, a CGA-based frailty assessment was conducted using the bedside Multidimensional Prognostic Index (MPI)[14]. After completion of the randomized trial, electronic medical records were retrospectively reviewed to collect clinical data corresponding to the checklist items. The project manager also recorded patterns of clinical decisions not captured in the CDI checklists. The review period extended from randomization to eight weeks after the final CDI-related treatment.

Geriatrics and gastroenterology specialists conducted a second review of the checklist, evaluating each item for alignment with best practice in geriatric care and applicability in clinical practice. Revisions were made based on these discussions with clinicians (Figure 2).

Data collection of patient characteristics

Patient characteristics for the development phases were collected at the time of a positive *C. difficile* PCR test. Data included socio-demographic variables, Charlson Comorbidity Index (CCI)[15], record-based MPI for frailty status in hospital-admitted patients[16], habitation status, *C. difficile* diagnosis site, toxin profile, and CDI definition classified as healthcare facility-onset, community-onset healthcare facility-associated, or community-associated CDI[17].

Statistical analysis

Descriptive statistics were used to summarize the clinical characteristics of patients in both the phases. Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. The distribution of activities was reported as counts and percentages.

All analyses were made in STATA version 18·0 (StataCorp LLC, College Station, Texas).

Ethical statement

Access to the patient electronic medical record as part of the study was approved by the hospital boards of directors at all participating hospitals and obtained on 14 March 2021 as part of the CLODIfrail initiative. The randomized quality improvement trial was conducted in accordance with the Declaration of Helsinki[18] and ensured all patients had access to standard medical care per national guidelines. The trial posed no project-related risks, experimental

213 treatments, or invasive biological sample collection. Participants could refuse treatment per
214 Danish Health Authority rules. The study design and its categorization as a quality improve-
215 ment study were approved by the Central Denmark Region Committees on Health Research
216 Ethics (j.no. 1-10-72-1-21).
217

Results

Phase I: Identification of key elements and initial CDI checklist design

Between 16 April and 14 October 2021, ten patients with CDI were treated at Aarhus University Hospital and Silkeborg Regional Hospital, Denmark. The patients' median age was 84 (interquartile range (IQR) 74-94) and 60% were females (Table 1). Eight patients (80%) were diagnosed during hospitalization and 5 (50%) had recurrent CDI.

The steering group emphasized a need for frailty assessment as part of the CDI management, given evidence that many older patients with CDI are severely frail[5]. They also emphasized the need for assessing rehydration and nutritional status, considering alternative reasons for diarrhea, and reviewing the medication list, particularly discontinuing antibiotics and proton pump inhibitors. Patient and public representatives called for targeted patient information on CDI (Supplementary text S1)[10] and for standardized communication procedures with primary healthcare providers, using predefined headings and corresponding letters (Supplementary Table S2)[10]. Iterative adjustments to the CDI checklist are presented in Supplementary Table S3.

Development phase I resulted in the first draft of the CDI checklist for treatment and care of older patients with CDI (Supplementary Figure S4)[10].

Phase II: Use and refinement of the CDI checklist

Between 1 September 2022 and 3 May 2023, a total of 217 patients were consecutively included in the randomized trial. Of these, 109 were assigned to CGA organizational care, and the checklist was used in 108 (99%); one patient died before the first study visit. The median age of the 109 patients was 79 years (IQR 74-84) and 56% were females. Ninety-six (88%) had a first CDI and 13 (12%) had recurrent CDI. Most patients were diagnosed during hospitalization (n=79, 72%), with the rest diagnosed in primary healthcare (16%) or during outpatient treatment (12%) (Table 1).

Adherence to the CDI checklist items is presented in Table 2. All patients underwent frailty assessment using the MPI and were evaluated for the indication for FMT treatment. Information materials and corresponding letters to primary healthcare were provided to all patients. Supportive nutritional and rehydration therapy remained key components of the checklist as 64 (59%) of 108 patients required additional nutritional therapy and monitoring, and 61 (56%) required rehydration therapy. Discontinuation of non-CDI-related antibiotics was undertaken in 26 (52%) of 50 patients (Table 2).

Additional factors not addressed in the initial CDI checklist were identified by the project manager and added to the checklist (Supplementary file 3). FMT was performed in 102 of the 109 (94%) patients. Post-FMT constipation requiring laxative treatment occurred in 17 of 102 patients (16%), prompting the inclusion of a reminder for clinicians to educate patients about constipation management following FMT.

Clinician feedback, gathered through steering group meetings and written correspondence, indicated that all predefined items on the checklist were considered relevant except for the MPI, which was considered too time-consuming for daily clinical practice and replaced with CGA[8,9] as part of clinical evaluation. To guide decision-making regarding FMT, a key question—"Can the patient tolerate recurrent CDI?"—was added. Clinicians also emphasized the critical need for coordinated CDI management across specialties to ensure continuity of care. Furthermore, the proton pump inhibitor and laxative treatment items were rephrased for clarity, and the prompt to consider other reasons for diarrhea was moved to the beginning of the checklist to minimize automation in CDI assessment and treatment. The checklist was subsequently revised to incorporate factors not addressed in the initial version, resulting in the current version (Figure 3).

Discussion

In this model development study, we created a CDI checklist to provide a structure for the management of older patients with CDI. The checklist encompassed multiple treatment and care domains, thereby promoting a more holistic approach to this population. A central consideration was the patient's ability to tolerate potential CDI recurrences, assessed through CGA-guided clinical judgement. The checklist was intentionally kept simple to serve as a pragmatic tool for decision-making in a complex patient group. In the randomized trial, its use ensured that all patients received structured CDI-related care planning, including assessment of the indication for FMT. The checklist also substantiated the importance of supportive care, such as nutritional and fluid therapy, and the discontinuation of established risk factors for recurrence, including non-CDI antibiotics and proton-pump inhibitors.

Increased awareness of CDI management was evident in the fact that all patients underwent systematic CDI assessment, including evaluation of the indication for FMT, as outlined in the CDI checklist. The structured approach may have contributed to the reductions in CDI recurrence, hospital readmissions, and length of stay in the CLODIfrail study[10] as it prompted clinicians to engage actively in treatment care planning. Timely, appropriate CDI treatment may alleviate symptoms and mitigate the impact on chronic comorbidities in older patients, thereby potentially lowering hospital readmission rates and days in hospital. Prior research has demonstrated that implementing evidence-based treatments and establishing critical care pathways improve clinical outcomes, underscoring the necessity for a proactive approach[19,20]. The present study extends this evidence by highlighting how a structured, geriatric-focused tool like the CDI checklist can operationalize management in a real-world setting for older patients. However, as the checklist was embedded within a broader organizational pathway, future studies should formally validate its independent utility.

The CDI checklist was developed and subsequently refined within a hospital-at-home context[10]. This approach aligns with the current healthcare policy priorities on equity, which

emphasize the delivery of care closer to citizens and the reduction of avoidable hospitalizations[21]. By supporting clinical decision-making outside the hospital setting, the checklist enhances accessibility and patient-centeredness, while also providing a structured framework applicable to CDI management in hospital settings. This dual utility broadens its applicability and underscores its relevance across multiple levels of care.

The checklist incorporated multiple aspects of treatment and care for older patients with CDI, extending beyond a narrow focus on CDI-specific therapy. Supportive elements—such as informing primary healthcare collaborators, involving relatives and patients through information material, and managing comorbid conditions—were considered equally important. This multiple-component approach aligns with prior research demonstrating that standalone interventions are less effective than bundled strategies in CDI management[22-25].

The CDI checklist was developed and refined collaboratively by geriatric physicians and nurses to ensure that it reflected the complex needs of older patients and supported shared clinical responsibility. Tailored to the geriatric clinical reality, it anticipates broader patient challenges throughout the treatment trajectory and promotes holistic, person-centered care. Because it was developed within a multidisciplinary geriatric framework, incorporating principles and structures tailored to older patients with complex needs, its application outside geriatric settings may require adaptation of both its content and structure.

Discontinuing non-CDI-related antibiotics was included as an element of the CDI checklist. According to the Centers for Disease Control and Prevention, up to 30% of all antibiotics prescribed in acute care hospitals are either "unnecessary or inappropriate"[26]. In Denmark, overall antibiotic use has declined; however, broad-spectrum antibiotic consumption has increased among older adults[27]. As antimicrobial stewardship programs have been found effective in preventing CDI[28], these trends underscore the need for active antimicrobial stewardship.

The need for nutritional and rehydration therapy highlights that effective CDI management requires complementary care. Providing supplemental fluids and nutritional support not only mitigates the immediate effects of the infection but also sustains the patient's overall health and functional reserve. Attending to these aspects alongside targeted antimicrobial therapy for CDI may optimize treatment outcomes and facilitate recovery.

Constipation following FMT emerged as a notable concern once patients had stabilized after CDI treatment, prompting its inclusion in the updated checklist. Immediate gastrointestinal symptoms after FMT for both first and recurrent CDI have been reported in the literature[29,30], with post-FMT constipation described in 3%-25% of patients within 1-3 months post-procedure[31,32]. In our study, weekly monitoring by the geriatric team for gastrointestinal symptoms may have led to an overestimation of constipation prevalence. Conversely, we recorded constipation only when laxative treatment was required, which may have led to an underestimation of the true rate.

Our study has several strengths. Most importantly, it included approximately half of all *C. difficile*-positive patients within a specific geographic area. This broad catchment ensured diverse representation of older patients with CDI across multiple healthcare facilities, thereby enhancing the study's generalizability. Furthermore, our research provides valuable insights into managing CDI in older adults and is grounded in real-world practice. By addressing the multifaceted needs and challenges of this population, our study moves beyond isolated interventions, advocating for a holistic, context-sensitive approach to CDI management in everyday healthcare settings.

Important limitations apply. First, the development and use of the CDI checklist were confined to geriatricians, which may limit its applicability to other medical specialties and underscores the need for collaboration with geriatric teams. Future research should explore its implementation beyond geriatric contexts. Second, while the CLODIfrail study[10] found that

CGA organisational care (including the CDI checklist) was associated with enhanced outcomes, the independent clinical effect of the checklist remains uncertain. Rigorous evaluation of its implementation against predefined outcomes is therefore warranted. Third, reliance on retrospective review of electronic medical records may have introduced data incompleteness, potentially impacting the accuracy of our findings; however, Danish electronic medical records integrate updated information from primary and secondary care, bolstering data sufficiency.

Future application of the CDI checklist will depend on effective dissemination to clinical end-users and accessibility at the point of care. Future studies should explore the feasibility of embedding the checklist as a pop-up tool in electronic health records or hyperlinking it directly within microbiology reports via national platforms such as the Danish Microbiology Database. Additionally, incorporating the checklist into regional and national clinical guidelines may support its adoption and standardize care for older patients with CDI.

In conclusion, the CDI checklist presents a practical, standardized framework for managing CDI in older patients, integrating treatment, care planning, and management of concomitant comorbidities. Future research should prioritize evaluating its implementation and long-term sustainability across diverse clinical settings to determine its impact on clinical outcomes and inform broader adoption.

Acknowledgements

The authors express their gratitude to the collaborators at the participating medical departments.

Author contributions

All authors meet the ICMJE criteria for authorship. Study concept and design: Tone Rubak (TR), Christian Lodberg Hvas (CH), Simon Mark Dahl Baunwall (SMB), Sara Ellegaard Paaske (SEP), Rikke Kongensgaard (RK), Troels Kjærskov Hansen (TKH), Marianne Ørum (MØ). Acquisition of data: TR. Analysis and interpretation: TR, CH, SMB, SEP, RK, TKH, MØ. TR drafted the first manuscript version. All authors revised the manuscript for intellectual content and approved the final review.

Conflicts of interest statement

Simon Mark Dahl Baunwall reports speaker honoraria from Tillotts Pharma. Christian Lodberg Hvas reports research support from the Novo Nordisk Foundation (j.no. NNF22OC0074080) and speaker honoraria from Tillotts Pharma. All other authors declare no conflicts.

Funding

The study was conducted at the Department of Geriatrics, Aarhus University Hospital. The Department of Geriatrics covered administrative personnel costs. Financial support was obtained from Helsefonden (grant number 22-B-0239). The FMT framework was supported by Innovation Fund Denmark (j.no. 8056-00006B). Christian Lodberg Hvas received research support from the Novo Nordisk Foundation (j.no. NNF22OC0074080). The funders had no

role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Data availability statement

Upon reasonable request, data will be provided in anonymized form in accordance with European data regulations, specifically the General Data Protection Regulation. Access to pseudonymized participant data requires a formal data access agreement, and where necessary, approval from an ethics committee is also required.

Table legends

Table 1. Patient characteristics, patients aged ≥ 70 years with *Clostridioides difficile* infection in the Central Denmark Region. Development phase I (from 16 April to 14 October 2021) and development phase II (1 September 2022 to 1 August 2023).

Table 2. The *Clostridioides difficile* infection checklist. Descriptive summary of activities in development phase II.

405 **Table 1.**

	Phase I (N = 10)	Phase II (N=109)
Age, years (median (IQR))	84 (74-94)	79 (74-84)
Gender, n (%)		
Female	6 (60%)	61 (56%)
Charlson Comorbidity Index score (median (IQR))	1.5 (1-2)	3 (2-6)
Terminal disease registration before date of positive PCR test for CDI, n (%)	0 (0%)	5 (5%)
Primary disease requiring admission[a], n (%)		
Enteral infectious disease	1 (12.5)	29 (37)
Gastrointestinal disease	-	4 (5)
Cardiovascular disease	-	7 (9)
Pneumonia	1 (12.5)	6 (8)
Sepsis	1 (12.5)	5 (6)
Renal disease	-	11 (14)
Urinary tract infection	3 (38)	1 (1)
Chronic obstructive pulmonary disease	-	1 (1)
Dehydration and electrolyte disturbance	1 (12.5)	1 (1)
Rheumatic disease	-	2 (3)
Lesions and intoxication	-	2 (3)
Cancer	-	1 (1)
Malnutrition	-	1 (1)
Erysipelas	-	1(1)
Anemia	-	1(1)
Other skin diseases	-	1 (1)
Hip fracture	1 (12.5)	1 (1)
Frailty level[b], n (%)		
Low (MPI-1)	0 (0)	11 (10)
Moderate (MPI-2)	6 (60)	36 (33)
Severe (MPI-3)	4 (40)	32 (29)
Unknown	0 (0)	30 (28)
Habitation status, n (%)		
Living in one's own home	8 (80)	101 (93)
Nursing home resident	2 (20)	8 (7)
***C difficile*, number of infections, n (%)**		
First infection	5 (50)	96 (88)
Recurrent	5 (50)	13 (12)
***C difficile* diagnosis, site, n (%)**		
Primary healthcare	2 (20)	17 (16)
Outpatients	0 (0)	13 (12)
Inpatients	8 (80)	79 (72)
***C difficile* toxin and subtype profile[c], n (%)**		
Toxin A	9 (47)	98 (90)
Toxin B	9 (47)	107 (98)
Binary toxin	2 (11)	9 (8)
Subtype 027	0 (0)	0 (0)
***C difficile* case definition[d], n (%)**		
Healthcare facility-onset (HO)	1 (10)	50 (45)
Community-associated, healthcare facility-associated (CO-HCFA)	5 (50)	29 (27)
Community-associated (CA)	4 (40)	30 (28)

406
407 [a]The diagnoses are accessible only for patients admitted to hospital.
408 [b]Record-based MPI was performed only in patients diagnosed with CDI during hospital admission. Patients diag-
409 nosed in primary healthcare or outpatient settings were registered with an unknown MPI because of missing in-
410 formation from electronic medical records.
411 [c]Patients can have a combined toxin profile, but data on combined toxin profile was not collected.

[d]HO: case of CDI collected > 3 days after admission to facility; CO-HCFA: case of CDI occurring within 28 days after discharge from a healthcare facility; CA: case of CDI occurring more than 28 days after discharge from a healthcare facility.

Abbreviations: PCR: Polymerase chain reaction; *C. difficile*: *Clostridioides difficile;* CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index.

418 **Table 2.**

Activity	N = 108 n (%)
1) CDI treatment care planning	
Describe CDI clinical status	108 (100)
Blood analyses (electrolytes, renal function, albumin, CRP, leucocytes, hemoglobin)	96 (89)
Start vancomycin peroral or bactocin oral suspension (probe) 125 mg x 4. Continue vancomycin at least 10 days or until the day before fecal microbiota transplantation (FMT).	108 (100)
Perform the Multidimensional Prognostic Index (MPI)	108 (100)
Geriatric assessment of indication for fecal microbiota transplantation (FMT) and treatment care planning.	108 (100)
Deliver information material to the patient	108 (100)
Deliver stool diary to the patient and/or primary caregivers.	108 (100)
Corresponding letter to the general practitioner and primary healthcare	108 (100)
2) Medication review	
Antibiotics (other than vancomycin): discontinue if possible (N = 50[a])	26 (52)
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent catheterization, etc.)	19 (18)
Laxative: discontinue (N = 15[a])	14 (93)
Proton pump inhibitor: discontinue if possible (N = 56[a])	39 (70)
Diuretics: consider reduction during active diarrhea (renal function) N = 60[a]	23 (38)
3) Rehydration and nutrition	
Nutrition: consider need for nutrition therapy and monitoring	64 (59)
Rehydration therapy: consider need for rehydration and monitoring	61 (56)
Consider other reasons for diarrhea! (e.g., inflammatory bowel disease, cancer, microscopic colitis)	62 (57)

419
420 [a]Only patients already in antibiotic, laxative, proton-pump inhibitor or diuretic treatment at the time of the CDI

421 Abbreviations: CDI: *Clostridioides difficile* infection; MPI: Multidimensional Prognostic Index; FMT: fecal mi-
422 crobiota transplantation
423

Figure legends

Figure 1. Driver diagram addressing treatment and care challenges in older patients with CDI.

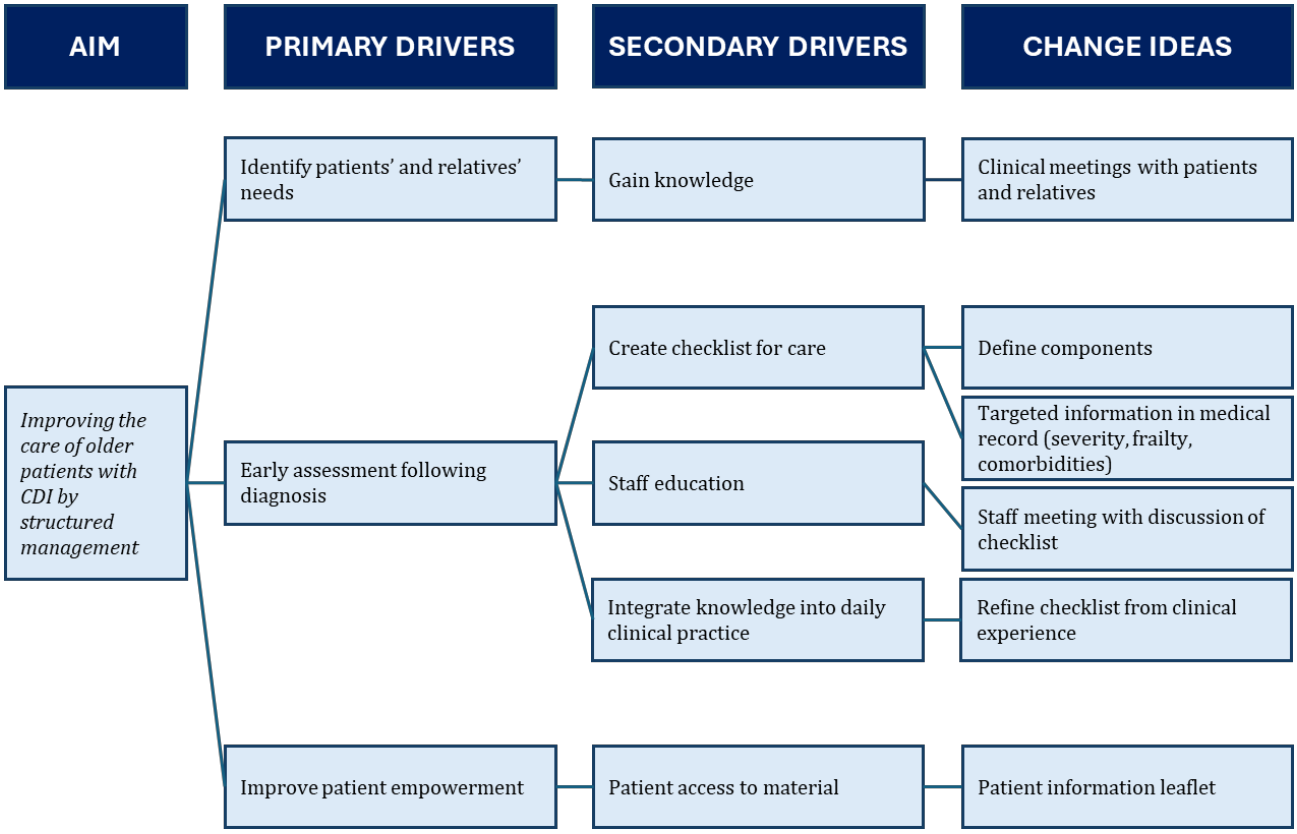
Figure 2. Steps for development of the *Clostridioides difficile* infection checklist. Method flow illustration according to the P: Plan, D: Do, S: Study, A: Act model[11].

Abbreviations: CDI: *Clostridioides difficile* infection.

Figure 3. *Clostridioides difficile* infection, revised checklist (phase II).

435 **Figure 1**

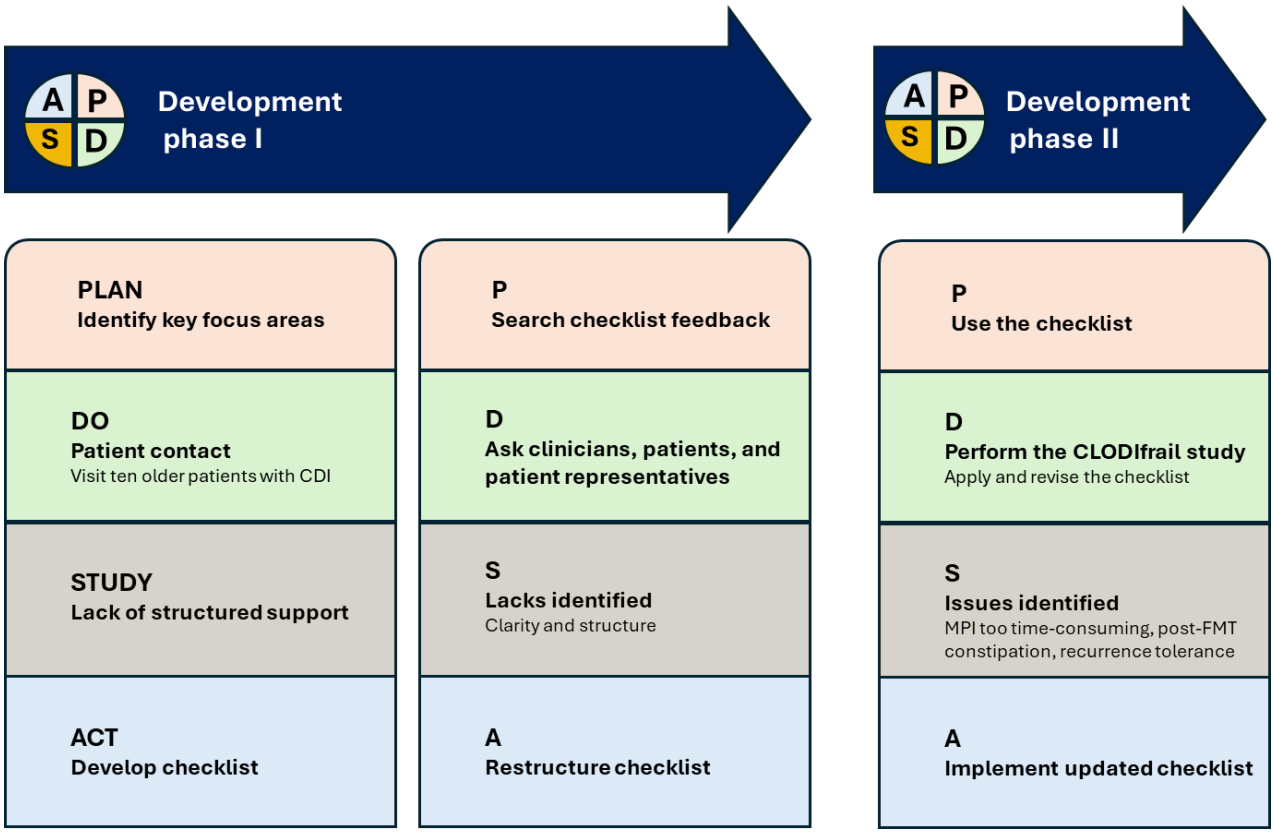
436



437

438 **Figure 2**

439



440

441

442 **Figure 3**

Patient label_____

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Clostridioides difficile infection – check list for older patients

***Clostridium difficile* infection (CDI), definition** ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.		
	Done	Not relevant
1) Care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin oral tablets or suspension (probe) 125 mg x 4 Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT) Evaluate clinical response on day 5-6. If no clinical response, consider other reasons for diarrhoea (e.g. inflammatory bowel disease, cancer, microscopic colitis) Consider shift of treatment to Fidaxomicin or rescue FMT	☐	☐
Perform Comprehensive geriatric assessment as part of clinical evaluation	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning. Consider whether the patient can tolerate recurrent CDI? Consider the need for coordination of CDI treatment across specialties.	☐	☐
Hand out patient leaflet about C. difficile infection and FMT, including information on risk of post-FMT obstipation	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent catheterization in case of significant post void residual etc.)	☐	☐
Laxative: discontinue if possible	☐	☐
Proton pump inhibitor: discontinue if possible. If discontinuation is not possible at time of assessment, reduced dose may be first step towards this ultimate goal	☐	☐
Diuretics: consider reduction during active diarrhea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
All patients have clinical contact to geriatric department once weekly or more frequently if clinical indication during 8 weeks from date of last FMT or completed vancomycin treatment		

All activities are registered in the electronic medical journal.

443

References

1. Leffler DA, Lamont JT. Clostridium difficile infection. *N Engl J Med* 2015; 372(16): 1539-48.
2. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; 372(9): 825-34.
3. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. *PLoS One* 2014; 9(6): e98400.
4. Ticinesi A, Nouvenne A, Folesani G, et al. Multimorbidity in elderly hospitalised patients and risk of Clostridium difficile infection: a retrospective study with the Cumulative Illness Rating Scale (CIRS). *BMJ Open* 2015; 5(10): e009316.
5. Rubak T, Baunwall SMD, Gregersen M, et al. Frailty level at discharge predicts mortality in older patients with Clostridioides difficile more accurately than age or disease severity. *Eur Geriatr Med* 2023; 14(3): 583-93.
6. Baunwall SMD, Dahlerup JF, Engberg JH, et al. Danish national guideline for the treatment of Clostridioides difficile infection and use of faecal microbiota transplantation (FMT). *Scand J Gastroenterol* 2021; 56(9): 1056-77.
7. Caupenne A, Ingrand P, Ingrand I, et al. Acute Clostridioides difficile Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality. *J Am Med Dir Assoc* 2020; 21(1): 110-4.
8. Parker SG, McCue P, Phelps K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* 2018; 47(1): 149-55.
9. Ellis G, Gardner M, Tsiachristas A, et al. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev* 2017; 9: Cd006211.
10. Rubak T, Baunwall SMD, Gregersen M, et al. Early geriatric assessment and management in older patients with Clostridioides difficile infection in Denmark (CLODIfrail): a randomised trial. *Lancet Healthy Longev* 2024; 5(12): 100648.
11. Langley G MR, Nolan K et al. The Improvement guide, 2nd edn. San Fransisco: Jossey-Bass A Wiley Imprint; 2009.
12. University A. Center for Faecal Microbiota Transplantation. Available at: www.cefta.au.dk. Accessed August 13, 2025.
13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42(2): 377-81.
14. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res* 2008; 11(1): 151-61.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40(5): 373-83.
16. Hansen TK, Damsgaard EM, Shahla S, Bruun JM, Gregersen M. A reliable and record-based frailty assessment method for older medical inpatients. *Eur Geriatr Med* 2020; 11(5): 803-12.

17. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; 66(7): 987-94.
18. World Medical Association. WMA Declaration of Helsinki - ethical principles for medical research involving human subjects. 2022. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/2024). Accessed August 13, 2025.
19. Cheng YW, Phelps E, Nemes S, et al. Fecal Microbiota Transplant Decreases Mortality in Patients with Refractory Severe or Fulminant Clostridioides difficile Infection. *Clin Gastroenterol Hepatol* 2020; 18(10): 2234-43.e1.
20. de Belvis AG, Barbara A, Giubbini G, et al. Impact evaluation of a Critical Pathway for patients with Clostridium difficile infection: A pre-post analysis in a Third Level Referral Center. *Int J Infect Dis* 2019; 80: 105-10.
21. Denmark IaHo. Health reform agreement 2024. Available at: https://www.ism.dk/publikationer-sundhed/2024/november/aftale-om-sundhedsreform-2024. Accessed August 13, 2025.
22. Dohrendorf CM, Unkel S, Scheithauer S, et al. Reduced Clostridioides difficile infections in hospitalised older people through multiple quality improvement strategies. *Age and ageing* 2021; 50(6): 2123-32.
23. Louh IK, Greendyke WG, Hermann EA, et al. Clostridium Difficile Infection in Acute Care Hospitals: Systematic Review and Best Practices for Prevention. *Infect Control Hosp Epidemiol* 2017; 38(4): 476-82.
24. Abbett SK, Yokoe DS, Lipsitz SR, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated Clostridium difficile infection. *Infect Control Hosp Epidemiol* 2009; 30(11): 1062-9.
25. Muto CA, Blank MK, Marsh JW, et al. Control of an outbreak of infection with the hypervirulent Clostridium difficile BI strain in a university hospital using a comprehensive "bundle" approach. *Clin Infect Dis* 2007; 45(10): 1266-73.
26. Centers for disease control and prevention. Core elements of hospital antibiotic stewardship programs. Available at: https://www.cdc.gov/antibiotic-use/hcp/core-elements/hospital.html. Accessed June 23, 2025.
27. Kristensen PK, Johnsen SP, Thomsen RW. Decreasing trends, and geographical variation in outpatient antibiotic use: a population-based study in Central Denmark. *BMC Infect Dis* 2019; 19(1): 337.
28. Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; 17(9): 990-1001.
29. Baunwall SMD, Andreasen SE, Hansen MM, et al. Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol* 2022; 7(12): 1083-91.
30. Hvas CL, Dahl Jorgensen SM, Jorgensen SP, et al. Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection. *Gastroenterology* 2019; 156(5): 1324-32 e3.

31. Agrawal M, Aroniadis OC, Brandt LJ, et al. The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated clostridium difficile infection in 146 elderly individuals. *Journal of clinical gastroenterology* 2016; 50(5): 403-7.
32. Saha S, Mara K, Pardi DS, Khanna S. Long-term Safety of Fecal Microbiota Transplantation for Recurrent Clostridioides difficile Infection. *Gastroenterology* 2021; 160(6): 1961-9.e3.

Supplemental material

Manuscript title

Development of a checklist to support management of older patients with *Clostridioides difficile* infection

Corresponding author

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Table of contents

Supplementary S1. Patient information material regarding *Clostridioides difficile* infection and treatment. The material is reproduced from supplementary of Rubak et al. Lancet Healthy Longev 2024; 5(12):100648.

Clostridioides difficile infection and fecal microbiota transplantation

Clostridioides difficile is a bacterium that can cause serious infection of the intestine. In the older patient, where other illness has caused weakness, infection with *Clostridioides difficile* can become serious. The infection tends to come back. What is typically experienced is numerous diarrhoea, nausea, reduced appetite, dehydration, fever, fatigue, weight loss, and increased sadness. Some patients lose the will to live because of a loss of energy.

We identify the infection using a stool sample supplemented with blood tests. Treatment is started with an antibiotic targeting the *Clostridioides difficile* bacterium, following supply of healthy intestinal bacteria.

Fecal microbiota transplantation

Supply of healthy intestinal bacteria is also called fecal microbiota transplantation (FMT). There are no known side effects or late effects of FMT in patients who do not have other bowel diseases. The healthy intestinal bacteria come from donors affiliated with the Department of Hepatology and Gastroenterology, Aarhus University Hospital. Strict requirements are placed on the donors equal to the Danish blood donor system. Donors are anonymous.

Fecal microbiota transplantation can take place in three ways:

1. Via capsules taken orally over 30-45 minutes
2. Via tube to the intestine
3. Via endoscopy of the intestine (colonoscopy)

Regardless of which type you are offered, we will follow up with you through the Department of Geriatrics.

Clinical follow-up contacts

Many older patients with *Clostridoides difficile* infection are severely weakened and need supportive treatment with fluids and nutrition including close monitoring of gastrointestinal symptoms. We offer clinical follow-up by staff trained in diseases in older patients. The purpose is to ensure an evaluation of the gastrointestinal symptoms and early start of treatment if indication for this.

How does the follow-up take place?

The follow-up involves a visit from the outgoing geriatric team when you have received the diagnosis and a weekly telephone contact regarding evaluation of the gastrointestinal-related symptoms. If there is a need for further visits, treatment, or supportive therapy, this will take place in your own home via the outgoing geriatric teams.

What should I be aware of?

In case of changes in bowel movements, abdominal pain, nausea, reduced fluid intake/nutrition, you/your relatives should contact the Department of Geriatrics. In need of antibiotics other than the antibiotics used to treat *Clostridioides difficile* infection, you must contact the Department of Geriatrics regarding treatment strategy because antibiotics can trigger a relapse of the infection. Transmission of the infection occurs with feces and bacterial spores in the immediate surroundings of the patient. Handwash followed by hand disinfection must be carried out before leaving the

patient. It is important to use water/soap or chloring alcohol. We recommend that health personnel wear plastic aprons and gloves to reduce infection transmission.

What are my responsibilities?

At termination we will ask you to deliver a stool sample to test for *Clostridioides difficile*. We will hand out a feces kit and ask you to send/deliver it to the Department of Microbiology.

Contact information

(…).

Supplementary Table S2. Standardised headlines for documenting *Clostridioides difficile* infection. The table is reproduced from supplementary of Rubak et al. Lancet Healthy Longev 2024; 5(12):100648.

Name (code)	Standard headlines
CDI clinical status at first contact (cdi1)	Abdominal pain? Number of stools per day? Bristol type? Fecal incontinence? Loss of appetite? Is the patient a candidate for fecal microbiota transplantation according to a geriatric assessment? Plan: The patient is affiliated with the Department of Geriatrics for the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile* (CDI). Please contact the Department of Geriatrics if there is an indication for antibiotics other than CDI-related antibiotics. Please contact the Department of Geriatrics in case of recurrent CDI. Contact information (…)
Correspondence letter for primary health care (cdi2)	The patient is affiliated with the Department of Geriatrics for the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile* (CDI).. Please send the weekly status of the following (correspondence letters/telephone contact): Abdominal pain? yes/no Number of daily stools Bristol type Appetite? Is the patient overall improving, status quo, or clinically worsening? Please contact the Department of Geriatrics if there is an indication for antibiotics other than CDI-related antibiotics. Please contact the Department of Geriatrics in case of increasing diarrhea, abdominal pain, or waning general condition. Contact information (…)
Correspondence letter for general practitioner (cdi3)	The patient is affiliated with the Department of Geriatrics for the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile* (CDI).. Please contact the Department of Geriatrics if there is an indication for antibiotics other than CDI-related antibiotics. Please contact the Department of Geriatrics in case of increasing diarrhea, abdominal pain, or waning general condition. Contact information (…)

Supplementary Table S3. The iterative adjustments to the *Clostridioides difficile* infection checklist during the development phase

Version	Change
Pre CLODifrail study	
01	Add a checkbox for easier item tracking
02	Add CDI definition Add planning for FMT, estimated date for FMT and plan for vancomycin initiation
03	Add preventive strategies to reduce antibiotic use Add reminder to clinicians of considering other diagnoses for diarrhea Add key contact information
04	Move CDI definition to the top to ensure diagnostic clarity
05	Add a field prompting use of standardized correspondence Add a field to ensure a plan for follow-up
06	Add stool diary to the patients and/or primary caregivers
07	Add hand out patient leaflet about *Clostridioides difficile* infection and FMT
08	Restructure the checklist into three core domains 1) CDI treatment and care planning, 2) medication review, 3) Rehydration and nutrition
Post CLODIfrail study	
09	Add "if possible" to ensure discontinuation of laxative treatment Add "If discontinuation is not possible at time of assessment, reduced dose may be the first step towards this ultimate goal" to proton-pump-inhibitor treatment
10	Move "consideration of other reasons for diarrhea" to the beginning of the checklist to avoid automation of CDI assessment and treatment
11	Add a reminder to educate patients undergoing FMT to manage constipation if it arises
12	Add the reminder: "Consider the need for coordination of CDI treatment across specialties"
13	Replace the MPI with CGA
14	In the geriatric assessment of the indication for FMT, add reminder to the clinicians to consider whether the patient can tolerate recurrence of CDI

Abbreviations: CDI: Clostridioides difficile infection; FMT: fecal microbiota transplantation; MPI: multidimensional prognostic index; CGA: comprehensive geriatric assessment

Supplementary Figure S4. *Clostridioides difficile* infection checklist (phase I). The figure is reproduced from supplementary of Rubak et al. Lancet Healthy Longev 2024; 5(12):100648.

Patient label_____

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Clostridioides difficile infection – check list for older patients

Patients with Clostridioides difficile infection (CDI) during hospital admission or at home.

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.		
	Done	Not relevant
1) CDI treatment care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin peroral or bactocin oral suspension (probe) 125 mg x 4. Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT).	☐	☐
Perform the Multidimensional Prognostic Index	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning.	☐	☐
Deliver information material to the patient	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent cathetherization etc.)	☐	☐
Laxative: discontinue	☐	☐
Proton pump inhibitor: discontinue if possible	☐	☐
Diuretics: consider reduction during active diarrhoea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
Consider other reasons for diarrhoea! (e.g. inflammatory bowel disease, cancer, microscopic colitis)	☐	☐
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT or completed vancomycin treatment.		

All activities are registered in the electronic medical journal.

12. Co-authorship declarations

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Tone Maria Mørck Rubak

This declaration concerns the following article/manuscript:

Title:	Frailty level at discharge predicts mortality in older patients with Clostridioides difficile infection more accurately than age or disease severity
Authors:	Rubak T, Baunwall SMD, Gregersen M, Hansen TK, Rosenbæk JB, Erikstrup LT, Hvas CL, Damsgaard EM

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Rubak T, Baunwall SMD, Gregersen M, et al. Frailty level at discharge predicts mortality in older patients with Clostridioides difficile more accurately than age or disease severity. Eur Geriatr Med 2023; 14(3): 583-93. doi: 10.1007/s41999-023-00772-3

If accepted or submitted, state journal: European Geriatric Medicine

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student designed the database and took active part in conceptualisation under supervision from all supervisors.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student collected all data from electronic medical records, entered all data in the database and coordinated and conducted the main part of data analysis with supervision from the supervisors.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student was primarily responsible for drafting the manuscript and wrote the first version and revised it according to input from co-authors.	
Submission process including revisions:	A

AARHUS UNIVERSITY

Free text description of PhD student's contribution ***(mandatory)***   The PhD student drafted the manuscript, revised it according to inputs from co-authors and led the drafting process.

Submission process including revisions:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student was responsible for submitting the manuscript, preparing the point-by-point response to reviewers, and revising the manuscript following peer review.	

Signatures of first- and last author, and main supervisor

Date	Name	Signature
12.8.25	Tone Maria Mørck Rubak	
14/8 25	Else Marie Skjøde Damsgaard	
12.8.25	Christian Lodberg Hvas	

Date: 12.8.25

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Tone Maria Mørck Rubak

This declaration concerns the following article/manuscript:

Title:	Clostridioides difficile infection in frail older patients, quality in treatment and care: the CLODIFrail study protocol for a multicentre randomized controlled trial
Authors:	Rubak T, Veilbæk H, Gregersen M, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Ørum M, Vinding RS, Sørensen CAK, Steves CJ, Baunwall SMD, Hvas CL, Damsgaard EM

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Rubak T, Baunwall SMD, Gregersen M, et al. Early geriatric assessment and management in older patients with Clostridioides difficile infection in Denmark (CLODIfrail): a randomised trial. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648 (Published as Supplementary file no 1)

If accepted or submitted, state journal: Lancet Healthy Longevity

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

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B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The PhD student designed the study question and the practial organisation of its conduct in collaboration with the supervisors.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** Given that this was a protocol article, no data acquisition or analysis was conducted. Nonetheless, the PhD student planned the data collection and statistical analysis in collaboration with the supervisory team and external statistical experts.	
Drafting the manuscript:	B

AARHUS UNIVERSITY

Free text description of PhD student's contribution ***(mandatory)***   The PhD student drafted the manuscript and prepared the first version. The subsequent revisions were made in consultation with the co-author group.
Submission process including revisions: A
Free text description of PhD student's contribution ***(mandatory)***   The PhD student did the submission and revisions.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
12.8.25	Tone Maria Mørck Rubak	
14.8.25	Else Marie Skjøde Damsgaard	
12.8.25	Christian Lodberg Hvas	

Date: 12.8.25

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Tone Maria Mørck Rubak

This declaration concerns the following article/manuscript:

Title:	Early geriatric assessment and management in older patients with Clostridioides difficile infection (CLODIfrail) – a randomised trial
Authors:	Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Asferg M, Barat I, Secher-Johnsen J, Riis MG, Rosenbæk JB, Hansen TK, Ørum M, Steves CJ, Veilbæk H, Hvas CL, Damsgaard EM

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Rubak T, Baunwall SMD, Gregersen M, et al. Early geriatric assessment and management in older patients with Clostridioides difficile infection in Denmark (CLODIfrail): a randomised trial. Lancet Healthy Longev 2024; 5(12): 100648. doi: 10.1016/j.lanhl.2024.100648

If accepted or submitted, state journal: Lancet Healthy Longevity

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

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Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student participated in the design of the study and designed the practical organisation of its conduct.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student screened and included approximately all patients in the project, treated patients, collected all data from the electronic medical records, led the data analysis and provided the first interpretation of data. Statistical assistance was provided.	
Drafting the manuscript:	A

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Free text description of PhD student's contribution ***(mandatory)***
The PhD student contributed actively in the revision process with revision up until final acceptance.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
12.8.25	Tone Maria Mørck Rubak	
14.8.25	Else Marie Skjøde Damsgaard	
12.8.25	Christian Lodberg Hvas	

Date: 12.8.25

Signature of the PhD student

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Tone Maria Mørck Rubak

This declaration concerns the following article/manuscript:

Title:	Development of a geriatric checklist to support management of older patients with Clostridioides difficile infection
Authors:	Rubak T, Baunwall SMD, Gregersen M, Paaske SE, Ørum M, Kongensgaard R, Hansen TK, Gregersen M, Hvas CL

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Journal of the American Geriatrics Society

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student formulated key elements of the integration of quality improvement framework.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student collected all data from electronic medical records, entered all data in the database and conducted the data analysis and interpretation.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student independently prepared the initial manuscript draft.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
The PhD student handled the submission process as corresponding authur, including cover letter, supplements, communication with the journal.

Signatures of first- and last author, and main supervisor

Date	Name	Signature
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