EPH73

Risk Factors for Recurrences of Clostridioides Difficile Infection in the Medicare Population Age 65+

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FERRING PHARMACEUTICALS

Introduction

- *Clostridioides difficile* infection (CDI) is the most common healthcare-associated infection in the U.S., especially in older patients, affecting an estimated 462,100 persons in 2017. Recurrent CDI remains one of the most difficult treatment challenges for clinicians, with estimates of 31,300 and 38,500 recurrences for community-associated and healthcare-associated cases, respectively, in 2017.[1-3]
- Up to 35% of patients who develop CDI will experience a recurrence (rCDI), and up to 65% of patients who develop at least one recurrence will develop a subsequent recurrence.[4-10] rCDI is associated with higher likelihood of death and higher healthcare utilization compared with primary CDI (pCDI).[11]
- Risk factors such as advanced age and history of partial colectomy have been associated with higher rates of CDI recurrence in the U.S.[12]

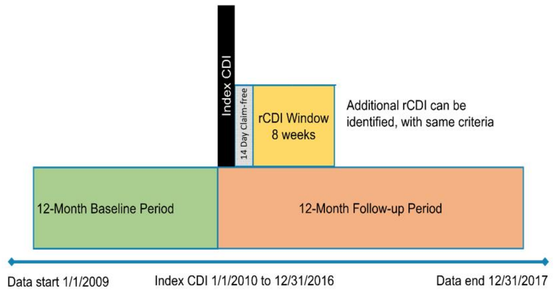
Objective

To assess risk factors and quantify rate of risk for CDI patients experiencing 1, 2, and 3+ recurrences.

Methods

- This retrospective study utilized 100% Medicare Fee-for-Service (FFS) claims data from 2009-2017 to identify patients age ≥65 with ≥1 CDI episode. The study population included patients with index CDI diagnosis between January 1, 2010 through December 31, 2016 and continuously enrolled in Parts A & B (medical), and Part D (pharmacy), for 12 months before CDI index date and up to 12 months after index CDI episode and with no evidence of CDI in pre-index period.
- The pCDI index episode began on the date of the first CDI medical claim and included all subsequent claims with CDI diagnosis with no more than a 14-day gap. (Figure 1)
- The pCDI episode was identified as ≥1 inpatient stay with CDI diagnosis code (primary or secondary diagnosis field) (ICD codes 008.45; A04.7, A04.71, A04.72), or ≥1 outpatient medical claim with CDI diagnosis plus evidence of CDI treatment (use of antibiotics including vancomycin, fidaxomicin, metronidazole, rifaximin, and bezlotoxumab, or fecal microbiota transplant).
- Recurrent (rCDI) episodes started within 8-weeks from the end of a previous CDI episode. CDI episodes starting beyond the 8-week window were considered new episodes and were excluded from the analysis.[13]

Figure 1. Primary CDI and Recurrent CDI Definitions



Statistical Analyses

- Baseline demographic characteristics were calculated on index date including age, gender, race/ethnicity, geographic region, dual eligible status for Medicare and Medicaid, and original reason for entitlement to Medicare (age 65 or disability and/or end stage renal disease), and Charlson Comorbidity Index (CCI).
- Multivariate logistic regression models were developed to assess probability of recurrence using 12-month pre-index baseline demographics and healthcare resource use.
- Odds-ratios (OR) were estimated to assess risk of 1rCDI vs. pCDI, 2rCDI vs. 1rCDI, and 3+rCDI vs. 2rCDI.
- Summary statistics included estimates, p-values, and odds ratios (OR)

RESULTS

Baseline Patient Characteristics (Table 1)

- 497,489 CDI patients were included; of these:
  - Patients who died were approximately 2 years older and more likely to be male, Black, and dual eligible for Medicaid (i.e., low income). They also had higher CCI scores indicating higher number of comorbidities.
  - 69.5% had pCDI only, 13.7% had 1rCDI, 7.4% 2rCDI, and 9.4% 3+rCDI.

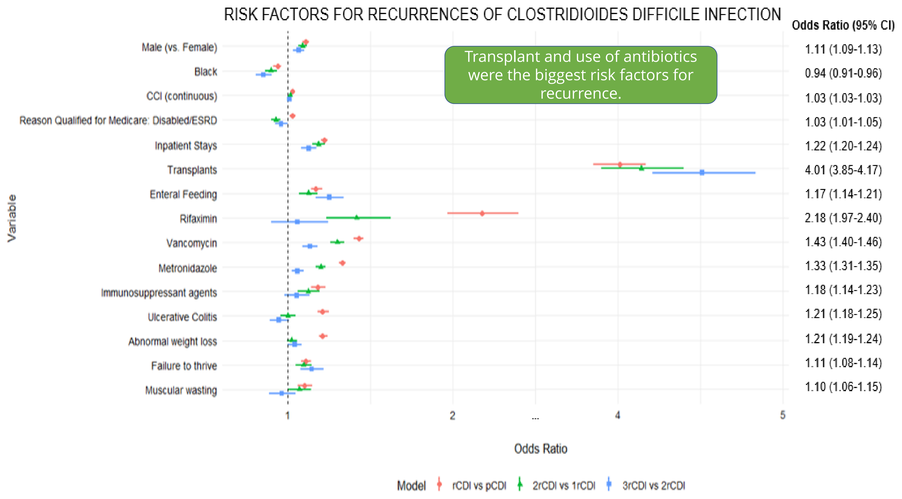
42.8% of all CDI patients died within the study period

Table 1. Baseline Patient Characteristics

		Primary CDI Only Cohort		1rCDI Cohort		2rCDI Cohort		≥3rCDI Cohort	
		Total Survived N = 186,996 (54.1%)	Total Deaths N=158,897 (45.9%)	Total Survived N = 40,277 (59.2%)	Total Deaths N = 27,806 (40.8%)	Total Survived N = 24,033 (65.4%)	Total Deaths N = 12,713 (34.6%)	Total Survived N = 33,428 (71.5%)	Total Deaths N = 13,339 (28.5%)
Baseline Characteristics									
Age	Mean (SD)	78.4 (8.0)	81.5 (8.5)	78.0 (7.9)	80.6 (8.3)	78.2 (7.9)	80.6 (8.3)	77.8 (8.0)	80.0 (8.6)
Gender (%)	Female	68.9	61.7	68.8	61.3	68.9	60.7	67.3	59.8
	Male	31.1	38.3	31.2	38.7	31.1	39.3	32.7	40.2
Race (%)	White	85.6	81.8	86.3	80.7	87.0	81.9	88.5	83.3
	Black	8.7	11.6	8.4	12.8	8.0	11.9	6.7	10.7
	Hispanic/Latino	2.2	2.6	2.0	2.6	2.0	2.7	1.9	2.4
	Asian	1.6	2.1	1.4	2.1	1.2	1.7	1.1	1.5
	Native American	0.6	0.5	0.6	0.5	0.5	0.5	0.5	0.6
	Unknown	1.3	1.4	1.3	1.3	1.2	1.3	1.3	1.5
Dual Eligible for Medicaid (%)		35.3	40.6	33.6	43.7	32.9	45.1	31.9	45.5
CCI Score	Mean (SD)	5.0 (3.4)	7.2 (3.6)	5.2 (3.4)	7.2 (3.6)	5.2 (3.5)	7.2 (3.6)	5.2 (3.5)	7.2 (3.6)
Medical Procedures and Treatments (N, %)									
Transplants		1.4	2.4	2.4	2.5	3.4	3.8	12.7	12.3
Gastrointestinal surgery		29.9	32.8	31.7	35.0	30.8	33.8	30.3	33.5
Enteral Feeding		3.9	8.4	4.5	9.0	4.1	8.7	4.2	9.9
Chemotherapy		43.7	51.4	45.1	52.3	45.7	54.5	49.8	58.0

CCI = Charlson Comorbidity Index score

Figure 2. Risk Factors for Recurrence (1rCDI vs. 2rCDI vs. 3rCDI) Outcomes



*Reference Groups: Reason Qualified: Age 65, Race/Ethnicity : White
**CDI: Clostridioides difficile infection; rCDI:recurrences of CDI; pCDI:pre-index primary CDI
***Showing values with a p value<0.05

Outcomes (Figure 2)

- Risk of recurrence was 4-4.5 times higher for transplant patients (p<0.0001)
- Antibiotic use during pre-index period was the next highest risk factor for recurrence:
  - Rifaximin increased likelihood of 1rCDI by 2.2 times and 2rCDI by 42% (p<0.0001).
  - Vancomycin increased likelihood of 1rCDI by 43%, 2rCDI by 30%, and 3rCDI by 13% (p<0.0001).
  - Metronidazole also increased likelihood of recurrences, including 33% higher risk of 1rCDI, 20% higher risk for 2rCDI, and 6% higher risk of 3rCDI (p<0.001).
- Use of immunosuppressant agents increased risk for first and second recurrences (OR: 1.18 1rCDI, 1.12 2rCDI; p<0.0001).
- Having an inpatient stay during baseline increased likelihood of rCDI by 22%, 2rCDI by 19%, and 3rCDI by 13%.
- A 1-point higher CCI score was associated with 3% greater likelihood of 1rCDI, 2% higher likelihood of 2rCDI, and 1% higher likelihood of 3+rCDI.
- Enteral feeding during pre-index period increased likelihood of 1rCDI by 17%, 2rCDI by 13%, and 3rCDI by 25%.
- Ulcerative colitis and abnormal weight loss were associated with 21% greater likelihood of 1rCDI (p<.0001) but did not increase risk of further recurrence.
- Pressure ulcer in baseline increased risk of 1rCDI by 17% (p<.0001), 2rCDI by 4% (p=0.032), and 3rCDI by 8% (p=0.001).
- Frailty conditions[14] were associated with higher likelihood of recurrences, including failure to thrive (11% higher risk of 1rCDI) and muscular wasting or weakness (8-10% higher risk of 1rCDI).
- Males were 11% more likely to have 1rCDI, 9% more likely to have 2rCDI, and 7% more likely to have 3rCDI (P<.0001) compared to females. Blacks were somewhat less likely to have recurrences (p<.0001).

CONCLUSIONS

- Transplant was the strongest predictor of multiple CDI recurrences, followed by antibiotic use prior to an index CDI. Having a prior inpatient stay was also associated with higher likelihood of recurrence.
- Male gender was associated with higher risk of recurrence while Black and other minority race was associated with lower likelihood of any recurrence.
- Ulcerative colitis was strongly associated with likelihood of 1 recurrence, but no significant association with further recurrences.
- New therapies to reduce CDI recurrences are needed to improve outcomes and reduce economic and clinical burden to patients, payers, and providers.

Limitations

- The Medicare claims data do not include claims for Medicare beneficiaries enrolled in private Medicare Advantage plans. Patients insured by other payers such as commercial, Medicaid and Veterans Administration coverage are not captured in the data.
- This study was descriptive in nature and cannot be used to determine cause and effect as temporality cannot be truly established with the use of claims data. In addition, the identification of the subpopulation conditions relies on accurate reporting of the ICD9/10 diagnosis codes on clams; therefore, misclassification of the cohorts is possible.

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- This study was sponsored by Ferring Pharmaceuticals (Parsippany, NJ)
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Disclosures

- Dr. Amy Guo is an employee of Ferring Pharmaceuticals
- Dr. Amin Alpesh serves as PI or co-I of clinical trials sponsored by NIH/NIAID, NeuroRx Pharma, Pulmotect, Blade Therapeutics, Novartis, Takeda, Humanigen, Eli Lilly, PTC Therapeutics, OctaPharma, Fulcrum Therapeutics, Alexion, unrelated to the present study; speaker and/or consultant for BMS, Pfizer, BI, Portola, Sunovion, Mylan, Salix, Alexion, AstraZeneca, Novartis, Nabriva, Paratek, Bayer, Tetraphase, Achogen LaJolla, Ferring, Seres, Eli Lilly, Spero, Millenium, PeraHealth, HeartRite, Aseptiscope, Sprightly, unrelated to the present study.
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REFERENCES

1. Ma, G.K., et al., Increasing Incidence of Multiply Recurrent Clostridium Difficile Infection in the United States: A Cohort Study. Ann Intern Med, 2017. 167(3): p. 152-158.
2. Guh, A.Y., et al., Trends in U.S. Burden of Clostridioides difficile Infection and Outcomes. N Engl J Med, 2020. 382(14): p. 1320-1330.
3. Magill, S.S., et al., Changes in Prevalence of Health Care-Associated Infections in U.S. Hospitals. N Engl J Med, 2018. 379(18): p. 1732-1744.
4. Cornely, O.A., et al., Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis, 2012. 55 Suppl 2: p. S154-61.
5. Deshpande, A., et al., Risk factors for recurrent Clostridium difficile infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol, 2015. 36(4): p. 452-60.
6. Garey, K.W., et al., Meta-analysis to assess risk factors for recurrent Clostridium difficile infection. J Hosp Infect, 2008. 70(4):
7. p. 298-304.
8. Leffler, D.A. and J.T. Lamont, Clostridium difficile Infection. N Engl J Med, 2015. 373(3): p. 287-8.
9. Smits, W.K., et al., Clostridium difficile infection. Nature Reviews Disease Primers, 2016. 2.
10. Leong, C. and S. Zelenitsky, Treatment Strategies for Recurrent Clostridium difficile Infection. Can J Hosp Pharm, 2013. 66(6): p. 361-8.
11. Rodrigues, R., G.E. Barber, and A.N. Ananthakrishnan, A Comprehensive Study of Costs Associated With Recurrent Clostridium difficile Infection. Infection Control and Hospital Epidemiology, 2017. 38(2): p. 196-202.
12. Dharbhamulla, N, et al., Risk factors associated with recurrent Clostridium difficile infection. J Clin Med Res, 2019. 11(1): p. 1-6.
13. Centers for Disease Control and Prevention. "Clostridioides difficile infection (CDI) tracking." https://www.cdc.gov/hai/eip/cdiff-tracking.html. ." (accessed April 21, 2022).
14. Kim DH, Schneeweiss S. Measuring frailty using claims data for pharmacoepidemiologic studies of mortality in older adults: evidence and recommendations. Pharmacoepidemiol Drug Saf. 2014;23(9):891–901.