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Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee. This manuscript adheres to the applicable Equator guidelines.

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Abstract:

Aim: A diverting ileostomy is typically performed to divert intestinal contents in high-risk colorectal anastomoses. Ileostomy closure is associated with high rates of post-operative Clostridium difficile infection (CDI). Risk factors for the development of CDI are unclear, however, a correlation has been observed with delayed closure. This study aims to assess the odds of developing CDI in patients who had a delay to reversal of ileostomy, compared to those who had no delay.

Methodology: A retrospective cohort study was conducted of patients undergoing reversal of ileostomy between 2010 and 2019 at a single tertiary centre. A delay to reversal of ileostomy was defined if the procedure was performed at >365 days following the index procedure. CDI was defined as the presence of Clostridium difficile toxin associated with diarrhoea. Univariable logistic regression analysis was performed to estimate odds of CDI for each co-variable, comparing patients who had a delay to reversal of ileostomy with those who did not. Multivariable logistic regression analysis was used to adjust for the potential confounding effects of covariables.

Results: Of 195 patients, 11 (5.6%), developed post-operative Clostridium difficile infection. Multivariable analysis showed that delay to reversal of ileostomy was associated with a nearly 7-fold increase in odds of Clostridium difficile infection (OR = 6.95, CI: 1.06-81.6; p-value =0.03).

Conclusion: A delay to reversal of ileostomy of >365 days was associated with a higher incidence of Clostridium difficile infection post-operatively. Careful consideration should be given to the timing of reversal and appropriate preoperative counselling of patients.

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What does this paper add to the literature?

This paper demonstrates a significant association between a lengthy delay to ileostomy closure and an increased risk of Clostridium difficile infection. It provides impetus for clinicians to advocate for earlier surgery in this cohort of patients.

Introduction:

Clostridium difficile (CD) is a gram-positive, anaerobic, spore-forming bacterium found in approximately 3% of the healthy population and is the leading cause of hospital associated gastrointestinal infection(1). The incidence of Clostridium difficile infection (CDI) has markedly increased in hospitalised patients since the turn of the 21st Century(2), and a parallel increase in severity has been also observed with the emergence of more virulent strains of CD(3). Previously seen predominantly in elderly or immunocompromised patients, CDI is increasingly emerging in younger, immunocompetent patients(2). CDI is associated with significant patient morbidity, length of stay and hospital expenditure (4).

Post-operative CDI has been reported in multiple case series following ileostomy closure(5-8). Although the exact mechanism by which reversal of ileostomy increases risk of CDI is unknown, altered bacterial colonisation of the de-functioned bowel is believed to play an important role(6). An alteration in the intrinsic intestinal immune system due to intestinal atrophy, in conjunction with a decrease in commensal bacteria due to the poor nutrient content of the diverted bowel, creates an environment for CD to thrive following restoration of intestinal continuity(6, 9).

A diverting ileostomy is typically performed to divert intestinal contents following a low rectal, coloanal or ileoanal pouch anastomosis, to reduce the morbidity and rate of reintervention if an anastomotic leak occurs(10). Ideally, reversal of ileostomy is performed at 3-6 months post-operatively, however, commonly it is performed much later due to adjuvant chemotherapy or waiting list pressure(7). At 6 months, >50% of patients typically still have their temporary ileostomy(11), and at 18 months the 2019 National Bowel Cancer

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Audit of England and Wales reported almost one third of patients still had their ileostomy(12).

Despite being perceived as a relatively minor procedure, reversal of ileostomy is associated with significant morbidity; a systematic review of 6107 patients demonstrated a significant morbidity rate of 17.3%(13). CDI was not reported as a recognised complication in any of the included studies, however, multiple studies report rates of symptomatic infection of up to 4.2%(5, 6, 8, 14). A systematic review of 11 articles identified the incidence of CDI post reversal of ileostomy to be 1.8%(7). Although uncommon, CDI is associated with significant morbidity and increased length of stay and hospital costs(8). Risk factors for the development of CDI post reversal of ileostomy are unclear, however, Rubio-Perez et al, in a retrospective analysis of 93 patients, found a significant correlation between delayed ileostomy closure and CDI(14).

We hypothesised that delay to reversal of ileostomy was associated with increased odds of development of CDI. The aim of this study was to utilise a clinical database from a metropolitan teaching hospital to assess the odds of developing CDI, comparing patients undergoing elective reversal of ileostomy without delay, with those who had delay to reversal of ileostomy (defined as occurring more than 365 days following the index operation).

Methods:

Patient population:

All patients undergoing elective ileostomy reversal between January 2010 and December 2019 at the Royal Melbourne Hospital (a metropolitan tertiary referral centre) were identified retrospectively through a local prospectively maintained, computerised operative database. Patients who had a reversal of ileostomy either via a peristomal incision or via a midline laparotomy were included; this included patients who had an ileocolic re-anastomosis procedure. Patients who had their reversal of ileostomy performed as an acute procedure or as part of another major abdominal procedure (such as liver resection) were excluded.

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Demographic and clinicopathological data were extracted from the patient's medical record and entered into an anonymised electronic database. The American Society of Anaesthesiologists (ASA) physical status classification and the Charlson Comorbidity Index (CCI) were used as surrogate measures of patient comorbidity. Diabetic status, the presence of systemic immunosuppressive therapy (including glucocorticoid, cytostatic and antibody treatment), and medication for gastroesophageal reflux disease was collected, due to the increased risk of CDI in these cohorts(15). The indications for original surgery and ileostomy, the operation performed, and details of neoadjuvant and adjuvant treatment were extracted. Perioperative antibiotic use was recorded as was any history of intervening surgical or endoscopic colorectal procedures between the index operation and reversal of ileostomy.

A delay to reversal was defined as those procedures occurring at greater than 365 days following the index procedure at which the ileostomy was created. A delay due to theatre access was defined as occurring if the time between booking and performing the reversal of ileostomy was greater than 365 days. A cut-off of 365 days was used as this is the timeframe in which reversal of ileostomy should be performed based on Australian national wait list categorisation.

Diarrhoea was defined as the passage of 3 or more loose stools in a 24 hour period, as based on the World Health Organisation definition. Stool culture results were reviewed for all patients who developed post-operative diarrhoea as documented in their records within 30 days following reversal of ileostomy. Stools samples were tested for CD toxin by enzyme-linked immunosorbent assay (ELISA) with confirmation by polymerase chain reaction (PCR). CDI was defined as the presence of CD toxin associated with diarrhoea post reversal of ileostomy. To ensure all patients with CDI were captured, the laboratory results of all patients undergoing reversal of ileostomy were reviewed; if a stool specimen was sent and was reported as liquid in consistency, these patients were also included.

Ethics:

Ethical approval was obtained from the Melbourne Health Human Research Ethics Committee

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Statistical Analysis:

Continuous variables were reported as medians with an interquartile range (IQR) and categorical variables as whole numbers and percentages. The principal exposure of interest was delay to reversal of ileostomy and the principal outcome of interest was odds of CDI. Univariable logistic regression analysis was performed to estimate odds of CDI for each co-variable, comparing patients who had a delay to reversal of ileostomy with those who did not.

Multivariable logistic regression analysis was used to adjust for the potential confounding effects of covariables. Delay to reversal of ileostomy was preserved as the principal exposure of interest for the multivariable regression and all covariables with p-value <0.1 from the univariable analysis were included. Evidence of effect modification between delay to reversal of ileostomy and adjuvant chemotherapy was assessed using likelihood ratio testing to compare models with and without an indicator variable. All analyses were performed using RStudio software (version 3.3.2; PBC, Boston, MA URL http://www.rstudio.com/) or SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA).

Results:

A total of 200 patients underwent reversal of ileostomy between January 2010 and December 2019 (Figure 1). Of these, 5 patients were subsequently excluded from further analysis: 3 patients had their reversal as part of another major abdominal surgery (liver resection n=2, laparotomy for metachronous cancer n=1) and 2 patients had reversal of ileostomy performed acutely. A total of 195 patients undergoing elective reversal of ileostomy were therefore included in subsequent analysis.

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All 195 patients received prophylactic cephazolin and metronidazole intravenously at the time of induction. No patients had antibiotics continued routinely post-operatively. A total of 43 patients developed diarrhoea post-operatively and had a stool specimen sent for analysis. Of these, 11 patients (5.6% of total) had positive results for CD and were defined as having CDI. All patients who developed CDI were successfully managed with antibiotic treatment and there were no cases of fulminant colitis or toxic megacolon. The median length of stay was 4.6 days in all patients, however, in those patients who developed CDI it was significantly longer at 13.2 days (p-value 0.03).

Demographic, clinicopathological and treatment details of the patient cohort are shown in Table 2. Median time to reversal was longer in those patients who developed CDI (451 days (IQR 441– 669)) compared to these who did not (315 days (IQR 210 – 459)). A total of 79 patients (40.5%) had a delay to reversal of ileostomy of greater than 365 days (Table 1). The delay was reportedly due to theatre access in 61 (77.2%), adjuvant therapy in 8 (10.1%) and was unclear in the remaining 10 patients. Of the 11 patients who developed CDI, 9 had a delay to their reversal. Of note, patients who had a delay to their reversal of ileostomy were older, more co-morbid and more of them had neoadjuvant chemoradiotherapy, adjuvant chemotherapy or an intervening procedure.

Results of univariable and multivariable analyses are shown in Table 2. From the univariable analysis, patients having a delay to their reversal of ileostomy had just over 7-fold increase in odds of CDI compared with patients having reversal under 1 year (OR = 7.33, CI: 1.82-49.00; p-value <0.01). Univariable analysis also showed that older patients, patients with more co-morbidity (ASA, Charlson Comorbidity Index), diabetics and those having neoadjuvant or adjuvant therapy had evidence of increased odds of CDI.

Multivariable analysis showed that delay to reversal of ileostomy was associated with a nearly 7-fold increase in odds of CDI when adjusted for the potentially confounding effects of age, ASA, Charlson Comorbidity index, diabetes, neo-adjuvant and adjuvant therapy (OR = 6.95, CI: 1.06-81.6; p-value = 0.03). Multivariable analysis also provided some evidence

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of association between high ASA score and CDI (OR = 3.07, CI: 1.39-7.48; p-value =0.04) but there was no evidence of association with the other measure of co-morbidity (Charlson Comorbidity Index). There was stronger evidence of association between adjuvant chemotherapy and odds of CDI on multivariable analysis than on univariable analysis, suggesting significant confounding by other co-variables (OR =10.7, CI: 2.15-70.3; p-value <0.01). However, this co-variable was not the major focus of the study. There was no evidence of effect modification between the variables of delay to reversal of ileostomy and adjuvant chemotherapy (p-value = 0.33).

Discussion:

This study highlights the frequency of CDI complicating reversal of ileostomy and provides evidence that delay to reversal was associated with a nearly 7-fold increase in CDI when adjusted for potential confounders. Creation of a diverting loop ileostomy has become a common procedure in the restorative treatment of rectal cancer with distal or high-risk rectal anastomoses. Despite their aim to reduce morbidity, their creation ties the patient to a second procedure, and their presence and subsequent reversal may be associated with significant patient morbidity. Although uncommonly reported in studies assessing morbidity following reversal of ileostomy, CDI appears to be more prevalent than previously thought. In the present study the incidence of CDI following reversal of ileostomy was 5.6% compared to an incidence of 0.01% for the general hospital population(16).

Similar results have been reported in other studies with a CDI incidence of 1.0 - 6.8% being described following reversal of ileostomy(5, 6, 8, 14). A systematic review of 11 articles by Harries et al. reported an overall incidence of 1.8%(7). In the present study, CDI was not associated with fulminant colitis, toxic megacolon, or mortality, however, multiple case reports and series describe instances of CDI with high rates of morbidity and mortality following reversal of ileostomy, thus making it an important clinical entity(14, 17, 18). In addition to an increased risk of morbidity and mortality, the cost of developing CDI post reversal of ileostomy, in terms of healthcare expenditure and length of stay, is significantly increased(8).

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The evidence from this study of an association between delay to reversal of ileostomy and CDI is supported by Rubio-Perez et al.(14) who, in a retrospective analysis of 93 patient undergoing reversal of ileostomy, identified an increased risk of developing CDI in patients who had their procedure beyond 6 months, with a reported defunctioning time for those affected ranging from 9 -15 months. The authors identified an apparently "safer period" between 3 and 6 months, which could be considered optimal and in their series the rate of complications post reversal of ileostomy was >30% after 9 months. To date, the present study is the largest conducted assessing an association between delayed reversal of ileostomy and the incidence of CDI.

In the present study a large number of patients (40.5%) had a delay of greater than 365 days to their reversal of ileostomy. Whilst this may be due to adjuvant treatment in some patients, in the majority it was due to waiting list pressures and the low priority given to this procedure. Despite being associated with poorer outcomes, delayed reversal is commonly seen in other studies, with up to 50% of patients waiting longer than 6 months (11). All studies included in the systematic review by Harries et al(7) reported a mean defunctioning time of greater than 6 months, highlighting the low priority given to this procedure.

Adjuvant chemotherapy use has been reported as being associated with colonisation of CD, likely as a result of altered microflora and gastrointestinal inflammation(19). In the present study, adjuvant chemotherapy was associated with a significant risk of developing CDI (OR 10.7, 95% CI: 2.15 – 70.3; $p<0.01$). We found no other studies examining the relationship between the development of CDI and chemotherapy usage prior to reversal of ileostomy. Adjuvant chemotherapy potentially may increase the risk of CDI by delaying reversal of ileostomy due to the time taken to administer chemotherapy, in addition to altering the microbiome of the defunctioned colon. Choi et al.(20) showed that reversal of ileostomy during adjuvant chemotherapy was clinically safe and did not alter oncological outcomes, however, further research in this area is needed before recommending concurrent reversal of ileostomy and chemotherapy as standard of care. An alternative approach is early reversal prior to commencement of adjuvant chemotherapy, with the EASY RCT demonstrating early closure at 8-14 days to be feasible in appropriately selected patients(21).

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Several limitations should be acknowledged when interpreting data from this study. The retrospective, observational nature of this study clearly limits its interpretation. However, the use of multivariable analysis has allowed adjustment of imbalances in measured, potentially confounding co-variables. Secondly the overall number of patients, and the number of patients who developed CDI was low thus limiting comparison and the precision of the results. Additionally, patients without diarrhoea during their admission were not screened for the presence of CD and may have developed symptoms post discharge. The diagnosis of CDI was also limited to inpatient analysis, patients who developed symptoms post-discharge may have been missed, and no follow up data was available. Finally, additional complications following reversal of ileostomy were not evaluated.

Preliminary results from this study need to be confirmed with large prospective studies and strategies for the identification and/or elimination of CD in defunctioned colons prior to reversal of ileostomy should be investigated. Future studies on the microbiome of defunctioned colon could provide insight into the pathophysiology of CDI following reversal of ileostomy and lead to preventative strategies.

Conclusion:

A delay to reversal of ileostomy of greater than 365 days was associated with a increased risk of developing symptomatic CDI post-operatively. Despite not being associated with the severe complications of fulminant colitis or toxic megacolon in this cohort, CDI results in increased patient morbidity and healthcare expenditure. Careful consideration should be given to the timing of reversal and appropriate preoperative counselling of patients. Based on the results of the present study, reversal of ileostomy should be performed within 365 days of the index procedure.

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None

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Table 1: Demographic, clinicopathological and treatment details comparing patients who had a delay to reversal of ileostomy of >365 days, compared to those who had a standard time to reversal.

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Patient variables		Standard RI ≤365 days (n=116)	Delay to RI >365 days (n=79) 40.5%
Clostridium Difficile Infection (n, %)	No	114 (98.3)	70 (88.6)
	Yes	2 (1.7)	9 (11.4)
Age (y)	Median	59.5	68
	(IQR)	(43 – 72)	(53 – 77)
(n, %)	≤65	73 (62.9)	34 (43.0)
	>65	43 (37.1)	45 (57.0)
Sex (n, %)	Female	46 (39.7)	33 (41.8)
	Male	70 (60.3)	46 (58.2)
ASA (n, %)	1 – 2	88 (75.9)	47 (59.5)
	3 – 4	28 (24.1)	32 (40.5)
CCI (n, %)	0-1	65 (56.0)	38 (48.1)
	2+	51 (44.0)	41 (51.9)
Diabetic on medication (n, %)	No	100 (86.2)	59 (74.7)
	Yes	16 (13.8)	20 (25.3)
Gastroesophageal Reflux Disease on Medication	No	87 (75.0)	47 (59.5)
(n, %)	Yes	29 (25.0)	32 (40.5)
Immunosuppressed (n, %)	No	107 (92.2)	76 (96.2)
	Yes	9 (7.8)	3 (3.8)
Original Operation (n, %)	Colon	22 (19.0)	17 (21.5)
	Rectal	94 (81.0)	62 (78.5)
Operation for Malignancy (n, %)	No	43 (37.1)	25 (31.6)
	Yes	73 (62.9)	54 (68.4)
Neoadjuvant Treatment (n, %)	No	81 (69.8)	42 (53.2)
	Yes	35 (30.2)	37 (46.8)
Adjuvant Treatment (n, %)	No	89 (76.7)	48 (60.8)
	Yes	27 (23.3)	31 (39.2)
Intervening Antibiotics (n, %)	No	102 (87.9)	65 (82.3)
	Yes	14 (12.1)	14 (17.7)
Intervening Procedure (n, %)	No	106 (91.3)	64 (81.0)
	Yes	10 (8.7)	15 (19.0)

Legend: ASA = American Society of Anaesthesiologists physical status classification score, CCI = Charlson Comorbidity Index, RI = Reversal of Ileostomy.

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Table 2: Univariable and Multivariable analyses of Clostridium Difficile Infection vs No Clostridium Difficile Infection

		Univariable Analysis			Multivariable Analysis	
Patient variables		**Clostridium Difficile Infection n=11, (5.6%)**	**Univariable Odds Ratio (95% CI)**	**p-value**	**Multivariable Odds Ratio (95%CI)**	**p-value**
Time to reversal >365 days	No	2 (1.7)				
	Yes	9 (11.4)	7.33 (1.82 – 49.0)	**<0.01***	6.95 (1.06 – 81.6)	**0.03**
Age (years) (n, %)	≤65	1 (0.9)				
	>65	10 (11.4)	13.6 (2.53 – 252)	**0.01***	2.21 (0.15 – 76.4)	0.60
Sex (n, %)	Female	4 (5.1)				
	Male	7 (6.0)	1.20 (0.35 – 4.73)	0.77		
ASA (n, %)	1 – 2	2 (1.5)				
	3 – 4	9 (15.2)	12.1 (2.98 – 80.9)	**<0.01***	3.07 (1.39 – 7.48)	**0.04**
CCI (n, %)	0 – 1	2 (1.9)				
	2+	9 (10.0)	5.72 (1.43 – 38.2)	**0.03***	1.87 (0.20 – 20.6)	0.58
Diabetic on medication (n, %)	No	6 (3.8)				
	Yes	5 (13.9)	4.11 (1.12 – 14.5)	**0.04***	3.11 (0.92– 14.5)	0.12
Gastroesophageal Reflux Disease on Medication (n, %)	No	7 (5.2)				
	Yes	4 (13.9)	1.27 (0.32 – 4.39)	0.71		
Immunosuppressed (n, %)	No	10 (5.5)				
	Yes	1 (8.3)	1.57 (0.08 – 9.41)	0.68		
Original Operation (n, %)	Colon	2 (5.1)				
	Rectal	9 (5.8)	1.13 (0.28 – 7.64)	0.88		
Operation for Malignancy (n, %)	No	1 (1.5)				
	Yes	10 (7.9)	5.73 (1.06 – 106)	0.11		
Neoadjuvant Treatment (n, %)	No	5 (3.6)				
	Yes	6 (10.3)	3.05 (0.88 – 11.0)	**0.08***	2.92 (0.55– 16.9)	0.21
Adjuvant Treatment (n, %)	No	3 (2.4)				
	Yes	8 (10.3)	5.00 (1.39 – 23.4)	**0.04***	10.7 (2.15 – 70.3)	**<0.01**
Intervening Antibiotics (n, %)	No	8 (4.7)				
	Yes	3 (11.5)	2.62 (0.55 – 9.83)	0.17		
Intervening Procedure (n, %)	No	8 (4.7)				
	Yes	3 (13.0)	3.07 (0.64 – 11.6)	0.12		

Legend: ASA = American Society of Anaesthesiologists physical status classification score, CCI = Charlson Comorbidity Index. n, % reported as number of CDI patients with respect to entire cohort. * Included in multivariable analysis.

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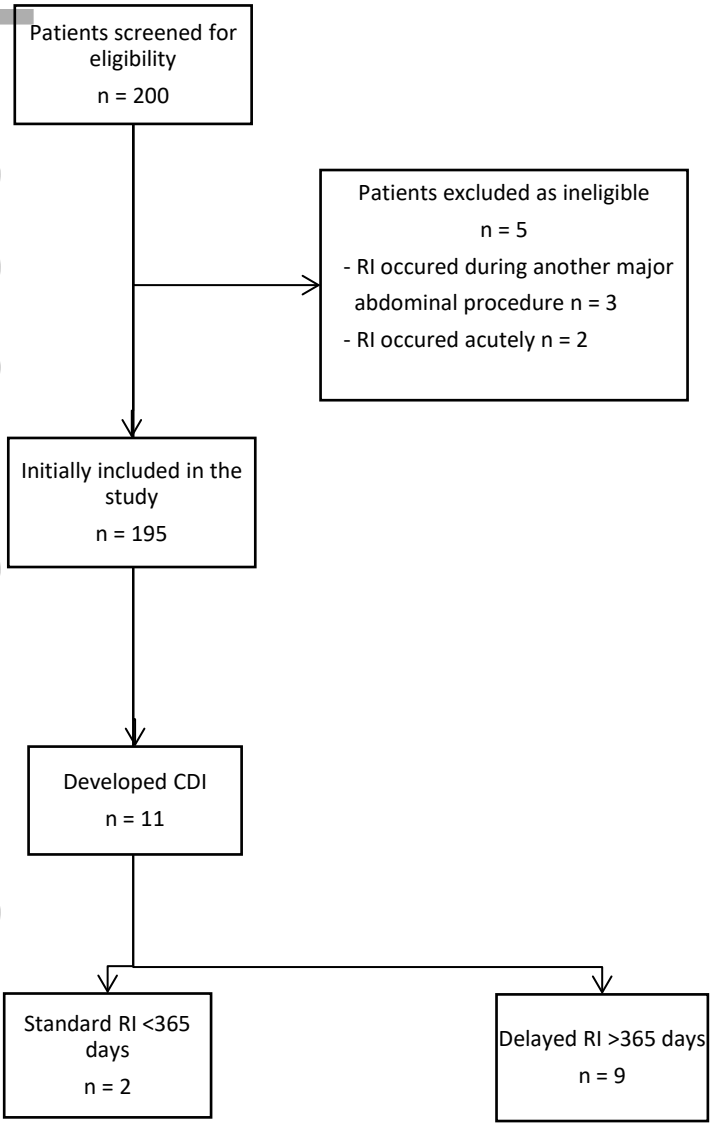
Figure 1: Patient recruitment flowchart



Legend: CDI = Clostridium difficile infection, RI = Reversal of ileostomy

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