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Title: Cross-sectional study of the prevalence, causes and management of hospital-onset diarrhoea

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Running Title:

Prevalence, causes and management of hospital-onset diarrhoea.

Summary

Background: The National Health Service in England advises hospitals collect data on hospital-onset diarrhoea (HOD). Contemporaneous data on HOD are lacking.

Aim: To investigate prevalence, aetiology and management of HOD on medical, surgical and elderly-care wards.

Methods: A cross-sectional study was performed in a volunteer sample of UK hospitals, which collected data on one winter and one summer day in 2016. Patients admitted ≥72 hours were screened for HOD (definition: ≥2 episodes of Bristol Stool Type 5-7 the day before the study, with diarrhoea-onset >48 hours after admission). Data on HOD aetiology and management were collected prospectively.

Findings: Data were collected on 141 wards in 32 hospitals (16 acute, 16 teaching). Point-prevalence of HOD was 4.5% (230/5142 patients; 95% CI 3.9-5.0%). Teaching hospital HOD prevalence (5.9%, 95% CI 5.1-6.9%) was twice that of acute hospitals (2.8%, 95% CI 2.1-3.5%; odds ratio 2.2, 95% CI 1.7-3.0). At least one potential cause was identified in 222/230 patients (97%): 107 (47%) had a relevant underlying condition, 125 (54%) were taking antimicrobials, and 195 (85%) other medication known to cause diarrhoea (laxatives in 150). 9/75 tested patients were *Clostridium difficile* toxin positive (4%). 80 (35%) patients had a

documented medical assessment of the diarrhoea. 144 (63%) patients were not isolated following diarrhoea onset.

Conclusion: HOD is a prevalent symptom affecting many thousands of patients across health systems each day. Most patients have multiple potential causes of HOD, mainly iatrogenic, but only a third had medical assessment. The majority were not tested for *Clostridium difficile* and not isolated, potentially missing cases and contributing to transmission.

Key words: Diarrhoea; nosocomial; hospital onset; hospital acquired; *Clostridium difficile*

Abbreviations:

BSC – Bristol stool chart

CDI – *Clostridium difficile* infection

HOD – hospital-onset diarrhoea

NHS – National health service

Introduction:

Guidelines from the National Health Service (NHS) in England encourage hospitals to collect data on the prevalence of hospital-onset diarrhoea (HOD), to facilitate detection of unexpected variations [1]. However, NHS hospitals do not collect such data and contemporaneous prevalence and risk factor information in developed countries are lacking.

HOD is known to affect patients and health services [2]. Causes such as *Clostridium difficile* infection (CDI) are associated with morbidity and mortality [3]. HOD also impacts staff time and hospital resources [3,4]. Single-centre cohort studies from the 1990s suggested it was common, affecting 22-32% of patients during admission, but were performed in settings with high CDI rates [5,6]. Whilst the prevalence was lower in more recent publications, they were performed in diverse ward/hospital settings using different definitions of HOD, making

results difficult to generalise [7-12]. Studies of the aetiology and management of HOD focus mainly on specialist areas (e.g. intensive care, oncology) [13,14]; there are few data from general medical, surgical and elderly-care settings, although they represent over half of adult hospital admissions in England [15]. To address these knowledge gaps and comply with NHS guidelines we undertook a cross-sectional study on general medical, surgical and elderly-care wards in the UK to describe the prevalence of HOD, its potential causes and management.

Methods

Ethics

The NHS Health Research Authority advised the study constituted a service evaluation, not requiring written patient consent or formal review by a research ethics committee. Appropriate local approval was required at participating sites.

Design

Prospective, observational, cross sectional study. The protocol was developed by the UK's National Infection Trainee Collaborative for Audit and Research, following the STROBE statement (checklist in supplementary material) [16].

Setting

The study was advertised through the British Infection Association, Healthcare Infection Society and Infection Prevention Society in autumn 2015. All acute and teaching NHS hospital trusts/health boards (administrative units typically covering 1-3 hospitals) were eligible to participate. Participating sites, which were self-selected, chose one day in each of two periods (11-22 January and 6-17 June 2016) for data collection. Data were collected in winter and summer to allow for potential seasonal variation. Sites identified at least two wards for data collection from a pre-specified specialty list (supplementary material, Table S1).

Participants

On each data collection day all patients on study wards were eligible for inclusion, except those receiving end-of-life care. Patients specifically declining to be involved were excluded.

Definitions and variables

HOD was defined as ≥2 episodes of unformed stools (Bristol Stool Chart (BSC) type 5-7) in the day before data collection, with diarrhoea onset >48 hours after hospital admission [7,17]. In patients with a stoma, HOD was defined as an acute increase in daily faecal effluent above that normally expected (by the patient or clinical team). If known, an effluent volume of >500mL/24hr for a colostomy or >1000mL/24hr for an ileostomy was considered significant.

Variables assessed included: diarrhoea frequency and duration, previous HOD episodes during that admission and possible causes of HOD (underlying medical conditions associated with diarrhoea, gastrointestinal infections, antimicrobials and other medication associated with diarrhoea).

Common causes of HOD were identified by literature search (see supplementary material), though investigators could report any condition, medication or intervention they believed was causing diarrhoea. For an iatrogenic exposure to be considered a possible cause of HOD it had to fulfil these criteria: exposure had to precede diarrhoea onset with exposure >48 hours, or $\geqslant$ two doses of a new medication (with either the second of these, or a subsequent dose, given in the 24 hours before diarrhoea onset) and the diarrhoea resolving once exposure ceased (if known on the study day) [5]. For enemas and bowel preparation a single dose was considered sufficient. Results from microbiological testing of faecal samples submitted ≤72 hours after data collection were included.

Data were also collected on hospital characteristics: size (small (<500 beds), medium (500-1000 beds) and large (>1000 beds)), type, isolation capacity, testing protocols for faecal samples and infection control policies. Definitions from mandatory reporting were used for hospital type ("acute" being medium-sized, general hospitals providing services for local populations, and "teaching" larger hospitals, providing medical training and local general services, plus specialised regional services).

Data sources, collection and analysis

Standardised data collection forms were developed and piloted at three hospitals (supplementary material Appendices 1-3). Investigators received telephone-based training and guidance notes for data collection. On each study day patients admitted >72 hours were questioned to ascertain whether they had HOD, using the BSC to ensure correct identification of diarrhoea. Evidence for HOD was also obtained through questioning of ward staff and chart review. If $\geqslant$1 source indicated a patient had HOD, further data were collected from the patient, ward staff, medical charts/records and laboratory results systems. All possible causes of HOD were documented; where multiple causes were identified no attempt was made to rank their importance.

Hospitals, wards and patients with HOD were given unique identifiers at each participating site. Anonymised patient data were then uploaded on to a standardised database (Microsoft Excel) and verified locally. Each site submitted their database for analysis in Leeds.

Sample size

Based on published studies the point prevalence of HOD was estimated to be ~10% [5-12]. It was assumed there would be ~25 patients per ward and 5 wards per hospital. There was no information about clustering effects to be anticipated, therefore an intra-class correlation coefficient was used for patients within wards and wards within hospitals. Without any adjustment for clustering, to achieve a 95% confidence interval of $\pm$1%, assuming a binomial model, would need 3600 patients. The design effect for wards was 1.24 and that for hospitals was 1.04. The sample size required to achieve $\pm$1% was therefore 1.24x1.04x3600 = 4643 patients.

Statistical Analysis

The primary outcome measure was the point-prevalence of HOD. Secondary outcomes were hospital characteristics associated with HOD, the proportion of cases with a potential cause(s) and the proportion of cases tested for CDI. Standards for the evaluation of HOD, including testing for CDI, were taken from national guidance [1].

Appropriate summary statistics were reported for continuous (normally and non-normally distributed) and categorical variables. As HOD patients could potentially influence ward prevalence, which in turn could affect hospital prevalence, a multilevel model was used with

patients clustered within wards and wards within hospitals. Random intercepts for ward and hospital were included in a variance components binomial regression. Clustering of hospitals within NHS trusts/health boards was not considered, since most trusts/health boards had one hospital represented in the study and none had more than two.

To seek explanation of the variance at different levels, several plausible explanatory variables were considered in a three-level binomial regression model and then a parsimonious model was presented featuring only statistically significant terms with random intercepts retained for wards and for hospital, to account for clustering. Prevalence estimates were presented from these results, complete with confidence intervals.

Fixed effects terms were included for season and speciality and were to be included for ward and hospital characteristics as appropriate, unless little clustering was seen by ward or hospital. Analyses were performed using R version 3.3.2 employing the Ime4 library version 1.1-12 [18,19].

Results

Settings & Recruitment

Thirty-two hospitals (16 acute, 16 teaching) at 25 NHS trusts/health boards participated (listed in supplementary material). One hundred and forty one wards were included: 63 (45%) medical, 52 (37%) surgical and 26 (18%) elderly-care (Table S1). Data were collected from 116 wards in both rounds, 20 just in winter, and 5 in summer only. Patient recruitment and results are summarized in Figure 1.

Multilevel model output

The multilevel model revealed minimal contribution to clustering either at ward or hospital level. Patient level variance was 3.28987, ward level 0.07115, and hospital level 0.00004. Likelihood ratio tests confirmed this finding, so simple single-level models were used.

Prevalence of HOD and influencing factors

The crude point-prevalence of HOD was 4.5% (230/5142 patients; 95% confidence interval (CI) 3.9-5.0%). Another 395 patients had one episode of unformed stool in the day before data collection.

HOD prevalence in teaching hospitals was 5.9% (163/2748, 95% CI 5.1-6.9%), more than twice the 2.8% prevalence in acute hospitals (67/2394, 95% CI 2.1-3.5%; odds ratio 2.2, 95% CI 1.7-3.0). Prevalence was unaffected by season, hospital size, or ward characteristics (specialty, number of beds and side-rooms).

Patient and HOD characteristics

The median age of HOD patients was 77 (IQR 66-85years); 52% were female. Median duration of hospitalisation at HOD onset was eight days (IQR 5-15 days). Patients reported a median of three episodes of diarrhoea the day before data collection; median symptom duration was two days (IQR 1-6 days). Sixty (26%) patients had experienced ≥1 previous episodes of HOD during their admission and 14 (6%) had a history of CDI.

Potential causes of HOD

Nearly all HOD patients (222, 97%) had at least one potential cause of diarrhoea (Table I). The majority (196 patients, 85%) had multiple possible causes (median 3; IQR 2-5). Almost half the patients, 107 (47%) had underlying conditions associated with diarrhoea (Table I). The commonest was constipation with overflow diarrhoea (39/230, 17%). Seven patients had no relevant diagnosed condition but reported longstanding diarrhoea.

Just over half (125, 54%) of HOD patients were exposed to ≥1 antimicrobial within the 24 hours before diarrhoea onset (Table II). In total, 123/201 (61%) antimicrobials administered were intravenous; 184 (91%) were started in hospital. Antibiotics are listed by group and stratified by risk of CDI in Table S2. The commonest groups were: beta lactam-beta lactamase inhibitor combinations (61/230, 27%), macrolides (17, 7%) and carbapenems (15, 7%).

Most patients with HOD (195/230, 85%) were prescribed ≥1 non-antimicrobial drug that can cause diarrhoea (median 2, IQR 1-3; Table II). Diarrhoea is reported as a “very common” (occurring with a frequency ≥1 in 10) or “common” side effect (occurring with a frequency ≥1 in 100) for all drugs listed, except steroids and levothyroxine, for which the frequency is

unknown [20]. The commonest were laxatives (150/230, 65%), proton-pump inhibitors (100, 44%) and selective serotonin-reuptake inhibitors (30, 13%). In total, 247/442 (56%) of medications were started before admission. Medication started pre-admission was the only potential cause of HOD in 21 (9%) of cases.

Microbiological investigation of HOD

Eighty patients with HOD (35%) had stool microbiology testing following diarrhoea onset; in 56/80 patients (71%) the stool sample was obtained within 24 hours. Seventy-five HOD patients (33%) were tested for CDI; this included 48 of the 125 (38%) patients exposed to antimicrobials. The proportion of patients receiving ≥1 antimicrobial associated with moderate to high risk of CDI (defined in Table S2) who were tested for CDI was only slightly higher (42/103, 41%). All laboratories followed a two-stage testing algorithm, consistent with UK guidance [21]. Nine HOD patients were faecal-toxin positive (4%); a further four were GDH positive with negative toxin assays, suggesting *C. difficile* colonization. There was no difference between patients who were tested for CDI (including those with the infection), and those not tested, in terms of frequency of diarrhoea, the median number and distribution of potential causes of HOD per patient (Table III). Only documentation of HOD in medical notes had a significant association with CDI testing (78% of those tested versus 38% not tested, $p<0.001$). Norovirus testing was undertaken in 16 patients; three were positive.

Patient management

Overall, 218/230 (95%) HOD patients had documentation of bowel movements; most commonly on a BSC (173, 79%). In 143 (62%) patients the number of diarrhoea episodes in the 24 hours before the study day was documented. In 80 cases the number of patient-reported episodes could be compared to the number documented: 21 patients (26%) reported more, 6 (8%) reported fewer, whilst for 53 (66%) there was no difference. The presence of HOD was documented in the medical notes in 115/230 (50%) of cases. For 94/115 (82%) it was within two days of diarrhoea onset. There was documented evidence of medical assessment of the diarrhoea for 80/230 (35%) patients. In 64/80 (80%) cases this took place either on the day of diarrhoea onset or the following day.

Not including faecal sampling, 93 (40%) patients had ≥1 additional investigation for HOD (range 1-4; Table S3). One or more treatments was stopped, started or adjusted owing to

HOD in 61 patients (27%; Table S4). Laxatives were stopped in 30/150 (20%) of those receiving them.

At the time of developing HOD, 40/230 (17%) of patients were already in isolation; a further 46 (20%) were placed in a side-room following diarrhoea onset. The remaining 144 (63%) HOD patients were not isolated. This included 25 patients who were tested for *C. difficile* (one of whom was toxin positive), though a significantly higher proportion of those tested were isolated (27/52 (52%) tested patients v 11/129 (9%) untested patients, $p<0.001$).

Discussion

Key findings

The point prevalence of HOD on general medical, surgical and elderly-care wards was 4.5%. HOD was associated with a prolonged hospital admission at symptom-onset and was recurrent in over a quarter of cases. Almost all patients had at least one identifiable potential cause of HOD; 85% had multiple potential causes. Only 35% of patients overall were tested for CDI, including only 38% of those receiving antimicrobials. Nine patients were *C. difficile* toxin positive (4%).

The rate of diarrhoea documentation was high, though a quarter of patients reported more episodes than documented. Only 35% of patients had a documented medical assessment of the diarrhoea. Of the patients not already in a side-room just 20% were isolated following diarrhoea onset. 48% of those tested for *C. difficile* were not isolated.

Strengths and limitations

This multicentre study is the largest published investigation of HOD, with data collected from multiple hospitals of different types across the UK. The narrow confidence intervals indicate the results could be used to estimate the prevalence of HOD on general wards in similar settings.

There are several limitations. The design precluded an assessment of the incidence and duration of HOD, which would require a cohort study. The hospitals involved were self-selected; their practices may differ from other hospitals in the NHS. Industrial action during

the winter data collection period led to a national reduction in the number of elective admissions. This may have led to under-representation of elective patients and lower bed occupancy rates for this period.

Patient recall bias or unrecognised cognitive impairment may have led to an underestimate of HOD prevalence, although to minimise this risk questions about diarrhoea were limited to the 24 hours before the study day and multiple information sources were reviewed for evidence of HOD. Data were mostly collected from the notes/electronic records, inaccuracies in which may have impacted the findings. (We did not collect data on clinical factors and blood test results that might have influenced decisions to test for CDI.)

Comparison with other studies

The prevalence of HOD was less than reported in most other studies, though meaningful comparison is difficult, owing to the diverse range of settings, lack of contemporaneous reports and varied definitions of HOD used [5-12]. It may reflect our exclusion of specialist units, where HOD prevalence is typically higher, e.g. intensive care, and the lower rate of CDI than some studies [5-7]. HOD prevalence was significantly higher in teaching hospitals, but unaffected by hospital and ward size, specialty, number of side-rooms and season. This suggests that patient factors and the complexity of their condition influences the risk of HOD, rather than differences in systems or processes, although unmeasured factors may have had an impact. The low level of norovirus activity in the UK during the study may explain why season had no effect [22].

Identifying the potential causes of HOD facilitates recognition of modifiable causes. Known causes of HOD include numerous medications, especially laxatives and antibiotics [23,24]. Almost two thirds of HOD patients were on laxatives. In only 20% were they stopped following the onset of diarrhoea, consistent with a previous study [8]. Constipation with overflow diarrhoea was the commonest underlying condition causing HOD. These related findings suggest that improvements in bowel care could reduce the occurrence of HOD. Antibiotic treatment was a predisposing factor in half of HOD patients; since the incidence of diarrhoea varies between antibiotics there may be an opportunity to modify this risk through better antimicrobial stewardship.

Most patients were not tested for CDI. This may reflect close adherence to UK guidance, which advises testing HOD for CDI is unnecessary if there is an alternative cause, and in almost all patients at least one was evident [21]. Alternatively, in hospitals where the definition of HOD included a minimum daily frequency of diarrhoea, not testing for CDI may reflect failure to identify and document all episodes of diarrhoea in some patients. Failing to diagnose infectious causes of HOD, such as CDI and norovirus, has negative consequences for patients and hospitals. Patients can undergo unnecessary investigations, whilst treatment and instigation of appropriate infection control measures may be delayed [25,26]. Forty percent of patients in this study had at least one investigation and 27% had some alteration to their treatment as a result of HOD, adding to patient morbidity and hospital costs.

Almost two thirds of patients had no documented medical assessment of their diarrhoea. It is unclear whether this reflected a lack of awareness of HOD amongst clinicians (a known problem [8]) or that they did not consider the diarrhoea to be significant. A previous study found HOD receives little attention after CDI is excluded [7].

The failure to isolate most patients with diarrhoea is contrary to published guidelines and may increase the risk of faecal pathogen transmission [27,28]. Reasons for not isolating those tested for CDI merit further investigation but may reflect limited availability of single-room accommodation in many NHS hospitals.

Implications

The overall economic impact of HOD has not been evaluated, though CDI and norovirus are known to place a financial burden on healthcare organisations [3,4]. The cost of HOD is likely to be significant, given the large number of patients involved. In England there are approximately 100,000 acute hospital beds in the included specialties [29]. Applying the 4.5% prevalence result this equates to approximately 3600 patients with HOD per day (1.3 million patient days of HOD/year). Given the scope of the problem, recommendations that healthcare organisations monitor their prevalence of HOD has significant implications for infection control teams and may not be feasible without additional resources.

All organisations in this study had policies requiring source isolation of patients with diarrhoea but compliance was poor, with most patients not isolated, perhaps because of

insufficient isolation capacity. Better management of HOD would facilitate more efficient use of side rooms.

UK guidelines advise against CDI testing when there is an alternative cause of HOD [20]. As the number and distribution of potential causes of HOD did not differ between patients tested for *C. difficile* (including those with CDI) and those not tested a more inclusive testing strategy should be considered, to avoid missing CDI cases and contributing to onward transmission [26, 29]. If the proportion of patients with CDI (4%) was the same in the cohort of untested HOD patients (n=155) six cases were missed. As documentation of HOD in medical notes was associated with CDI testing, mandating medical assessment in all cases of HOD (which did not happen in most patients), could help to identify potentially infectious diarrhoea and encourage CDI testing and prompt isolation, consistent with published recommendations [28]. It could also shorten HOD duration, by ensuring appropriate management of non-infectious causes. Of note, NHS Improvement has given notice of its intention, from 2020, to examine both diarrhea sampling and CDI testing rates in NHS hospitals [30].

Commented [MW[1]:
NHS Improvement. Clostridium difficile infection objectives for NHS organisations in 2019/20 and guidance on the intention to review financial sanctions and sampling rates from 2020/21 Available at: https://improvement.nhs.uk/documents/808/CDI_objectives_for_NHS_organisations_in_2019_Feb19.pdf Last accessed 05 March 2019.

Conclusions

The prevalence of HOD on general medical, surgical and elderly-care wards in NHS hospitals was 4.5%, suggesting there are over a million patient days of HOD on these wards in UK hospitals each year. Multiple potential causes of HOD can be identified in most patients, complicating its management, including decisions around CDI testing. Work to reduce impact on patients and healthcare organisations should focus on ensuring patients with HOD undergo medical assessment focussed on the need for CDI testing and isolation and identifying and managing other common, modifiable causes.

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Conflict of interest statement

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698 Tables

	N	% (n=230)
Number of underlying conditions		
Any	107	47
1	84	37
2	18	8
3	4	2
4	0	-
5	0	-
6	1	<1
Underlying condition		
Constipation with overflow diarrhoea	39	17
Previous bowel resection or recent abdominal surgery	35	15
Diverticular disease (including diverticulitis)	18	8
Severe sepsis (non-gastrointestinal source)	11	5
Colorectal cancer (in the past 5 years)	8	4
Inflammatory bowel disease	8	4
Stoma	8	4
Gastrointestinal bleed (within the last 72 hours)	7	3
Liver disease	6	3
Pancreatitis	4	2
Biliary sepsis	2	1
Irritable bowel syndrome	2	1
Short bowel syndrome	2	1
Other*	20	9

699 *Alcohol withdrawal, anxiety, bile acid malabsorption, bowel perforation, colonoscopy with extensive
700 irrigation, faecal incontinence, fruit induced (2 cases), gastric cancer, graft versus host disease, high-output
701 stoma, ileal ulceration, intravenous drug use, ischaemic colitis, non-compliance with medication, pancreatic
702 insufficiency, peritoneal dialysis, rectal prolapse, small bowel fibrotic stricture, thyrotoxicosis
703
704 **Table I: Number (percentage) of underlying or pre-existing conditions associated with diarrhoea in**
705 **HOD patients**
706

Medication	Total n	Total % of all HOD patients (n=230)	Started pre-admission n	Started pre-admission % of patients on that medication	Started post-admission n	Started post-admission % of patients on that medication
Laxatives	150	65	67	45	83	55
Antimicrobials*	125	54	17	8	184	92
Proton pump inhibitors	100	44	81	81	19	19
Selective serotonin reuptake inhibitors	30	13	28	93	2	7
Steroids	25	11	14	56	11	44
Iron (oral)	22	10	14	64	8	36
Metformin	21	9	20	95	1	5
Enteral feed	18	8	4	22	14	78
Enema (in the preceding 24hr)	14	6	0		14	100
Glycerine suppositories	10	4	1	10	9	90
Metoclopramide	10	4	1	10	9	90
Immunosuppressants other than steroids	7	3	5	71	2	29
Bowel preparation	5	2	0		5	100
Donepezil	3	1	3	100	0	0
Nutritional supplements	3	1	0		3	100
Chemotherapy	2	1	1	50	1	50
Levothyroxine	2	1	2	100	0	0
Magnesium salts	2	1	0	0	2	100
Phosphate and potassium salts	2	1	0	0	2	100
Other**	15	7	5	38	8	50

*Figures (and percentages) shown for the timing of when antimicrobials were started are based on the total number of antimicrobials prescribed (n=201), as some patients were on a combination of antibiotics started both before and after admission at the time of diarrhoea onset.

**Other medication judged by investigator to be a potential cause of HOD (whether started before or after admission not known in 2 cases): allopurinol, bisoprolol, calcium/vitamin D, colchicine, furosemide, Gastrografin, lithium, iopanoic acid, opiates (patient reported), pancrelipase (2 cases), quetiapine, ranitidine, sevelamer, simvastatin.

Table II: Prescriptions of medications associated with diarrhoea in patients with HOD

	No CDI test, No. (%)	CDI test, No. (%)	Adjusted OR (95% CI)	P value
Total	155	75	-	-
Age (mean ± SD)	73 ±17	73 ±15	1.00 (0.98, 1.03)	0.80
Sex (m)	76 (49)	34 (45)	0.85 (0.45, 1.63)	0.70
No. of potential causes of HOD/ patient (median)	3	3	-	-
No. of diarrhoea episodes in 24 hr before the survey (median)	3	3	1.10 (0.94, 1.29)	0.26
Any underlying condition associated with diarrhoea	74 (48)	33 (44)	0.77 (0.40, 1.49)	0.70
Receiving antimicrobials	78 (50)	47 (63)	1.73 (0.89, 3.37)	0.11
Any other medication that can cause diarrhoea	130 (84)	65 (87)	1.38 (0.52, 3.62)	0.72
Medication started pre-admission only potential cause of HOD	17 (11)	4 (5)	0.42 (0.11, 1.59)	0.25
HOD documented in medical notes	59 (38)	58 (78)	6.47 (3.31, 12.66)	<0.001

Table III: Clinical features and potential causes of HOD in patients tested for CDI versus those not tested for CDI.

Figures

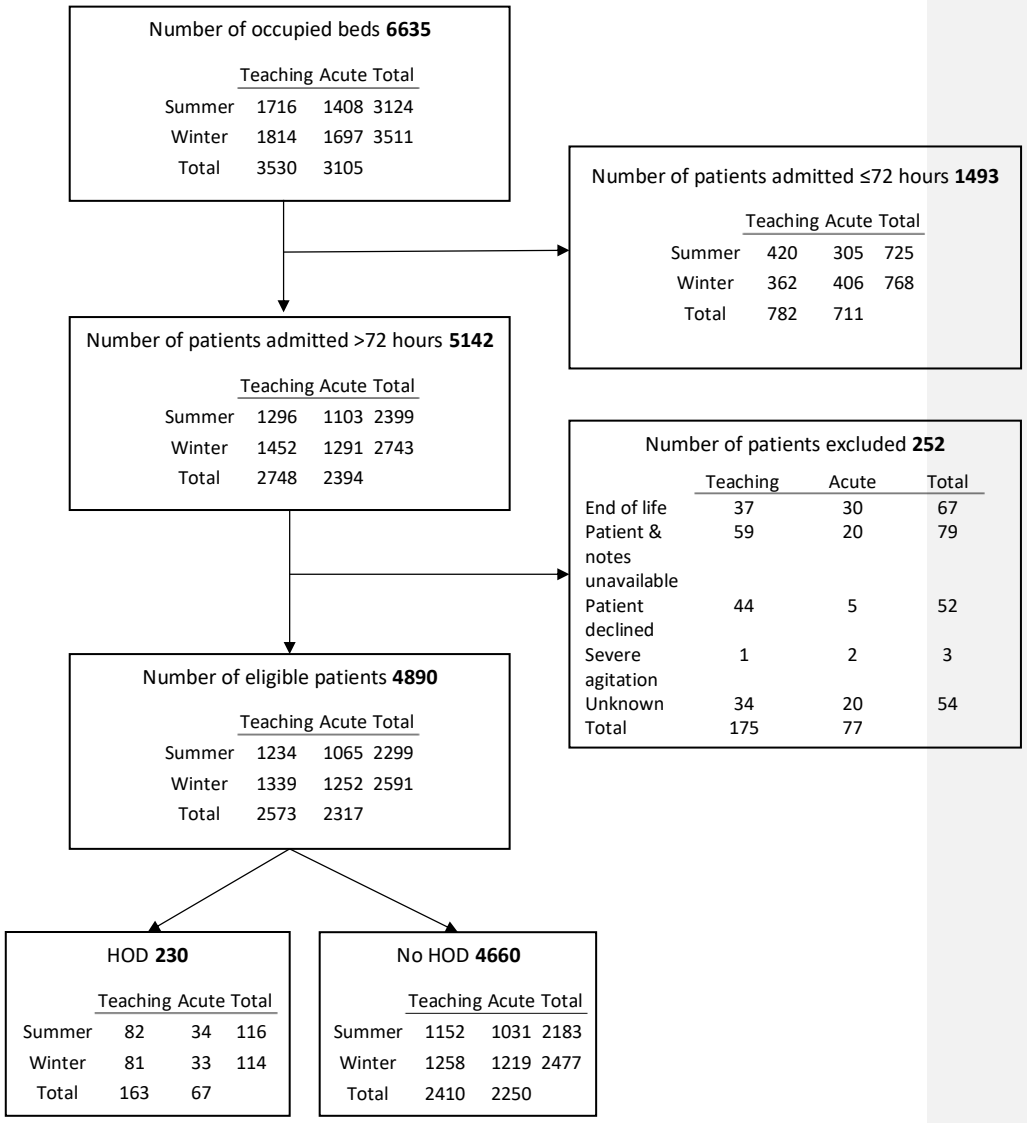

Figure 1: Flow diagram showing patient recruitment and results, both overall and by season and hospital type.