Introduction

Diarrhoea, defined as ≥3 loose or liquid stools per day with a volume of greater than 200g/day[1], affects 9.7-41% of Intensive Care Unit (ICU) patients [11-14]. Here, it impacts negatively on patient dignity, mobility and self-care; increases nursing workload; and can cause fluid and electrolyte imbalance, impaired nutritional state and dermal injury. Such factors may contribute to the increased patient length of stay cost of care and mortality with which it is associated[3,4,5,6,7, 10].

The pathogenesis of diarrhoea in the critically ill is poorly understood[8], but factors including infection (e.g. *C. difficile,* norovirus), pancreatic exocrine failure, and the administration of feed and or medications (e.g. laxatives, antibiotics)[2]. as well as changes in the gut microbiome, and the structure, function and perfusion of the gut mucosal surface[9].

In 2016, we reported that 12.9% of 9,331 consecutive patients admitted to the large, mixed general ICU at a Central London teaching hospital (University College London Hospitals, UCLH) suffered diarrhoea. We also reported that non-infective causes appear to predominate, with one fifth of patients receiving laxatives before diarrhoea onset. Finally, we found diarrhoea to be independently associated with ICU length of stay and mortalit.y[10]

We sought to determine whether these observations were more generally applicable, by studying the ICU patients of a smaller North London district general hospital.

Methods

We performed a service evaluation, registered as an audit with the Whitingto Hpspital NHS Trust. All data analysed were fully anonymised. As such, no ethical approval was required.

The Whittington Hospital is a 360-bed teaching hospital located in North London with 42,000 admissions per year. Computerised records were analysed to identify patients > 18 years old who were admitted to its 15-bed mixed medical/ surgical ICU/high dependency unit (HDU) for level 2 or 3 care in the 60 months between 1/2/2013 to 1/2/2018. The Whittington ITU has clearly defined protocols for sending stool samples for microbiological or virological analysis, based on the Bristol Stool Chart scoring system. Consistent with our previously published methodology[10], patients who had a stool sample sent during their admission were judged to have suffered from an episode of diarrhoea.

Stool samples were analysed by microscopy and culture (from February 2013 – June 2017), and using bacterial PCR from July 2017 onwards. Based on patient presentation and symptoms, samples were also analysed for *Clostridium difficile* toxin A and B using an immunoassay enzyme, *C. difficile* glutamate dehydrogenase antigen, and Norovirus 1 and 2. The presence of *C. difficile* antigen indicates the presence of a potentially toxin-producing organism which is likely associated with disease; therefore the presence of toxin positive and toxin negative/ antigen positive samples were classified as positive infectious samples.

Demographic data, including age, sex, admission category (medical or surgical), and Acute Physiology and Chronic Health Evaluation (APACHE) II score, were collected. Laxatives (including lactulose, senna, macrogol, sodium docusate and ispaghula husk), enemas (phosphate) and suppositories (glycerol) received during admission were also documented. Measures of outcome including length of stay (LOS) and mortality were recorded.

Patient data were extracted from the ICU database and stool data from the hospital laboratory software (ICE Anglia). A

Statistical Analysis

Data were compared between patients suffering from diarrhoea, and those not suffering diarrhoea. We sought to describe the prevalence of diarrhoea; the proportion of cases in which an infective agent was identified; any association with laxative or enema use; and the relationship of diarrhoea with ICU length of stay and mortality. xxxx

Data were analysed using Microsoft Excel 2010.

Results

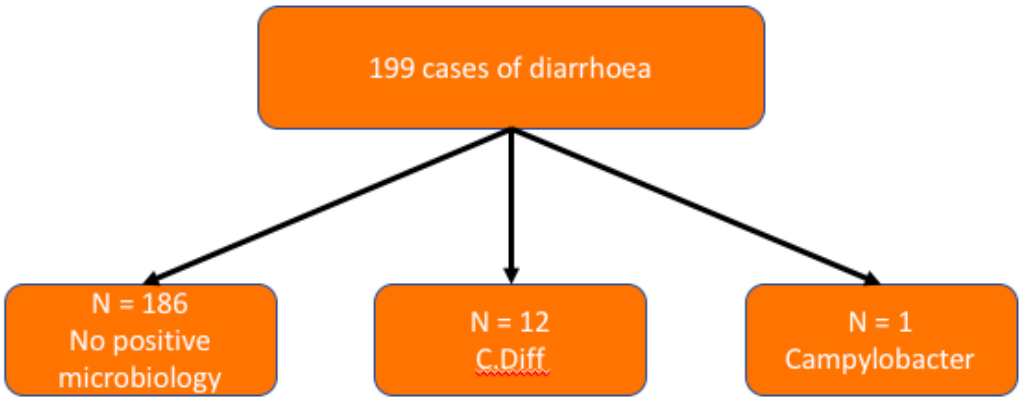
Diarrhoea Prevalence:
Between 1/2/2013 and 1/2/2018, a total of 3,737 patients were admitted to the Whittington Hospital ICU (mean +/- xx age 61 +/- 18.9), 1,912 (51.1%) male, 1,328 (35.5%) from surgical admissions, median APACHE II score 14 (interquartile range 9-19). Diarrhoea was found in 199 patients (prevalence of 5.3%).

Infective aetiology:
Of the 199 admissions associated with diarrhoea, stool sample analysis suggested an infective aetiology in 13 (7%) (see Figure 1): 1/175 (0.006%) of samples sent for bacterial microscopy and culture/ PCR, 12/175 (6.9%) of stool sample sent for *C. difficile* and 0/2 (0%) of sample sent for virological analysis. The single positive stool microscopy and culture was for *Campylobacter*.

Out of 12 positive *C. difficile* samples, 10/12 (83.3%) were antigen positive only, and 2/12 (16.7%) were toxin positive. *C. difficile* was the most common infective agent, occurring in 12 admissions and 11 individual patients (mean age +/- SD 65.6 +/- 14.2, 67% male, 67% medical admissions). Three patients were post-operative, with the most common medical reason for admission being sepsis (5/9). xxx

No patient tested positive for more than 1 pathogen at any time.

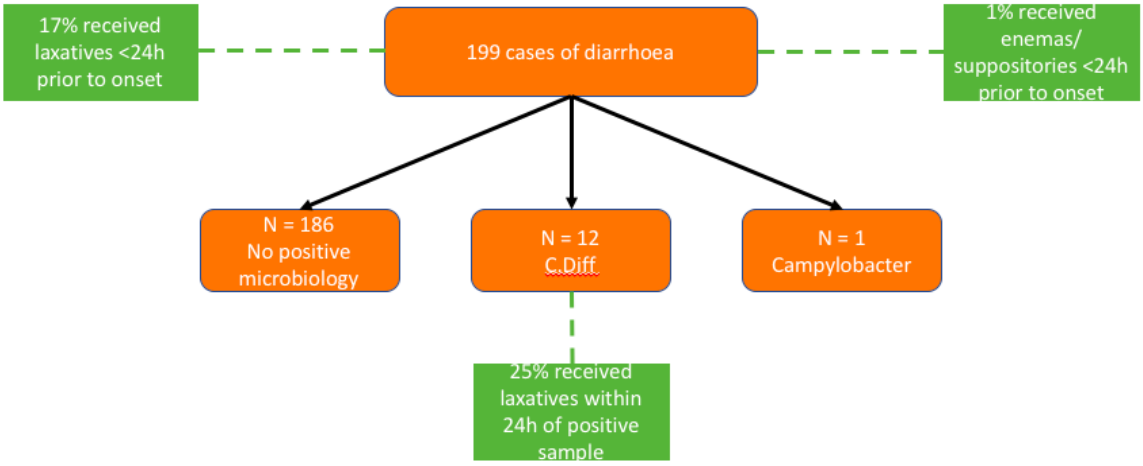
Figure 1: Diarrhoea in the Whittington ITU



Laxatives, suppositories and enemas:
Of 3,727 ICU patient admissions, 1,005 (26.9%) received laxatives during their stay. Of 199 diarrhoea cases, 34/199 (17.1%) received laxatives < 24h prior to onset of diarrhoea, while 3/12 (25%) of C. Diff cases received laxatives within 24h of a positive sample.

Of 3,727 ICU admissions, ^^ received enemas/ suppositories during their stay. Of 199 diarrhoea cases, 2/199 (1%) received enemas/ suppositories < 24h prior to its onset.

Figure 2: Laxatives administration



Clinical outcomes:

Median ICU LOS was 2.5 days (interquartile range 1.1 - 5.5 days) and mortality 11% (412/3,737). When compared to those without diarrhoea, patients admitted with diarrhoea experienced greater median ICU LOS (median (IQR) 2.3 (1.0-5.0) days vs 10 days (5.0-22.0)) and greater ITU mortality (9.5% (356/3,727) vs 18.1% (36/199)).

Median ITU LOS for *C. difficile* patients was 11.5 days (IQR 2.0-14.3). Five out of 12 (42%) of patients with either *C. diff* toxin or antigen positive samples died during their admission. Neither *C. diff* toxin positive patient (0/2) died during their ITU admission.

Figure 3: Median length of stay

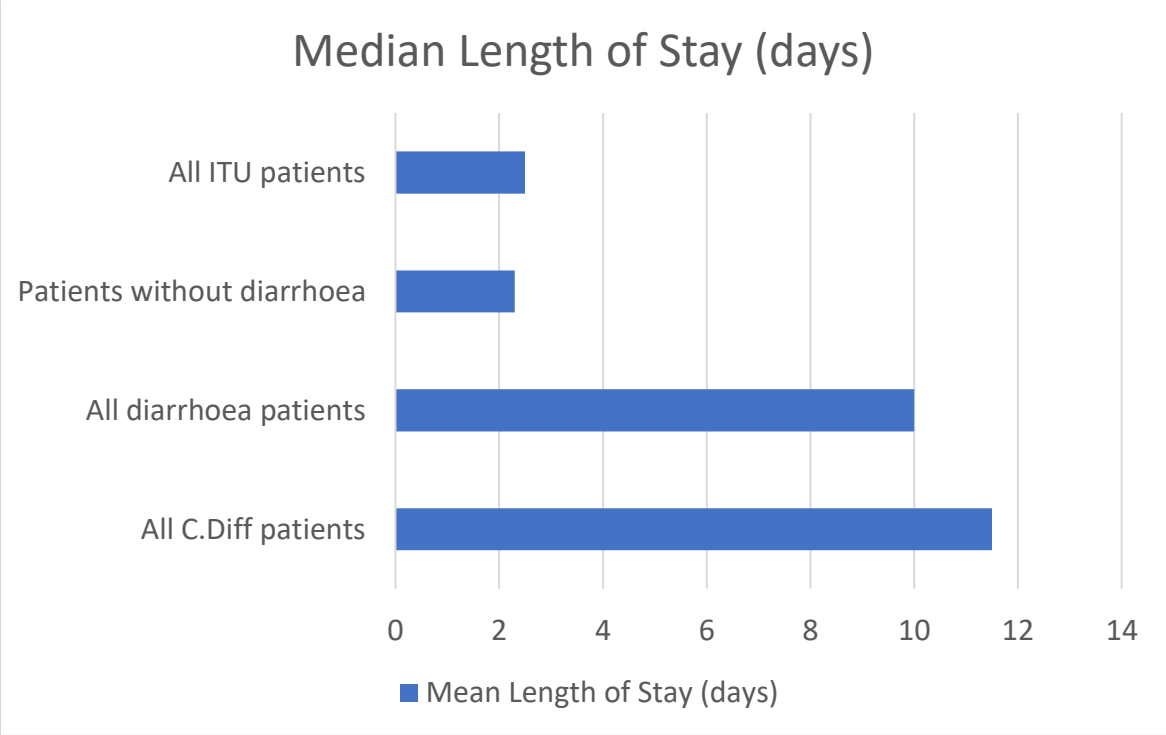
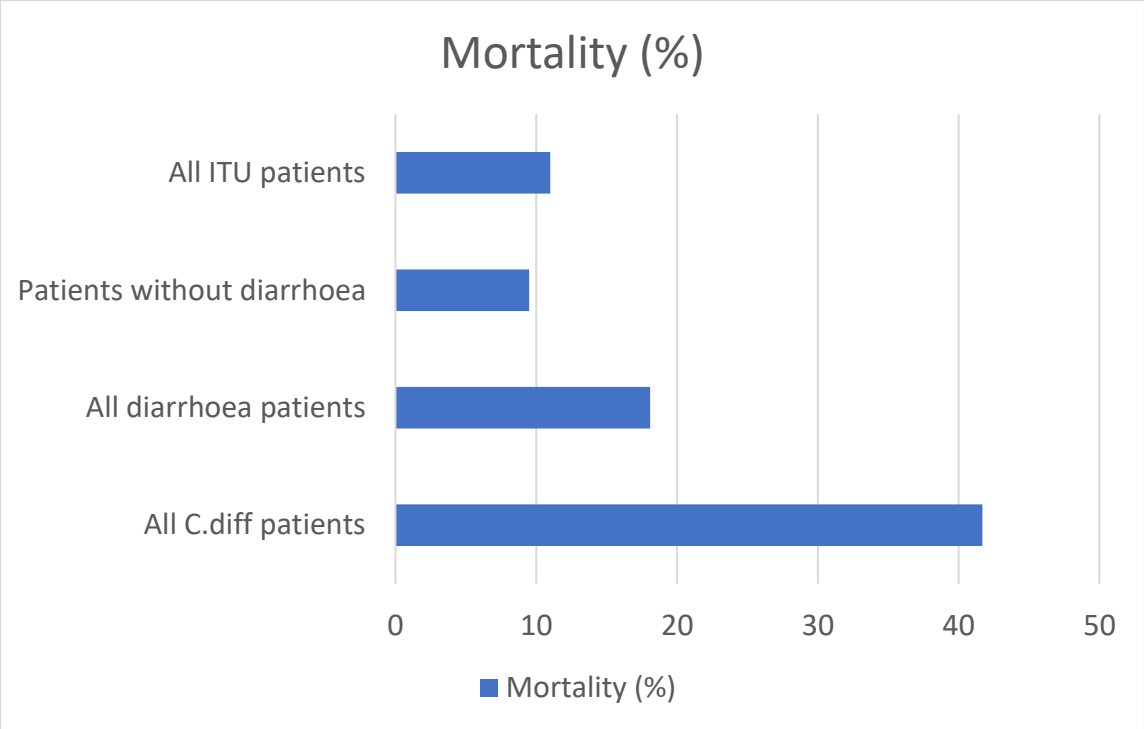


Figure 4: Mortality



Discussion

We found diarrhoea to be common, affecting nearly 1 in 20 admissions to a small district general ICU/HDU. It was associated with greater ICU LOS (data, p-value) and also mortality (data, p-value). Infective aetiology was uncommon (less than 7% of cases) and use of laxatives prior to diarrhoea onset was common (17.1%).

The prevalence of diarrhoea in our unit was lower than the 12.9% that which we had previously reported in a large central London ICU (University College London Hospital, UCLH)[10], and others report a prevalence of 9.7-41%[11-14]. This may reflect differences in case-mix: for instance, the proportion of surgical and long-term gastroenterology patients was greater at UCLH [data], where the use of tube-feeding was also more common [data]. Median APACHE II scores also differed in the two studies(14 at the Whittington vs 16 at UCLH- p values for comparison?). Our diagnosis of diarrhoea was dependent on a stool sample being sent to the laboratory: whilst this was the same criterion which we had used before [ref 10}, the prevalence of milder cases may have been underestimated when compared to the studies of others.

In 93% of cases, no enteric infection could be identified in cases (none viral, *C. difficile* in 6% and other bacterial infection in 0.5%). These data are similar to those at UCLH (prevalence of pathological stool samples 7% vs 9.2%; and proportion with non-*C Difficile* bacterial infection 0.5% at both site). However, the proportion of cases with *C. difficile* infection was lower (6% vs 9.3%, p xx) as were the proportion with viral infection (0% vs 5.2%). These differences might partly reflect the smaller sample size of the Whittington study, and improved antibiotic stewardship as awareness of the deleterious effects of *C. difficile* become more apparent. Other reports in the literature?]

Overall, 26.9% of admissions received laxatives- a greater proportion than we reported at UCLH (17.5%). This difference might be accounted for, in part, by laxatives being a part of an electronic software "prescribing bundle" on the unit. [data reported from other units in the literature?}
Some 17.1% of patients received laxatives prior to diarrhoea onset, compared to xx% of non-diarrhoea cases (p xx). [comment- possible causative role? Compare to what we reported before?
Whilst fewer total patients received laxatives prior to diarrhoea onset when compared to the UCLH data (17.1% vs 20.2%), more of our *C. diff* patients (25% vs 13.4%) received laxatives within 24h of a positive sample, and fewer received enemas or suppositories (1% vs 11.4%) less than 24h prior to diarrhoea onset. Taken together, these data suggest that laxative use may be a contributory factor in its aetiology. [other literature? Is such prescription part of guidelines?]

Patient length of stay was greater in those affected by diarrhoea than in those unaffected: [our data xx vs yy; p value]. This finding matches that which we made at UCLH (xx vs yy respectively, p nn). [case mix adjustments? Report nature/ analysis, and comments as per the last paper. Discuss possible causality, with caveats that 'sicker and longer stay may get more chance to have diarrhoea etc.. as per last paper].] We had previously shown that this association persists after adjustment for confounding factors- including time from ITU

admission to developing diarrhoea[10], This suggests that a possible causal role for the presence of diarrhoea itself in increasing LOS. Such a role is plausible, as diarrhoea may impair nutrient intake, contribute to dermal injury and to fluid and electrolyte imbalance, and increase dependency on higher levels of nursing care.
C diff LoS data and discussion

Similarly, crude mortality was greater in patients affected by diarrhoea than in those without (xx vs yy%, p nn). These data match those identified at UCLH (xx vs yy, p nn). [unadjusted and adjusted data; analysis and discussion as per last paper.].
C dfiff data and discussion.

There were several limitations to this study. As previously stated, the prevalence of diarrhoea may have been higher than reported as the diagnosis of diarrhoea depended on a stool sample being sent to the laboratory. However, robust ICU protocols exist to ensure that stool samples are sent promptly if an infective cause is suspected. Analysis of electronic records did not allow us to adjust for potential iatrogenic confounders, such as antibiotic administration, enteral feeding or electrolyte replacement, which have been shown to be independent risk factors for diarrhoea[15]. Moreover, we could not determine any relationships of diarrhoea with patient-specific variables, such as the level of organ support, co-morbidities or reason for admission. Despite studying data covering a full five year period, the number of diarrhoea cases was relatively small. A large-scale prospective study would help clarify the imlact of such factors in diarrhoea pathogenesis. Doing so might identify factors amenable to intervention, thus mitigating the financial, morbidity and mortality burdens associated with ICU diarrhoea.

In the meantime, robust and regular review of patient's gastrointestinal status, with prompt recognition, investigation and treatment of diarrhoea in light of its association with worsening patient outcomes, should be performed. At the Whittington, a trial of removing laxatives from the prescribing bundle, and protocolised care to ensure appropriate identification of the cause of diarrhoea, management of reversible aetiology, and appropriate laxative prescribing, have been suggested as possible ways to reduce the burden of this condition. The low diagnostic yield of laboratory investigations for diarrhoea suggest that rationalising of investigations could help reduce the financial cost to the department; indeed, Manthey et al (2018) suggest that testing for enteric pathogens other than *C. difficile* in ITU should be avoided, and is only reasonable when diarrhoea commenced less than 48h after hospital admission[16].

In summary, diarrhoea has a prevalence of 5.3% in the Whittington ICU, less than that seen in previous studies. The infective burden is low, suggesting another aetiological cause for diarrhoea in the critically unwell. Over 17% of our patients with diarrhoea received laxatives in the 24h prior to its onset, indicating a need to rationalise prescribing. There is an association with increased length of stay and patient mortality in patients with diarrhoea, which is increased further in patients with *C. difficile*.

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