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Co-morbidities as predictors of mortality in *Clostridium difficile* infection and derivation of the ARC predictive score

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SUMMARY

Clostridium difficile associated diarrhoea (CDAD) has increased significantly in the last 15 years, but predictors of outcome are inadequately understood. This was a cohort study of 2761 patients in North East England between 2002 and 2009, with the end-point of mortality at 30 days. The role of age, gender and co-morbidities was examined by binary logistic regression. Rounded odds ratios were used to develop a predictive score. A predictive score based on age, renal disease and cancer (ARC score) differentiated groups with differing risk of 30-day mortality (risk for score of 0–3 was 9–21%, score of 4–7 was 31–48% and score of 8 was 66%). Co-morbidities were shown to be important predictors of outcome in CDAD, and can be combined with age in the ARC score to assess the likelihood of survival. This requires further validation in other populations, but has important implications for clinical and research practice.

Introduction

Clostridium difficile associated diarrhoea (CDAD) is a healthcare-associated infection that has increased significantly in the UK, from less than 1000 cases/year in the early 1990s to 36,097 cases in 2008/2009.[1,2] Outcome measures in CDAD are not yet well defined, but death at 30 days is probably the best measure.[3] It is often difficult to attribute death to a specific cause in patients with CDAD as they often have multiple co-morbidities. Many previous studies of outcome in CDAD are difficult to compare because they do not use absolute mortality as the end-point, and vary in their definitions of how death is attributed to CDAD or otherwise. However, mortality among these patients is high. For example, a previous study of all the patients diagnosed with CDAD in a specific UK National Health Service (NHS) hospital trust between 2002 and 2008 reported absolute mortality at 30 days of 32.7%, with no significant difference between the study years or between hospitals.[3] This is similar to the absolute mortality rates reported from enquiries at the Vale of Leven Hospital and Stoke Mandeville Hospital: 32.7% and 34.5%, respectively.[4,5] Mortality rose incrementally from 3.4% in patients aged <40 years to 41% in those aged >90 years.[3]

Previous studies of factors associated with outcome in CDAD are summarized in Table I. Co-morbid illness or system dysfunction has not been studied extensively as a predictor of 30-day mortality. Ischaemic heart disease,[16] cardiorespiratory failure,[15] and pre-existing pulmonary and renal disease[9] are associated with higher mortality. Liver disease[10] and cognitive impairment[13] have also been identified in small studies as predictors of severe disease, although not of death. A higher score on the Charlson Co-morbidity Index ($4.34 + 1.71$ vs $3.42 + 2.08$; $P = 0.02$), which is a measure of the overall burden of co-morbidity, has been found to be a significant risk factor for 90-day mortality[8] and for 'severe disease'.[11] However, it has not been studied for its effect on 30-day mortality, which is possibly a better indicator of the effect of CDAD than 90-day mortality.

Previous studies have investigated diverse populations in diverse clinical situations, generally in relatively small or specialized cohorts, and have either used absolute or attributable mortality. There is, therefore, inadequate understanding of the co-morbidities associated with poor outcome, and a better understanding of the pattern and cause of mortality in patients with CDAD is desirable. By establishing significant predictors of 30-day mortality in *C. difficile* infection, patients at high risk of poor

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Table I
Previous studies of factors associated with *Clostridium difficile* associated diarrhoea (CDAD) outcome

Study	Sample size	Factors	Notes
Andrews *et al.*, 2003[6]	153	Age >70 years Increasing co-morbid illness Recurrent CDAD	Risk factors for severe CDAD
Bishara *et al.*, 2008[7]	217 patients, 52 had CDAD	Univariate analysis: – Renal failure – Leukocytosis – Hypoalbuminaemia – Occult blood in stool Multi-variate analysis: – Elevated serum urea level	Factors associated with increased all-cause 28-day mortality
Cadena *et al.*, 2010[8]	129	Higher Charlson Co-morbidity Index Severe *C. difficile* infection Use of piperacillin/tazobactam or meropenem	Factors associated with increased 90-day mortality
Dudukgian *et al.*, 2010[9]	398	Higher APACHE II score Higher American Society of Anesthesiologists class Lower diastolic blood pressure Pre-existing pulmonary and renal disease Use of steroids Evidence of toxic megacolon Higher white blood cell count Clinical signs of sepsis and organ dysfunction (renal and pulmonary)	Factors associated with increased all-cause mortality
Gravel *et al.*, 2009[10]	1430	Advanced age Hospital admission from another hospital/long-term care facility Liver disease Receipt of vancomycin as initial treatment Change in initial treatment	Factors independently associated with severe outcome
Hardt *et al.*, 2008[11]	124	Higher 30-day mortality Higher proportion of longer hospital stay >14 days Charlson Co-morbidity Index Serum C-reactive protein at diagnosis	Predictors for severe CDAD
Keneally *et al.*, 2007[12]	278	Septic shock Ward-to-ICU transfer Increasing APACHE II score	Independent predictors for 30-day mortality in patients with CDAD admitted to ICU
Kyne *et al.*, 1999[13]	73	Endoscopy Cognitive impairment	Independent predictors of severe CDAD
Marra *et al.*, 2007[14]	58	SOFA score at onset of CDAD Advanced age	Independent predictors of all-cause mortality
Sailhamer *et al.*, 2009[15]	199 (fulminant *C. difficile* colitis)	Age ≥70 years Severe leukocytosis or leukopenia or bandaemia Cardiorespiratory failure	Independent predictors of all-cause mortality
Wilson *et al.*, 2010[16]	128	Ischaemic heart disease Hypoalbuminaemia	Independent predictors of 30-day all-cause mortality

ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

outcome could potentially be identified for recruitment to intervention studies. Outcomes could also be better compared between different healthcare providers.

Scoring systems for predicting outcome at the bedside are prevalent in clinical medicine. They can be used in individual patient care for prognostication (e.g. to keep patient and family informed) and to help decide the intensity of treatment required or appropriate. They are useful in comparing outcomes between units by adjusting outcome for severity. Examples used routinely in gastroenterology include those used to predict outcome in liver disease (e.g. UKMELD score[17] and Glasgow alcoholic hepatitis score[18]), and those used to predict the course of gastrointestinal bleeding (e.g. Rockall score[19]). There is no standard and validated predictive measure for CDAD. Recently, a scoring system based on age, temperature, leukocytosis, albumin and concomitant antibiotic use (ATLAS) was described. In the validation cohort, the majority of patients had scores of 1–7 with mortality rates of 0–14%.[20] The mortality rate was 56% for those with a score of 8. However, this study used 'mortality due to CDAD' and not absolute mortality as its end-point. Most predictive scores use absolute mortality as the end-point they are trying to predict (e.g. Rockall score[19] and Glasgow alcoholic hepatitis score[18]).

Ideally, a predictive score should be consistent, simple to calculate, reliable in its predictions (and remain reliable in diverse patient populations), and clinically useful in separating groups with differing risk.

As such, the aim of this study was to establish the predictive power of age and co-morbidities on mortality at seven and 30 days, and to develop a predictive score based on co-morbidities and age.

Methods

The study cohort has been described in detail previously.[3] Briefly, patients diagnosed with CDAD between 2002 and 2009 within a single acute care NHS hospital trust were identified using the microbiology reporting system, and were included if tested within the laboratory with a first positive result using the VIDAS *Clostridium difficile* toxin A and B immunoassay (bioMérieux UK Ltd, Basingstoke, UK) on a faeces sample with consistency of Bristol stool type 6 or 7.[21] Only first episodes were included. Information about vital status was obtained by two methods, namely by examining the Trust Patient Administration System and from individual mortality data files tracked using the National Tracing Service, a service run for the NHS by Connecting for Health and based on central registration from death certificates.