Malnutrition in healthcare settings and the role of gastrostomy feeding

Matthew Kurien1,2*, Jake Williams2 and David S. Sanders1,2
1Academic Unit of Gastroenterology, Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield S10 2RX, UK
2Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

Malnutrition can adversely affect physical and psychological function, influencing both morbidity and mortality. Despite the prevalence of malnutrition and its associated health and economic costs, malnutrition remains under-detected and under-treated in differing healthcare settings. For a subgroup of malnourished individuals, a gastrostomy (a feeding tube placed directly into the stomach) may be required to provide long-term nutritional support. In this review we explore the spectrum and consequences of malnutrition in differing healthcare settings. We then specifically review gastrostomies as a method of providing nutritional support. The review highlights the origins of gastrostomies, and discusses how endoscopic and radiological advances have culminated in an increased demand and placement of gastrostomy feeding tubes. Several studies have raised concerns about the benefits derived following this intervention and also about the patients selected to undergo this procedure. These studies are discussed in detail in this review, alongside suggestions for future research to help better delineate those who will benefit most from this intervention, and improve understanding about how gastrostomies influence nutritional outcomes.

Malnutrition: Nutrition support: Hospitals: Gastrostomy

Malnutrition describes a state in which a deficiency, excess or imbalance of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition), function or clinical outcome(1). It is a recognised global public health problem affecting both industrialised and emerging countries(2). Presently, the state of food insecurity estimates that about 795 million people in the world (just over one in nine people) are malnourished(3). Poverty, social isolation and substance misuse contribute significantly to the burden in developed countries; however the mainstay of problems are derived from disease related malnutrition, through reduced dietary intake, increased metabolic demands and impaired absorption or loss of nutrients(4). The consequences of malnutrition can be profound, leading to deleterious effects on both physical and psychological function. This can adversely impact clinical outcomes such as morbidity, mortality, hospital length of stay, hospital readmissions and healthcare costs(3,5). Despite the prevalence of malnutrition and its associated health and economic costs, malnutrition remains under-detected and under-treated in healthcare settings(6).

Prevalence of malnutrition in healthcare settings

In 1994 a landmark paper published by McWhirter et al. in the British Medical Journal raised concerns that 40% (200/500) of patients admitted to an acute UK hospital were malnourished(8). A further concern highlighted in this study was that patients continued to lose weight during their hospital stay (mean weight loss of 5.4%). Since the publication of this seminal paper, there have been numerous other studies performed in the UK, demonstrating a prevalence of malnutrition in UK hospitals...
ranging between 11 and 45%\(^9\). Although considerable heterogeneity exists between these published studies, findings collectively suggest that malnutrition in hospitals remains highly prevalent in the UK today. These findings are supported by a recent publication from the British Association for Parenteral and Enteral Nutrition using the Malnutrition Universal Screening Tool (discussed later)\(^10\). This report estimates adult malnutrition to affect: 30% on admission to hospitals, 34% in hospital wards, 35% admitted to care homes, 35% already resident in care homes, 18% admitted to mental health units, >15% attending hospital outpatient clinics and 10% of patients visiting general practitioners\(^10\).

Problems with malnutrition in healthcare settings are not confined to the UK. In a multicentre study evaluating 21,007 patients from 325 hospitals across Europe and Israel, 27% of patients were subjectively identified as being at nutritional risk\(^11\). In Latin America, a recent systematic review of sixty-six studies encompassing 29,474 patients from twelve countries, demonstrated a prevalence of disease-related malnutrition on hospital admission between 40 and 60%. Similar findings have been reported from other industrialised nations across the globe\(^12\)-\(^15\).

**Improving nutritional care through screening and assessment**

Over recent decades several publications from differing professional bodies and patient organisations have raised concerns about the detection of malnutrition\(^16\)-\(^19\). Consequently, an array of screening and assessment tools has been devised to help assess malnutrition and determine nutrition risk. Nutritional screening refers to a rapid and simple means of predicting malnutrition risk, whereas nutritional assessments determine whether malnutrition is actually present\(^20\). The benefits of screening tools are that they can be used by an array of trained healthcare professionals, whereas nutritional assessments require greater expertise, and are most frequently performed by trained dietitians.

The Malnutrition Universal Screening Tool is the nutrition screening tool most frequently used in the UK, incorporating present BMI, unintentional weight loss and the presence of any acute disease effect that could compromise nutritional intake for >5 d\(^21\). It has been shown to have high predictive validity in both the community and hospital environments (length of hospital stay, mortality in elderly wards, discharge destination in orthopaedic patients)\(^21\)-\(^23\). Another screening tool adopted is the Nutritional Risk Screening 2002, which includes four questions about: BMI (if it is <20-5), presence of weight loss in the past 3 months, presence of low dietary intake in the past week and the severity of disease\(^24\). This Nutritional Risk Screening 2002 was advocated in the 2002 European Society for Clinical Nutrition and Metabolism consensus definition for malnutrition\(^23\),\(^25\).

Other tools used in clinical practice include the Mini Nutrition Assessment, the Subjective Global Assessment and the Short Nutrition Assessment Questionnaire\(^26\)-\(^28\). Despite the benefits of nutritional screening in healthcare settings and the requirement to do so in certain countries (e.g. UK, USA), the use of these tools remains highly variable, with no one tool being universally adopted in all settings\(^29\),\(^30\).

**Economic costs of malnutrition**

Although the physical and psychological manifestations of malnutrition have been extensively investigated, until recently there has been limited work evaluating the economic costs of malnutrition. This paucity of work highlights the difficulties in attributing monetary value to certain consequences of malnutrition that may be influenced by disease status, socioeconomic status, life expectancy, alongside the perspective from which the economic analysis is being undertaken (e.g. patient, healthcare professional or general public)\(^31\). In European countries the annual costs of disease related malnutrition have been calculated in The Netherlands (2011), Germany (2006), UK (2012) and Ireland (2007) equating to €1-9 billion, €9 billion, €19-6 billion and €1-5 billion, respectively\(^32\),\(^33\). As a cost per adult (>18 years) capita for these four individual nations, costs translate to €135, €134, €370, €500, respectively. These variations in outcomes highlight the differences in methodology used to calculate costs, with the UK data considering all healthcare costs, e.g. total general practitioner visits and costs for providing domiciliary and home care, compared with the findings from the Netherlands that only assesses additional costs due to disease related malnutrition\(^32\). Improving the understanding of direct healthcare costs of malnutrition (e.g. cost of travelling expenses to patients and carers to receive nutrition support), and of the indirect healthcare costs such as reduction in work productivity, would help enhance costing calculations.

The benefits of health economics data in this field can be demonstrated when considering the effectiveness and efficacy of interventions for treating malnutrition. This has recently been the subject of a Cochrane systematic review, supporting the use of nutritional therapy in reducing healthcare costs. This work also highlights the need for future work to investigate the impact nutritional therapies have on malnutrition and on hospital readmission rates\(^34\).

**Nutrition support**

Nutrition support involves the provision of nutrition beyond that provided by normal food intake using oral supplementation, enteral tube feeding and parenteral nutrition\(^19\). The goals of nutrition support are to ensure attainment of an individual’s nutritional requirements. Oral nutrition using special diets and supplements is usually considered the first line therapy in managing malnutrition, however certain individuals may require enteral...
or parenteral nutrition when oral intake is reduced or when swallowing is unsafe\(^\text{35}\). Of these modalities, enteral nutrition is usually preferred in the context of a normally functioning gastrointestinal tract as it is physiological, cheaper and may help maintain gut barrier function\(^\text{36,37}\). Most patients requiring nutrition support therapy have treatment for less than 1 month\(^\text{38}\). When short-term enteral feeding is considered, nasogastric and orogastric tubes are most frequently used, reflecting their ease of insertion and removal (Fig. 1). Tubes range in length and diameter and can be inserted either at the bedside, at endoscopy or using radiological guidance. When nutritional intake is likely to be inadequate for more than 4–6 weeks then enteral feeding using a gastrostomy is most frequently considered (Fig. 2)\(^\text{39}\). This intervention for providing nutritional support is discussed in further detail later.

**History of gastrostomies and techniques of insertion**

A gastrostomy describes a feeding tube placed directly into the stomach via a small incision through the abdominal wall (Fig. 2). It can provide long term enteral nutrition to patients who have functionally normal gastrointestinal tracts but who cannot meet their nutritional requirements due to an inadequate oral intake\(^\text{39}\). Infrequently, they may also be used for decompressing the stomach or proximal small bowel following outflow obstruction or volvulus.

The concept of a gastrostomy was first proposed by Egeberg, a Norwegian army surgeon in 1837, however it was only in 1876 when Verneuil used a silver wire to oppose visceral and parietal surfaces that success was achieved in inserting a surgical gastrostomy\(^\text{40}\). Post-procedural peritonitis was the most frequent limitation to previous attempts at surgical insertion, with death ensuing in individuals who developed this complication. Stamm modified Verneuil’s surgical technique in 1894, prior to modifications being developed by Dragstedt, Janeway and Witze in the 20th century\(^\text{41}\).

In 1979, Michael Gauderer and Jeffrey Ponsky revolutionised gastrostomy practice by pioneering an endoscopic method of insertion in Cleveland, Ohio\(^\text{42}\). The two paediatricians performed the very first percutaneous endoscopic gastrostomy (PEG) in a 6-month old child, using a 16 French DePezzar (mushroom tipped) catheter, which they replicated again in a further five paediatric cases\(^\text{43}\). Ponsky then utilised this technique in a cohort of adult patients with dysphagic strokes, which heightened interest in this novel endoscopic technique\(^\text{43}\). The ‘pull technique’ that they pioneered is presently one of the three endoscopic methods frequently used today in clinical practice. When compared with previously used surgical methods, endoscopic insertion was favourable, as it was minimally invasive and incurred lower morbidity and mortality.

Two years later in 1981, Preshaw in Canada used fluoroscopic guidance to insert the first percutaneous radiological gastrostomy\(^\text{44}\). Like endoscopic methods, modifications of the original radiological technique have occurred since the original method was conceived. However, despite these advances endoscopic techniques remain the most popular methods of insertion internationally, with percutaneous radiological gastrostomy insertion most frequently reserved for high-risk patients, oropharyngeal malignancy and when endoscopic passage is technically difficult\(^\text{45,46}\).

**Indications for gastrostomy**

Since the introduction of endoscopic and radiological insertion techniques for gastrostomy, there has been increasing demand for this intervention, for an increasing number of clinical indications. A broad list of indications

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Fig. 1. (Colour online) Methods of enteral feeding.

Fig. 2. (Colour online) A gastrostomy feeding tube.
for which patients are presently being referred for gastrostomy is given in Table 1. Despite being widely performed, the evidence base to support gastrostomy feeding in certain patient groups is lacking. This is reflected in the National Confidential Enquiry into Patient Outcome and Death report, which reviewed mortality outcomes of post-percutaneous endoscopic gastrostomy insertion between April 2002 and March 2003, identifying a 30-d mortality rate in a cohort of 16648 patients of 6 % (47). Subgroup analysis alarmingly showed that 43 % died within 1 week of undergoing PEG insertion, of whom in 19 % the intervention was felt to have been futile. Interestingly, the National Confidential Enquiry into Patient Outcome and Death data identified a high prevalence of acute chest infections (40 %) in those undergoing PEG placement, which could have influenced these mortality outcomes. The present evidence regarding gastrostomy feeding in certain patient subgroups is discussed later.

**Gastrostomy feeding and dementia**

Patients with dementia frequently develop feeding problems, leading to weight loss and nutritional deficiencies. Up to 85 % of these problems develop prior to death suggesting that difficulties with feeding are an end-stage problem, associated with advanced disease (48). Whether or not to use gastrostomies to feed patients with dementia is an emotive and controversial issue. This controversy is further compounded by the fact that in the late stages of the illness, individuals lack capacity to express their wishes. The 2010 British Artificial Nutrition Survey gives insights into the frequency of insertion for dementia, highlighting that registration of home enteral tube feeding (mainly by gastrostomy) for this indication declined from 7 % in 2004 to 3 % (48/1560) (49). This decline reflects concerns raised in the medical literature about inserting gastrostomies for this indication.

There is presently a limited number of prospective studies examining outcomes in dementia that could help inform clinical practice (50,51). In a retrospective cohort study of 361 patients, mortality was found to be significantly higher in dementia patients compared with any other patient group (54 % 30-d mortality and 90 % at 1 year) (52). Our group has recently replicated this finding in a prospectively followed cohort (n 1023), however the number of insertions performed for dementia was low (n 5) (53). These concerns have been highlighted in a Cochrane systematic review, which showed no improvements in survival, quality of life, nutritional status, function, behaviour or in psychiatric symptoms in patients with advanced dementia receiving enteral tube feeding (54).

**Gastrostomy feeding in stroke patients**

Dysphagia is common in patients after a stroke ranging between 23 and 50 % (55). While neurological recovery does occur in some patients leading to improvements in swallowing function, many remain at high risk of developing aspiration pneumonia and malnutrition. Enteral nutrition is widely advocated in these individuals; however, controversy exists as to the optimal mode of delivery. Two small randomised studies evaluating PEG vs. nasogastric feeding demonstrated improved mortality outcomes, hospital length of stay and nutritional indices in patients who had a PEG, suggesting derived benefit (56,57). However, since these studies were published the FOOD trial, a multicentre study evaluating enteral nutrition in stroke patients has questioned the potential merits of PEG feeding (58). Consisting of three pragmatic randomised controlled trials, the FOOD trial aimed to determine whether routine oral nutritional supplementation of a normal hospital diet improved outcomes after stroke (trial 1); whether early tube feeding improved the outcomes of dysphagic stroke patients (trial 2); and whether tube feeding via a PEG resulted in better outcomes than nasogastric feeding (trial 3). Results showed no benefit of oral supplements; however, survival improved when tube feeding was commenced early but at the cost of poorer functional outcomes. In trial 3 the best outcome was achieved in the group fed by nasogastric tube. These findings have led to reviewing present practice and questioned the optimal timing of gastrostomy feeding in these patients.

**Gastrostomy feeding in oropharyngeal malignancy**

Patients with oropharyngeal malignancy are at risk of malnutrition due to direct effects from the tumour (e.g. reduced appetite, host response, problems ingesting food due to tumour size) and also from the anticancer therapies themselves (e.g. radiation induced mucositis). Gastrostomies are widely performed in this patient group as a prophylactic measure (prior to radiotherapy and chemotherapy), but also when swallowing problems occur directly because of the malignancy itself. Despite the potential merits of enteral feeding in this patient group, there has only been one randomised controlled trial evaluating gastrostomy feeding in comparison with other enteral feeding methods (59). This has led to a recent Cochrane review concluding that there is insufficient evidence to determine the optimal method of enteral feeding in patients with head and neck cancer receiving radiotherapy and/or chemoradiotherapy (60).

### Table 1. Conditions where gastrostomy feeding is considered

<table>
<thead>
<tr>
<th>Neurological indications</th>
<th>Obstruction</th>
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<tr>
<td>Cerebrovascular disease</td>
<td>Oropharyngeal cancer</td>
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<tr>
<td>Motor neurone disease</td>
<td>Oesophageal cancer</td>
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<tr>
<td>Multiple sclerosis</td>
<td>Oesophageal stricture</td>
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<tr>
<td>Muscular dystrophy</td>
<td>Miscellaneous</td>
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<td>Parkinson’s disease</td>
<td>Burns patients</td>
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<td>Cerebral palsy</td>
<td>Fistulae</td>
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<td>Dementia</td>
<td>Cystic fibrosis</td>
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<td>Reduced conscious level/cognition</td>
<td>Short bowel syndromes (e.g. Crohn’s disease)</td>
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<tr>
<td>Head injury</td>
<td>Mental health (Anorexia/ Learning Difficulties)</td>
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<td>Intensive care patients</td>
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Malnutrition in healthcare settings 355
Gastrostomies are increasingly being used in the treatment of patients with neurogenic dysphagia. While the exact aetiology of the neurogenic dysphagia is frequently unknown, it is commonly encountered in patients with motor neurone disease (amyotrophic lateral sclerosis), Huntington’s chorea, multiple sclerosis and in patients with Parkinson’s disease. When bulbar weakness develops leading to dysphagia and dysphagia, gastrostomies are frequently considered to aid nutrition, reduce choking episodes and to minimise the risk of aspiration pneumonia.

There are presently no randomised controlled trials evaluating outcomes of patients with chronic neurodegenerative conditions following gastrostomy insertion. Of the observational studies that have been performed, findings are frequently conflicting, retrospective and predominantly from motor neurone disease cohorts. Based on the limited available literature, the most recent Cochrane review tentatively concludes that gastrostomy feeding may confer a survival and nutritional advantage in those with motor neurone disease, however further work is required with regard to evaluating quality of life. The recent ProGas study has provided further insights into this area since the Cochrane review, evaluating methods of gastrostomy insertion and optimal timing.

Gastrostomy feeding in other patient sub-groups

Gastrostomy insertion is performed for a number of other indications (highlighted in Table 1), however evidence to support its use in these differing sub-groups is questionable. An example of this is in patients who suffer head injuries following road traffic accidents, falls, violence or sport who are often considered for gastrostomy while on intensive care units. Presently, the latest Cochrane review of nutritional support in head injury patients (analysis of eleven trials) suggests early feeding may improve survival and disability, however this benefit may be best derived from total parenteral nutrition rather than enteral nutrition methods. When comparing nasogastric feeding with gastrostomy feeding in this patient group, gastrostomy feeding may reduce pneumonia rates but does not derive any mortality benefit.

Another group of patients seen in adult services with gastrostomies are patients with cerebral palsy. Gastrostomy insertion is increasingly being performed in children with this condition with the aim of improving weight, nutritional indices and quality of life. These individuals are then moved into adult services as they reach adulthood. Unfortunately, as in many other areas of gastrostomy feeding there is a paucity of well-designed randomised controlled trials evaluating gastrostomy feeding in this patient group, leading to uncertainty regarding the merits of this intervention. This uncertainty is reflected in other conditions (anorexia nervosa, achalasia, frailty, burns patients) and highlights the need for well-conducted studies, to help better inform clinical practice.

Enteral feeds can be delivered via gastrostomies using continuous, bolus or intermittent infusion methods. These feeds are nutritionally complete (containing protein or amino acids, carbohydrate, fat, water, minerals and vitamins) and are available in fibre free and fibre enriched forms. Determining the type of feed used is influenced by an individual’s nutritional requirements, gastrointestinal absorption, motility and also by their co-morbidities, such as renal or liver disease. Continuous infusion provides patients with feed over 24 h and is most frequently reserved for very ill patients. This regimen is associated with an increased risk of drug nutrient interactions and may also increase intragastric pH leading to bacterial overgrowth. Bolus feeding describes the delivery of 200–400 mL feed (administered either by push or gravity methods over 15–60 min) periodically throughout the day, permitting medications to be given at times different to feeds. This can lead to abdominal bloating, diarrhoea and symptoms analogous to those seen in the dumping syndrome where rapid gastric emptying occurs. Intermittent infusions provide feeds over a longer duration than bolus feeding using an infusion pump, thereby minimising the adverse symptoms but also permitting breaks for the patients unlike continuous feeding.

The nutritional benefits derived from gastrostomy feeding are not clearly established. The uncertainties that exist reflect the heterogeneity in populations previously assessed, the paucity of data examining long-term nutritional outcomes and confounders such as timing of gastrostomy feeding that may have influenced reported outcomes. In addition, the assessment of nutritional status is highly variable. In stroke patients, a frequently cited historical paper showed that gastrostomy feeding was better than nasogastric feeding at improving weight gain and anthropometric measurements at 6 weeks. This landmark study has helped inform future clinical practice; however it is to be recognised that results were derived from only thirty patients from two UK centres. The more recent and significantly larger, multicentre FOOD trial has enhanced understanding about the timing and method of enteral feeding in stroke patients; however uncertainty still remains about how gastrostomies impact nutritional status in these individuals.

The ProGas study provides insights into how gastrostomy feeding influences nutritional outcomes in motor neurone disease. This study was not a randomised controlled trial; however, its importance to clinical practice has been widely recognised by being the first multicenter, longitudinal cohort study in this field. In this study, the authors report outcomes of 170 patients who had valid weight measurements 3 months post-gastrostomy insertion. Findings showed that in eighty-four (49%) patients, weight loss was more than 1 kg compared with baseline values. These findings suggest...
nutritional gains may be limited in this group of patients; however, to determine the timing of gastrostomy insertion may be critical to achieve maximal gains in the future. The uncertainties highlighted here emphasise the need for better studies looking at nutritional outcomes in gastrostomy patients. This would also help improve understanding of the efficacy of this intervention in reducing malnutrition.

Optimising referral for gastrostomy insertion and aftercare

There has been increasing interest in improving patient selection for gastrostomy insertion\(^{(76-78)}\). One method used internationally to optimise referral practice is to employ institutional guidelines that use a standardised referral protocol. Use of a multidisciplinary team in assessment of patients and dissemination of evidence can allow both carers and healthcare professionals to make an informed decision. This approach has been shown (in observational studies) to improve the selection of patients referred for gastrostomy\(^{(79-81)}\).

When considering whether insertion of a gastrostomy tube is appropriate, the question that must be asked is whether gastrostomy feeding would maintain or improve a patient’s quality of life. This question must be answered in the context of the underlying diagnosis and prognosis, considering moral and ethical issues, as well as respecting the patient’s wishes. Guidelines exist to aid clinicians in making decisions on gastrostomy feeding; however the decision to insert a feeding tube should always be made on an individual basis\(^{(19,82)}\).

Another factor that may be influencing outcomes following gastrostomy insertion is variations in the organisation of aftercare services. In the UK study, looking at provision of services for gastrostomy, only 64 % of units had a dedicated aftercare service\(^{(83)}\). The benefits of dedicated home enteral feed teams have been shown to reduce costs and morbidity associated with gastrostomy feeding\(^{(84,85)}\). Given that most complications of gastrostomy feeding occur following hospital discharge, effort should be made to improve the delivery of aftercare and procurement of these services for the benefit of patients.

Ethical and legal considerations of gastrostomy feeding

Gastrostomy feeding raises ethical and legal issues. Both the Royal College of Physicians and the General Medical Council in the UK have provided guidance on oral feeding and nutrition\(^{(86,87)}\). Artificial feeding is considered a medical treatment in legal terms and requires valid consent prior to commencement. For consent to be valid the person giving consent must have the capacity to do so voluntarily after being given sufficient information to guide informed choice. When a patient has capacity their wish to consent to or refuse treatment should be upheld, even if that decision may lead to death. When a patient lacks capacity an independent mental capacity advocate should represent that individual. The multidisciplinary team caring for the patient is responsible for giving, withholding or withdrawing treatment, including artificial feeding and hydration and should consider any advance directives, the patient’s prognosis and the likely benefits of gastrostomy feeding when making decisions. A limited trial of feeding may sometimes be used but strict criteria regarding what constitutes success should be determined prior to starting gastrostomy feeding\(^{(74)}\). Conflicts sometimes arise between health care professionals or between the professionals and those close to the patient. In such circumstances it may be necessary to seek legal advice or seek resolution through a local clinical ethics committee\(^{(85)}\). Anecdotally, such conflicts appear to be rising with increased patient and family demands for intervention, which may in turn be influenced by emotion or by cultural beliefs.

The National Institute for Health and Care Excellence dementia guidelines highlight the importance of quality of life in advanced dementia and support the role of palliative care in these individuals from diagnosis until death. Best practice in these patients could be to encourage eating and drinking by mouth for as long as tolerated, utilising good feeding techniques, altering food consistencies and to promote good mouth care. Assisting hand feeding in this way has recently been shown to be of benefit in elderly patients, with volunteer assistance improving oral intake and enjoyment of meals\(^{(89)}\). When disease progression is such that the patient no longer wants to eat or drink, then rather than inserting a gastrostomy tube, end of life care pathways might be considered. Views held by carers and medical staff may prevent progression to end of life care pathways. A questionnaire survey demonstrated that allied health care professionals were more likely than physicians to consider gastrostomy feeding when presented with patient scenarios relating to malnutrition\(^{(90)}\).

Conclusion

Malnutrition is a global public health concern. These problems are not only restricted to emerging countries, but also highly prevalent in healthcare systems in developed countries. Despite advances in nutritional care, evidence from across the globe suggests that detection of malnutrition remains sub-optimal. Presently, billions are being spent on the consequences of malnutrition, when simple corrections of patient’s nutritional statuses appear to be overlooked or not considered as a sufficient medical problem. To help ease this burden to patients and healthcare systems, detection and appropriate treatment need to be significantly improved, alongside improvements in the evidence base for selected treatments. This has particular relevance to gastrostomy feeding where the benefits for malnourished individuals and their caregivers remains uncertain. Future gastrostomy research should aim to better delineate those who will benefit most from this intervention; determine the optimal timing of this procedure and enhance understating
on how gastrostomies can improve nutritional outcomes in malnourished individuals.

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Conflict of Interest
None.

Authorship
M. K. designed and drafted the article and is the guarantor. J. W. revised the article and approved the final manuscript. D. S. S. designed and revised the paper and approved the final manuscript.

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