Nutrition Management of Spinal Cord Injured Patients: An Investigation of Resources and Interventions in UK Spinal Cord Injuries Centres

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Abstract

Introduction: Spinal cord injured (SCI) patients have complex physical and psychological needs. Malnutrition (including under- and over- nutrition) is common after SCI, and is associated with adverse clinical outcomes such as increased risk of infection. To date, limited information is available to guide clinicians to identify, prevent and manage nutrition related complications in SCI patients. This gap in evidence has promoted a series of research studies addressing the following research aims: (1) To review and understand the variations in nutritional management in SCI centres (2) To evaluate whether currently implemented nutrition interventions (e.g probiotics use in preventing antibiotic associated diarrhoea (AAD) and Clostridium difficile infection (CDI) are evidence based and to discuss the potential barriers to good nutritional care in SCI centres; (3) To evaluate three original studies (bariatric surgery case studies; the use of oral nutritional supplement (ONS) and vitamin and minerals (VMS) and; the use of Lactobacillus casei Shirota (LcS) in preventing AAD. A total of seven peer-reviewed papers, utilising a range of mixed research methodologies (observational studies, case study, surveys, randomised-controlled trials and systematic review protocol) were undertaken to demonstrate the effectiveness of nutrition interventions in patients admitted to SCI centres with a critical commentary.

Results: (1) Although most SCI centres use validated nutrition screening tool, the resource allocation for nutritional care appeared to be relatively limited; (2) Definition for AAD, CDI, under- / over-nutrition risk and choice of probiotics in preventing AAD / CDI are varied across SCI centres. (3) Three studies attempted to demonstrate an improvement in SCI patient's quality of care are reported. These include: (i) the use of nutritional supplements in SCI patients at malnutrition-risk (undernutrition risk, serum albumin and haemoglobin level are predictors of oral nutrition supplements use); (ii) the first UK bariatric surgery in a morbidly obese SCI patient who failed all non-surgical interventions (an improvement in functional, anthropometrical and nutritional biochemistry was found after surgery) and (iii) the use of probiotics in preventing antibiotic associated diarrhoea (AAD). (*Lactobacillus casei* Shirota was found to prevent AAD when compared to a control, 17.1% v 54.9%, $p<0.01$).

Conclusion: Our studies suggest that resources allocated in SCI centres varied. Without sufficient nutritional resources in SCI centres, malnutrition will be under-detected and under-treated. In addition, carefully planned nutrition / dietetic interventions could improve outcomes in SCI patients if nutritional care is embedded in the SCI care-pathway. Development of clinical nutrition practice guidelines are warranted, and further well-designed randomised controlled trails are required to confirm whether the effect of nutrition (and probiotic) intervention is cost- and clinically-effective.

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List of Abbreviations

AAD	Antibiotic Associated Diarrhoea
AHP	Allied Health Professions
AIS	AISA Impairment Scale
AISA	American Spinal Injury Association
BAPEN	British Association of Parenteral and Enteral Nutrition
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CDAD	*Clostridium difficile* Associated Diarrhoea
CDI	*Clostridium difficile* Infection
CNS	Central Nervous System
EIA	Enzyme Immunoassays
ISCOS	International Spinal Cord Society
LcS	*Lactobacillus casei* Shirota
LOS	Length of (hospital) stay
MASCIP	Multidisciplinary Association of Spinal Cord Injury Professionals
MND	Motor Neurone Disease
MS	Multiple Sclerosis
MUST	Malnutrition Universal Screening Tool
NICE	National Institute for Health and Clinical Excellence
NSIC	National Spinal Injuries Centre
NST	Nutritional Screening Tool
ONS	Oral Nutritional Supplements
PPI	Proton Pump Inhibitor
RCT	Randomised Control Trial
RMR	Resting Metabolic Rate
RTA	Road Traffic Accident
SC	Spinal Cord
SCFA	Short Chain Fatty Acids
SCI	Spinal Cord Injury
SNST	Spinal Nutrition Screening Tool
VMS	Vitamin and Mineral Supplements
WTE	Whole-Time-Equivalent

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Declaration

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Role of the investigator

This thesis would not have been possible without the help and support of many individuals and organisations listed in the acknowledgements. My involvement in nutrition research began in May 2004 during a year working toward my final year dietetic research project in the Department of the Nutrition and Dietetics at the Robert Gordon University, Aberdeen. I completed an MSc in Human Nutrition with specialisation in Public Health Nutrition at the University of Glasgow (2005-6) and an MPhil in Clinical Nutrition at University College London in 2010-2014 (part-time). I have worked at Stoke Mandeville as a Dietician since 2005 before choosing to specialise in spinal cord injury in 2007 and became Lead Dietitian at the National Spinal Injuries Centre at Stoke Mandeville Hospital in 2011. I have a long and on-going interest in research into the management of malnutrition and associated problems. My research has explored the role of probiotics in preventing bowel problems, and the management of obesity following spinal cord injury. I have a track record of obtaining external funding from charities (The Waterlow Foundation, The Healthcare Infection Society) and industry (Aventis Pharma, Abbott Nutrition and Yakult UK/Yakult Europe). I was the principal investigator on six research projects (leading to my MSc (Med Sci) and MPhil degrees. Since 2005, I have produced a significant number of peer-reviewed abstracts (54) and 18 full length articles, seven of which are submitted for the PhD degree by prior publication at City, University of London.

I was responsible for developing and implementing the studies I described in this thesis. This involved developing detailed clinical protocols, ethics and NHS Trust's Research and Development applications, data collection and maintaining the study databases. I was responsible for the study database with input from Dr. Shashivadan P Hirani and led the major analyses described in this thesis. For all the published papers submitted for this PhD (by prior publication), I was the lead (first) author responsible for writing the first version of the paper, coordinating and editing inputs from co-authors and submitting the final manuscripts.

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Chapter 1 Introduction

Overview

Disease-related malnutrition is both a cause and consequence of disease, and as such, it cannot be eliminated. (Elia, 2003) There is sound evidence from the literature that delivery of improvement in the quality of nutritional care significantly reduces adverse clinical outcomes such as harm whilst improving an individual's quality of life and reducing morbidity and mortality (NICE, 2006a). The impact of malnutrition in spinal cord injury (SCI) patients is more evident as they tend to have a long hospital stay after acute injury (Wong et al, 2012a; Wong et al, 2013). After a SCI, patients are expected to transfer to a specialist SCI centres for ongoing rehabilitation before they can re-integrate into the community. It is not known how staff in SCI centres identify or manage malnutrition after SCI and this will consequently alter the clinical decisions made for the management and ultimately, may have an impact on clinical outcomes. SCI contributes to both sensory and functional impairments and greatly impairs activities of daily living for SCI patients. A multicentre study found that at least 45% of SCI patients were overweight and 15.3% were obese (Wong et al, 2012a). If malnutrition after SCI goes undetected and unmanaged, it could cause a significant problem, including longer hospital stay (Wong et al, 2013), increase risk of infections (Schneider et al, 2004) increase in-hospital mortality (Wong et al, 2013), pressure ulcers (Consortium of Spinal Cord Medicine, 2014) and the development of nutrition-related complications such as obesity and other cardio-metabolic complications (NICE, 2006a).

Newly-injured SCI patients require anticoagulation therapy to prevent venous thromboembolism. This increases the risk of gastric ulcers, so patients often receive a proton pump inhibitor (PPI) to protect the stomach against this adverse effect. (Consortium for Spinal Cord Medicien, 2004) Literature reports show that patients on PPI have an increased risk of contracting *Clostridium difficile* infection (CDI) compared with patients who are not taking PPI (Tariq et al, 2017). In addition, increased use of invasive devices such as urinary catheters increases the risk of adverse effects of antibiotic use, including CDI (Evans et al, 2008). In SCI patients, antibiotic associated diarrhoea (AAD) and / or CDI can contribute to or complicate any pressure ulcer management as it leads to moisture and bacteria that could potentially contaminate pressure ulcers. Recurrent diarrhoea also depletes the body of electrolytes which are

key in wound healing, and chronic episodes lead to loss of micronutrients such as magnesium and zinc (Worth et al, 2016). The microbiota has an important role in human health. Changes in microbiota can confer resistance to or promote infection by pathogenic bacteria. Antibiotics have a profound impact on the microbiota that alters the nutritional landscape of the gut and can lead to the expansion of pathogenic populations. Therefore the interactions between the microbiota, probiotics, the host and pathogenic bacteria will produce strategies for manipulating the microbiota against AAD / CDI. (see section 1.6).

1.1 Aims and objectives of the thesis

To date, limited information is available to guided clinician to identify, prevent and manage nutrition related complications in SCI patients. This gap in the evidence promoted a series of research studies addressing the following research questions:

- How would SCI centres identify patients at risk of malnutrition?
- Are current nutrition intervention (e.g. oral nutrition supplement and vitamins and minerals supplements) evidence base?
- Would nutrition intervention (e.g. probiotic) improve patient's clinical outcome such as antibiotic associated diarrhoea (AAD)?

The over arching hypothesis of this thesis was to review if implementing evidence based nutritional interventions could improve decision making and clinical outcomes of SCI patients through three specific aims.

Aim 1:

To review and understand the variations in nutritional management in SCI centres from the perspective of staff and SCI patients.

Objectives:

- To review their choice of nutrition screening tools for identifying malnutrition risk.
- To discuss the variation in dietetic provision in SCI centres with reference to other multidisciplinary team members from wider allied health professionals.

- To generate expert opinion (knowledge, attitude and practice) in obesity management amongst SCI centres in the UK, Ireland, Belgium and the Netherlands.

Aim 2:

To evaluate whether currently implemented nutrition interventions in SCI centres are based on sound research evidence, and potential barriers to good nutritional care in SCI centres.

Objectives

- To discuss centre based variation in the diagnostic criteria of malnutrition risk; diarrhoea and *CDI* and;

- To report the development of a systematic review protocol on the use of probiotic in preventing AAD and CDI.

Aim 3:

To report three original studies (from a case study to a randomised trial) that explore how nutritional interventions may influence clinical outcomes in SCI patients.

Objectives

- To discuss the impact of bariatric surgery (the first case in the UK) on a morbidly obese SCI patient, as a way to instigate body weight loss following the failure of other non-surgical interventions.

- To report on the impact of nutritional supplements in SCI patients at risk of undernutrition, using a validated SCI-specific nutrition screening tool, the Spinal Nutrition Screening Tool, SNST.

- To report the effectiveness of a commercial probiotic, *Lactobacillus casei* Shirota (LcS) in preventing AAD and CDI.

A total of seven reported studies, covering a range of methodologies (Table 1.1) were undertaken to demonstrate the vital role that dieticians play in the nutritional management of people with SCI.

1.1.1 Outline of the thesis

Within the thesis, section 1.2 provides brief details of the anatomy of the spinal cord and nature of SCI, which helps to understand the physical and psychological impact after SCI. This is followed by a brief description of SCI centres, their functions and the concept of multidisciplinary rehabilitation as the key to successful SCI rehabilitation.

A critical review of the first study (Paper 5) will accompany in chapter one and it will discuss the variation of nutrition resources allocation across SCI centres and the impact of this variation. The prevalence, cause and consequence of malnutrition after SCI are discussed in section 1.4 covering both the acute and chronic phases of SCI. This is followed by a review of current literature in general and SCI populations with particular focus on the unique metabolic changes in those with SCI in both the acute and chronic phase of SCI. The subsequent sections describe potential complications after SCI, the concept of gut microbiota and the use of probiotic in manipulating gut microbiota in preventing AAD / CDI.

In chapter 2, attention will be given to the steps in identification of malnutrition risk and effect of malnutrition after SCI (section 2.1). The potential limiting factors obstructing optimal nutrition practice in SCI centres will be discussed. I also review the criteria for the the identification of overnutrition risk, choice of treatment and prevention strategies of obesity after SCI (Paper 4).

SCI patients are susceptible to infections during their stay in SCI centre. Antibiotic associated diarrhoea could lead to additional healthcare costs and adverse consequence such as CDI. There is increasing evidence that probiotics when administered in adequate amounts confer a health benefit on the host, particularly in diarrhoea related to antibiotic used. To date, little evidence exists to support this concept in SCI patients. Therefore, the second study presented in chapter 2, provided unique insight into whether SCI centres use a standardised definition for malnutrition risk and AAD / CDI.

In addition the evidence on the use of probiotic in preventing AAD / CDI after SCI will be discussed. (Paper 6 and 7).

In chapter 3, three original studies exploring how nutritional interventions may influence SCI patient's clinical outcomes were critically reviewed. The first study discussed the result on the use of nutritional supplements in SCI patients. The appropriate use of nutritional supplements was believed to be evidence-based in treating patients with an undernutrition risk. (Paper 1) The cause of obesity and its link with SCI must also be addressed (section 3.1). Although weight loss has been advocated as a primary strategy for the condition, to date, there is little guidance to support the nutritional management of morbid obese patients with SCI. Therefore, I discussed the impact on the first published bariatric surgery case report in SCI patients in the second study. (paper 2). This study recommends a carefully planned bariatric surgery with input from a multidisciplinary team could be an effective way to reduce the body weight of morbid obese SCI patients when they failed all non-surgical intervention. Finally, the effect on the use of probiotic (*LCS*) in preventing AAD in SCI patients was discussed in the third study. (paper 3)

Finally, the findings of each of the linked seven studies and their implications for the nutritional management in SCI patients are discussed in chapter 4. Limitations of our studies are discussed as well as proposals for further areas of research in SCI patients.

In summary, malnutrition after SCI is known to have a negative impact on clinical outcomes. The high burden to SCI patients and the healthcare system have recently been recognised, with a demand of timely specialist assessment and intervention. The studies undertaken and discussed in this thesis have contributed to the gap in the literature by identifying variations to the clinical management of SCI patients across SCI centres. As bed capacity in SCI centres is unlikely to change in the near future, this study proposes to improve early identification and management of malnutrition after SCI through implementation of nutrition screening tool and best practice recommendations. It is hoped that this will become embedded into routine clinical care and facilitate earlier focused interventions to improve outcomes in SCI patients with malnutrition.

1.1.2 Peer Reviewed Publications for Assessment

Seven first authored papers are included for assessment. These papers clustered into four themes (section 1.1). These include 1) Complications related to malnutrition and its association to adverse clinical outcomes; 2: Current nutrition practice in SCI centres; 3: Role of nutrition intervention to treat / prevent nutrition related complications and; 4: Potential limiting factors for good nutritional care. They are summarised in Table 1.1 and Figure 1.1, and are listed in chronological order beginning in 2013 through to 2015.

1. **Wong S**, Graham A, Green D, Hirani S, Grimble G & Forbes A (2013) Nutritional supplement use in patients admitted to spinal cord injury centre, *J Spinal Cord Med* **36**, 645-651.

2. **Wong S**, Forbes A, Barnes T, Coggrave M, Pounds-Cornish E, Appleton S & Belci M (2013) Morbid obesity after spinal cord injury: an ailment not to be treated? *Eur J Clin Nutr* **67**, *998-999.*

3. **Wong S**, Jamous A, O'Driscoll J, Sekhar R, Weldon M, Yau CY, Hirani S, Grimble G & Forbes A (2014) A *Lactobacillus casei* Shirota probiotic drink reduces antibiotic-associated diarrhoea in patients with spinal cord injuries: a randomised controlled trial. *Br J Nutr* **111**, 672-678.

4. **Wong S**, van Middendorp J, Belci M, van Nes I, Roels E, Smith E, Hirani S, Forbes A (2015) Knowledge, attitudes and practices of medical staff towards obesity management in patients with spinal cord injuries: an international survey. *Spinal Cord* **53**, *24-31.*

5. **Wong S**, Graham A, Hirani SP, Charlton D, Colawood S, McKeown E, Taylor C & Saif M (2015) Review of dietetic service provision and activity in spinal cord injury centres: a multicentre survey in the UK and Republic of Ireland. *Spinal Cord*. **53,** 855-859.

6. **Wong S**, Saif M, O'Driscoll J, Kumar N, Smith E, Roels E, van Nes I, Faber W, McKwown E, Hirani SP, Jamous A (2015) Survey on the use of probiotics in preventing antibiotic associated diarrhoea and *Clostridium difficile* associated diarrhoea in spinal cord injuries centres. *Int J Probiotics and Prebiotics* **10**, 85-90.

7. **Wong S**, Jamous A, O'Driscoll J, Sekhar R, O'Driscoll S, Lewis S, McKeown E & Hirani SP (2015) Effectiveness of probiotic in preventing antibiotic associated diarrhoea (AAD) and *Clostridium difficile* associated diarrhoea (CDAD) in patients with spinal cord injury: a protocol of systematic review of randomised controlled trial. *Syst Rev* **24**, 170. Doi: 10.1186/s13643-015-0159-3.

Table 1.1: Summary of papers for assessment

Aim	Author Year Journal	Objective	Research approach	Setting subject	sample size	data collected	Main results	Conclusion
3	1.Wong et al 2013 J Spinal Cord Med	To (1) assess food intake ; 2) establish prevalence of dietary supplement use; 3) identify characteristics of supplement user in SCI patients	prospective observational study (survey)	single centre SCI patient	n=73	use of supplement vitamins and mineral (VMS) and oral nutritional supplement (ONS)	19.1% receive ONS 46.5% receive VMS patient at under-nutrition risk were found to consume more ONS than the lower risk (p=0.05)	Use of supplements in common in SCI patient, particular in older adults and those with poor nutritional status.
1, 2	2. Wong et al 2013 Eur J Clin Nutr	To report the first UK morbidly obese SCI patient who has undergone bariatric surgery	case-report	SCI patient	n=1	weight, body-mass-index (BMI), mid-arm circumference (MAC), triceps-skinfold thickness (TSF) and lipid profile.	Clinical significant weight loss (32.4 kg) after the surgery There were improvement in BMI, waist circumference, TSF, MAC, lipid profile and functional improvement.	The provision of bariatric surgery should be consider as an option for morbid obese SCI patient if all non-surgical interventions have been tried.
3	3.Wong et al 2014 Br J Nutr	To 1) assess the efficacy of *Lactobacillus casei* Shirota (LcS) in preventing diarrhoea associated with antibiotic (AAD) and C. diff (CDAD) 2) determine if undernutrition risk and proton pump Inhibitor (PPI) use is risk factor for AAD/CDAD	Open-labelled randomised controlled trial	Single centre SCI patients	n=164 n=76 receive LcS n=82 receive control (routine) care	occurrence of diarrhoea defined as 2 x type 5 or above loose stool (Bristol stool scale). undernutrition risk using SNST score ≥11	Intervention (LcS) group had significant lower incidence of AAD (17.1 v 54.9%, p=0.022) Undernutrition and PPI use are associated with AAD. poor appetite (OR 5.04) and no LcS (OR 8.46) were found as independent risk factors for AAD.	LcS could reduce incidence of AAD in hospitalised SCI patients. a placebo-controlled RCT is needed to confirm this apparent benefit
1,2	4.Wong et al 2015 Spinal Cord	To 1) examine the opinions of medical staff working in SCI centres (SCICs); 2) evaluate their knowledge, attitudes and Practices towards obesity Prevention and management 3) report number of beds and dietitians available at SCICs	Prospective observational study (survey)	multicentre n=18 SCI centres	n=18 SCI centres	37-item questionnaire to identify current knowledge, attitude and practices of medical staff.	little (2.8%) medical staff receives training in obesity management. 61% of doctor did not consider BMI is appropriate after SCI Respondents also indicated the need for weight management guideline.	Appropriate training should be considered for all medical staff Development of SCI specific weight management guideline should be considered.

Theme	Author Year Journal	Objective	Research approach	Setting subject	sample size	data collected	Main results	Conclusion
1	5.Wong et al 2015 Spinal Cord	To 1) establish and compare how much time dietitians spend in direct and indirect contact with patients; 2) document current nutritional screening practice	Prospective observational study (survey)	multicentre n=12 SCI centres	n=12 SCI centre	total SCI beds and whole time equivalent (WTE) dietitians, medical staff, nurses and other allied health staff. dietitians were ask to fill in A week work sampling tool	8/12 SCI centres responded 6/8 SCI centres used validated nutrition screening tool. staffing level varied and below recommended level. Dietitians spend 39.1% time in direct patient activities	Resources allocated to nutritional care appear to be varied and limited in SCICs. No recommendation currently made for dietitians working in SCICs further workforce planning for dietitian should be considered.
2	6.Wong et al 2015 Int J Prob & Preb	To 1) determine if SCIC stock probiotics; 2) determine whether the use of those probiotic was Evidence-based; 3) document C. diff infection (CDI) practice	Prospective observational study (survey)	multicentre n=9 SCI centre 4 in the UK 1 in the Republic of Ireland 1 in Belgium 3 in the Netherlands	n=12	centre's demographic number of bed days use of probiotics indication of probiotics incidence of CDI CDI practice definition of diarrhoea	5/9 SCIC stoked probiotic 5 probiotic were identified LcS (44.4%), *L. casei DN-114001* (22.2%), *L. acidophilus* (22.2) and Ecologic Pro-AD (11.1%) were choice for AAD prevention. Mean CDI was 0.307 per 10,000 patients-days. (range 0 to 1.08) Definition of diarrhoea were varied among SCICs	There is a need to use a standardised definition of diarrhoea when conducting AAD/CDAD research
2	7.Wong et al 2015 Sys Rev	To report a systematic review protocol in assessing the protocol effectiveness of probiotic in preventing and treating AAD and CDAD in SCI Patients.	systematic review	N/A	N/A	Cochrane library; Centre for Reviews and Dissemination; CINAHL; PsycINFO Embase; Medline; AMED; International Clinical Trials Registry	N/A	This systematic review will provide information on probiotic therapy for and CDAD in SCI population. Preliminary search identified only 2 studies reported using probiotic to prevent / treating AAD / CDAD. (Paper 3)

Aim 1: To review and understand the variations in nutritional management in SCI centres from the perspective of staff and SCI patients.

Aim 2: To evaluate whether currently implemented nutrition interventions in SCI centres are based on sound research evidence, and potential barriers to good nutritional care in SCI centres.

Aim 3: To report three original studies (from a case study to a randomised trial) that explore how nutritional interventions may influence clinical outcomes in SCI patients.

ONS: oral nutritional supplement; VMS: vitamin and mineral supplements; SCI: spinal cord injury; AAD: antibiotic associated diarrhoea; CDAD: Clostridium difficile associated diarrhoea; CDI: Clostridium difficile infection.

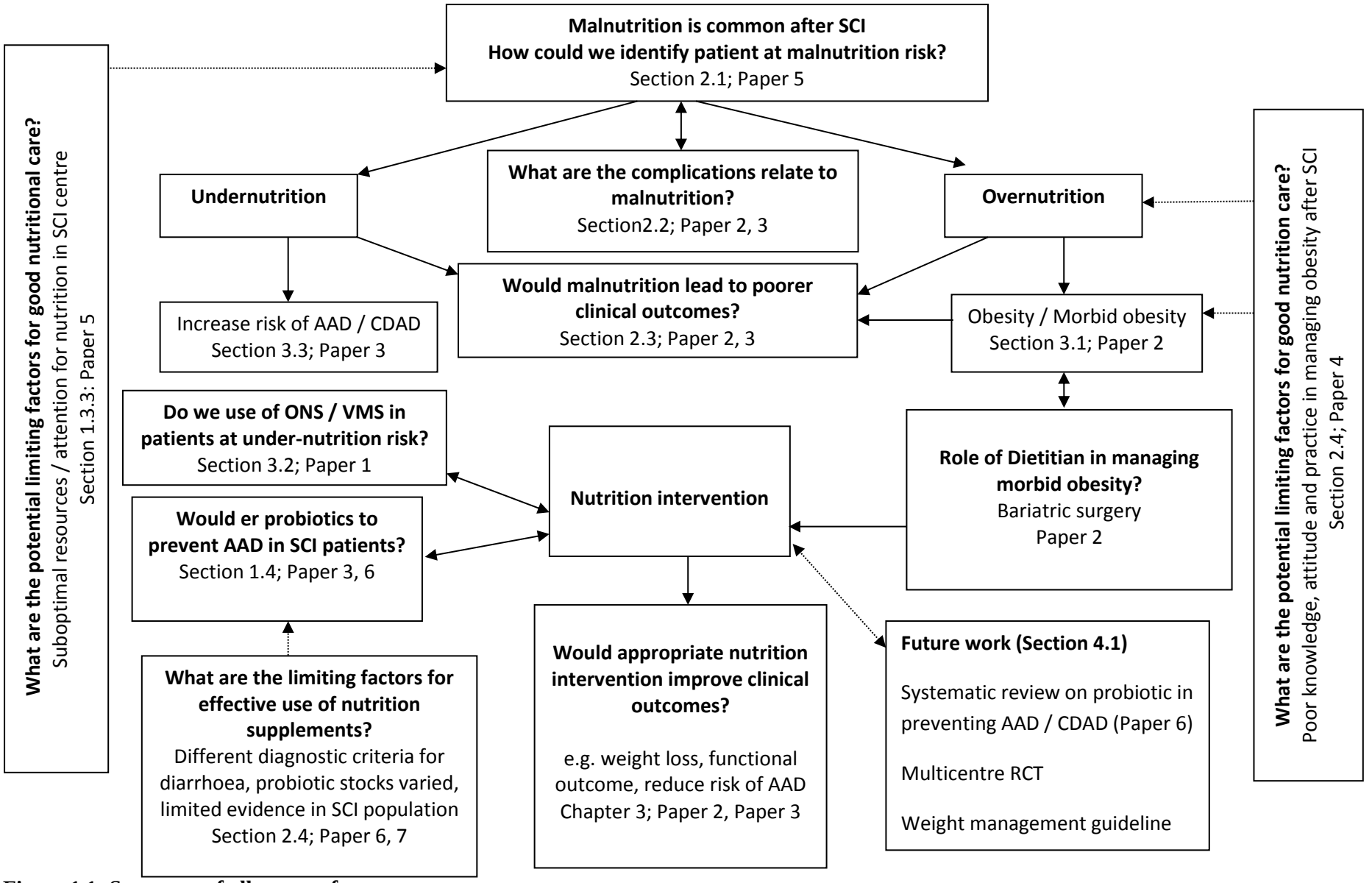


Figure 1.1: Summary of all papers for assessment

1.2 Spinal Cord Injury

SCI occurs when the spinal cord (SC) is damaged, usually due to fracture of the vertebral column, which normally encases and protects the SC. (Figure 1.2) However, SCI may be present even without osteoligamentous injury, one example is SCI without radiographic abnormality (SCIWORA), (Consortium of Spinal Cord Medicine, 2004) The paediatric population is predisposed to SCIWORA because of the laxity of cervical spine ligaments. Importantly, SCI causes all of the systems of the body to function differently to those of a non-paralysed person, and in addition leads to other issues, such as loss of sensation or movement and spasm. The level of SCI may affect organ function. For example, cardiovascular, respiratory, bladder and bowels, metabolic and psychological, and sexual functions.

The most common mechanism of SCI is a sudden, unexpected, impact or deceleration on the SC, which accounts for approximately 73 % of all SCI cause. The rest of the SCI are non-traumatic SCI (27 %). (Spinal Injury Association, 2009). Road traffic accidents (RTA) are the most common cause of traumatic SCI, which accounts for 36 % of all causes of SCI, followed by domestic and industrial accidents (37 %), sports and recreational accidents (21 %) and finally self-harm and criminal assault (6.5 %). (Spinal Injury Association, 2009)

Non-traumatic SCI is any damage to the SC that has not been caused by a major trauma such as infection (inflammatory or infectious), loss of blood supply (vascular), compression (neoplastic) or slow degeneration of spinal bones, such as osteoarthritis (degenerative). Non-traumatic SCI contributes to approximately one third of all SCI causes and there is a growing population of admissions for rehabilitation (Ho et al., 2007).

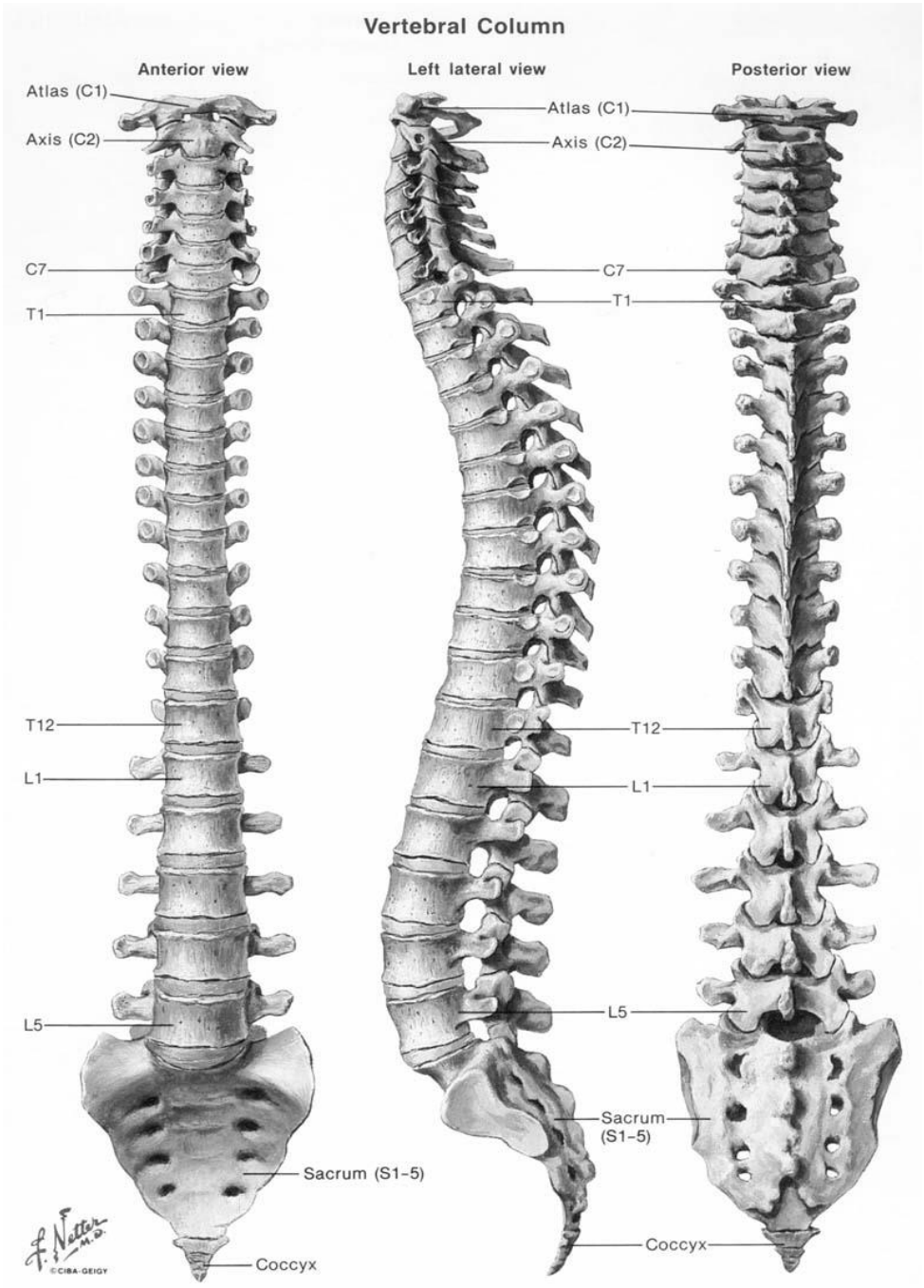


Figure 1.2: The human spine

The cervical spine extends from C1 to C7, the thoracic spine from T1 to T12, the lumbar spine from L1 to L5, followed by the sacrum and coccyx.

The first published report of SCI was translated by James Henry Breasted in 1930. This document, known as the Edwin Smith papyrus, contained details of an unknown Egyptian physician accurately describing the clinical features of traumatic tetraplegia (quadriplegia). The documents, dating to 2500BC, describe 48 traumatic cases, six of which involved the cervical injury. The Edwin Smith papyrus described that the patient would have priapism (erection), and incontinence of urine and semen. It also revealed an awareness of the awful prognosis of SCI with chilling advice: "an ailment not to be treated". (Hughes, 1988) This Egyptian physician suggested that the two SCI cases were not to be treated at all, probably due to their poor prognosis. Obviously, this physician had sufficient knowledge of anatomy and the surgical skills of his days; however, he may have also been aware that his resources were limited, preventing SCI patients to recover and return to their normal life.

More recently, during the First World War, 90% of patients who suffered a SCI died within a year of being wounded, and approximately only 1% survived for more than 20 years. This survival rate after SCI has greatly improved since the introduction of modern multidisciplinary and comprehensive SCI management, which was first promoted by Sir Ludwig Guttmann (Guttmann, 1970). The model SCI Centre system was described by John Young (1919-1990) such that it "*must be able to meet the needs of a person with SCI by competently treating the direct injury as well as all organ systems affected (of which there are many), the functional deficits that result, by providing training and equipment, the psychological adjustments that must be made, the vocational pursuits that must be changed, and provide long term specialised care*". (Silver, 2003) In addition, he also outlined the core components of such a system which must include emergency medical services, emergency trauma centre, acute hospital care, acute rehabilitation care and on-going rehabilitation treatment.

1.2.1 Terminology and classification

SCI is an injury to the SC from traumatic or non-traumatic causes. SCI are classified according to the level of the corresponding vertebra (cervical spine, thoracic spine, lumbar spine or sacral spine) at which the injury to the SC occurs. For example, a break in the fourth segment of cervical spine is called a C4 injury. After SCI, depending on

the level and severity, an individual will experience complete or partial loss of sensory (sensation) or motor (movement) functions below the injury.

Damage to neural elements within the cervical area result in tetraplegia (quadriplegia), and depending on the specific location and severity of injury, varying degrees of motor and sensory impairment will occur in the arms, trunk, legs, bowel, and bladder. For example, injuries at C1/2/3 levels will often result in loss or reduced diaphragm function and the patient will be very likely to need life-long ventilation; injury at C4 level will result in significant loss of function at the biceps and shoulders; at C5 level will result a complete loss of function at the wrists and hands; at C6 level will result a limited wrist control and complete loss of hand function; C7 and T1 level will result in lack of dexterity in the hands and fingers. (Fig 1.4 and Fig. 1.5)

Damage to the thoracic, lumbar, or sacral segments results in paraplegia. Paraplegics will experience a variable degree of motor and sensory function loss in the trunk, legs, bowel and bladder. The arms are spared in paraplegia.

In 1982, the American Spinal Injury Association (ASIA) published its first edition of the Standards for Neurological Classification of Spinal Injured Patients. (ASIA, 1992) These standards arose from a need for more precise definition of neurological levels and the extent of incomplete injuries. The ASIA standards focused on 10 key muscles and 10 key sensory points to be tested during a neurological assessment. The ten key muscles, five in the upper limb and five in the lower limb, are tested while the patient is lying in the supine position and require minimal movement of the spinal column. Likewise, key sensory points are selected to represent each sensory dermatome from C2 through to S4-S5.

The muscles of both extremities are very important for classification of injury level after SCI. An accurate evaluation of voluntary motor function is very important because it will provide a starting point for the therapeutic programme and it is also a reflection of neurological level of injury. A standardised form to be used as a flow chart for classifying SCI was also developed by ASIA as shown in Fig. 1.4 and Fig. 1.5. An AISA Impairment Scale (AIS): A indicates a complete SCI; there is no motor or sensory function preserved in the sacral segments S4-5. AIS B, C and D are incomplete SCI.

AIS B only preserved sensation below the neurological level, including sacral segments S4-5. AIS C preserved motor function below the neurological level and the majority of muscles having a grade less than 3 out of 5. AIS: D preserved motor function below the neurological level and the majority of key muscles below the level having a grade 3 or greater and AIS E indicates that motor and sensory function is normal.(Fig 1.5) These standards were endorsed by the International Medical Society of Paraplegia (now the International Spinal Cord Society (ISCOS), www.iscos.org.uk) creating the *International Standards for Neurological and Functional Classification of Spinal Cord Injury*. (ASIA, 2015)

Sacral-sparing is evidence of the physiological continuity of SC long tract fibres (with the sacral fibres located more at the periphery of the cord). This translates into a simple definition of "complete SCI" if they do not have motor and sensory function in the anal and perineal region representing the lowest sacral cord at S4 and S5 (as this is the last part of the SC). Indication of the presence of sacral fibres is of significance in defining the completeness of the injury and the potential for some motor recovery. (ASIA, 2015) (Figure 1.3 and Figure1.4).

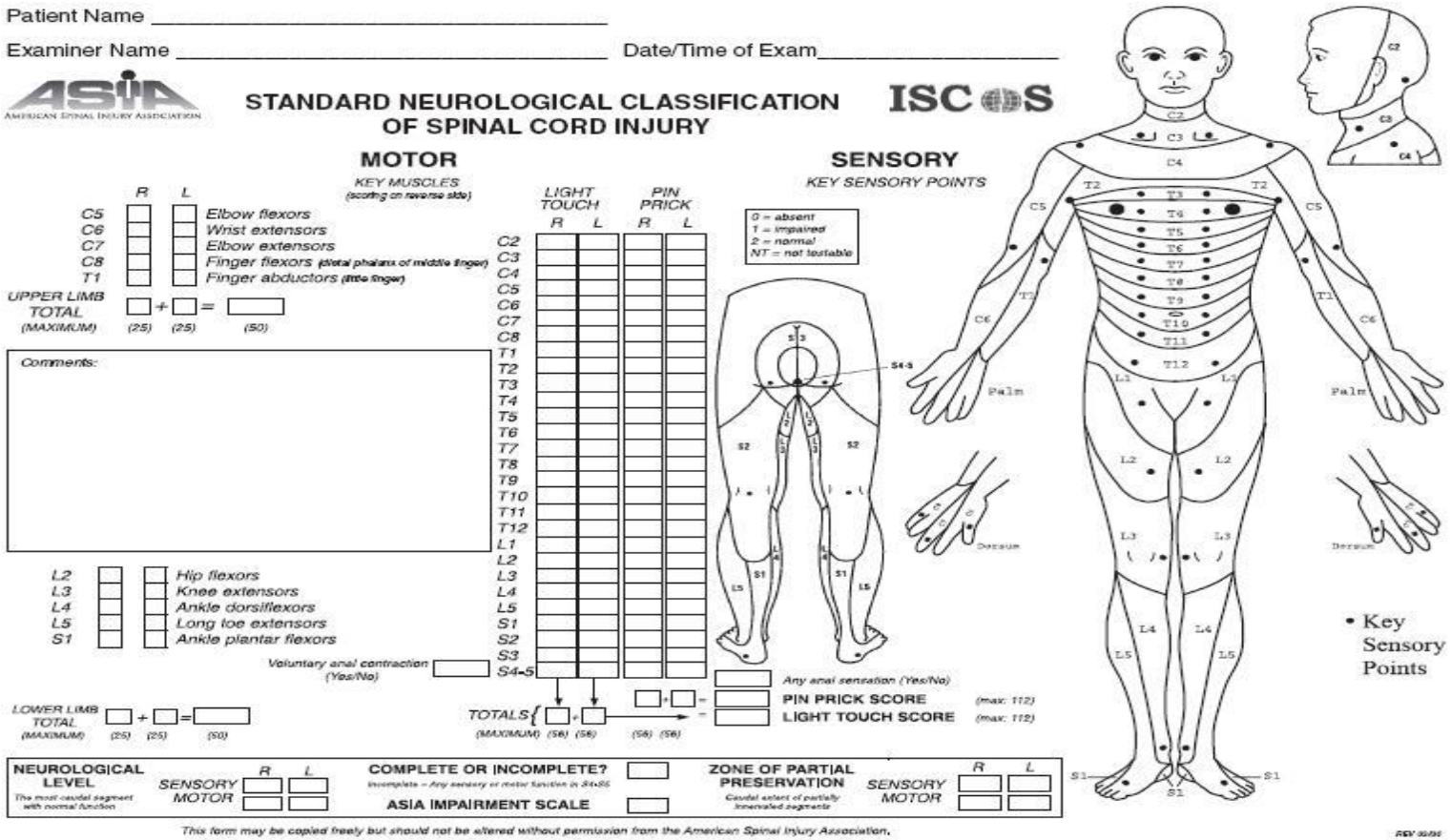
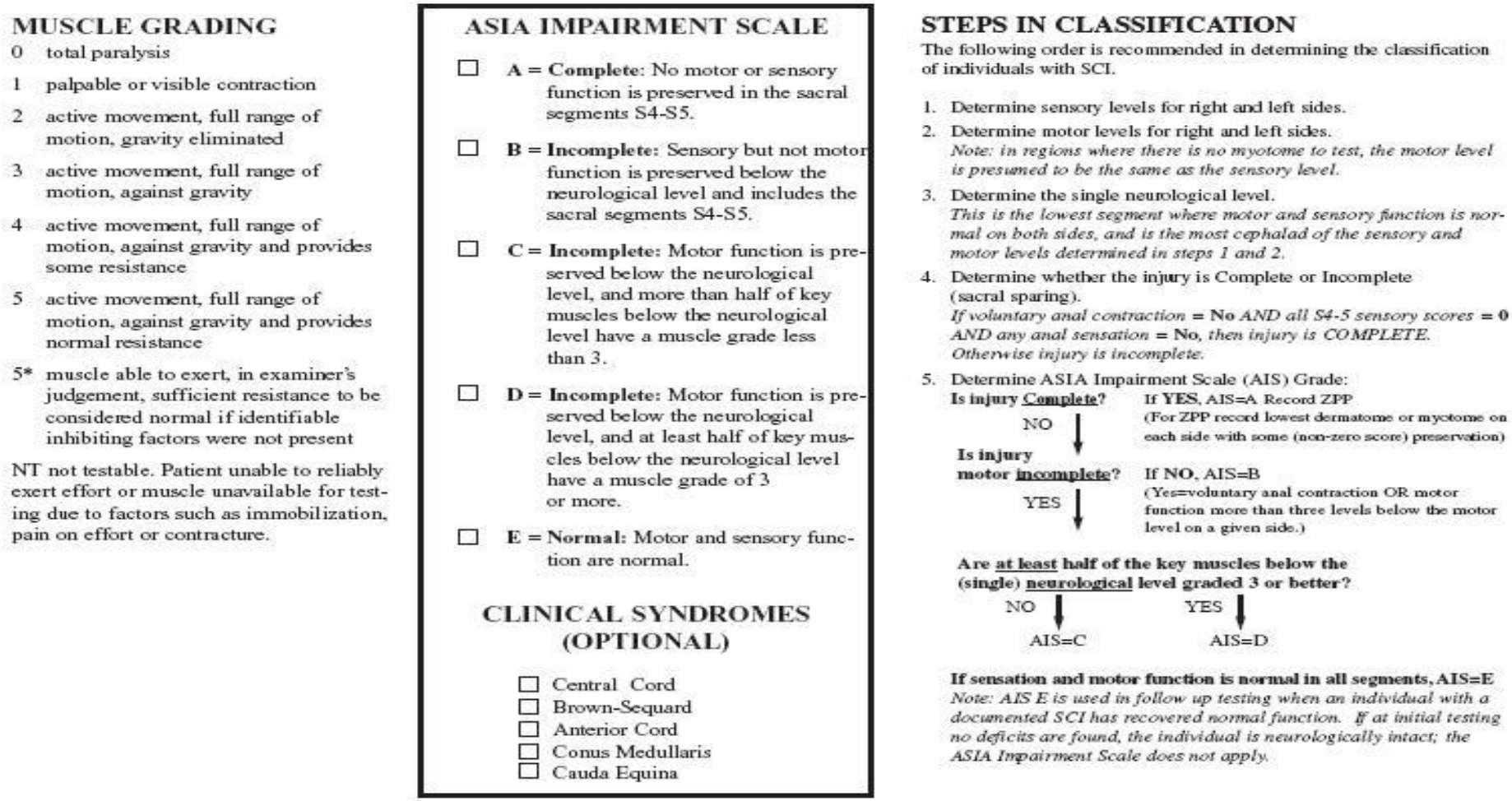


Figure 1.3: International standard for neurological classification of spinal cord injury. Reproduced with permission of the American Spinal Cord Injury Association.



MUSCLE GRADING

0 total paralysis

1 palpable or visible contraction

2 active movement, full range of motion, gravity eliminated

3 active movement, full range of motion, against gravity

4 active movement, full range of motion, against gravity and provides some resistance

5 active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

ASIA IMPAIRMENT SCALE

☐ **A = Complete:** No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central Cord
☐ Brown-Sequard
☐ Anterior Cord
☐ Conus Medullaris
☐ Cauda Equina

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores* = **0** *AND any anal sensation* = **No**, *then injury is COMPLETE. Otherwise injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If **YES**, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)

NO ↓

Is injury motor incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)

YES ↓

Are at least half of the key muscles below the (single) neurological level graded 3 or better?

NO ↓ AIS=C

YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Figure 1.4: ASIA impairment scale grading: International standards for neurological classification of spinal cord injury. Reproduced with permission of the American Spinal Injury Association

1.2.2 Physical and psychological effect after SCI

The level and severity of injury to neural tissue determines the symptoms produced by SCI. There are primary and secondary effects after SCI. The primary effects include paralysis (section 1.5), spasm and reduced or loss of sensation or movement. The level of SCI may affect organ function. Due to prolonged decreased mobility, patients with chronic SCI can also develop a variety of secondary effects (complications) on skin (pressure ulcers), respiratory, circulatory, gastrointestinal, urinary, metabolic and bone.

Many patients are depressed and disinterested in eating after SCI. Studies reported 20 – 62% of patient will suffer from depression after acute SCI. (Judd et al, 1991) Some may be confused or have a decreased level of consciousness especially during acute the phase of SCI. (Consortium for Spinal Cord Medicine, 2008)

In addition, tetraplegic with a particularly high level of injury may also lose the ability to breathe for themselves; therefore, they may have to rely on mechanical ventilation. Table 1.2 & Table 1.3 summarise the primary and secondary physical effects after SCI and Fig 1.3 summarises the physical and physiological consequences of SCI.

Table 1.2: The primary effects and change in organ functions after spinal cord injury

Primary effects	**Effects**	**Treatment options**
Paralysis	Unable / difficulty to move the body in space	
Spasticity	Development of contracture Muscle shortening and reduction of range of motion Difficulty in positioning	Botulinum toxin Use of baclofen, tizanidine and dantrolene Intrathecal baclofen to help those who do not respond to oral medication
Disruption of sensation	Discoordination of body movement Vulnerable to trauma Impaired body awareness	
Decreased range of motion	Deformities Limited functional capacity	
Organ functions		
Respiratory	Reduction in inspiratory & expiratory ability Increased energy of breathing Inability to breathe without mechanical ventilation (high cervical SCI); Paralysis / weakness of diaphragm Diminished tidal volume and vital capacity	
Gastrointestinal	Decreased oesophageal motility Faecal impaction	Prokinetics, help stomach to empty faster laxatives
Bowel and bladder continence	Urinary retention Loss of voluntary bowel and bladder control Bladder infection and bowel obstruction	Urodynamics to examine the bladder function to inform best treatment approaches
Genital function	Disruption of sexual functions Infertility in men	
Cardiovascular function	Bradycardia (slowing heart rate) Hypotension Orthostatic hypotension	
Thermo regulation	Hypothermia Absence of shivering Loss of sweating in response to a rise in body temperature	

Table 1.3: The secondary effects after spinal cord injury, their complications and available treatment options.

Secondary effects	**Complications**	**Treatment options**
Pressure ulcers	Osteomyelitis	Infection being treated by antibiotics
	Sepsis	Conservative / Surgical procedure to enhance wound healing
	Death	
Respiratory complications	Atelectasis	Infection being treated by antibiotics
	Pneumonia	
Decreased range of motion	Cosmetic problems	Botulinum toxin
	Increase vulnerability to pressure ulcers	physiotherapy and occupational therapy
Osteoporosis	Increase vulnerability to fracture	vitamin D, calcium supplementation
Gastrointestinal complications	Stress gastric / duodenal ulcers	proton pump inhibitor / H2 blocker
	Paralytic ileus	Parenteral nutrition
	Gastric dilatation	laxatives
	Faecal impaction	surgical procedure (e.g. colostomy) in severe case
	Bowel obstruction	
Urinary tract complications	Bladder infection	infection being treated by antibiotics
	Urinary reflux	urodynamic to examine bladder function to inform best treatment option
	Kidney & bladder stones	Electro-hydraulic lithotripsy
	Hydronephrosis & pyelonephrosis	
	Kidney failure	
	Septicaemia	
Metabolic / nutrition related complications	Osteoporosis	vitamin D supplementation
	Change in body composition	Dietetic assessment / intervention
	Change in nutritional requirements	Dietetic assessment / intervention
	Increase risk of developing metabolic syndrome	

1.2.3 Epidemiology and financial impact

The annual incidence of SCIs throughout the world is 15 to 40 cases per million (Sekhon & Fehlings, 2001). It is estimated that there are around 500 to 700 cases of SCI each year in the UK (Spinal Injury Association, 2009), and based on a total UK population of 62.3 million, this is equivalent to 8 – 11 cases per million (Office for National Statistics, 2010). In 2009, it is estimated that there are currently 40,000 people living with SCI in the UK. (Spinal Injury Association, 2009)

The cost of medical care for people with a SCI continues beyond the first year after injury, and once the condition of individuals with a SCI has stabilised, they require the services of health-care practitioners on a continuing basis. Some people undergo recurring hospitalisation for a variety of reasons associated with their SCI, ranging from chronic issues that are directly linked to the injury or secondary complications, such as pressure ulcers, pneumonia, muscular/joint problems, and obesity. Individuals with a chronic SCI require a much higher level of medical maintenance and follow up than the able bodied population because their medical symptoms are often masked by the lack of sensation following a SCI. There is limited analysis on the money spent in the UK on SCI patients. Berkowitz and colleagues (Berkowitz et al, 1998) estimated that the cost for continuing medical care for a person with SCI was $9,000AUD (£5,769) a year, with higher costs associated with more severe injuries. In addition, older adults incur a higher cost than their younger counterparts, and women incur slightly higher costs than men.

Using an estimate incidence of 8 to 12 cases per million per year, and the total 40,000 SCI patients living in the UK currently, the initial costs of treatment after SCI will be £86 to £130 million with a further £2.3 billion being spent on continuing care per year.

1.3 Spinal cord injury centre

In 1941 Ludwig Guttmann was asked by the Medical Research Council to report on the current situation regarding the treatment and rehabilitation of patients who had suffered a SCI. The result of this report caught the attention of Colonel George Riddoch, a neurologist and Chair of the Peripheral Nerve Committee of the Medical Research Council of England. Subsequently, Ludwig Guttmann was put in charge of establishing a new spinal unit under the supervision of the Ministry of Pensions, and chose Stoke Mandeville Hospital in Aylesbury. This was as its facilities were all at ground level with wide corridors, therefore accessible for wheelchairs. In 1944 the National Spinal Injuries Centre (NSIC) at Stoke Mandeville Hospital was opened.

Currently, the UK's SCI centres form a highly specialised NHS rehabilitation service, which supports individuals with SCIs from their initial injury and throughout their life. Each centre has its own out-patient department providing lifelong follow up for their patients. An early Canadian study compared outcomes for SCI patients before and after their introduction of specialist SCI centres (Tator et al, 1995). The authors reported reduced mortality and length of hospital stay (LOS) for all SCI patients when managed in a SCI centre. More recently, an Australian study (New et al, 2011) looked at the impact on patients admitted to different types of centres and identified a lack of uniform standards affecting outcomes. A systematic review of the impact of acute care in SCI centres with regards to LOS, complications and mortality (Parent et al, 2011) identified 15 studies with reported outcomes for a cohort of at least 10 patients. The authors reported patients who were transferred to a SCI centre promptly after injury, tends to had a shorter LOS, fewer complications and greater neurological recovery, supported by staff with clinical expertise. Although the evidence generated was weak, the authors recommended to facilitate early transfer to SCI centre and to engage multi-disciplinary staff to reduce the severity and rate of complications and overall mortality.

A Cochrane review of SCI centres for acute management (Jones & Bagnall, 2004) noted that the majority of complications of SCI can occur in the first 24 hours. However, they found insufficient evidence to support conclusions concerning the benefits or disadvantages of immediate referral versus late transfer to SCI centres, suggesting the need for a well-designed prospective study to address this question. Aito (2003) noted

that pressure ulcers and respiratory complications were much more common among patients who were treated in non-specialised units or who had experienced delays in their transfer to a SCI centre. Aung and el Masry (1997) showed that patients admitted to an SCI centre within one week of a SCI suffered a lower rate of complications compared to those admitted later. Similarly, DeVivo et al. (1990) found statistically significant reductions in acute care, and in the total length of stay, coupled with a highly significant reduction in pressure ulcers among patients admitted to SCI centres within one day of a SCI, compared to an otherwise comparable group of patients admitted to a SCI centre for rehabilitation only supporting the concept of SCI centres and potential benefit of transferring to SCI centre at early stage of their SCI.

Across the UK and Ireland, there are 12 SCI centres, with eleven in the UK, eight in England, one in Scotland, one in Wales and one in Northern Ireland, providing a total of 458 in-patients beds for the rehabilitation of people who have a SCI. The total number of beds in these units is under pressure and unable to meet the demands. As referral numbers exceed the capacity, this leads to significant delays in transfer of patients to SCI centre leading to an increased report of complications. Whilst SCI centre capacity are unlikely to change, ensuring a consistent approach to nutritional care would improve clinical outcomes and improve a patient's quality of care. This study sought to understand the variation in nutrition practice across UK SCI centres.

1.3.1 The National Spinal Injuries Centre at Stoke Mandeville Hospital

The NSIC at Stoke Mandeville Hospital is the oldest and one of the largest SCI centres in the world, providing a total of 115 beds for people with a SCI; 62 of these are for active rehabilitation, and there is a dedicated young person's rehabilitation unit consisting of 9 beds. The remaining beds are for acute admissions, people who are medically unstable, and for secondary elective admissions.

1.3.2 Dietetic services within SCI Centres

Although dieticians have been widely accepted as core multidisciplinary team members across other medical specialties, such as intensive care (Intensive Care Society, 2015), unfortunately dietetic therapy and resources in SCI centres is widely under-utilised. (Wong et al, 2012c) Indeed, low staffing level issues were also highlighted in recent

international SCICs survey. (New et al, 2013) Therefore, we conducted an update survey of service provision at SCI centres across both the UK and the Republic of Ireland in 2015. Paper 5 will be used to support this section.

> Paper 5: Wong S et al. (2015) Review of dietetic service provision and activity in spinal cord injury centres: a multicenter survey in the UK and Republic of Ireland. *Spinal Cord*. **53**: 855-859.

In order to understand the potential impact on the variations in nutritional resources allocation and management in SCI centres, we surveyed all twelve SCICs surveyed (11 in the United Kingdom and 1 in the Republic of Ireland) again in 2014. Eight (66.7%) centres respondents (7 in the UK and 1 in the Republic of Ireland) completed and returned the questionnaire. The centres represented 390 of 531 (73.4%) UK and Ireland SCI beds (1 SCIC in the Republic of Ireland (n=36), 7 SCICs in the United Kingdom (n=354). There is no current guidance on nutrition screening after SCI, although all SCICs reported that they used a nutritional screening tool, only six of eight SCICs (75%) used a validated nutrition screening tool (n=3: Malnutrition Universal Screening Tool; n=3: SNST and the remainder (n=2) used a local non-validated tool.

Variations were observed across the UK SCI centre's nutrition practice since our first report in 2008 (Wong et al, 2012c). Six of eight (75%) SCICs reported they aim to complete nutritional screening within 24 hours of admission and two of eight SCICs (25%) aimed to complete nutritional screening within 48 hours. We found one WTE dietician covering between 60-160 patients (national average of 99.5 patients) and six out of the eight centres surveyed were below the clinical recommendations (Wong et al., 2012c; Paper 5).

Insufficient resources may impact greatly on the nutritional knowledge of patients and staff at these centres and is likely to contribute to the under-recognition and under-treatment of malnutrition. Only three of eight (37.5%) SCICs meet the recommended dietitian to bed ratio 1:60 set by the SCI dietitians group of the British Dietetic Association (Wong et al, 2012c). Additionally, dietitians in five of eight (62.5%) SCICs still report covering more than 100 patients per WTE. A study by Windle (2008) found that the allocation for dietitians in the adult intensive care unit was also under resourced.

The variation in staff levels could be due to each SCIC having its own unique needs and challenges and therefore comparisons do have limitations (especially over a small sample of centres). However the impact remains; recent literature suggests malnutrition, including both under- and over-nutrition (obesity) is common in patients with SCI and it is associated with poorer clinical outcomes and increased healthcare costs. (Wong et al, 2013) Our previous study (Wong et al, 2012d) from SCI centres reported staff agreed that poor oral intake or prolonged intubation were criteria for artificial nutrition support. Our recent study (Wong et al, 2012a), reported undernutrition is common in SCI patients suggesting that clinical guidance may not be routinely applied in SCI centres.

At the present time, no formal recommendation has been set by the specialist commissioners for an optimal staffing level for dietitians. (NHS England, 2013) Our study found the provision of dietitians did not significantly improve in the last five years (Table 1.4) that the number of staff in different SCICs still varied considerably (34 to 160 beds per WTE dietitian) suggesting malnutrition may continue to be under-detected and under-managed.

There are some limitations of this study. Formal sample size calculation was not performed as the present study surveyed all SCI centres in the UK and Republic of Ireland, with a response rate of 66.7%. The response rate was comparable in literatures and we believed the study's result could apply to UK SCI centres. However, the study did not address the non-response bias. Non-response bias is the bias that results when respondents differ in meaningful ways from non-respondents. Indeed, non-response is often a problem with mail surveys, where the response rate can be very low. It would be recommended in future study to assess non-response bias formally, and perhaps use more face to face resources to get more complete information.

The present study's questionnaire contains 37 items. It was based on previous published literatures. (Wong et al, 2011; Ward et al 2014) No data / responses were excluded from the analysis. Therefore, results derived from this sample of SCICs could be considered representative for the UK and the Republic of Ireland. Overall, in absence of empirical evidence, the result of this survey would provide an insight into current nutrition practice in the approach to nutritional management across SCI centres to identify consistent practices and areas requiring further development.

Table 1.4: Human resources allocation in participating spinal cord injury centres

Staff category	Total WTE Staff	number of beds per WTE staff Median; range	2009 figures median; (range)	p-value	National recommendations
Consultants (n=7 SCICs)	18.0	18 (15.3-31)	15.0 (10.5-24.4)	0.153	15-20
Other grades of medical staff	33.0	12 (6.2-46)	10.1 (7.5-20.0)	0.701	-
Nurses (n=6 SCICs)	325.7	1.3 (0.5-1.5)	1.3 (0.6-1.8)	0.748	2-3
Dietitians (n=7 SCICs)	4.63	93.4 (34-160)	136 (30-387)	0.272	-
Physiotherapists (n=7 SCICs)	65.49	5.9 (4-8)	5.6 (3.75-10.5)	0.848	5-7
Occupation therapist (n=6 SCICs)	30.3	10. (3.7-12.9)	10.5 (3-16.6)	0.617	6-8

SCIC: spinal cord injury centre; WTE: whole time equivalent

1.4 Malnutrition after a SCI

Studies from general populations have suggested that undernutrition is an important predictor of poor hospitalisation outcome, including increased length of hospital stay (Bauer et al., 2002; Burr et al., 1993; Kagansky et al., 2005; Stratton et al., 2004; Van Nes et al., 2001; Wong et al, 2012c)' premature mortality (Van Nes et al., 2001; Sullivan et al., 1999; Studley et al., 1936; Kagansky et al., 2005; Desport et a.l, 1999; Wong et al, 2012c), post-operative complications (Hennessey et al., 2010), infections (Schneider et al., 2004), pressure ulcers (NICE, 2005), poor wound healing (NICE, 2005), compromising of the immune system (Cruse et al., 2000), and impaired muscle and respiratory function (Sullivan et al., 1999; Kagansky et al., 2005).

The prevalence of undernutrition-risk in SCI patients is estimated to be high (44.3%) (Wong et al., 2012a). A higher prevalence of undernutrition risk was observed in patients with the following associated features: high cervical injury (60.7%), and the use of mechanical ventilation (56.3%) (Wong et al., 2012a). There are various possible causes of undernutrition; some may be present prior to hospital admission, whereas others develop during an inpatient stay (Persson et al., 2002). These include:

- Inadequate food intake
- Anorexia, dysphagia, vomiting, diarrhoea (undernutrition)
- Poor availability of food due to social deprivation or variation in hospital practice
- Reduced physical ability to eat due to arthritis, SCI
- Reduced desire to eat due to chronic pain, neuropathic pain, depression or apathy may lead to loss of interest in food
- Patients' clinical state/disease process may increase metabolic rate and nutritional requirements
- Unbalanced food intake
- Defect in food digestion/absorption
- Malabsorption issues, e.g. short bowel syndrome

1.4.1 Metabolic response in patients with acute SCI

The early stages post-SCI, known as the acute phase could last up to 12 weeks after SCI. Malnutrition associated with this phase may be directly due to a suboptimal nutritional intake of calories and protein to meet the nutritional requirements due to hyper-metabolism post-injury, SCI related comorbidities, infection, and also dependence on ventilation (Kearns et al., 1992).

The degree of hyper-metabolism may vary in severity depending on factors such as the degree of inflammation, age, and body composition (Frankenfield et al., 1997). Metabolic changes are also present due to the initially elevated catabolic hormonal and cytokine responses, including increased blood levels of counter regulatory hormones (e.g. cortisol and catecholamines), increased blood and tissue levels of pro-inflammatory cytokines (e.g. interleukin-1, interleukin-6 and tumour necrosis factor α), and peripheral-tissue resistance to endogenous anabolic hormones (e.g. insulin and insulin-like growth factor).

Extensive multiple organ trauma, soft tissue injuries and fractures, may further increase the hyper-metabolic response. Evidence suggests that, in contrast to trauma and head injury, there is a reduction in energy expenditure during the acute SCI phase, but further evidence is needed to determine specific nutritional requirements post-injury (Buchholz & Pencharz, 2004).

Similar to a state of starvation, a negative energy balance will result in the accelerated utilisation of fat and protein for energy due to the depletion of glycogen stores. This depletion may be caused by catabolism, nitrogen loss, and reduced protein synthesis, which when coupled with immobilisation and muscle atrophy, can lead to significant loss of lean muscle mass, up to 900g/day (Hadley, 2002). In addition, the administration of glucocorticosteriods after a SCI may increase the catabolism of protein. The loss of nitrogen in the urine, mainly due to muscle atrophy secondary to a SCI, increases with the severity of an injury, and a negative nitrogen balance is correlated with the level and extent of an injury, potentially lasting up to 2 months post-injury. This in turn may result in reduced gastrointestinal mucosal integrity, a compromised immune system, and an increased risk of infections.

It is recommended to use indirect calorimetry to determine energy requirements for nutrition support in both acute and chronic SCI settings (Consortium for Spinal Cord Medicine, 2008; section 1.5.5). However, in absence of an indirect calorimeter, standard predictive energy equations should be adjusted to reflect caloric needs during the acute phase, to reduce risk of overfeeding. The American Dietetic Association guidelines recommend Harris-Benedict equation with an activity factor of 1.1 (for bedbound patients) and a stress factor of 1.2. The guidelines also recommend protein intake of 2g/Kg body weight but these requirements may need to be adjusted with level of injury and AIS grade (ADA, 2009).

In clinical practice, the timing to start feeding patients in the acute setting may be difficult to determine. In non-SCI traumas, early nutrition support (48-72 hours) is recommended to improve outcomes. (ADA, 2009) Complications of trauma, surgery and medications may increase risk of paralytic ileus. Patients with paralytic ileus, which generally occurs for the first 48-hours post-injury but may extend for a prolonged period, are generally kept nil by mouth for this period and oral or enteral nutrition initiated once signs of ileus are resolved. Parenteral nutrition (PN) may be indicated in patients with mechanical bowel obstruction or prolonged ileus until the bowel begins to recover and EN or oral diet is initiated. Both EN and PN have shown to reduce gastric ulceration in acute SCI and PN may also reduce the incidence of upper gastrointestinal bleeding in patients with poor oral intake. Table 1.5 summarises the impact on metabolism, nutritional status and nutrition requirements in acute and chronic phase of SCI.

1.4.2 Psychological state after acute SCI

The psychological consequences of having suffered a SCI should not be underestimated. Many patients are depressed and disinterested in eating and therefore may refuse to eat and or drink. Indeed, quality of life is often greatly reduced and secondary complications tend to increase morbidity and mortality. Studies reported 20 – 62 % of patient will suffer from depression after acute SCI. (Judd et al, 1991) Some may be confused or have a decreased level of consciousness especially during acute the phase of SCI. (Consortium for Spinal Cord Medicine, 2008)

Table 1.5 Impact on metabolism, nutritional status and nutritional requirements in acute and chronic phases of SCI

Phase	Acute		Chronic
Impact on metabolism	Depleted energy stores, utilisation of body fat and protein for energy, accelerated catabolic rate driven by inflammatory stress response, rapid nitrogen loss and reduced protein synthesis. Nutrient deficiencies.		Increased appetite and oral intake, reduced physical activity and immobilisation, muscle atrophy causing BMR reduction. Body composition changes: reduced fat free mass and increased fat mass
Impact on nutritional status	Loss of lean muscle mass, increased risk of infection, impaired wound healing, muscle atrophy, loss of gastrointestinal mucosal integrity, paralytic ileus, gastric ulcers.		Increased risk of overweight and obesity, metabolic syndrome, hypercholesterolemia, increased risk of CVD, Diabetes type 2 and pressure ulcers.
Nutritional requirements	Energy	Normal metabolism: 90-130% metabolic state Hypermetabolism: > 130% of metabolic state	Tetraplegia: 22.7 Kcal/Kg BW Paraplegia: 27.9 Kcal / Kg BW.
	Protein	2g / KG BW / day	0.8-1 g / KG BW

1.5 Complication after SCI

1.5.1 Infections after SCI

Infections such as chest, bladder and urinary tract infections are more common in patients with SCI. The frequency of pulmonary complications parallels the degree of respiratory impairment, increasing with progressively higher levels of SCI. Studies have reported that respiratory complications such as atelectasis, and pneumonia occur in 50 to 67 % of patients with SCI at any level. (Fishburn et al, 1990) Due to the need for long term bladder catheterisation patients are particularly vulnerable to infections of the urinary tract or kidneys. It was reported that 80.4 % of SCI patients suffered from urinary tract infection (UTI) or bacteriuria. (Stover et al, 1999)

1.5.2 Pressure ulcers

Patients with SCI are susceptible to pressure ulcers (PU) and subsequent infection (Cruse et al, 2000a; Cruse et al, 2000b; Kaufman et al, 1985; Young et al, 1987). Developing PU is a significant risk for people with SCI (Consortium of Spinal Cord Medicine, 2008). A PU results when insufficient blood flow and decreased oxygen is delivered to specific pressure points in the body. This may be due to externally applied pressure for a prolonged period of time over bony prominences (Krause & Broderick, 2004). After SCI, individual's ability (sensation) to feel pain in a pressure area is impaired due to sensation loss and they are also unable to shift weight naturally due to mobility loss (Krause & Broderick, 2004). The level of SCI lesion is a significant factor in the development of PUs. An observational study carried out by Waters and colleagues (Waters et al, 2009) found that patients with complete SCI had more PU episodes per year than those with incomplete SCI, reinforcing the importance of sensory function as a risk factor for PU. When a PU is severe and not treated aggressively, it can lead to further disability, surgical interventions, amputations and fatal infections (Consortium of Spinal Cord Medicine, 2014).

PU account for nearly one fourth of the cost of care for individuals with chronic SCI. In the US, the cost of care for PU is about 1.2 to 1.3 billion US dollar annually, with prevention costing one tenth of this. (Jones et al, 2003) A recent study (Krause & Broderick, 2004) reported that nearly 90 % of PU is preventable and significant protective measures including life style, exercise and diet are essential. There is minimal research investigating the relationship between nutritional status and prevention and /or healing of pressure ulcers. Limited high quality studies do exist, however, that either quantify amounts of nutrients needed to prevent pressure ulcers or optimises the healing process once a pressure ulcer occurs in the SCI patients. (Chapman et al, 2011) Table 1.6 summarises the nutritional consideration for those with a pressure ulcer.

1.5.3 Swallowing difficulties

SCI patients may also suffer from swallowing dysfunction that hinders their ability to tolerate oral food which may occur as a result of lying flat. Studies have reported that 16 % of patients have dysphagia after SCI. (Seid et al, 2010) Ventilator support and tracheostomy may present physical barriers to eating and drinking (Wong et al, 2012a). Kirshblum and colleagues (Kirshblum et al, 1999) suggested that the presence of a tracheostomy appears to be a risk factor in causing dysphagia. If dysphagia remains undetected and untreated, aspiration pneumonia could result.

1.5.4 Gastrointestinal complications

Gastrointestinal factors such as dysphagia, ileus, nausea, vomiting, gastrointestinal bleeding, diarrhoea or constipation, early satiety and abdominal injuries may adversely affect patient's nutritional status. (Consortium of Spinal Cord Medicine, 2008) In addition, a compromised gut due to spinal shock could lead to gastric content aspiration and abdominal distension which could compromise dietary intake and ventilation. (Cheshire & Coats, 1966)

Table 1.6 Suggested supplementation for pressure wound healing versus Dietary recommended values (DRVs)

Nutrient		Energy (Kcal)	Protein (g)	Vit. A (µg)	Vit. C (mg)	Zinc (mg)	Iron (mg)
DRV: EAR energy, RNI other nutrients	Males	EAR: 2340 -2550 kcal / day	53.3 – 55.5	700	40	9.5	8.7
	Females	1877 - 1940	45 – 46.5	600	40	7	8.7 – 14.8
Supplementation suggestions for specific deficiencies with PU in SCI	PU Stage I - II	30-40 Kcal / KG BW Or BMR x 1.2*	1.2 – 1.5 g/Kg BW / day)	3000 to 15000 (up to 10 days)	100 – 200	220mg twice /day (or 50 mg elemental zinc) for 2-3 weeks	Supplementation should be provided as indicated to correct iron deficiency anaemia.
	PU stage III = IV	30-40 Kcal / KG BW Or BMR x 1.5*	1.5 – 2 g/Kg BW / day)		1000 – 2000		

**Harris-Benedict predictive energy equation times stress factor*
Abbreviations –
DRV: Dietary Reference Values;
EAR: Estimated Average Reference;
RNI: Reference Nutrient Intake
PU: pressure ulcer

1.5.5 Obesity

Obesity is a common secondary complication of chronic SCI and is associated with adverse metabolic consequences. Recent studies suggested that up to 60% of patients with chronic SCI were overweight (body mass index: BMI >25 kg/m^2) (Gupta et al, 2006), and up to 30 % of patients are obese (BMI >30 kg/m^2). A positive energy balance increases the risk of obesity. Total energy expenditure (TEE) is compromised due to a reduced basal metabolic rate (BMR) due to muscle atrophy (change in body composition), and a reduction in physical activity level (PAL). In addition to those conditions common to the able-bodied population, a reduced function below the level predicted by the neurological lesion, pain, and compromised mobility are unique in obese patients with SCI. (Boninger et al, 1999)

Total energy expenditure (TEE)

TEE is composed of several different components including the body's basal metabolic requirements (Basal Metabolic Rate: BMR), typically taken in a subject resting in a reclining position, after 8 hours of sleep and 12 hours of fasting; physical activity level (PAL), diet induced thermogenesis (DIT) and non-exercise activity thermogenesis (NEAT).

$$TEE = BMR + PAL + DIT + NEAT$$

BMR accounts for approximately 60 to 70 % of TEE. Resting energy expenditure (REE), the amount of energy required for a 24-hour period by the body during a non-active period, is generally observed to be lower in people with SCI than those without (Buchholz et al, 2003; Liusuwan et al, 2007; Monroe et al, 1998), lower than predicted (Barco et al, 2002; Buchholz & Pencharz, 2004; Cox et al, 1985; Kearns et al, 1992; Supngen et al, 2003) and related to SCI level. (Mollinger et al, 1985)

DIT is the increase in energy expenditure associated with digestion, absorption and storage of food, and accounts for approximately 10% of TEE.

Activity thermogenesis is the thermogenesis that accompanies physical activities, therefore, can be divided into exercise and non-exercise activity thermogenesis (NEAT). After SCI, most individuals do not partake in purposeful sporting exercise, therefore, their NEAT could be as low as zero; for those who do exercise / train regularly,

exercise-related energy expenditure is generally 10% of the TEE. NEAT or the "energy expenditure of spontaneous physical activity" encompasses the combined energy cost of physical activities of daily living, spontaneous muscle contraction, fidgeting and maintaining posture when not recumbent and accounts for the remainder of the TEE.

TEE can be predicted or measured. At a clinical level, BMR is often expressed as a function of body weight using predictive equations such as the Schofiled equation (Schofield, 1985) and Harris & Benedict's equation (Harris & Benedict, 1919), the majority of them are validated in able-bodied subjects.

When used in the SCI population, such predictive equations overestimate measured requirements by 5 to 32 % (Barco et al, 2002; Buccholz & Pencharz, 2004; Cox et al, 1985; Jeon et al, 2003; Mollinger et al, 1985; Shedlock & Laventure, 1990; Shizgal et al, 1986; Spungen et al, 2003), most markedly in tetraplegic patients (Cox et al, 1985; Mollinger et al, 1985). Similarly, measured BMR has been found to be 14 to 27 % lower in people with chronic SCI than in able – bodied controls (Buccholz & Pencharz, 2004; Jeon et al, 2003; Monroe et al, 1998). It is recognised that not all clinical rehabilitation centres will have access to an indirect calorimeter to measure BMR. (Consortium for Spinal Cord Medicine, 2008) To avoid over- and under- feeding SCI patients during an acute phase and overnutrition in a chronic phase of injury, development of a new equation to predict requirements in SCI is needed. In addition, this new equation should be validated and prospectively tested in a large sample of men and women with complete and incomplete tetraplegia and paraplegia. In absence of disease specific predictive equations, the use of general equations could lead to obesity. Practitioner working in SCI centre should be cautious when using predictive equations.

Two possible mechanisms to explain the reduced BMR in patient with chronic SCI has been proposed: 1.) Change in body composition: reduced fat free mass (FFM) and; 2.) Altered sympathetic nervous system activity.

Reduced fat free mass (FFM)

Body composition changes after SCI in response to reduced physical activity, immobilisation or disease. This causes a reduction in metabolically active tissue (FFM) and increase in adiposity levels and as a consequence, energy balance becomes more

difficult to maintain. In a cross sectional study of 133 SCI males (Spungen et al, 2003), it was found that body composition changes were exaggerated with advancing age and resulted in increased body fat and loss of FFM (muscle). The result was significantly greater than those of an ethnicity-matched able-bodied cohort.

BMR is predominantly determined by FFM which accounts for over 70 % of the variation in BMR. This is due to the numerous high energy processes which occur in organs and muscles, including ion pumps, synthesis and degradation of cell constituents and various biochemical cycles. Patients with chronic SCI have a reduced FFM (Jeon et al, 2003). Therefore, a decrease in FFM may result in a decrease in BMR.

Altered sympathetic nervous system activity

Sympathetic activity is dependent on the neurological level of the lesion; high level SCI, is associated with markedly decreased sympathetic activity (Schmid et al, 2000). Because of this, it has been questioned whether the BMR should be adjusted for body composition or sympathetic nervous system activity when comparing those with and without SCI. A study by Jeon and colleagues (Jeon et al, 2003) attempted to answer this question; they proposed a low BMR observed in paraplegia and tetraplegia is due to reduced FFM, and in tetraplegia, also to reduce sympathetic nervous system activity. Differences in BMR (measured by indirect calorimeter) between persons with or without SCI become non-significant when the BMR was adjusted for body composition, suggesting that the metabolic activity of FFM does not differ in these patients.

Diet induced thermogenesis (DIT) and brown adipose tissue (BAT)

Decreased DIT may be an important risk factor for weight gain, (D'Alessio et al, 1988) and concomitantly mammalian brown adipose tissue (BAT) plays a critical role in maintaining energy balance by thermogenesis, (Cannon & Nedergaard, 2004) the dissipation of energy in the form of heat. The mechanisms whereby diet stimulates energy expenditure are not fully understood and knowledge of the effect and role of BAT in SCI patients is limited, (Bucchholz & Pencharz, 2004) Stimulating the energy-dissipating function of BAT may serve to counteract fat accumulation. (Nedegaard et al, 2011) The post-meal rise in metabolic rate is a significant contributor to daily heat

production and body weight homeostasis, and has a potential role in counteracting the development of obesity.

Physical activity level (PAL)

As a third component of TEE, if neither the BMR, nor the obligatory phase of the diet induced thermogenesis (DIT), is different between people with and without SCI. The decrease of REE in the SCI population is most likely due to a decreased PAL. However, the data on PAL in the SCI population are limited. Data is limited to the cardio respiratory response, such as heart rate or oxygen consumption during crutch or walker-assisted ambulation (Ulkar et al, 2003) or during wheelchair propulsion measured during exercise testing (Kolpek et al, 1989). It is not surprising that individuals with SCI have significantly lower PAL than those who are able-bodied (Buchholz et al, 2003; Shizgal et al, 1986; Yamaski et al, 1992). Tetraplegia is associated with lower PAL than paraplegia (Dearwater et al, 1985), and participation in sports decreases post injury (Tasiemski et al, 2000). Studies seem limited to either measurements of PAL indirectly by questionnaire (Dearwater et al, 1985; Tasiemski et al, 2000), or in respiratory chambers (Monroe et al, 1998).

Yamasaki and colleagues (Yamasaki et al, 1992) found patients with SCI can perform the same as able-bodied individuals if they are actively participating in exercise. But generally their TEE was significantly lower when compared to their more active days or to the control days of able-bodied individuals. Therefore, individuals with chronic SCI should be encouraged to engage in increased frequency, intensity and / or duration of structured physical activity to offset population specific sedentary activities. It is acknowledged, however, that patients with SCI are engaged in sedentary activities of daily living unique to the SCI population, such as pressure relief, bowel programmes, or standing in a standing frame which therefore limits the opportunity for exercise.

It is also reported that the TEE was 25 % and PAL was 18 % lower in individuals with complete rather than incomplete lesions (Yamasaki et al, 1992). This finding was not surprising as complete lesions result in absent sensory and motor function below the level of injury and thus might be expected to result in more limited movement. Taking this in to account, we can anticipate that individuals with tetraplegia and those with complete lesions may be at a particular disadvantage.

These factors, in addition to the lack of volitional control below the level of SC lesion and the disruption to systemic autonomic control, provide a unique challenge for individual to maintain energy balance after SCI.

1.6 Gut microbiota

The gut microbiota has a tremendous potential to impact our physiology, both in health and in disease. They contribute to metabolic functions, protect against pathogens, and educate the immune system, and through these basic functions they directly or indirectly affect most of our physiological functions (Antoine, 2010). When clinically indicated, antibiotics will be used to treat infections, however, the use of antibiotics also have a profound impact on the gut microbiota that alters the nutritional landscape of the gut and can lead to the expansion of pathogenic species, such as CDI. Changes in microbiota can confer resistance to or promote infection by pathogenic bacteria, such as CDI.

1.6.1 Role of the gut microbiota in specific disease conditions

The gut microbiota can influence human physiology, and it is no surprise that there is great interest in studying microbiota changes associated with disease states or antibiotic use, often referred to as dysbiosis. (Figure 1.5). Gut microbiota dysbiosis has been reported to be associated with malnutrition (Smith et al, 2013; Subramanian et al, 2014) The relationship between dysbiosis with malnutrition and disease pathogenesis remains uncertain at this time. It is not often clear that gut microbiota changes associated with diseases are meaningful, and distinguishing between cause and effect is inherently challenging. It is intriguing to speculate that dysbiosis may cause disease as we learn more about how the gut microbiota can influence the host. It has also been noted that the diseased state can lead to changes to the gut microbiota through various mechanisms, including changes in eating habits and bowel function, as well as through the addition of medication, such as antibiotics.

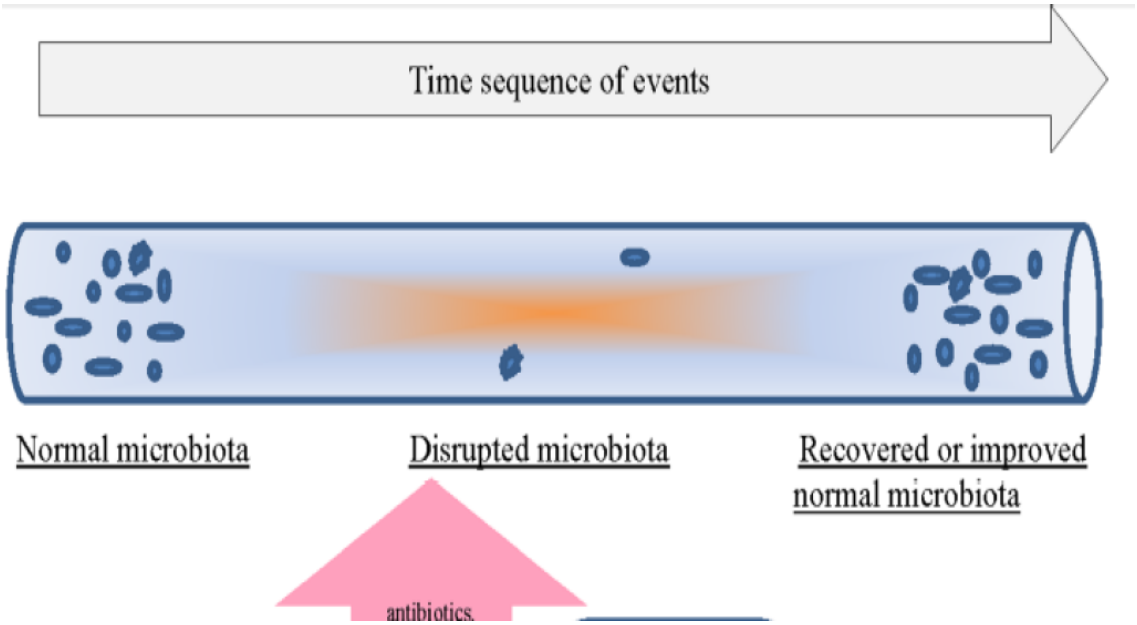


Figure 1.5: Effect of antibiotics on gastrointestinal microbiota, an illustration of dysbiosis (McFarland, 2013)

1.6.2 Manipulating the gut microbiota using probiotics to prevent AAD/CDI

Probiotics are defined as '*live microorganisms which, when administered in adequate amounts, confer a health benefit on the host*' (WHO, 2002). In 2014, the definition was further reviewed by an expert panel, with just a small change to improve its grammar to '*live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host*' (Hill et al., 2014).

Probiotics are commonly recommended as an adjunct to prevent AAD / CDI in general patients (McFarland, 2006; Segarra-Newnham, 2007; Snydman, 2008). However, no probiotic has been demonstrated to be efficacious in the prevention of recurrent CDI when studied rigorously. Several recent meta-analyses have indicated that probiotics may be effective as a primary prophylaxis for AAD / CDI. (section 1.6.3).

1.6.3 Evidence on the use of probiotic in preventing AAD / CDI

Probiotics could maintain and restore the gut microbiota balance through receptor competition, competition for nutrients, inhibition of epithelial and mucosal adherence of pathogens, the introduction of a lower colonic pH favouring the growth of non-pathogenic species, stimulation of host immunity, or general antimicrobial effects. A recent meta-analysis examined randomised, double-blinded, controlled trials of

probiotics in the prevention of AAD (Videlock & Cremonin, 2012: pooled relative risk, 0.53, 95% CI 0.44 to 0.63) and CDI (Johnston et al., 2012), and suggested the use of probiotics over a placebo in general patients. (pooled relative risk, 0.34, 95% CI, 0.24 to 0.49).

A double-blind RCT suggested that probiotics (*Lactobacillus casei* DN1005) were effective in preventing AAD in general patients. The study was conducted on 135 adults (n= 66: antibiotics and placebo; n=69 antibiotics and probiotics), and showed that a drink containing *L. casei, L. bulgaricus* and *S. thermophilus* twice daily prevented AAD and diarrhoea caused by *CDI* (7 of 57 patients in the probiotic group, compared to 19 of 56 in the control group developed AAD). However, only 135 out of a total of 1760 hospitalised patients taking antibiotics were randomised in this trial (randomisation rate: 7.6%), which may limit the applicability of the findings (Hickson et al., 2007).

A few meta-analyses have been conducted to build on the current evidence regarding the use of probiotics in AAD in the general patients group. Kale-Pradhan et al. (2010) reported a meta-analysis of 10 RCTs (n=1,862) in paediatric and adult patients who received a single *Lactobacillus* strain or placebo for preventing AAD. *Lactobacillus* prophylaxis throughout the antibiotic treatment (5-14 days) reduced the risk of AAD in adults but not paediatric patients. Six trials included patients aged 18 years or more, whereas four included patients less than 18 years of age (ranging from 2 weeks to 14 years), while the follow-up period ranged from 2 days to 3 months. The combined risk ratio of developing AAD was significantly lower for *Lactobacillus* vs. placebo (risk ratio: 0.35, 95% CI: 0.19 – 0.67). In a sub-group analysis, this held true for adults (risk ratio: 0.24; 95% CI: 0.08 – 0.75). Two meta-analyses have examined randomised, double-blinded, controlled trials of probiotics in the prevention of AAD in general patients (Cremonini et al., 2002; D'Souza et al., 2002).

Another meta-analysis also published in 2012 by Hempel and colleagues included 63 studies with a total of 11,811 participants. They evaluated probiotics for the prevention and treatment of AAD. This review included parallel RCTs that compared probiotic use as an adjunct to antibiotic treatment with a concurrent control group. Eighty-two RCTs met the inclusion criteria and were included in the analysis. In the 63 trials that reported the number of participants with diarrhoea and the number of patients randomised to

both treatment groups, probiotic use was associated with a lower risk ratio of developing diarrhoea when compared with a control group (Pooled risk ratio: 0.58; 95% CI: 0.50-0.68; p <0.001; I2: 54%; risk difference: -0.07, 95% CI: -0.10 to -0.05). These results were consistent across a number of sub-groups, and sensitivity analyses based on probiotic interventions, participant and setting characteristics, and across varying indications for antibiotic use. The researchers reported a beneficial treatment effect with a number needed to treat of 13 (95% CI: 10.3 to 19.1). The review concluded that probiotics are associated with a reduction in AAD.

A more recent Cochrane review of probiotics for the prevention of CDI in adults and children included 23 studies with a total of 4,213 participants. (Goldenberg et al., 2013) It was reported that probiotics significantly reduced the risk of CDI by 64%, and the incidence of CDI was 2.0% in the probiotic group, compared to 5.5% in the placebo, no treatment group, control groups (risk ratio: 0.36, 95% CI: 0.26 – 0.51) (Goldenberg et al., 2013). The review concluded that the moderate-quality evidence suggested that probiotics are both safe and effective for preventing CDI.

These meta-analyses confirm an odds ratio of 0.39 and 0.37, respectively, in favour of probiotic over placebo in preventing AAD. However, the heterogeneity of the studies makes it very difficult to draw definite conclusions for disease specific populations, such as SCI population indicating further research is needed to determine which probiotics, patient's group and antibiotics are associated with the greater efficacy.

1.6.4 Safety issues of probiotics

Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. They are generally regarded as being safe, and severe adverse event such as mortality or intensive care unit admission have rarely been reported. Safety issues are related to bacterial translocation and sepsis, and to the risk of harbouring antibiotic resistance transposons that may increase resistance to antibiotics. The theoretical risk is the translocation of bacteria from the intestine to other areas in the body, resulting in an iatrogenic infection, and two cases of bacteraemia have been reported (Snydman, 2008).

LcS is considered safe to use in clinical settings and has been used in a broad range of patients (Matsuzaki et al., 2005; Srinivasan et al., 2006; Stadlbauer et al., 2006).

Evidence from human studies suggests that LcS predictably increases the number of beneficial intestinal bacteria (Matsumoto et al., 2010), and it has been shown to help with constipation (Sakai et al., 2011), to modulate immune function (Dong et al., 2013) , to reduce the global infection risk (Gleeson et al., 2011), and to reduce the risk of diarrhoea (Sur et al., 2011).

Summary for chapter 1

We have discussed the aim of the thesis and included seven first authored papers for assessment of PhD by prior publication. The terminology, mechanism, classification, epidemiology and financial impact of SCI were discussed in section 1.2. The history of SCI centre and dietetic research were presented in section 1.3. The cause and consequence of malnutrition after SCI were discussed in section 1.4 and 1.5. and in section 1.6 we report the concept of using probiotics to manipulate the gut microbiota to prevent AAD / CDI. Currently, there is limited evidence on the use of probiotic in preventing AAD / CDI in SCI patients. The effectiveness of probiotic in preventing AAD / CDI in SCI patients will also be discussed in section 3.3.

Chapter 2 Identification of malnutrition risk and potential barriers for implementing good nutritional care in SCI Centres

The nutritional needs and management of patients who have sustained an SCI and are still recovering from the acute trauma and those who are stable and undergoing rehabilitation are quite different. This chapter is designed to report the nutrition management of SCI patients admitted to a SCI centre. It's sub-divided into four sections, first the prevalence of undernutrition risk after SCI and the use of a nutrition screening tool to identify patients at risk of becoming undernutrition will be described (section 2.1), then complications related to malnutrition (section 2.2) and the association with adverse clinical outcomes in SCI patients (section 2.3: papers 2 and 3) are reported, finally, the potential limiting factors for implementing good nutritional care in SCI centres are discussed. (section 2.4).

2.1 Identifying patients at risk of malnutrition

Elia (2003) describes malnutrition as a state in which a deficiency, excess or imbalance of energy, protein and other nutrients causes adverse effects on body form, function and clinical outcomes. It was refined further by the international consensus committee in 2010 that varying degrees of acute or chronic inflammation are key contributing factors in the pathophysiology of malnutrition associated with disease or injury. (Jensen et al, 2010) The committee propose the following nomenclature for nutrition diagnosis in adults. 1. "starvation-related malnutrition", where there is chronic starvation without inflammation; 2. chronic disease-related malnutrition", where inflammation is chronic and of mild to moderate degree and; 3. "acute disease or injury-related malnutrition", when inflammation is acute and of severe degree. (Jensen et al, 2010). In 2015, European Society for Clinical Nutrition and Metabolism (ESPEN) has published criteria for the definition of malnutrition (Cederholm et al, 2015), namely BMI ≤18.5 kg/m2 , or weight loss >10% (indefinite of time) or 5% (in 3 months) and BMI <20 kg/m2 for patients <70 years or <22 kg/m2 for patients ≥70 years or fat free mass index (muscle) (below <15 and <17 kg/m2 in women and men, respectively) to identify malnutrition risk.

Previous studies have consistently revealed the inadequacy of any single method or tool in assessing a patient's nutritional status and the use of threshold BMI values as in

malnutrition universal screening tool (MUST) may produce false results in SCI patients because of changes in body composition after SCI (Laughton et al., 2009).

In the absence of a gold standard, researchers have been led to develop various nutritional indices that could be used to identify patients at an increased risk of poorer outcomes because of malnutrition. The use of a valid nutrition screening tool (NST) could assist the process of accurately identifying those patients who are at risk of developing malnutrition. Appropriate identification and early intervention could improve clinical outcomes and reduce health-care costs (NICE, 2006). In addition, it is well known in the literature that not all tools are suitable for all patients (e.g. patients with liver diseases, Morgan et al., 2006) including SCI patients. In the absence of a universally accepted definition of malnutrition, it is difficult to establish the validity of any newly developed NST. Consequently, it is important to establish the extent to which a new NST agrees with previously used and established methods for identifying malnutrition (Stratton et al., 2004).

To address this within the SCI population, I previously reported the prevalence of malnutrition in SCI patients using the MUST (Wong et al., 2012a: 44·3% of patients were undernourished or at risk of undernutrition). Next, in the same group of patients, we validated a disease specific tool, the SNST (Wong et al, 2012b; figure 2.1) against the pragmatic reference standard of a full dietetic assessment, assuming that an assessment by a dietician is the most likely to be accurate, as it reflects additional knowledge and training (Wong et al., 2012d: I found that the SNST is an acceptable and reliable nutrition screening tool with reasonable reproducibility and valid when compared with another validated nutrition screening tool (MUST) and a full dietetic assessment. (Wong et al., 2012b) The SNST had substantial agreement with MUST (k: 0.723, 95% confidence interval (CI): 0.607–0.839) and the dietitian assessment (k: 0.567, 95% CI: 0.434–0.699). The SNST had a moderate to substantial reliability (inter-rater reliability: k: 0.5, 95% CI: 0.2–0.8; intra-rater reliability: k: 0.64, 95% CI: 0.486–0.802). When compared with dietetic assessment, the SNST had a numerically lower specificity (76.1% vs 80.4%) and similar agreement to MUST (k: 0.57 vs 0.58) but SNST showed a numerically higher sensitivity (85.7% vs 80.4%) and a numerically higher negative predictive value (92% vs 89.2%) than MUST.) Finally, I also demonstrated that undernutrition-risk score using the SNST, were associated with

adverse clinical outcomes, including length of hospital stay and 365 days mortality rate after admission (Wong et al., 2013).

Although the SNST is not superior to the widely used generic nutrition screening tool (the MUST). My data does however confirm that the SNST is valid to screen SCI patients' nutritional risk. (Wong et al, 2012b) The SNST is a locally developed screening tool, which has been used in some major UK SCI centres including the NSIC at Stoke Mandeville Hospital and the Duke of Cornwall Spinal Injuries Centre at Salisbury District General Hospital since 2004. There was a reluctance to abandon this disease specific tool, which was familiar to the users. Recently, more SCI centres (who are not routinely screening their patients) are now considering using SNST for nutrition screening. I consider that my data permits us to condone this more comfortably than was previously the case. In addition, I see this as something of an organisational advantage as to continue to use the SNST in SCI centres where it is established is easier than switching to an alternative and preferable to having several tools in use in a small discipline. The UK NICE highlights the importance of using a validated NST, and MUST is only one of the recommended choices. I failed to find any published literature indicating whether in SCI patients should use a generic NST or a disease specific NST. I hope my (now published) data helps to fill this void and add insight into future clinical research in SCI medicine. I hope that promotion of this tool will convince other SCI professions to use a common disease specific NST.

It was noted nutritional therapy is seen to be under-utilised in the SCI centres. Several organisational factors, I published previously, including sub-optimal dietetics provision (section 1.3.3; Wong et al., 2012c), inadequate nutrient intake (Wong et al., 2012c), together with poor nutritional knowledge (Wong et al., 2012d) are thought to be barriers of implementing good nutritional care.

Figure 2.1: The Spinal Nutrition Screening Tool (Reproduced from Wong et al, *Eur J Clin Nutr* 2012; **66**: 382-387)

To be completed by nursing staff

Patient name _____ Hospital number _____

Est. Pre-injury Height _____ **Weight** _____ **Body Mass Index** _____ **(See ready reckoner chart)**

Date completed _____

					Score
Weight History	**0** No weight loss	**1** Some unintentional weight loss. BMI 19-21	**3** Moderate unintentional weight loss. BMI 16-18	**4** Marked unintentional weight loss. BMI <16	
Age	**1** 18-30yrs	**2** 31-60yrs	**3** over 60yrs	**4** under18yrs	
Level of SCI	**1** S1-S5	**2** L1-L5	**3** T1-T12	**5** C1-C8	
Other medical conditions	**0** None **1** Chronic condition E.g. diabetes/substance abuse	**2** Acute Trauma Fractures/Head Injury **3** Infection/Post surgery	**4** Requires ventilation	**5** On ventilatory support with tracheostomy	
Skin Condition	**0** Intact **1** Red mark or Grade 1	**2** Superficial skin damage or Grade 2	**3** Full thickness skin damage or Grade 3	**5** Deep multiple pressure ulcers or Grade 4/5	
Diet	**0** Normal diet and fluids	**1** Parenteral or enteral nutrition	**2** Modified texture diet +/-nutritional supplements	**3** Nil by Mouth	
Appetite	**0** Good, eating all meals	**1** Poor, > ½ left	**2** Not accepting food & drink or unable to eat	**3*** Vomiting and diarrhoea	
Ability to eat	**1** Able to eat independently	**2** Requires some help	**3** Needs to be fed		

TOTAL=

Score each risk factor, using highest score if more than one is relevant.	**Total these row scores to obtain Initial total Score and record risk level**	**Risk level** 0-10 = **Low** 11-15 = **Moderate** >15 = **High**

* Investigate cause and treat.

SCI: spinal cord injury; C1-C8: Cervical SCI; T1-12: Thoracic SCI; L1-L5: Lumbar SCI; S1-S5: Sacral SCI

Many patients, AHPs and hospital managers do not realise how common malnutrition is within hospitalised patients (Wong et al, 2012d: that 60% of doctors and 29.3% of nurses are correct in estimating the prevalence of malnutrition). I previously proposed that poor nutritional knowledge among SCI nurses and doctors is probably another barrier to implementing good nutritional management (Wong et al, 2012d; without proper training it can be assumed that front line healthcare staff will continue to fail to identify patients at nutritional risk, and subsequently to offer appropriate choice of treatment (Wong et al., 2012c).

In addition, despite high awareness of obesity as a medical significant issue (NICE, 2006a), the magnitude of the obesity epidemic remains high and is worsening, particularly in patients with SCI (Wong et al, 2012a: 45% of SCI patients are at-risk of over-nutrition) A more detailed understanding of knowledge, attitudes and practice of SCI staff is necessary to determine the best way to facilitate the contribution of SCI medical staff in addressing obesity after SCI. Although there are standard published recommendations for SCI management and optimal staffing levels (Paper 5), these documents do not make specific recommendations on obesity management. In 2012, a study was conducted to determine the nutritional knowledge, attitudes and practices of medical staff towards weight management in patients with SCI so that it could be decided whether additional training might improve detection and treatment of malnutrition in SCI patients. (Paper 4)

> **Paper 4: <u>Wong S</u>** et al (2015) Knowledge, attitudes and practices of medical staff towards obesity management in patients with spinal cord injuries: an international survey. *Spinal Cord* **53:** *24-31*.

During October 2012 and May 2013, I surveyed senior medical staff working in 23 SCI centres from four European countries (Belgium: n=3, the Republic of Ireland: n=1; the Netherlands: n=8, and the United Kingdom: n=11, with a covering letter addressed to the local medical lead explaining that findings would be used to identify current knowledge, attitude and practices of medical staff and to identify areas for improvement.

The overall SCIC response rate was 78.4% (18/23 SCICs; 59 individual responses, 2-12 responses per SCIC, 63.6% in the United Kingdom (n=7), 66.7% in Belgium (n=2), 62.5% in the Netherlands (n=5) and 100% in the Republic of Ireland (n=1). Whilst the majority of the respondents felt that they are confident in dealing with overweight (74.5%) and obese (66.1%) SCI adults, less than half (44.1%) are confident in treating overweight and obese SCI children. The respondents also highlighted the need to practice malnutrition (obesity) prevention and management but that there was a lack of suitable training on offer. (Paper 4) No junior/trainee doctors reported that they had received formal training in obesity management of SCI patients and only 2 (6.3%) senior doctors reported that they had formal training in this area.

SCI specialists have been identified as important potential contributors to the prevention and treatment of overweight and obesity, in part, because of continued involvement during rehabilitation. SCI medical staff are therefore in a unique position to provide guidance to patients. In the UK and Republic of Ireland, SCI consultants will continue to see their patients as part of a life-long follow up. They are the most frequently used source of information about weight control and are perceived to be the most reliable formal source of information.

Among medical staff, knowledge, attitudes and practices in the management of obesity have been studied in various English-speaking countries, especially amongst General Practitioners (Thuan & Avignon, 2005). However, despite high awareness of obesity as a medically significant issue (Kristeller & Hoerr, 1997), the magnitude of the obesity epidemic remains high (NICE, 2006a) and is worsening, particularly in SCI patients. (Wong et al, 2012a) However, weight management is not commonly offered to SCI patients, at least not in the UK. (Wong et al, 2011)

The main strength of this study is that it is the first official European survey conducted in four European SCI centres which obtained an overall 78.4% response rate from across four European countries. Therefore it was not possible to compare the present study's response rate with the literature.

This study has a number of limitations. The selection of the SCICs in each country was at discretion of the principal investigators. Although the number of SCICs per country

was small. The survey was sent to all SCI centres with a high response rate, and with no data / response were excluded from the analysis .Therefore, I believed the results derived from this sample of SCICs could be considered representative of each country and I hope the data is generalisable to other European SCI centres.

Formal sample size calculation was not performed as I surveyed all SCI centres. The present study reported a response rate of 78.4%, the response rate was comparable in literatures. However, I did not address the non-response bias. It would be recommended in future study to assess non-response bias formally.

The centres' response rate varied from 2–12 responses per SCIC, some larger centres may be over-represented in the results. In addition, our technique of secondary invitation of respondents by selected lead individuals within a SCIC could introduce selection bias and I acknowledge this; however, guidance was provided to them to circulate the questionnaire to all medical staff, with varying degrees of experience and special interest, working in the SCI centres. Although the respondent sample size (n=59) was small, I feel that this still reflects the views of SCI doctors working in SCICs. To our knowledge, this represents at least 46.8% of all senior medical staff in the UK and Ireland SCICs (15 out of a total 32 centres) which is comparable with the literature (53% response rate).

Apart from the UK, I did not include junior staff from Ireland, Belgium and the Netherlands. There was a predominance of respondents from the UK (n=40) compared to non-UK respondents (n=19). Although this arguably over-represents from one country's perspective, it does not reflect the reality of staff-mix in the SCI centres. The number of senior medical staff surveyed was comparable in the UK and non-UK centres (14 vs 19).

The present study's questionnaire contains 37 items. It was developed based on previous published literatures. (Al-Ghawi et al, 2009; Campbell et al, 2000; Bocquier et al, 2005; Fogelman et al, 2002) Therefore, I believe the questionnaire is likely to be valid and reliable.

In summary, this was the first study to document the need for obesity management among SCI professionals. Limited knowledge and experience among medical staff together with variation in dietetic provision (paper 4, 5) in SCIC are probable barriers to effective weight management for SCI patients. Our results indicate that more structured teaching about obesity classification and its treatment should also be provided for all front line staff, especially more senior staff that has previously been denied this opportunity. Without proper guidelines and training, it is unlikely that healthcare staff will have sufficient knowledge to identify at-risk patients or to offer appropriate treatment. This study reinforces the need to consider collaborating with national professional bodies to develop SCI-specific weight management guidelines which include clear guidance on optimal dietetic service provision within the SCICs.

2.2 Potential limiting factors for implementing good nutritional care in SCI centres

The potential barriers limiting the implementation of good nutritional care and in SCI patients were discussed in section 2.1. These include sub-optimal and variation in dietetic resources within UK SCI centres, (section 1.3.2), and poor knowledge among staff at SCI centres concerning the management of malnutrition (section 2.1). In this section, I will discuss specific limitations for conducting nutrition research in SCI patients with emphasis on my research. These include lack of universal diagnostic criteria for *CDI*, and diarrhoea management practices varying among SCI centres (section 2.2.1), lack of a universal definition of malnutrition and diarrhoea (section 2.2.2) and limited evidence available for the use of probiotic in SCI patients (section 2.2.3 and section 2.2.4). Paper 6 will be used to support this section.

Paper 6: **Wong S** et al. Survey on the use of probiotics in preventing antibiotic associated diarrhoea and *Clostridium difficile* associated diarrhoea in spinal cord injuries centres. *Int J Probiotics and Prebiotics* **10**, 85-90.

2.2.1 C. difficile - practice varies between SCI Centres – dose SCI centre have standardised *C. diff* infection policy?

Although there is promising evidence to support the use of probiotics to prevent AAD and CDI (section 1.4.1), there are no recommendations published to provide guidance to

physician regarding the use of probiotic in preventing CDI and AAD in SCI patients and consensus exists on optimal diagnostic criteria for CDI.

In 2014, I surveyed nine SCI centres from four European countries (UK, Ireland, the Netherlands and Belgium) with an aim to investigate SCI centres' CDI management strategies (including diagnostic procedures and presence of national surveillance) (paper 6). In addition, it was also documented whether they stocked probiotics, and the reason for the use of probiotics.

All nine SCI centres responded to the survey. It was found the current diagnostic tests to detect the presence of *C. difficile* or its toxins in stools are not uniform. Only five out of nine SCICs reported they have a CDI policy. Five SCICs reported CDI cases and the median CDI cases per 10,000 days were 0.56 (range: 0-1.08). The methods for diagnosing CDI, culturing *C. diff*, definition of diarrhoea and treatment options are varied and these are summarised in Table 2.1.

Four out of nine (44.4%) centres did not stock any probiotic products. Three SCICs stocked only one probiotic product, and two SCIC stocked more than one probiotic product. Of the five SCICs that stocked probiotics, the products were used for preventing AAD (n=4) and CDI (n=2) and/or constipation (n=1).

The stocking of probiotics for the prevention of AAD/CDI was not found to be common in SCI centres (section 2.1.3), and the definition of diarrhoea (section 2.1.2) and management of CDI varied, suggesting inconsistency in patient's care and potentially missed opportunity in improving patient's care. The results highlighted the need for a standardised definition within this vulnerable population group. Since the study was published, I have discussed with the ISCOS about setting a universal definition of diarrhoea / *C. difficile* management standards, as this would not only help in identifying and treating SCI patients but also in future AAD/CDI research (for common study outcome).

The survey (in paper 6) had some limitations. Firstly, the selection of the SCI centres in each country was at the discretion of the principal investigator and the number of SCI centres per country was small. I acknowledged the snowball sampling technique was

not ideal (see as per paper 4) However, the SCI centres selected represented approximately 40% of the SCI centres in Belgium, the UK and the Netherlands, and 100% within the Republic of Ireland. Therefore, I believe results derived from this sample can be considered relatively representative of each country.

Table 2.1: Summary of CDI management in SCI centres (Paper 6)

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6	Centre 7	Centre 8	Centre 9
C. difficile policy	*	Yes	Yes	*	Yes	Yes	Yes	Yes	Yes
C. difficile outbreak	No	No	No	*	No	No	No	No	No
Number of CDI in SCIC	0	*	0	*	2	1	1	1	0
CDI cases per 10,000 patient days (SCIC)	0	-	0	-	0.56	1.08	0.63	0.76	0
C. difficile diagnostic criteria	1	1	1,5,6	1	1	1	1	1	1
Medium for culturing *C. difficile*[b]	1	1	1	1	3	4	1	4	1
First line treatment of CDI [c]	1	2	2	2	1	2	1	2	1
Criteria for diarrhoea[d]	1	2	3	2	1	4	1	1	2

CDI: *Clostridium difficile* infection; SCIC: spinal cord injury centre

[a]*C. difficile* diagnostic criteria: 1: Enzyme immunoassays (EIA) for C. diff toxin A and / or toxin B; 2: EIA for C. diff toxin A only; 3: Cytotoxicity test; 4: culture for toxin producing C. difficile; 5: Enzyme for *C. difficile*- specific glutamate dehydrogenase; 6: PCR

[b]1.Cysloserin-cefoxtin-fructose agar; 2: Cycloserin-cefoxitin-mannitol agar; 3: Brazier medium; 4: Polymerase chain reaction

[c]First line treatment of CDI: 1: Vancomycin 125mg 6 hourly PO for 10-14 days; 2: Metronidazole 800mg loading dose then 400mg 8 hourly PO for 10-14 days

[d]Definition of diarrhoea: 1: ≥2 watery liquid stools type 5,6 or 7 (Bristol stool scale) over 24 hours; 2: 2: ≥ 2 stools per day for ≥3 days; 3: ≥ 3 loose or liquid stools per day; 4 other

2.2.2 Lack of a standardised definition for malnutrition risk and diarrhoea

There is no universal agreement of the definition of malnutrition risk (section 2.1) and malnutrition. Elia (2003) describes malnutrition as a state in which a deficiency, excess or imbalance of energy, protein and other nutrients causes adverse effects on body form, function and clinical outcomes. This was refined further by the International Consensus Committee in 2010 that varying degrees of acute or chronic inflammation are key contributing factors in the pathophysiology of malnutrition associated with disease or injury (Jensen, 2010). The committee proposed the following nomenclature for nutrition diagnosis in adults: (1) 'starvation-related malnutrition', where there is chronic starvation without inflammation e.g. medical conditions like anorexia nervosa; (2) 'chronic disease-related malnutrition', where inflammation is chronic and of a mild to moderate degree such as organ failure or pancreatic cancer; and (3) 'acute disease or injury-related malnutrition', when inflammation is acute and of a severe degree such as major infection, burns, trauma or head injury (Jensen et al., 2010).

Diarrhoea is thought to be clinically significant if there are more than three loose stools per day (Hogenauer et al., 1998; O'Donnell et al., 1990). However, our recent survey in four major European SCI centres found that the definition of diarrhoea varies among SCI centres. (paper 6) Up to four different definitions of diarrhoea were reported from nine SCI centres. Of nine centres surveyed, four SCI centres use ≥2 watery liquid stools type 5,6 or 7 (Bristol stool scale) over 24 hours; Three SCI centres use ≥ 2 stools per day for ≥3 days; One SCI centre uses ≥ 3 loose or liquid stools per day and one SCI centre reports they do not a have standardised definition but are using clinical judgement. With different diagnostic criteria, there is the potential for making inconsistent clinical diagnosis and false positive results for CDI and increases inconsistency in CDI research.

Indeed, using different criteria definitely creates inconsistency in both making a clinical diagnosis and has an implications on research outcomes. Using a standardised definition of study outcome including diarrhoea and malnutrition, would improve the quality of future research studies, especially systematic reviews and meta-analyses as currently it uses inconsistent criteria. It is recommended to use a standardised criterion for diarrhoea, CDI and detecting malnutrition risk as this would facilitate a variety of other

projects (clinical and research), ranging from clinically based nutrition intervention studies to health economic studies, including an investigation into the cost of malnutrition in SCI patients.

2.2.3 SCI centres stocking of different probiotic supplements

I found five (55.5%) out of nine centres stocked probiotics. Five different types of probiotic strains were identified. Although, four probiotics strains were reported by one centre's clinician as being of use for AAD/CDI prevention, only one of four probiotic strains (*LcS*) had been studied for use in a SCI population paper 3).

Different SCI centres tended to stock different types of probiotics, and the diagnostic criteria for diarrhoea varied amongst SCI centres, suggesting that SCI clinicians need to be reminded of the concept that the probiotic effect is strain-, dose- and disease-specific and there is a need for standardised policy for CDI. It also highlights the importance of reviewing the evidence for each probiotic before offering it to SCI patients as the probiotic effect is strain-specific (Goldenberg et al, 2013). A systematic review was planned and a meta-analysis to assess the effect of probiotics in preventing and treating AAD and CDI in the SCI population (Papers 7). A systematic review protocol was published in December 2015 (Paper 7)

2.2.4 Limited evidence on the use of probiotics in preventing AAD/CDI in the SCI population

In this section, I will focus on assessing the quality of evidence on the use of probiotic in preventing AAD / CDI in SCI populations. Two key papers (paper 6 and paper 7) will be used to support the section.

Paper 7: Wong S et al. (2015) Effectiveness of probiotic in preventing antibiotic associated diarrhoea (AAD) and *Clostridium difficile* associated diarrhoea (CDAD) in patients with spinal cord injury: a protocol of systematic review of randomised controlled trial. *Syst Rev* **24**, 170. Doi: 10.1186/s13643-015-0159-3.

Drinking probiotics (paper 3) is often recommended with antibiotic use to maintain a healthy gut microbiota and to prevent harmful bacteria overgrowth, such as by *C. difficile* which could overwhelm the gut and cause CDI (section 1.6.1). However, the evidence of its use in SCI patients is currently unknown. Therefore, the aim of this section was to report our plan to evaluate the evidence on the use of probiotic in preventing AAD / CDI in SCI patients.

A systematic literature review to determine whether the probiotics that were stocked were supported by any clinical research was undertaken. Of five different probiotic strains reported, I performed a systematic literature search restricting our search to randomised controlled trials that assessed probiotics in SCI patients exposed to antibiotics. I searched the Cochrane Central Register of Controlled Trials, Health Technology Assessment Database; CINAHL; PsycINFO; EMBASE; Medline; AMED and DARE from the date of inception to Feb 2015 using the following terms (with synonyms and closely related words): "spinal cord injuries" combined with "antibiotic-associated diarrhoea" and "probiotic". Our search identified only one study reporting evidence of probiotic benefit against AAD in an SCI population, which was one of those probiotics: LcS. (Paper 3)

Our review did not find any studies conducted in SCI populations that investigated use of probiotics for preventing or treating CDI and constipation in the SCI population, although there are several studies with the general population (section 1.6.3). I found that *LcS* and *L. Casei* DN-14001 appear to be the choice of probiotic for prevention of AAD / CDI in SCI centres. Overall, no probiotic was supported by a strong evidence base, mainly due to the lack of consistent benefit from different studies.

Only 25% and 50% of SCICs stocked *LcS* and *L. Casei* DN-14001, respectively, whereas 50% of SCICs stocked at least one probiotic that was supported by low or no evidence. These results suggested that a majority of SCICs stock a probiotic that lacks reliable evidence. Although I only found only one study reporting the efficacy of probiotic in preventing AAD in SCI patients, the other probiotic strains may also be effective.

Recent meta-analyses from general population examining randomised, double-blinded, controlled trials of probiotic in the prevention of AAD (Cremonini et al, 2002; D'Souza et al, 2002; Hempel et al, 2012; Goldenberg et al, 2013) and CDI (Goldenberg et al, 2013) suggested that the use of probiotics could reduce the occurrence of diarrhoea when compared to placebo. However, the heterogeneity of studies varies in disease conditions (e.g. SCI), probiotic strains, dose and duration of probiotic and the definition of diarrhoea makes it very difficult to draw definitive conclusions.

Most previous probiotic research has involved small, single centre studies of variable quality, and even when a meta-analysis is carefully performed it is limited by the quality of the included studies, and therefore could introduce additional bias through study selection and data pooling methods. Although the study by Allen et al. (2014) is by far the largest RCT, they only used two strains of probiotic bacteria (LcS and *B. bifidum*) within a specific patient group. With newly published data and conflicting evidence to support the association of reduced rates of AAD with probiotic use, it is difficult to draw definite conclusions for the SCI population.

This study has a number of limitations. The selection of the SCICs in each country was at the discretion of the principal investigators. At present, the number of SCI centres per country was small. The study authors justified to include one SCIC for each country with fewer than 10 million inhabitants or fewer, two for countries with between 10 and 20 million inhabitants, and four for those with more than 20 million inhabitants, with a balance between academic and non-academic institutions. All survey SCI centres responded. Therefore, results derived from this sample of SCICs could be considered representative of each country and hope the data is generalisable to other European SCI centres.

The SCI centres selected represented approximately 40% of the SCICs in the Belgium, UK and the Netherland, and 100% in the Republic of Ireland. Therefore, results derived from this sample of SCICs could be considered representative of each country. (at least in this four Western European Countries) and I hope the data is generalisable to other European SCI centres.The present study reported a response rate of 100%. Therefore, the author did not address the non-response bias in the present paper. The sample

selected was representative, at least to the UK, Belgium, the Netherlands and the Republic of Ireland. All surveys were sent to all medical leads working in the SCI centres. It would be recommended in future studies to survey all SCI centres in the country of interest.

In summary, there is increasing evidence to support the preventive role of probiotics in AAD. (Cremonini et al, 2002; D'Souza et al, 2002; Hempel et al, 2012; Goldenberg et al, 2013) However, they have also highlighted some common limitations, such as heterogeneity between studies, poor documentation of probiotic strains, and a lack of assessment of probiotic-specific adverse events. Identification of the population who may benefit most from probiotic therapy remains unclear, and further research is needed to determine the optimal dose of probiotic therapy, as well as the comparative effectiveness of different probiotic regimens in specific patients group.

Summary for chapter 2

In chapter 2, I have discussed how to identify SCI patients at risk of malnutrition (section 2.1), and the cause and consequences of malnutrition were discussed in section 2.2 and 2.3. In addition, the potential limiting factors for implementing good nutritional care in SCI centres were discussed in section 2.4, these included CDI practice variation amongst SCI centres, and lack of standardised definition for malnutrition and diarrhoea. Currently, there is limited evidence on the use of probiotic in preventing AAD / CDI in SCI patients. To guide SCI clinical practice, I devised a systematic review protocol to investigate the effectiveness of probiotics in preventing AAD / CDI in SCI patients but unfortunately, limited studies were identified to indicate the benefits (or not) on the use of probiotics in SCI patients.

Chapter 3 Nutrition interventions in SCI Patients with malnutrition risk

Many studies from general populations have suggested that the clinical consequences of malnutrition such as length of hospitalisation (section 2.3); obesity (section 3.1), and diarrhoea (section 2.3; 3.3) could be reduced, avoided or reversed by appropriate nutritional interventions.

The evidence on the use of different nutritional intervention in SCI patients is currently limited by various factors, mainly related to limited resources invested in nutrition and dietetic research for SCI patients. (section 1.3.2) Nevertheless, limited trials have been published in this field. To date, studies included the use of specific amino acid in healing pressure ulcers (Brewer et al, 2010: arginine supplement group had a significant shorter healing time when compared with control group: 10.5 $\pm$ 1.3 weeks v 21 $\pm$3.7 weeks, $p<0.05$)); the use of cranberry in preventing or treating urinary tract infection (Opperman et al, 2010: that no evidence to support the use of cranberry could prevent urinary tract infection) and weight management clinic for SCI patients (Chen et al, 2006; Wong et al, 2011; Rimmer et al, 2013: that structure weight management programme could help SCI patients to lose weight without compromising lean body mass). The trials results are summarised in Table 3.1

In this chapter, three original nutrition studies I tried in our SCI patients are discussed. These include the role of nutrition interventions using a range of different interventions to treat/prevent nutrition related complications, including using bariatric surgery to treat morbidly obese SCI patients (section 3.1), use of nutritional supplements in patients at malnutrition risk (section 3.2), and the use of probiotic Lcs to prevent AAD / CDI and AAD in SCI patients (section 3.3).

Table 3.1: Selected nutritional trials in spinal cord injured patients

Author Date Journal	**Objective**	**Research approach**	**Setting subject**	**sample size**	**data collected**	**Main results**	**Conclusion**
Brewer et al 2010 J Wound Care	To determine whether or not the use of an arginine-containing Nutritional supplement in pressure ulcer management	case-control study ulcer	SCI patients with pressure	35 18 intervention receiving 9g of arginine/d until full healing occurred 17 historical control	Ulcer healing time	intervention group had a significant shorter mean ulcer healing time when compared with control 10.5 $\pm$ 1.3weeks vs. 21 $\pm$ 3.7 weeks, $p<0.05$	Arginine may aid pressure ulcer healing in SCI patients
Opperman 2010 Spinal Cord	To determine whether the literature support the use of cranberry in Preventing or treating urinary tract infection (UTI)	Literature review	SCI patients	5 studies 436 patients 388 prevention of UTI 48 treating UTI	Incidence of UTI	3 studies found no significant effect 1 reported significant reduced biofilm load 1 reported fewer UTI	Mixed messages More rigorous clinical research is needed
Rimmer JH et al 2013 Am J Phy Med Rehab	Examined the effect of a 9 months remote telephone-based weight management program	RCT 3 arms	Adult with physical disabilities	102 24 SCI (9 control; 7 POWERS; 6 POWERS+)	Body mass index B-PADS score Physical activity, mins/week Nutrition score	Significant reduction in BMI; B-PADS score in POWERS group and POWERS+ group	Web-based remote coaching tool could be effective strategy for assisting over-weight adult with physical disabilities in maintaining or reducing weight

Author Date Journal	Objective	Research approach	Setting subject	sample size	data collected	Main results	Conclusion
Chen et al 2006 Spinal Cord	To assess the effectiveness of weight loss program	A single group uncontrolled trial	Adult with chronic SCI	16 chronic SCI patients	weight, body mass index skinfold, blood Pressure, lipid Profile, nutrient Intake, Psychosocial and Physical function	Significant reduction in body mass index, c anthropometric measurements and fat mass and improvement in diet quality and psychosocial and physical function	weight management clinic covering diet and exercise can help SCI individual to loose weight without compromising total lean body mass.
Wong et al 2011 Food Nutr Sci	To assess the effectiveness of weight management clinic trial	A single group uncontrolled	Adult with SCI	38 SCI patients	body mass index (BMI), mid-upper arm circumference (MUAC), triceps Skinfold (TSF), Mid arm muscle circumference, Blood pressure	Significant reduction in weight, BMI, TSF, systolic blood pressure.	Simple dietetic intervention can help SCI people to loose weight without compromising lean body mass.

3.1 Using oral nutritional supplements and vitamin and mineral supplements in SCI patients at under-nutrition risk

Medical nutrition can support individuals who cannot meet their nutritional requirements through a normal diet and / or help them to manage their condition. ONS are an essential part of a care pathway for those patients who are unable to support themselves through conventional nutrition, as well as being a clinically and cost-effective way to manage malnutrition when prescribed and monitored appropriately. (NICE, 2006b) SCI patients at risk of undernutrition may require dietary supplements such as oral nutritional supplements (ONS) and/or vitamin and mineral supplements (VMS) in order to correct their nutritional deficits. Opperman et al (2010) reported that the use of dietary supplements was high in SCI patients living in the community, but prior to 2013, there is limited literature reporting on the usage of supplements in an in-patient setting (SCI centre). Therefore, this section discusses whether nutritional supplements are used appropriately and Paper 1 is used to support this section. This study also aimed to assess food intake and to establish the prevalence of ONS and VMS usage in a representative sample of SCI patients from the NSIC; and to identify the characteristics of supplement users.

> **Paper 1:** Wong S et al. (2013) Nutritional supplement use in patients admitted to spinal cord injury centre, *J Spinal Cord Med* **36**, 645-651.

In an attempt to understand the utilisation of nutritional supplements in a SCI centre, I conducted a survey during February 2012 to access the food intake and use of ONSs in the NSIC. Sixty-seven of the 73 returned questionnaires included a food record chart. The meal intake data was collected via a food record chart (nil by mouth, less than half, half, more than half and all eaten), this was used in our previous study (Wong et al., 2012e) and the method had been validated by Hiesmayr et al in the European Nutrition Day study. (Hiesmayr M et al, 2006) Twenty-one of the 67 (31%) patients consumed three full meals a day. Approximately one in ten patients (7 of 67) ate less than half of their breakfast. Eighteen (26.8 %) patients were found to miss one or more meals. A significantly higher proportion of patients missed their evening meal rather than either breakfast or lunch. (28.3%, 10.4%, and 8.9% respectively, χ^2: 11.67, p =0.003) Snacks

were not provided to the great majority of patients (90%), and 31 (42.5%) of patients reported that they required assistance to eat.

I found that the use of a ONS and VMS was common in SCI patients in an in-patient setting (19.1% took an ONS and 46.5% a VMS), especially in older patients with an undernutrition risk (62.1%) (paper 1). The study also found a high prevalence of patients at risk of undernutrition using the SNST (47.9%) (Wong et al, 2012b), which is comparable with our previous findings (Wong et al., 2012a).

Undernutrition risk (SNST score ≥11, p=0.005), low serum albumin (<30g/L, p=0.012) and haemoglobin level (<11, p=0.043) were identified by the univariate logistic regression analysis as predictors of ONS usage.

Food is the treatment for most malnourished patients in hospital. I found that more than one-third (39.8%) of patients did not eat all the food served. Based on the UK's estimate of average requirements (EAR) and reference nutrient intake (RNI) (Department of Health, 1991), the deficit from a single missed meal would be equivalent to 300-600 kcal and 15-20g protein per day (16-33% of daily requirement). In addition, I found that snacks, which can contribute substantially (e.g. 400kcal, 6g protein, or ~15% of daily requirement), were not provided to the majority of patients (90%), indicating an important missed opportunity in SCI patients with additional nutritional requirements, such as pressure ulcers.

It is known that the prevalence of supplement use has increased over recent years in the UK. One of the largest studies of its kind, the UK National Dietary and Nutrition Survey (NDNS) (Henderson et al., 2003) assessed the UK general population's diet, nutrient intake and nutritional status via a continuous, cross-sectional survey. The NDNS reported that the number of respondents (n=1,724) taking supplements had increased, with 40% of women and 29% of men taking some form of dietary supplement in 2000/2001, compared to 17% of women and 9% of men in 1986/1987. The NDNS's were from the general population, our present study found a higher proportion of patients (50% of females and 45.7% of males) to be receiving a VMS, but the very fact of hospitalisation in SCI centre is obviously important. Increasing interest in normalising the micronutrient profile to improve health outcomes may also have

contributed, such as those with pressure ulcers. (NICE, 2005; Consortium of Spinal Cord Medicine, 2014)

The main limitation of our study was that only one day's food intake was assessed, and therefore assumptions have necessarily been made concerning food provision and net intake across a sometimes very prolonged hospital stay. It is expected a larger sampling of their food intake, than a single data collection, would provide stronger evidence to permit a more conclusive comparison with the national standards (Department of Health/Public Health England, 2014). However, I believe that it is highly probable, had we asked for longer diary data, that this would have adversely affected the response rate and itself diminished the generalisability of the conclusions for different reasons. Indeed, the uses of computer technology such as a pictorial food diary, weight food diary or smart phone applications are worthwhile to consider in future studies, but this is not applicable for the present study as this was a clinical audit.

I believed this was the first study formally reporting the pattern on the use of nutritional supplements in patients admitted to a SCI centre. This would make formal sample size calculation difficult. The sample size of the present study (n=73 out of 105 respond) are comparable with other published literatures. (Opperman et al, 2010; Wong et al, 2012) The present study survey (using a questionnaire) all patients admitted to the NSIC. Although I failed to perform sample size calculation, I believe the sample size represented a significant proportion of samples studied and comparable to other published studies. The percentage of female participants (19.2%) are similar to published literature (20% of SCI population were female, Ho et al, 2007) describing SCI population, suggesting the risk of non-response bias is small. The inevitable disabilities and the need for extended hospitalisation for acute care and rehabilitation in this group of patients renders extrapolation from generic hospital populations unwise. I believe that when compared with the published literature in SCI population, our sample size and response rate lends sufficient weight for our conclusions to be meaningful, that use of ONS and VMS is common amongst SCI population, if used appropriately in those at risk of under-nutrition, this could be a cost effective treatment. (Opperman et al., 2010).

Formal ethical permission to conduct the study was not required by the institution's review board as this was considered a clinical audit not involving active patient's participation.

In conclusion, the data from this study indicates that nutrient intake from hospital meals alone was often insufficient to meet patients' requirements and the use of ONSs and/or VMSs is likely to be beneficial to protect against and to treat both macro- and micro nutrient deficiencies and their related complications. Given that a high proportion of SCI patients will require assistance to eat (especially true for complete-tetraplegic patients), a further study should focus on whether additional feeding assistance could improve patients' food intake in this context.

3.2 Treating morbidly obese SCI patients

Obesity has become an unavoidable issue in the SCI population due to their enforced inactivity secondary to paralysis and subsequent change in body composition. (section 1.5.5) Whilst, limiting trials report the effectiveness of dietary modification in treating obesity (Chen et al, 2006; Wong et al, 2011), there was limited evidence in reporting how dietitians could contribute in treating morbid obese patients with SCI. This section will discuss how dietitians (as part of multidisciplinary team) could contribute in treating morbidly obese SCI patients using bariatric surgery (section 1.2.1 and 2.1). Paper 2 will be used to support this section.

Paper 2: <u>Wong S</u> et al. (2013) Morbid obesity after spinal cord injury: an ailment not to be treated? *Eur J Clin Nutr* **67**, *998-999.*

There are limited data on the rate of weight gain post SCI in the UK. An unpublished retrospective audit carried out amongst patients attending the outpatient clinic at the NSIC at Stoke Mandeville Hospital in 2007, showed that BMI increased by 2 kg/m^2 for males and 3 kg/m^2 for females after their SCI. When comparing this with the national survey data in the UK, (Henderson et al, 2003) patients with SCI (Gupta et al, 2006) seem more likely to become overweight and obese than the able-bodied population (60 % vs. 40 %). If I extrapolate from these estimated figures, it is predicted that at least 18,000 individuals with SCI may be overweight or obese in the UK.

Many of these conditions relating to obesity could be managed or prevented by appropriate nutritional interventions. In 2006, the NICE published guidelines on managing overweight and obesity. (NICE, 2006a) They recommended a reduction in energy intake, following the eat-well plate set by the government, (Food Standard Agency, 2002) and increased physical activity in conjunction with behaviour modification support for obesity management. Although weight loss has been advocated as a primary treatment strategy for the condition, to date, little high quality evidence exists to support this concept in patients with SCI. (section 1.5.5) To our best knowledge, only two trials has been published on the effect of dietary intervention in obese SCI individuals. Chen's study demonstrates that a carefully planned programme with restricted dietary intake and lifestyle modification could be an effective way to

reduce the body weight of obese SCI patients without compromising total lean body mass and overall health. (Chen et al, 2006) . I replicated Chen's (Chen et al, 2006) idea in NSIC and reported that a simple weight management clinic proved to be able to help overweight SCI individuals to lose weight without compromising lean body mass (Wong et al., 2011). The most important therapeutic finding of that study was that dietary intervention results in a clinically meaningful reduction of weight in overweight SCI individuals. Overall weight was reduced by 3.9 % in this study, a similar finding to that of the study by Chen and colleagues (3.8 %). (Chen et al, 2006) However, despite well-documented positive outcomes of bariatric surgery in ambulatory patients (NICE, 2006a), little information (paper 4) is available to guide both clinician and patients regarding the choice of bariatric (weight loss) surgery despite the UK NICE guideline recommends if all non-surgical interventions have been tried without success, then bariatric surgery could be an option to consider for patients who are morbidly obese. (NICE, 2006a)

In 2012, a morbidly obese patient with SCI underwent a gastric bypass surgery in a UK-based SCI centre. Following bariatric surgery, the patient (Subject A: paraplegia) showed gradual functional and anthropometric improvement, over a period of 7 months, and the patient's laboratory investigations were stable (Table3.2). Subject A was discharged with a prescription for a general multivitamin/mineral preparation, vitamin D and thiamine supplements. A structured follow-up dietary programme was put in place that included from the first two weeks (liquid diet), weeks 3-4 (puree diet), weeks 5-6 (soft-texture) and then he progressed to a normal diet from week 7. This was followed by 3 monthly, 6 monthly and annual follow-ups. For the first 7 months after surgery, subject A's total weight loss was 32.4 kg. He also showed further functional improvement at the 18 months follow up. From the baseline, at 7 months and 18 months: 6 minutes walking distance: 91, 144 and 190m and Berg balance score: 19 (2 elbow crutch), 51 (2 elbow crutch) and 44 (one elbow crutch) suggesting a positive clinical improvement (mobility) after bariatric surgery.

Two years after publishing the first report, in 2014, another SCI patient (Subject B: paraplegia) underwent bariatric surgery after reporting a weight gain from 126.5kg to 134.3kg after her SCI. Subject B was 44 years old and had sustained a T10 incomplete paraplegia, AIS: B due to a fall. A laparoscopic Roux-en-Y gastric bypass was

successfully performed in May 2013 and Subject B was also discharged with a prescription for a general multivitamin/mineral preparation, vitamin D supplements and thiamine supplements. For the first 7-months after surgery the total weight loss was 22 kg for Subject B, and again I successfully demonstrated that there were important clinical improvements in both functional outcomes (6 minutes walking distance, Berg balance score), anthropometric measurements (BMI, waist circumference, mid-upper arm circumference, triceps-skinfold thickness, mid-arm muscle circumference) and nutritional blood biochemistry (Lipid profile, blood glucose, HbA1c and other micronutrients) (Table 3.2).

The main limitation was that the evidence generated from a case report may not be generalisable to all SCI patients. This case study report was published as I realised that there were valuable lessons to be shared to other SCI clinicians. While the feasibility of implementing a multidisciplinary and long-term approach remains challenging (paper 4 and paper 5). The aim of this published case report was to demonstrate bariatric surgery could be an option for morbid obese SCI patients if all non-surgical interventions have been tried but unsuccessful. In addition, there is a potential for excellent control of measurement and complete description of the treatment when publishing. However, the prospective case report could suffer from the possibility that the case was managed differently from the usual care because of the desire to publish the results in the future. Ethics approval was not required as this was a case report, but written informed consent was obtained from patient and patient's consultant (M. Belci) before data collection and case report publication. I acknowledge the provision of bariatric surgery to all patients with obesity would not be practical; however, I should take into account the potential benefits of reducing/reversing comorbid conditions in order to ensure that bariatric surgery is as cost-effective an intervention as possible. I hope that the presentation of these cases will be useful to health-care professionals in dealing with similar cases. As discussed in section 2.2.1 and paper 4, the present study support the need for a practice guideline to help clinicians working in the SCI centres to manage obesity after SCI.

Table 3.2: Characteristics of subjects at baseline and 7 months after bariatric surgery

Parameters	Subject 1			Subject 2		
	Baseline	7-months after surgery	% change	Baseline	7-months after surgery	% change
Functional outcomes						
6-mins walking distance (m)	91	144	58	N/A non walker	N/A non walker	N/A non walker
Berg balance score	19	51	168	N/A	N/A	N/A
Anthropometric measurements						
Body mass index (kg/m^2)	59.8	49.8	16.7	48.3	40.8	15.5
Waist-circumference (cm)	165	146	11.5	N/A	N/A	-
Mid-upper arm circumference (cm)	53.8	42	21.9	32.9	29.1	11.6
Triceps-skin fold thickness (mm)	43.8	20	54.3	41.6	36.2	12.9
Mid-arm muscle circumference (cm)	40	35.7	10.7	32.9	29.1	11.5
Laboratory investigation						
Total cholesterol (mmol/L)	4.5	3.5	22.2	4.4	4.1	6.8
HDL-cholesterol (mmol/L)	1.1	1.2	9.1	1.4	1.4	-
LDL-cholesterol (mmol/L)	2.7	1.8	33.3	1.7	1.5	11.8
Triglycerides (mmol/L)	1.5	1.1	26.7	1.7	1.5	11.8
25 hydroxy-vitamin D (nmol/L)	20.6	33.9	64.5	30.8	68.9	123.7
Folate (ng/ml)	1.4	16.9	1107	6.4	9.4	46.8
Ferritin (ng/ml)	85	179	110	229	93	59.4
Vitamin B12 (pg/ml)	250	274	9.6	701	422	39.8
Abbreviations: HDL: High density lipoprotein; LDL: low-density lipoprotein						

3.3 Use of probiotics Lactobacillus casei Shirota in Preventing AAD/CDI in SCI patients

The evidence on the use of probiotic in preventing AAD / CDI in SCI patients is limited. (section 1.6.2) It appeared logical to assess the efficacy of probiotics in SCI patients because these patients are particularly vulnerable to infections and subsequently, AAD for many reasons. I therefore planned an open-labelled, randomised controlled trial to assess the efficacy of a commercial probiotic (LcS) for the prevention of AAD and CDI in adults with SCI. The objectives of this study were i) to determine the potential efficacy of LcS for the prevention of AAD and that caused by CDI for the duration of antibiotic use; and ii) to determine whether undernutrition-risk and the use of PPI are risk factors for AAD and CDI.

In this section the impact of diarrhoea in SCI patients and risk factors for AAD and CDI are discussed, together with the efficacy of using probiotics for preventing AAD and CDI in SCI patients. Papers 3 is used to support this section.

> **Paper 3:** **Wong S** et al. (2014) A *Lactobacillus casei* Shirota probiotic drink reduces antibiotic-associated diarrhoea in patients with spinal cord injuries: a randomised controlled trial. *Br J Nutr* **111**, 672-678.

I undertook an open-labelled RCT to assess the efficacy of a commercial probiotic (LcS) for the prevention of AAD and CDI in adults with a SCI. Ethical approval was granted by the NRES Committee (Ref: 10/H0605/19) and approval from the local institution's research board. Written informed consent was obtained from all patients before data collection and intervention. I randomized 158 SCI patients who required antibiotics; 76 received a commercially produced probiotic containing at least 6.5×10^9 live *LcS*, and 82 received no probiotic. The probiotics were administered once daily during the antibiotic treatment and for 7 days afterward. The SNST was used to assess patient's undernutrition risk (SNST score $\geq$11) at baseline, and 65% were found to be at risk for undernutrition. SCI patients (n=76) who took a commercial probiotic preparation of live LcS showed a significantly reduced risk of AAD when compared to

the control (no LcS) group (17.1 vs. 54.9%, p<0.001). Only one CDI (1.2%) was observed, and this was in the control group (n=82). Other than probiotic consumption, there were no significant differences between the two groups in nutrient intake or the number of antibiotics used. The use of proton-pump inhibitors and the occurrence of CDI were similar in the two groups. The strongest risk factors for antibiotic-associated diarrhoea were undernutrition (64.1% vs 33.3%; P < .01) and the use of proton-pump inhibitors (38.4% vs 12.1%; P = .022).

Our study also identified that poor appetite (nil by mouth), which can lead to under-nutrition, is an independent risk factor for AAD (Paper 3). This is in line with our previous work that a significant number of patients tend to miss one or more of their hospital meals, and this can contribute to a substantial loss of energy and protein. (section 3.2: Paper 1)

LcS was chosen as the probiotic for this study (Paper 3). To date there are no studies which have examined the effect of probiotics on the prevention of diarrhoea in SCI patients. Therefore it was logical to perform such an experiment using a commercially available probiotic at a relatively low cost. I acknowledge that this preparation is a 'commercial' probiotic but it is important to note that the results of the study were not influenced by commercial considerations.

There were some limitations associated with the un-blinded nature of the study. Due to the lack of a true placebo for this trial, the use of a heat-treated LcS was considered while planning this study but the production and quality control requirements for this were not possible. Heat treatment may not have killed all of the bacteria and may have led to undesirable taste changes which would have affected compliance within the control group. Furthermore, heat-treated bacteria can have some immune-modulatory effects. Therefore, I had little choice but to elect to have an open-label study and to use no intervention for the control group. It should be noted that a recent study has also used the same design (Dong et al., 2013).

Our study only collected nutrient intake as estimated by food record charts (nil by mouth, less than half, and half, more than half and all eaten), so it was not possible to perform individual dietary analysis. After taking an average of our hospital menu, I

compared patients' nutrient intake, including total energy, protein and dietary fibre, but could not find any statistical difference between the two groups. The probiotic product I chose had an energy value of 114.2 kJ (27.3 kcal). As described, although under-nutrition was common, I failed to identify any significant difference in nutrient intake in both groups. Therefore, I would not expect this extra 114.2 kJ to have made any significant impact, although this could be a potential limitation to our study.

Our study (Paper 3) reports an encouragingly low incidence of CDI, probably reflecting the adoption of the protocol recommended by the UK Department of Health, which focuses on strict hygienic practices, strict antibiotic use, restricted use of laxatives and PPIs, and isolation wards for confirmed and suspected CDI. However, the numerical data does not contradict a possible additional benefit from LcS.

I noted that our study found a higher incidence of AAD (36.1%) than in some previous reports (~25%) (Bartlett, 2002). This may be attributed to a longer follow up period (30 days) than in many of the other published trials (often only 7-14 days) (Hickson, 2011), as diarrhoea may occur up to two months after discontinuing antibiotic treatment (McFarland, 2000).

Furthermore, the nurses were not blinded to the group into which patients had been recruited but they were only aware if the patients were on LcS, and were not aware if patients had been recruited to the control group (routine care). All nurses were trained in using the Bristol Stool Scale and were only responsible for recording bowel motions according to the routine clinical procedure. The patients were not blinded to which arm they were being recruited into, and as lead researcher I too was not blinded to the study. The study outcome (occurrence of diarrhoea) was collected by the researcher according to an agreed definition from the clinical notes. In the absence of a placebo, I believe this approach is sufficiently robust.

Although this was not a double-blinded placebo RCT, there was an appropriate randomisation sequence, allocation concealment and the results were analysed on an intention-to-treat basis. Due to the limited number of trials in the literature, more research is required to determine if probiotics can reduce the incidence of AAD/CDI in SCI patients (Paper 3).

In conclusion, based on the present observation of a significant decrease in the incidence of AAD in patients with SCI, I can now consider LcS as a valid treatment option for the prevention of AAD in patients with SCI admitted to SCI centres. To confirm these findings and to evaluate the effectiveness of LcS in reducing the consequences of AAD/CDI, I am leading a multi-centre randomised placebo-controlled trial in the NSIC and Midland Centre of Spinal Injuries. (Efficacy of Consuming LcS In Spinal cord injury Patients (ECLISP); ISRCTN13119162; DOI 10.1186/ISRCTN13119162)

Chapter 4 Discussion

The research presented within this thesis sets out to achieve three key aims, the first to review and understand the vatiation in nutritional management in SCI centres. Secondly, to evaluate currently implemented nutrition interventions are based on sound research evidence and to discuss the potential limiting factors obstructing optimal nutrition practice in the SCI centres. Thirdly, to discuss whether nutritional interventions can improve SCI patient's outcomes and finally, make recommendations for further research in SCI patients.

In absence of a cure for SCI, research focuses on maximising a SCI patient's quality of life and reducing complications secondary to SCI. Since Sir Guttmann opened the first SCI centre in Stoke Mandeville Hospital and introduced modern multidisciplinary and comprehensive SCI management, a SCI patient's life expectancy has greatly improved (section 1.2.2). However, malnutrition, including under- and over- nutrition, becomes an apparent and unavoidable issue due to their enforced inactivity secondary to paralysis and subsequent change in body composition. Malnutrition is associated with increased morbidity, length of hospital stay and healthcare costs (section 2.3). Oral nutritional supplements (section 3.1), and artificial nutrition support are related to improved outcome, but have shown to mitigate the impact of patient's clinical outcome (section 1.5). The prescription of nutrition therapy by a dietitian can help in matching SCI patient's changing needs (section 1.4.2; section 3.3).

I discussed that nutrition management practices vary considerably by countries (UK, the Netherlands, Belgium and Republic of Ireland). Various limiting factors in implementing evidence based nutritional interventions in SCI patients were discussed (section 2.4). These are mainly related to the poorly defined clinical outcomes such as definition of under- and over- nutrition risk after SCI (section 2.4.2); the definition of diarrhoea (section 2.4.2) and inadequate knowledge in managing malnutrition (section 2.4.2). In addition, the lack of dietetic provision in SCI centres (section 1.3.3), will have a direct impact on availability of nutrition and dietetic expertise working in the SCI centre and to conduct clinical research. I have reported several organisational factors, including sub-optimal dietetics and meal provision and poor nutritional knowledge

within these centres that are thought to contribute to the insufficient use of NSTs and a lack of inconsistency in providing adequate nutrition support needed for SCI patients.

A key limitation to the survey studies (paper 4, 5, and 6) was the need to involve multidisciplinary staff's engagement. The survey required responses from professionals to provide representation of team decisions across centres. Reflecting the size of the various centres, it captured more respondents from the larger centres and fewer respondents from the smaller centres. This may have influenced the results towards the action of the larger centres. However, we provided possible rationales in that I believe this may still be considered representative of clinical practice; The completion of the survey were all above 65%, and comparable to other published literatures, reflecting a high level of cooperation and participation and; staff who were less familiar with the clinical management of SCI patients may have excluded themselves, limiting the generalisability of results.

The snowball methodology in selecting participants brings a potentially wide range of participants but does not allow for control over the number and type of participants, thus does not ensure representativeness of samples. (Faugier & Sargeant, 1997) Nevertheless, these surveys provide baseline data of current nutrition management of SCI patients in the UK, highlight differences in dietetic services and practice in the management of obesity in four European countries. The results from the survey studies strongly supported the need for SCI specific, evidence-based practice guidelines that can lead to improvement in care and patient health when implemented appropriately. These surveys could be repeated in future years to identify possible developments or progress in nutrition / obesity management in the UK.

Ideally, it would have been valuable to target specific staff in particular centres to participate in the survey, but it was not possible to identify specific staff working in these centres, especially if they work across other services, as is often the case for dietitians. This relied on the sample being self-selective. To minimise bias, the survey was disseminated through a number of multi- and uni- professional networks (ISCOS and MASCIP).

The summary data are presented in this thesis as means and standard deviations (s.d) or median and range unless otherwise indicated. Missing data is an important factor that reduces the study power and worsens the precision of estimates. (Kang, 2013) In this thesis, the nutrition risk score, occurrence of diarrhoea, CDI are the main outcomes. The clinical measures including SCI level, AIS grade, weight, height, blood pressure, blood biochemistry were collected on admission or during the clinic visit. Participants who did not attend had their clinical, nutritional or biochemistry data measured on recruitment and follow up will result in missing values. One way of dealing with missing data is omitting that data, i.e. complete case analyses. However, by omitting subjects with any missing data, the study power is reduced, and the precision of the estimates could be worse. In this thesis, missing data values were managed with multiple imputation using the SPSS (SPSS Inc, Birmingham, UK) Monte Carlo Markov Chain (MCMC) multiple imputation function. Thereafter, standard multiple imputation procedures were used to combine the multiple scalar and multivariate estimates quantities produced from the multiple analyses of the imputed datasets using SPSS version 19.0 (SPSS Inc, Birmingham, UK) to produce final results. Statistical and PhD supervisor (Dr. Shashi Hirani from University College London (2010), City, University of London (2011 onwards) was available throughout the study period and helped with the missing values imputation and the multivariate regression analysis. There were no missing data in respect of the primary end-points of the study in paper 3 (i.e. occurrence of AAD / CDI).

I decided formal ethics review is not necessary for some of our paper (survey paper 1, 4, 5 and 6) as these study is limited to secondary use of information previously collected in the course of normal care. The Health Research Authority also states the research ethic committee review is excluded when the study / research undertaken by staff within a care team using information previously collected in the course of care for their own patients and no patient identifiable data is used at any stage of the manuscript preparation. (The Health Research Authority, 2017) The above with discussed all participating centres in the UK and other European centre's review board that formal ethics permission was not required. Although I did not perform sample size for our survey papers (1, 4, 5 and 6) as I believe the sample size represent a significant proportion of samples studied and comparable to other published studies.

There have been numerous clinical trials investigating the efficacy of nutrition intervention in general patients, however, there were limited trials in SCI patient with majority of these only including a small number of patients. Our reports (case-report; observational studies (surveys), systematic review, and RCT) are therefore to be welcomed; however, the study has a number of methodologic flaws that may impact on the validity of results.

Without proper nutrition expertise in SCI centre, i.e. dietitian, the effectiveness of nutritional intervention will be difficult to implement and evaluate (such as use of probiotic in preventing AAD: section 3.3). SCI patients will receive poor evidence based clinical practice (section 2.4.4) ultimately, leading to poorer clinical outcomes and increased healthcare costs. An on-going initiative with the ISCOS, MASCIP and dietitians are underway to develop an evidence based clinical nutrition guideline in managing obesity after SCI. Through multidisciplinary collaboration, it is also expected to provide a practical solution to eliminate existing limitations, and disseminate new practice to clinicians working in the SCI centres.

By following this body of work, I now have the potential limiting factors obstructing the implementation of good nutritional care in SCI centres and better understanding of what nutrition screening tool should be used in SCI patients. In addition, a number of novel nutritional interventions / management approach were tested in SCI patients with a malnutrition-risk. The results of these studies indicated that it is possible to improve SCI patient's clinical outcomes if nutrition care is embedded appropriately in the SCI centre's policy.

The key themes in this thesis are summarised in table 1.1 and the research findings have had an impact on the SCI centre's practice. These include change in clinical practice, policy, organisational and development of new guideline. These are summarised in table 4.1. This body of work will support the implementation of the SNST across UK SCI centres. Through proper nutrition screening, at risk individuals will then be referred for detailed nutrition assessment and nutritional intervention by the dietitian.

Table 4.1 Research impact

Aim	Author Year Journal	Main outcomes	Research Impact	Clinical	Policy	Organisational	Guideline
3	1.Wong et al 2013 J Spinal Cord Med	Nutrient intake often insufficient to meet requirements and it likely to is beneficial to use ONS and or VMS To protect against and to treat . malnutrition	Further research on usage patterns of dietary supplements and potential health economic effect of dietary supplements in SCI patients is needed	√			
1, 3	2. Wong et al 2013 Eur J Clin Nutr	I reported the first morbidly obese SCI patients who has undergone gastric bypass surgery	Highlights that the provision of bariatric surgery as a option to consider if all non-surgical interventions have been tried Developemnt of clinical practice guideline: weight management guideline	√	√	√	√
1, 3	3.Wong et al 2014 Br J Nutr	LcS could be consider as a valid measure for the prevention of AAD in SCI patients.	To confirm the findings and evaluate the Effectiveness of LcS in preventing AAD and CDI, a larger placebo-controlled Trial in different geographical location is indicated.	√	√		
1, 2	4.Wong et al 2015 Spinal Cord	Limited knowledge among medical staff and variation in dietetic provision in SCI centre are probably barriers to effective weight management.	Establishing multi-disclipinary SCI-specific weight management guideline	√	√		√

Theme	Author Year Journal	Main outcomes	Research Impact	Clinical	Policy	Organisational	Guideline
1, 2	5.Wong et al 2015 Spinal Cord	The study highlighted staffing level varied across SCI centres and some are below professional recommendations	Further study is warranted to assess whether optimal dietetic resources could prevent nutrition related complications		√		√
1, 2	6.Wong et al 2015 Int J Prob & Preb	Stocking probiotics for the prevention of AAD / CDAD are not common. Definition of AAD / CDI are vary acroos SCI centres	Further effort in review the supporting Evidence for each probiotic before stocking. Systematic review on the effectiveness of probiotic in preventing AAD / CDAD in SCI patients is warranted.	√			
2	7.Wong et al 2015 Syst Rev	Systematic review protocol is published	To carry out systematic review on the effectiveness of probiotic in preventing AAD / CDAD in SCI patients	√			

Aim 1: To review and understand the variations in nutritional management in SCI centres from the perspective of staff and SCI patients.

Aim 2: To evaluate whether currently implemented nutrition interventions in SCI centres are based on sound research evidence, and potential barriers to good nutritional care in SCI centres.

Aim 3: To report three original studies (from a case study to a randomised trial) that explore how nutritional interventions may influence clinical outcomes in SCI patients.

4.1 Putting the results of this thesis into practice / research Impact

To improve the accuracy of identifying at-risk patients, I recommend that the SCI centre should use the SNST as a measure to screen for malnutrition. The research in this thesis has resulted in a change of practice in SCI centres in the UK and beyond. The ISCOS has now incorporated the SNST as the choice of nutrition screening tool. The SNST is now being choice of Nutrition Screening Tool in six SCI centres in the UK and Ireland. All patients on admission will be nutritionally screened by the SNST and at-risk individuals will be referred to a dietitian for nutrition assessment and nutrition risk is required to be repeated at regular intervals.

To help a SCI centre implement the use of SNST, I have developed a nutrition screening pathway for the centre's reference (Figure 4.1). The aim of this pathway is to make sure there is equitable treatment across the UK SCI centres and that nutrition care is provided to malnourished patients with SCI.

Locally, in the NSIC, I have successfully implemented the following projects within my practice. Since 2011:

- Made nutrition screening training mandatory for all nursing staff when they join the NSIC.
- Established a ward nutrition link nurse system, whereby ward dieticians provide in-depth training to the ward nutrition-link nurse who can then disseminate this to other clinicians involved in their care.
- Have ensured that equipment (e.g. hoist scale/bed scale) is available, as this is one of the major barriers for nutrition screening.
- To provide weekly and monthly update on nutrition screening compliance (performance indicator) to dietitians, ward and hospital management. (Wong et al, 2018)

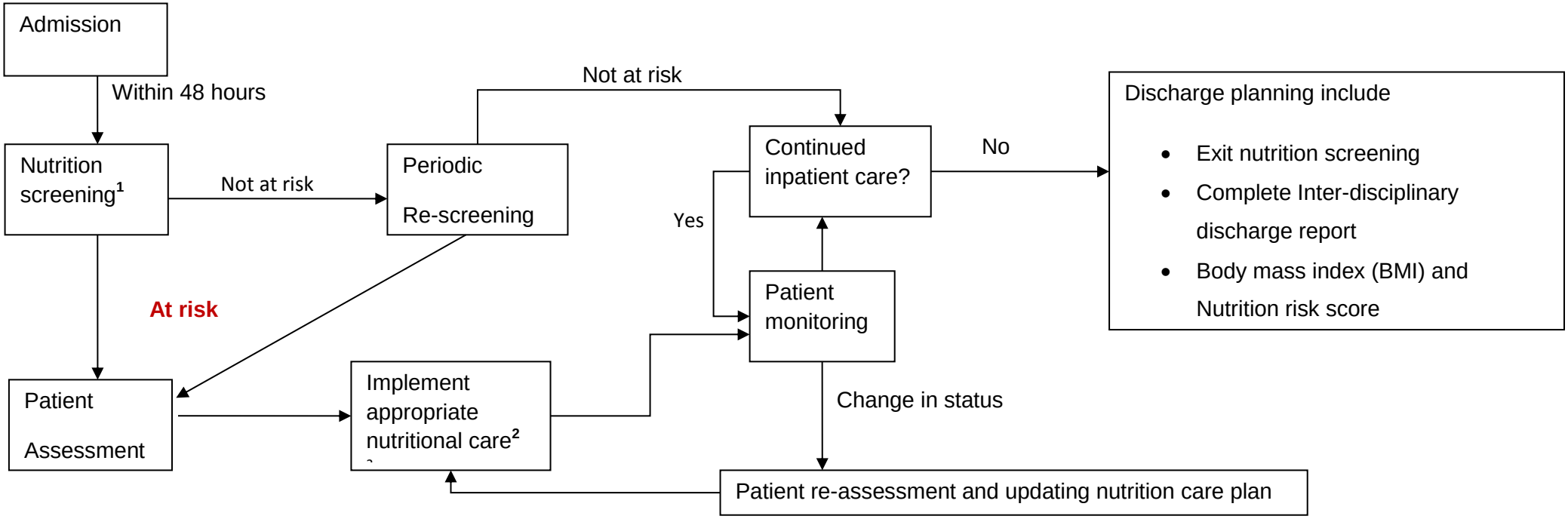
The results of this thesis and knowledge I acquired through my clinical practice and research have been shared with the national and international society for spinal cord injuries. I contributed in developing two sets of clinical guidelines (including the UK MASCIP older adult guidelines in 2009, and the ASIA pressure ulcer guidelines in 2014), and was invited to contribute in three book chapters (The British Dietetic

Association's Manual of Dietetic Practice in 2014, Advanced Nutrition and Dietetics in Nutrition Support in 2016, and the ISCOS textbook on the Comprehensive Management of Spinal Cord Injuries in 2015). In addition to publishing 18 peer-reviewed scientific journals, I have been asked to be a referee for 15 international peer-reviewed journals, including *Clinical Nutrition, British Journal of Nutrition, Journal of Spinal Cord Medicine, Spinal Cord, Clinical Rehabilitation, the British Medical Journal, and Archives of Physical Medicine and Rehabilitation*.

To address the complex nutritional needs of this unique population group, I proposed the Specialised Clinical Commissioning Group to review the need to include a dietitian within the core SCI care team and I am pleased to report that dietetics is now included as part of the essential team for a SCI centre's service within the NHS standard contract (NHS England, 2013).

The wide dissemination of my work has also led to nominations to sit on the nutrition sub-committee of the ISCOS and other national bodies, including the Neuroscience Specialist Group of the British Dietetic Association and MASCIP). In recognition of my outstanding scientific contributions to the ISCOS official journal, Spinal Cord, I was awarded with the prestigious Silver Medal Spinal Cord Prize by the ISCOS in September 2012. The ISCOS, which has a membership of over 1,000 clinicians and scientists from 87 countries, awards the Spinal Cord Prize every two years to encourage its younger members to submit original work for publication.

Following the publication of some of the research (paper 4; Wong et al, 2012e) included in this thesis, I have received invitations from local SCI consultants to address their staff training and also from the British Society of Rehabilitation Medicine and ISCOS to update their curriculum for nutrition for doctors in training. I am pleased to report that this has led to the inclusion of the first nutrition education module for doctors training in SCI, both locally and nationally.



[1] **Paediatric:** STMAP nutrition screening tool;
Adult: Spinal Nutrition Screening Tool
[2] **Nursing Nutrition care plan**: In IMS / for further instruction – "Nutrition Care Plans How to.pdf"
Frequency of re-screen / monitoring:
Acute floor: weekly
Rehab floor: monthly (routine screening); weekly if at-risk of malnutrition
Further reference can refer to
Guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children, NICE Clinical guideline 43, 2006;
NSIC Nutritional Pathway for children with Spinal Cord Injury;
Spinal weight management pathway (adult);
Prepared by Samford Wong on behalf of the NSIC nutrition group, Buckinghamshire Healthcare NHS Trust. Contact Tel: 01296315775 July 2012.

Figure 4.1: Nutrition pathway for the National Spinal Injuries Centre

At a local hospital level, I have established the Spinal Nutrition and Dietetics research group in 2012 with the aim of gaining insight into the effectiveness of an optimised nutrition state via nutrition intervention in SCI patients. At the NSIC, dietetics itself consists of 3.73 whole-time-equivalent (WTE) staff; there are 1.83 WTE dieticians working in clinical areas and 1.6 WTE research dieticians (Figure4.2). This department represents a very important contribution to the clinical and academic development of spinal dietetics in the UK SCI centre, both nationally and internationally. The group maintains a strong collaborative stance within the Buckinghamshire Healthcare NHS Trust (clinical researchers and basic scientists) where it has many productive links, including with commercial organisations. There are joint research programme collaborations with Higher Education Institutes and NHS organisations.

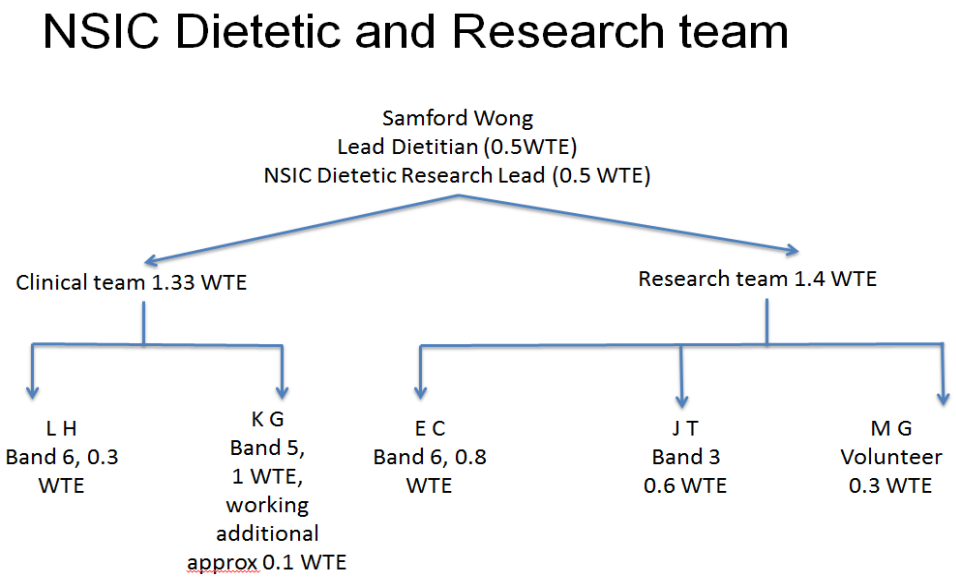


Figure 4.2: NSIC dietetic and research team organizational chart
WTE: Whole time equivalent.

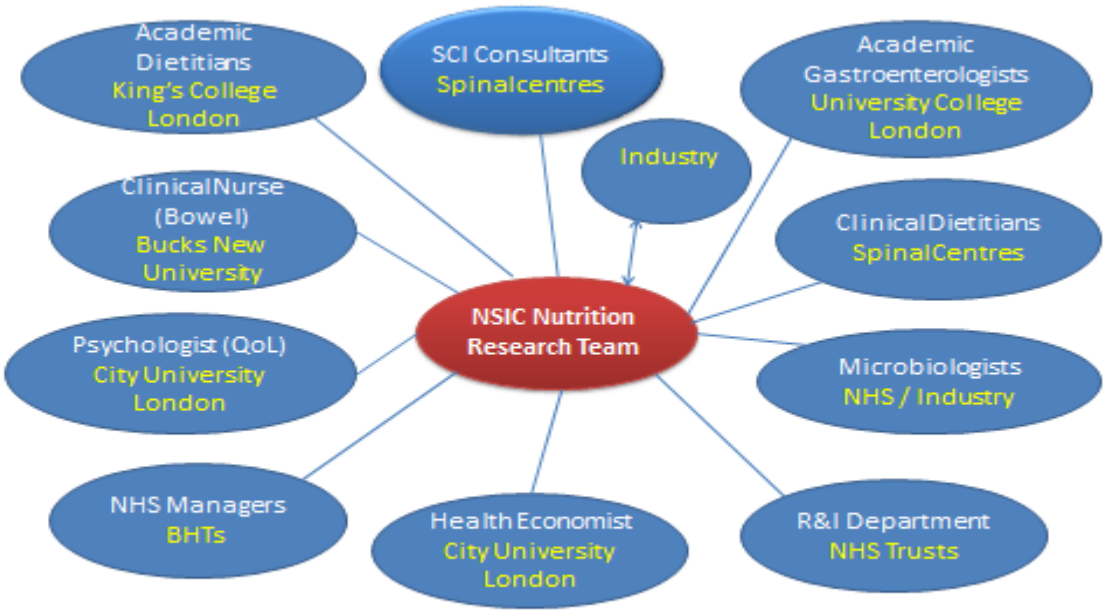


Figure 4.3: Collaborators diagram

Since 2007, I have produced over 65 peer-reviewed abstracts, and have been privileged to present my work at various national and international meetings. The research impact of my papers are summarised in Table 4.1 I have successfully completed six research projects, ranging from case report (paper 1), observation studies (survey paper 2, 4,5 and 6) to randomised controlled trials (RCTs) (paper 3) and systematic review (protocol paper 7) helping me to develop as an independent clinical researcher. Fig 4.4 and 4.5 summarises the seven papers submitted for assessment and it's critical appraisal summary (figure 4.5).

Figure 4.4: Summary of studies presented for assessment

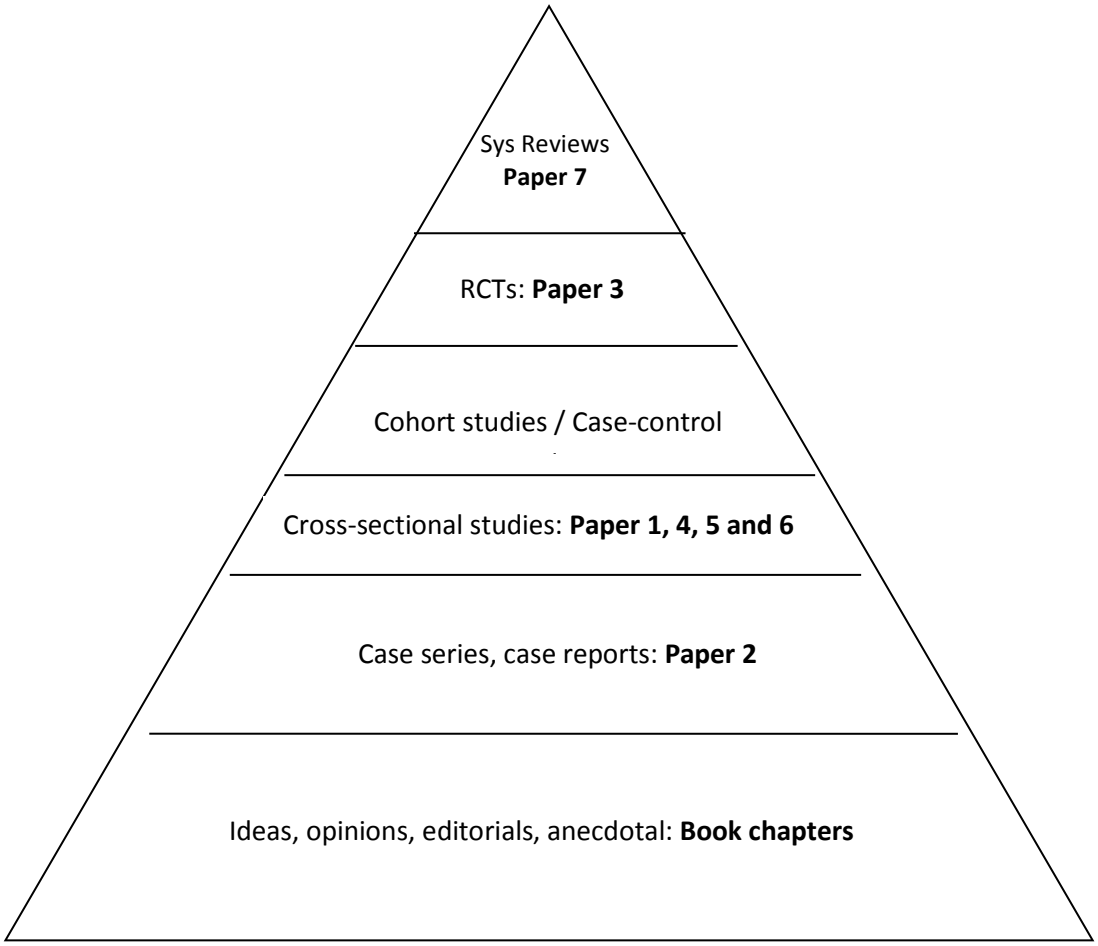


Fig 4.5: Critical appraisal summary of the 7 studies presented for assessment

	Paper 1: Supplement use	Paper 2: Bariatric surgery case report	Paper 3: Open label probiotic RCT	Paper 4: Obesity knowledge, Attidide and practice survey	Paper 5: Survey dietetic Resources in SCI centres	Paper 6: Survey of probiotic use in SCI centres for preventing AAD / CDI	Paper 7: Systematic review protocol for probiotic in preventing AAD / CDI
Study aims and objectives clear?	+	+	+	+	+	+	+
Study sample size justified?	-	NA	+	-	NA	-	NA
Sample taken from appropate population?	-	NA	NR	-	+	+	NA
Random sequence generation (selection bias)?	NA	NA	+	NA	NA	NA	NA
Measures to address non-responders?	-	NA	NA	NA	NA	NA	NA
Study methods for collecting data clearly described?	+	+	+	+	+	+	+
Were the groups similar at start of the trial?	NA	NA	+	NA	NA	NA	NA
Allocation concealment (selection bias)?	NA	NA	-	NA	NA	NA	NA
Were participants and researcher "blind" to treatment? (performance bias)	NA	NA	-	NA	NA	NA	NA
Were participants and researcher "blind" to outcome? (detection bias)	NA	NA	-	NA	NA	NA	NA
Incomplete outcome data (attrition bias)	NA	NA	+	NA	NA	NA	NA
Limitations of the study discussed?	+	+	+	+	+	+	+
Potential conflict of interest?	+	+	-	+	-	-	-
Was ethical approval or consent of participants attained?	NA	NA	+	NA	NA	NA	NA

+	probably low risk of bias
-	probably high risk of bias
NR	Not reported
NA	Not applicable

RCT: randomised controlled trial

SCI: spinal cord injury

AAD: antibiotic associated diarrhoea

CDI: Clostridium difficile infection

4.2 Conculsions and recommendations

The studies covered in this thesis were originally conceived and developed from the perspective of a clinician (S. Wong) working in a specialised SCI centre with a background awareness of mixed practice for nutritional management across both district general hospitals and teaching hospitals. Delayed admissions for those requiring specialist SCI interventions have increased over time in the UK due to growing demand and reduced bed capacity. Those with malnutrition often have correspondingly complex nutritional needs, requiring assessment and intervention by a specialist dietitian. Limited studies todate report the nutrition care of SCI patients in SCI centre. The primary research aim of the research was to review and understand the variations in nutritional resources and management in SCI centres in the UK and Republic of Ireland.

Chapter 1.4 provides a review of the literature on the use of probiotics in preventing AAD and CDI. These studies are predominantly from general patients, therefore providing limited generalisability to SCI patients. Therefore the second aim was to evaluate whether the current implemented nutrition practice / interventions in SCI centres are based on sound research evidence and to evaluate the potential barriers to good nutritional care in SCI centres. I found variations in clinical management of AAD / CDI; definition of malnutrition risk and diagnostic criteria of AAD / CDI in SCI patients across SCI centres. This was explored through a mailed survey of clinical staff working in SCI centres reported in chapter 2.4. The following study, chapter 3,3, reported the effectiveness on the use of a probiotic (LcS) in preventing AAD / CDI. In addition, a systematic review & meta-analysis protocol was devised to assess whether probiotics could prevent AAD / CDAD in SCI patients. The data from these studies would contribute to whether probiotic have a role in preventing AAD / CDI in SCI patients.

The third and final aim of this thesis was to explore how nutritional interventions may influence clinical outcomes in SCI patients. Chapter 3.1 describes the use of nutritional supplements in patients at risk of undernutrition using a SCI-specific nutrition screening tool, the SNST. Chapter 3.2 describes the first UK bariatric surgery case in morbid obese SCI patients as a way to generate body weight loss who failed all other non-surgical interventions. Chapter 3.3 reports the effectiveness of a commercial probiotic, LcS in preventing diarrhoea associated with antibiotics and CDI. The data from these

three studies would contribute evidence in the literature and would help to guide further recommendations for SCI management.

The results from the studies presented in this thesis, have answered some of the questions addressed, but have also highlighted other issues that require further investigations. In this section, I will outline some possible future research directions.

Research directions

Malnutrition including both under- and over-nutrition has substantial adverse effects on health, disease and well-being in patients with SCI. Yet despite good evidence that specific efforts to correct the problems improve health outcomes, it appears that there are recurrent inconsistencies in the implementation of malnutrition screening. When malnutrition goes unrecognised and untreated, malnutrition also have a substantial impact on the health economy with increased demands on health services such as out of hours services and increased rates of transition across pathways of care. To tackle malnutrition after SCI effectively and efficiently, our body of work has recommended that malnutrition (under- and over-nutrition) risk needs to be screened, identified and managed appropriately. Further effort could focus on evaluating whether using group setting education rather than individual consultation could be a strategy to improve efficiency of service, particularly in the rehabilitation phase and weight management patients as this could help alleviate time and funding pressure. The development and implementation of NSTs for assessing nutrition-risk in SCI patients will facilitate a variety of projects, ranging from clinically based nutrition interventions studies to health economic studies, including an investigation of the cost of malnutrition in SCI patients. Furthermore, it is also indicated that the use of ONS and other evidence-based nutrition interventions should be promoted and recognised as an integral part of the management of SCI patients that require nutrition support, alongside food.

After SCI, patients are particularly vulnerable to infections and subsequently, AAD for many reasons. Probiotic use could be a cost-effective intervention to prevent AAD, however, as probiotic effect is strain-specific, the effect of other strains is not known.

A multi-centre study is underway to investigate the efficacy of probiotic *LcS* in preventing AAD / CDI in SCI patients using a randomised double-blinded, placebo-controlled approach.

Without proper guidelines and training, it is unlikely that healthcare staff will have sufficient knowledge to identify at-risk patients or to offer appropriate treatment. Our work reinforces the need to consider collaborating with national professional bodies to develop SCI-specific weight management guidelines which include clear guidance on optimal dietetic service provision within the SCICs. In response to the need to develop specific clinical guidelines for SCI medical staff, the UK MASCIP has commissioned a multidisciplinary guidelines group to provide up-to-date information on overweight and obesity in SCI adults based on a systematic review of the literature.

Conclusions

This thesis has reported a range of studies using different methodologies from case studies to RCT and systematic review. (Figure 4.4) Although it has not included cohort/case-control studies, these have been described in my previous research work (Wong et al., 2011; Wong et al., 2012a). The body of work has demonstrated that it is possible to improve a SCI patient's clinical outcomes if nutrition care is embedded in the SCI care-pathway. It has also raised a number of questions, provided a platform for subsequent research, and has pointed to several areas where further research could productively be directed to improve clinical practice within SCI care.

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Appendix 1: Full Text Articles for Assessment

Paper 1:

Wong S, Graham A, Green D, Hirani S, Grimble G & Forbes A (2013) Nutritional supplement use in patients admitted to spinal cord injury centre, *J Spinal Cord Med* 36, 645-651.

Statement of contribution

Paper 2:

Wong S, Forbes A, Barnes T, Coggrave M, Pounds-Cornish E, Appleton S & Belci M (2013) Morbid obesity after spinal cord injury: an ailment not to be treated? *Eur J Clin Nutr* 67, *998-999.*

Statement of contribution

Paper 3:

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Paper 4:

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Statement of contribution

Paper 5:

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Paper 6:

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Paper 7:

Wong S, Saif M, O'Driscoll J, Kumar N, Smith E, Roels E, van Nes I, Faber W, McKwown E, Hirani SP, Jamous A (2015) Survey on the use of probiotics in preventing antibiotic associated diarrhoea and Clostridium difficile associated diarrhoea in spinal cord injuries centres. *Int J Probiotics and Prebiotics* 10, 85-90.

Statement of contribution

Appendix 2: Supporting Evidence: Additional Papers Published by S. Wong

1. Wong S, Graham A, Grimble G & Forbes A (2011) Spinal Clinic for Obese Out-patient Project (SCOOP) – a 1 year report. *Food Nutr Sci* **2**, 901-907 DOI: 10.4236/fns.2011.28123

2. Wong S, Derry F, Grimble G & Forbes A (2012) How do spinal cord injury centres manage malnutrition? A cross-sectional survey of 12 SCIC in the UK and Ireland. *Spinal Cord* **50**, 132-135. DOI: 10.1038/sc.2011.118

3. Wong S, Derry F, Jamous A, Hirani SP, Grimble G & Forbes A (2012) The prevalence of malnutrition in spinal cord injured patients - a UK multicentre study. *Br J Nutr* **108**, 918-923. DOI: 10.1017/S0007114511006234

4. Wong S, Derry F, Jamous A, Hirani SP, Grimble G & Forbes A (2012) Validation on the Spinal Nutrition Screening Tool (SNST) in patients with spinal cord injuries (SCI) – result form a multicentre study. *Eur J Clin Nutr* **66**, 382-387. DOI: 10.1038/ejcn.2011.209

5. Wong S, Graham A, Hirani SP, Grimble G & Forbes A (2012) Profile and prevalence of malnutrition in children with spinal cord injuries - assessment of the Screening Tool for Assessment in Paediatrics (STAMP). *Spinal Cord* **50**, 67-71. DOI: 10.1038/sc.2011.139

6. Wong S, Derry F, Graham A, Grimble G & Forbes A (2012) An audit to assess awareness and knowledge of nutrition in a UK spinal cord injuries centre. *Spinal Cord* **50**, 446-451. DOI: 10.1038/sc.2011.180.

7. Wong S, Graham A, Green D, Hirani SP, Grimble G & Forbes A (2012) Meal provision in a UK National Spinal Injury Centre – a qualitative audit of service users and stakeholders. *Spinal Cord* **50**, 772-777. DOI: 10.1038/sc.2012.43

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10. Wong S, Santullo P, O'Driscoll J, Jamous A, Hirani SP, Saif M. (2017) Use of antibiotic and prevalence of antibiotic-associated diarrhoea in patients with

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11. Wong S, Santullo P, Hirani SP, Kumar N, Chowdhury JR, Gracia-Forcada A, Recio M, Paz F, Zobina I, Kolli S, Kiekens C, Draulans N, Roels E, Martens-Bijlsma J, O'Driscoll J, Jamous A, Maif M (2017) Use of antibiotics and the prevalence of antibiotic-associated diarrhoea in patients with spinal cord injuries: an international, multicentre. *J Hosp Infect* **97**, 146-152. 10.1016/j.jhin.2017.06.019

12. Johnston BC, Lytvn L, Mertz D, Lo C K-F, Allen SJ, Wang D, Szajewska H, Miller M, Ehrhardt S, Sampalis J, Duman DG, Mozzoni P, Colloi A, Lonnermark E, Selinger CP, Wong S, Plummer S, Hickson M, Pancheva R, Hirsch S, Klarin B, Goldenberg JZ, Wang L, Mbuagbauw L, Foster G, Thabane L (2018) Microbial preparations (probiotics) for the prevention of Clostridium difficile infection in adults and children: an individual participant data meta-analysis. *Infection Control and Hospital Epidemiology* **39**, 771-781. Doi: 10.1017/ice.2018.84

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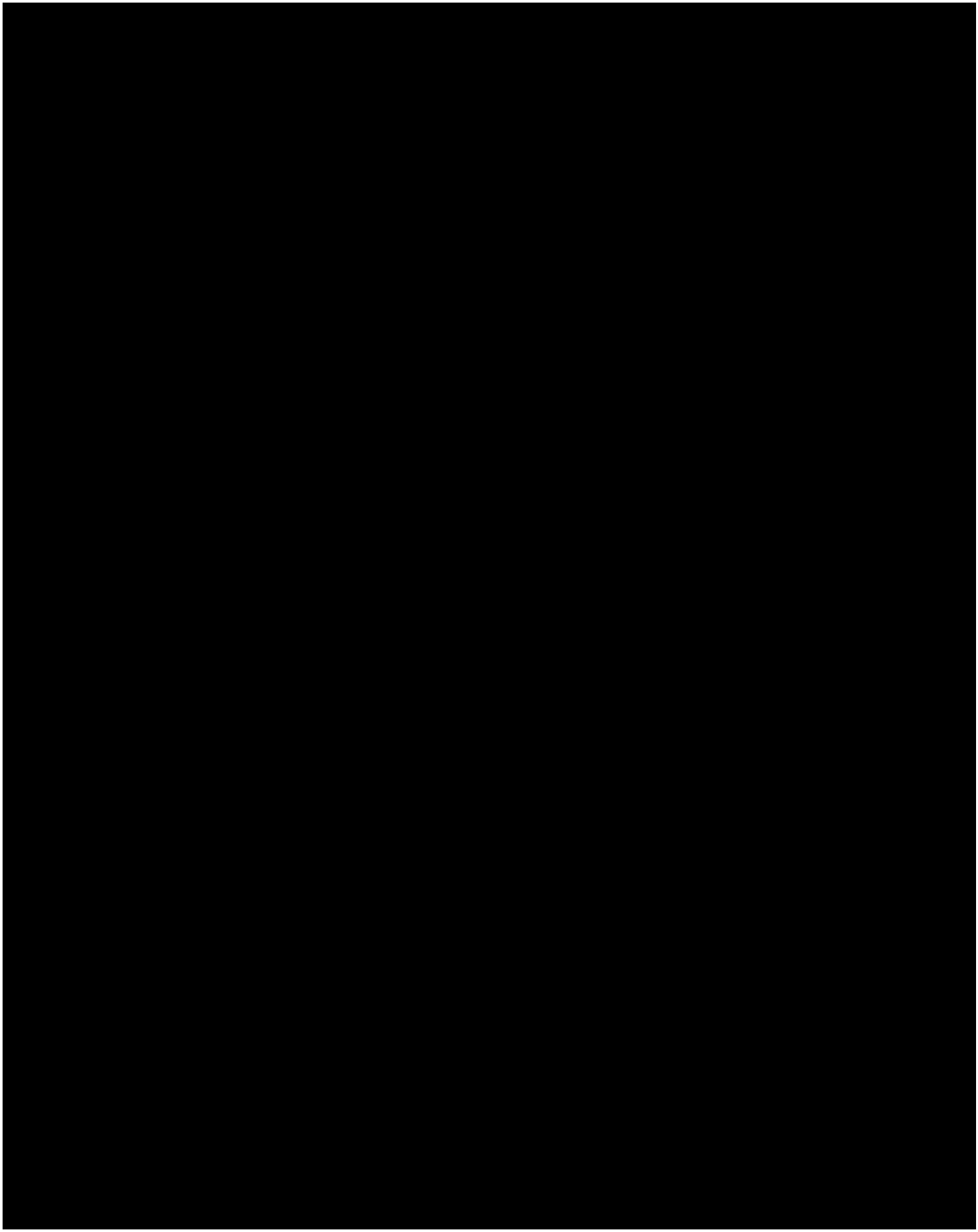

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