Prevention of pneumonia after stroke: The effect of metoclopramide on aspiration and pneumonia in stroke patients fed via nasogastric tubes

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Abstract

Introduction: Pneumonia contributes significantly to the morbidity and mortality in stroke patients, especially those fed via nasogastric tubes.

Methods: This project was conducted in two steps;

1. A randomised controlled trial: The efficacy of prokinetic agent metoclopramide was tested in a double-blind randomised controlled trial. Acute stroke patients with no pneumonia needing nasogastric feeds were randomized to 10 mg metoclopramide or placebo three times daily via the nasogastric tube for 21 days or until feeds discontinued. Participants were examined daily for clinical evidence of pneumonia.
2. A secondary analysis of data collected for the diagnosis of pneumonia. This was performed to identify early diagnostic markers of post-stroke pneumonia.

Results:

1) For the MAPS study 60 patients (mean age 78 years, mean NIHSS 19) were randomized, 30 in each group. Pneumonia was diagnosed in 26/30 and 08/30 in placebo and treatment group respectively ($p < 0.001$).

2) Signs and symptoms of 47 radiologically confirmed pneumonia revealed that hypoxia, tachypnoea and inspiratory crackles were the most consistent signs in early pneumonia and pyrexia, cough, and purulent sputum were less commonly observed. CRP of 40 mg/l had the best predictive value for early diagnosis of post-stroke pneumonia.

Conclusion: Treatment with metoclopramide treatment was associated with a significant reduction of aspiration and pneumonia. However, the incidence of pneumonia in the control

gourp was very high and may have led to a false positive result. The findings of this study should therefore be confirmed in a larger study. A raised CRP of 40 mg/l or above was a senditive and specific diagnostic marker for post-stoke pneumonia.

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List of abbreviations

A&E	Accident and Emergency
AF	Atrial Fibrillation
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
CCF	Congestive Cardiac Failure
CT	Computer Tomography
COPD	Chronic Obstructive Pulmonary Disease
CRP	C – reactive proteins
CVA	Cerebro Vascular Accident
EPR	Electron Paramagnetic Resonance
ESR	Erythrocyte Sediment Rate
GCS	Glasgow Coma Scale
H-2	Histamine 2
Hb	Haemoglobin
ICH	Intra Cranial Haemorrhage
IDDM	Insulin dependent Diabetes Mellitus
IHD	Ischaemic Heart Disease
I l	Interleukin
LACS	Lacunar Syndrome
LREC	Local Research Committee
MAPS	Metoclopramide on Aspiration and Pneumonia in Stroke study
MCA	Middle Carotid Artery
MRI	Magnetic Resonance Images
MRS	Modified Rankin Score
NG	Nasogastric
NHS	National Health Services

NIDDM	Non Insulin dependent Diabetes Mellitus
NIHSS	National Institute of Health Stroke Scale
NICE	National Institute of Clinical Excellence
OCSP	Oxford Community Stroke Project
PACS	Partial Anterior Circulation Syndrome
PaO_2	Partial pressure of Oxygen in arterial blood
$PaCO_2$	Partial pressure of Carbon dioxide
PE	Pulmonary Embolism
PEG	Percutaneous Endoscopic Gastroscopy
PET	Positron Electron Tomography
PO_2	Partial pressure of Oxygen
POCS	Posterior Circulation Syndrome
PPI	Proton Pump Inhibitor
RCT	Randomised Controlled Study
ROC	receiver operating characteristic
SA	Sleep Apnoea
SALT	Speech and Language Therapy
SD	Standard Deviation
SSS	Scandinavian Stroke Scale
TACS	Total Anterior Circulation Syndrome
TIA	Transient Ischaemic Attack
UTI	Urinary Tract Infection
WHO	World Health Organization

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Publications and Presentations from the work undertaken for the PhD

Publications

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(2) Warusevitane A, Karunatilake D, Roffe C. Effect of metoclopramide on survival, aspiration, hypoxia and pneumonia in acute stroke patients fed via nasogastric tubes. Cerebrovascular Disease 2013;35(Supple 3):13-4.

(3) Warusevitane AB, Karunatilake D, Lally F, Roffe C. Does metoclopramide reduce pneumonia in acute stroke patients on nasogastric feeds? International Journal of Stroke 2012 Dec;7(Supple 2):10.

(4) Warusevitane A, Karunatilake D, Sim J, Roffe C. High C-reactive protein is a better predictor of pneumonia after stroke than raised white cell count. Cerebrovascular Disease 2014;37(Suppl 1):703.

(5) Warusevitane A, Karunatilake D, Lally F, Roffe C. Diagnosis of pneumonia in acute stroke patients: is it different to any other pneumonia. Cerebrovascular Disease 2014;37(Suppl 1):705.

Presentations

(1) Oral presentation at European Stroke Conference London 2013. Effect of metoclopramide on survival, aspiration, hypoxia and pneumonia in acute stroke patients fed via nasogastric tubes.

(2) Oral presentation at UK Stroke Forum at Harrogate UK 2012. Does metoclopramide reduce pneumonia in acute stroke patients on nasogastric feeds?

(3) Poster presentation at European Stroke Conference Nice, France 2014. C. High C-reactive protein is a better predictor of pneumonia after stroke than raised white cell count.

(4) Poster presentation at European Stroke Conference Nice, France 2014. Diagnosis of pneumonia in acute stroke patients: is it different to any other pneumonia.

(5) Poster Presentation at 2nd Heart & Brain International Conference at Paris 2014. Effect of patient's positions and activity on witnessed aspiration in stroke patient on nasogastric feeds.

(6) Presentation at Stroke and Rehabilitation workshop at Institute of Science and technology in Medicine, Keele University Staffordshire, January 2014. Effect of metoclopramide in the incidence of aspiration and pneumonia in acute stroke patients who are on nasogastric feeds.

(7) Presentation at West Midlands Research Network, June 2013. Effect of metoclopramide on survival, aspiration, hypoxia and pneumonia in acute stroke patients fed via nasogastric tubes.

Chapter 1 Introduction

1.1 Project background

Stroke is the third leading cause of mortality in England and Wales[1;2]. The severity of the initial cerebral injury and intra-cranial complications such as cerebral oedema due to large cerebral infarction, and the effects of haemorrhage are responsible for mortality within the first few days. After the first few days medical complications such as aspiration pneumonia, pulmonary embolism, urinary tract infection, and urosepsis contribute significantly to mortality and morbidity[3]. Amongst these pneumonia is the leading cause of post-stroke morbidity and mortality and is directly related to post-stroke dysphagia[4-6].

There are three stages of swallowing, oral, pharyngeal and oesophageal, and these are all affected by stroke[7]. A high incidence of dysphagia following acute stroke has been demonstrated in numerous studies, with an incidence of 25 to 70% depending on the study population and the criteria used[8;9]. Several studies have shown that aspiration and pneumonia are common complications in dysphagic patients following acute stroke and contribute significantly to morbidity, length of stay, poor stroke outcome and mortality[10;11]. Patients with severe dysphagia or patients too drowsy to assess are maintained nil by mouth to prevent aspiration and nasogastric tube remains the main method of feeding in these patients. However, aspiration and pneumonia remains a common complication even when the patients are maintained nil by mouth and fed via nasogastric tubes[12-14]. This is partly due to continuing oropharyngeal dysfunction and aspiration in the presence of the nasogastric tube[15-18] and partly due to dysfunction of the lower oesophageal sphincter and the stomach following severe stroke resulting in gastroparesis, increased gastric volume, and regurgitation[19-21]. Presence of a nasogastric tube in the already dysfunctional lower

oesophageal sphincter increases regurgitation. Neutralisation of gastric acid by nasogastric feeds, migration of Gram negative bacteria from the oropharynx and biofilm formation on the nasogastric tube result in colonisation of the gastric contents by pathogenic bacteria[22-24]. Micro-aspiration of regurgitated infected gastric contents contributes to the development of pneumonia[17;25].

Several studies[26-29] have been done to assess the efficacy of different agents in reducing the incidence of pneumonia in post-stroke patients with varying success. Though some studies have been performed to assess prevention of pneumonia in patients fed via nasogastric tubes, limited information is available in stroke patients fed via nasogastric tubes. Metoclopramide is a dopamine 2 receptor antagonist of the upper gastrointestinal tract and is a commonly used prokinetic agent[30]. It increases lower oesophageal sphincter tone, improves gastric contractions, and forward peristalsis of the stomach which should in theory reduce reflux, micro-aspiration, and pneumonia[30].

The aim of this chapter is to provide a comprehensive background to stroke and the concomitant relationship with dysphagia, aspiration, and pneumonia, and the effect of a nasogastric tube on lower oesophageal sphincter and aspiration. In addition, methods currently available to prevent pneumonia in critically ill patients and patients fed via nasogastric tubes will be reviewed. Finally, actions of metoclopramide and mechanisms of how regular treatment with metoclopramide would reduce the incidence of pneumonia in acute stroke patients fed via nasogastric tubes will be explored.

1.2. Stroke

1.2.1. Definition and aetiology

The World Health Organisation defines stroke as a neurological deficit of sudden onset resulting in focal rather than global dysfunction, with symptoms lasting 24 hours or more or result in death within 24 hours and after adequate investigations the symptoms are secondary to a non traumatic vascular lesion[31]. If neurological symptoms resolve completely within 24 hours of onset clinical presentation is defined as a transient ischaemic attack (TIA)[32]. Crescendo TIAs are TIAs which occur with increasing frequency and duration or several episodes occurring within few days[33].

Cerebral infarction and primary intra-cerebral haemorrhage are the two most common causes of stroke[34]. Cerebral infarction occurs when an area of the brain is deprived of its blood supply due to an occlusion of its arterial blood supply leading to death of neurones secondary to lack of oxygen. Atheromatous carotid or vertebral artery occlusion, atheromatous arterial thrombosis within cerebral vessels or an arterial embolus from a distal site can lead to this vessel occlusion resulting in cerebral ischaemia and infarction[34]. Intracranial perforating striate small vessel disease, mainly secondary to hypertension, can lead to lacunar infarcts deep in the brain especially in the basal ganglia, internal capsule or pons. These lacunar infarcts are small (less than 1.5cm in diameter) and can be multiple. Slow accumulation of such infarcts can give rise to vascular dementia[34]. Rare causes of ischaemic stroke include hyper-coagulable status, autoimmune vasculitis, bacterial endocarditis and anti-cardiolipin antibody syndrome[34].

Primary intracranial haemorrhage accounts for 8% of strokes[35]. Cerebral haemorrhage is caused by rupture of micro-aneurysms and degeneration of walls of small blood vessels of small deep penetrating arteries. In older normotensive patients weakening of cerebral blood vessels due to cerebral amyloid angiopathy can give rise to cerebral bleeds [34]. Less common causes are bleeding into a cerebral tumour or bleeding from an arterio-venous malformation. Rupture of a berry aneurysm usually produces a subarachnoid haemorrhage[35].

1.2.2. Symptoms and classification

Common presenting symptoms of stroke are unilateral weakness with or without sensory impairment, speech disturbances or visual defects. Due to the sudden nature of the symptoms, either the patient or an observer can usually give an exact time of the disease onset. Sometimes the patient first notes symptoms of a stroke on waking in the morning (wakeup stroke) or stroke signs will be evident on examination of a patient who is brought into the hospital due to symptoms such as acute confusion, fall or collapse in the community[36].

Depending on the signs and symptoms stroke can be classified clinically into four distinct syndromes as defined by the Oxfordshire Community Stroke Project,[37] e.g. Total Anterior Circulation Syndrome (TACS), Partial Anterior Circulation Syndrome (PACS), Lacunar Syndrome (LACS), and Posterior Circulation Syndrome (PoCS). The classification provides a good estimate of the affected territory, prognostic factors such as survival, residual disability and risk of recurrence. TACS strokes, account for 15% of all strokes, and have a mortality of 50% within the first month, and 50% of survivors are dependent at 12 months following stroke. PACS strokes account for 35% of all strokes. Lacunar strokes and posterior circulation strokes are associated with 10% to 15% mortality within the first

month of stroke and 20% to 40% of the survivors will be dependent after 6 months[37]. These stroke types are explained in more detail in appendix 1.

1.2.3. Impact of stroke on the individual and society

Each year 110,000 people in England and Wales have their first stroke and 30,000 people go on to have further strokes[38]. As people live longer, stroke is the most common cause of disability in the world and is the third largest cause of death in the United Kingdom[1;2]. Stroke is also the leading cause of major disability in England and Wales accounting for around 53,000 deaths each year with over 450,000 people who are disabled due to stroke[39;40]. Stroke patients occupy up to 20% of all acute hospital beds, 25% of the long stay beds and about 40% of nursing home beds[41]. In Staffordshire, a district of around 500,000 people, there are approximately 1000 new cases of stroke per year. Eighty percent of stroke patients are admitted to hospital with an average stay of four weeks[42].

Strokes are not only devastating to the individual involved but also to their families, carers and society. In the United Kingdom there are about 110,000 new strokes each year which are responsible for about 5% of the total National Health Services budget[43]. In the United States almost 800,000 people experience a new or recurrent stroke each year which accounts for 5.5% of all deaths and a cost of $73 billion[42]. Compared with other medical and psychological problems, stroke is associated with the highest odds of incurring a wide range of disabilities which costs around £8.9 billion to the National Health Service and society every year in lost productivity and in formal care[44;45]. The extent of recovery from stroke is not only determined by the extent of neurological defects at stroke onset, but also by post-stroke complications such as hypoxia, infections, thrombosis and malnutrition[4]. This makes post-stroke care such as reducing infections, early mobilisation, and improving

nutrition as important as hyper acute stroke care such as thrombolysis and other interventional procedures.

1.3. Dysphagia

1.3.1. Neurological control of swallowing

Dysphagia is a disruption to normal swallowing. Central control of swallowing is organised at two levels involving both the cerebral cortex and the brainstem. The primary brain-stem swallowing mechanism is thought to originate from the medulla as a pre-programmed reflex. The swallowing sequence can be activated even after the removal of cortical and sub cortical areas above the brain stem[46]. The swallowing centre acts as a "Central pattern generator" and is localised in the medulla, with two levels of interoperation, namely the *Nucleus Tractus Solitarius* and the *Nucleus Ambiguous* with its surrounding reticular formation. Both have sensory inputs from cerebral and peripheral pathways with delivery of the final swallowing sequence by efferent cranial nerves[47]. These impulses reach the muscles of mastication via the mandibular branch of the trigeminal nerve and the facial nerve, tongue movements via hypoglossal and first two cranial roots and muscles of the palate, pharynx and larynx by the vagus nerve[48]. Sensory feedbacks are carried along in the 9^{th}, 10^{th} and trigeminal cranial nerves and terminate in the spinal nucleus of the trigeminal nerve and the dorsal region of the brain stem swallowing centre[49]. They also receive sensory input from the higher cortical areas. The *Nucleus Tractus Solitarius* is involved in the initiation of swallowing and the organization of the swallowing sequences. The reticular formation surrounding the *Nucleus Ambiguous* serves primarily as a connecting pathway to various motor neurons coordinating the swallowing sequelae. These two regions are bilaterally represented in the brainstem and are interconnected extensively. This allows either side of the brain the ability to coordinate the pharyngeal and laryngeal phases

of swallowing. Afferent fibres from the peripheral areas enter into the afferent receptor portals of this swallowing centre and synapse on "premotor neurons". This information can initiate or modify ongoing motor activity of the swallowing process [50],[51].

While reflexive swallowing depends on the swallowing centres in the brainstem, voluntary initiation of swallowing involves corresponding motor areas of the cerebral cortex. Cortical sensory and motor areas of swallowing regulation influence mastication and swallowing via cortico-bulbar pathways. They receive afferents from the receptors of the gastro-intestinal tract[52]. In addition reflexive swallowing also show bilateral activity concentrated to the primary motor-sensory regions in the cortex. Centres involved in voluntary swallowing are located in multiple areas of the brain which include the right orbital frontal cortex, bilateral sensory motor cortices, bilateral tempero-polar cortices, left mesial pre-motor cortex and cingulate, supplementary motor area, pre-cuneus, cuneus, bilateral insular cortices, putamen, thalamus, globus pallidus, left cerebellum and dorsal brain stem[52]. Of these most important areas are located in the sensory motor cortex, anterior cingulate cortex, adjacent supplementary motor areas, insula, operculum and precuneus[53]. This indicates swallowing involves the recruitment of a neural network with areas outside the primary motor cortex and the medullary brainstem. Within the motor cortex, the representation of swallowing muscles are somatotrophic, with oral muscles more lateral and pharyngeal muscles being more medial.

Cortical control of swallowing is bilaterally represented and is multifocal with some potential for spatial facilitation between the responses from each hemisphere[54]. However, there is asymmetrical somatotrophic representation of the midline swallowing muscles in the motor cortex, which is suggestive of a functionally dominant swallowing hemisphere[55]. The dominant hemisphere for swallowing is probably independent of handedness and the

speech centre[56]. This may partly explain the difficulties in the correlation of the extent, side and location of the ischaemic brain injury with the severity of gastrointestinal dysfunction following an acute stroke. Damage to the hemisphere with overall dominant swallowing function can lead to significant dysphagia. Some studies have shown swallowing related activities are lateralised to the left hemisphere both for involuntary swallowing (of saliva) and for voluntary swallowing[57-59].

1.3.2. Swallowing dysfunction after Stroke

Dysphagia due to cortical lesions is secondary to involvement of various neural connections from the precentral gyrus and the internal capsule[60]. They can affect the voluntary actions of the pharyngeal and laryngeal musculature of the contralateral side with peristaltic dysfunction and spasticity. Lesions of the lower inferior precentral gyrus and posterior portion of the inferior frontal gyrus in either hemisphere can cause a delay in the initiation of the pharyngeal response due to interference of pharyngeal feedback. A lesion in the insular region which has multiple close functional connections to several areas of the brain coordinating swallowing which include the lateral and mesial premotor cortex, the primary and secondary somotosensary cortex and the frontal, parietal and temporal opercula can increase the swallowing threshold and a delay in the pharyngeal phase of swallowing[60;61].

A brainstem stroke can affect the serial activation of the cranial nerve motor neurones (bulbar swallowing cortex) by the central patterns generator which is located in nucleus of *Tractus Solitarius* and *Nucleus Ambiguus* and motor neurones in the Nucleus of *Tractus Solitarius* and the dorsal motor nucleus of the Vagus which innervate the muscles of deglutition. Bulbar swallowing centre is also partly responsible for the initiation of the

voluntary triggering of the swallowing reflex in addition to spontaneous reflexes due to facilitatory fibres from the cortex. Thus there will also be a delay in the initiation of swallowing due to the affection of these corticobulbar fibres following an acute stroke. Less commonly, in more severe corticobulbar disease, the voluntary oropharyngeal swallowing reflex cannot be initiated at all though the reflex swallowing can still be initiated by the bulbar swallowing centre acting alone without the cortical input[62]. There is also a pyramidal inhibitor of the swallowing reflex which is relayed on the bulbar centre via corticobulbar pathways. Thus, corticobulbar involvement not only alters the excitatory influences but also affects the neuronal network which has an inhibitory control. This is supported by some stroke patients who have increased mandibular and palatopharyngeal reflexes and patients with amyotrophic lateral sclerosis who have suprabulbar palsy with increased brainstem reflexes[63], [64] [65]. Patients with combined cortical and brainstem strokes associated with bilateral lower cranial nerve dysfunction are at greatest risk of dysphagia and aspiration. In addition patients with bilateral supratentorial, bilateral hemispheric strokes are associated with a higher incidence of severe and prolonged dysphagia rather than a patient with unilateral hemispheric stroke due to the damage to the swallowing dominant hemisphere and the absence of contralateral cortex to reorganize and take over the control of the swallowing process[66].

1.3.3. Oesophageal sphincter and gastric dysfunction following acute stroke

Dysphagia is only one aspect of gastro-intestinal dysfunction following stroke. After acute stroke, patients display a spectrum of gastro-intestinal dysfunctions such as gastro-intestinal haemorrhage secondary to stress ulcers, delayed gastric emptying, gastro-oesophageal sphincter dysfunction and colorectal dysfunction[67]. This may be due to disruption of several centres in the brain responsible for gastro-intestinal motility and is not fully understood. It is thought to involve cortical and medullary centres, in a multifocal and bilateral pattern with a dominant hemisphere which is independent of the patients'

handedness[67]. As lower oesophageal and gastric dysfunction following stroke has a direct relevance to the work done in this thesis, these changes are discussed in more detail in this section.

Ischaemic brainstem strokes can affect the Nucleus of *Tractus Solitarius* and the *Nucleus Ambiguous* and are associated with decreased tone of the lower oesophageal sphincter and variable tone (which may also be increased) of the upper oesophageal sphincter. These neurones are usually tonically active and inhibited first and later forcefully activated again during the swallowing process[68]. Motor neurones to the smooth muscles of the oesophagus including the lower oesophageal sphincter are located in two sub regions of the dorsal motor nucleus of the Vagus in the medulla. Its rostal region contains neurones that mediate excitation and the caudal region mediates the inhibition of the oesophagus[69]. A study on the effects of an ischaemic stroke on oesophageal peristaltic function demonstrated significant peristaltic dysfunction during early phase of stroke including higher number of non-peristaltic oesophageal contractions in patients with unilateral hemispheric stroke irrespective of the presence of dysphagia[70;71].

To ensure the swallowed food bolus effectively enters the stomach, a potent proximal gastric relaxation is triggered by the vagal afferent mechano-sensors in the lower oesophagus. It causes a reduction in the intra-gastric pressure an increase in the gastric volume. These neurones of Nucleus of *Tractus Solitarius* which are activated by oesophageal distension project heavily to the dorsal motor nucleus of the Vagus and offer the primary source of pre-ganglionic autonomic control of the stomach[72]. Vagal control over gastric tone and motility is affected by the activity of two antagonistic vagal efferent projections. Activation of pre-ganglionic cholinergic neurones in the gastric mucosa results

in vagal mediated increasing gastric tone and motility. Rapid gastro inhibition can occur by inhibition of these neurones.

It has been demonstrated that there is a delay in gastric emptying and drug absorption by the stomach following acute stroke[73]. Intolerance to enteral nutrients and increased incidence of Helicobacter pylori colonisation as a result of delayed gastric emptying also have been demonstrated following stroke[73]. Similarly in patients with ischaemic stroke, colorectal dysfunction occurs due to a combination of lesions of the central and peripheral nervous system, immobility, dehydration and altered dietary habits. The colonic transit time is prolonged, especially in the right side of the colon. Intestinal pseudo-obstruction either due to defective enteric neurons, smooth muscles or both is not uncommon. All these can result in abdominal distension and increased intra-abdominal pressure which would lead to further dysfunction of the stomach and gastro-oesophageal reflux[74].

1.3.4. Dysphagia following stroke

Dysphagia after stroke is common and impairment of the swallowing mechanism has been shown in 25 – 70 % of patients with a stroke [75]. This wide range is due to the variations in study designs and methods used for the diagnosis of dysphagia[5]. About 50% of stroke patients are diagnosed as having dysphagia by clinical criteria and over 64% by video-fluoroscopy [8]. In the context of stroke, oropharyngeal dysphagia can be defined as a disruption of the passage of the bolus through the mouth and pharynx. Abnormal lip closure, lingual in-coordination and a delayed or absent swallowing reflex may lead to disturbances in the oral and pharyngeal stages of swallowing. Consequences of these include incomplete oral clearance, pharyngeal pooling, regurgitation and aspiration[76]. Early

identification is important in the management of stroke patients as many studies have demonstrated the association between impaired swallow and aspiration following stroke[8;10;77].

Various types of abnormalities of all three stages of the swallowing process can be seen in patients following an acute stroke. Larger hemispheric strokes and brain stem strokes are associated with significant and persistent swallowing difficulties[61]. Damage to the motor cortex or internal capsule in a hemispheric stroke can affect the musculature of the pharynx and the larynx in addition to the contralateral hemiparesis[61]. Total laryngeal paralysis is not seen after a hemispheric stroke due to bilateral supra-nuclear vagal innervations[61]. However, a brain stem stroke can affect the glossopharyngeal, vagal and hypoglossal nuclei which can give rise to dysfunction of the pharynx, palate and the larynx[61]. Smithard et al found an association between the side of the stroke and aspiration at one month after an acute stroke but this association was not seen in when assessed within the first week[78].

Following stroke, there may be dyspraxia and food pocketing in the lateral sulcus between cheeks and gum margins in the oral phase of swallow. This is due to the reduced tone of the buccinator muscle, which is innervated by the lower half of the facial nerve[79]. Also poor coordination of swallowing and talking can lead to the bolus entering the pharynx when the airway is not protected[78]. Tongue movements are reduced which affects the bolus size, chewing and movements of the bolus inside the mouth[80]. There is also a reduction in the resting salivary flow[80]. All these factors contribute to a delay in the oral phase[81]. Reduced tongue movements also lead to food collecting along the palatal vault and impairment of formation of a cohesive bolus[79]. This and reduced oral sensation can result in premature entry of the food bolus in to the pharynx which can potentially enter the airway[79]. In frontal lobe damage the “tongue thrust” pattern of swallowing may occur, with anterior movement

of the tongue rather than coordinated posterior movements, leading to rejection of food from the mouth which often perceived as patient is spitting his food out[79].

The cough reflex is frequently weak or absent following a stroke and there is also a delay or loss of triggering of the swallowing reflex [61;79]. Both these impairments can lead to penetration or aspiration of the food bolus which depends on the patient's posture and size and consistency of the food bolus[7]. Paralysis or changes in the soft palatal movement can lead to nasal regurgitation. Impairment of pharyngeal and laryngeal sensation can further increase the risk of aspiration[82]. There is also impairment of the laryngeal ascent, laryngeal adductor reflex and impaired vocal fold mobility which also can increase the risk of aspiration, especially if there is reduced sensation of the pharyngo-laryngeal region[83]. There is a reduction of pharyngeal peristalsis following a stroke which can lead to incomplete pharyngeal clearance, collection of food particles in the valleculae and the pyriform sinus, impaired relaxation of the crico-pharyngeal muscles and delay in transit of the bolus, all of which can lead to possible overflow of food material in to the airways during the swallow[82]. Impaired upper oesophageal sphincter relaxation can lead to an increased post swallow residue with increased risk of aspiration[84].

Research into changes of oesophageal function and peristalsis following an acute stroke is limited. It has been shown that there is a reduction in the oesophageal peristalsis and failure of relaxation of the lower oesophageal sphincter following an acute stroke[79]. Further studies have demonstrated that resting lower oesophageal sphincter tone is reduced following stroke predisposing to reflux and aspiration, especially if there is increased residual gastric volume due to gastroparesis[79;85;86].

Association of dysphagia with lesions affecting the brainstem as it interferes with glossopharyngeal and vagus nuclei, which control the pharyngeal muscles and bilateral hemispheric lesions due to its affection of bilateral cortico-bulbar fibres, have been known for a long time[35]. However, the association of dysphagia with unilateral hemispheric strokes was not well established until mid 1980s. One of the first studies of dysphagia after acute stroke was done in the late 1980s by Gordon *et al* who investigated one hundred patients who had an acute stroke and dysphagia within the first 48 hours after admission and demonstrated that 45% of these patients had problems of swallowing[76]. Contrary to the then common belief that dysphagia is mainly seen in brainstem strokes or in bilateral hemispheric strokes, the majority of patients in this study had unilateral hemispheric strokes and these dysphagic patients had a higher incidence of chest infection, dehydration and death. One can argue that this study overlooked patients with bilateral cortico-bulbar lesions secondary to bilateral lacunar infarcts in the basal ganglia, presenting with symptoms of bilateral cortical lesions. However, in this study dysphagia wasn't restricted to patients who had other risk factors such as previous cerebrovascular disease, hypertension or diabetes, leading to an increased risk of bilateral lacunar infarcts affecting cortico-bulbar tracts in both hemispheres. A larger study on 357 unilateral hemispheric stroke patients confirmed that 30% had dysphagia within the first 48 hours of admission but only 6% had persistent dysphagia after one month [87]. Similarly another study demonstrated that 39% of 124 patients with acute non-haemorrhagic stroke failed the initial swallowing screening and 19% of patients needed enteral nutrition during their acute care[11].

All these studies confirm that dysphagia is common after a hemispheric stroke. Identification of dysphagia in stroke is important as this predisposes a patient to aspiration[88]. About one third of acute stroke patients with swallowing difficulties will

develop aspiration pneumonia[11]. Lower respiratory tract infections were more common in aspirators (68%) than in the non-aspirators (6%)[8]. Keeping the patient nil by mouth did not prevent the occurrence of chest infections in these patients who were shown to aspirate suggest that they continue to aspirate their oropharyngeal secretions silently, which were colonised by pathogenic organisms[89]. A literature review demonstrated that there was an increased risk of pneumonia in patients with dysphagia and this was even greater in patients with aspiration[75]. Aspiration pneumonia is a major cause of morbidity and mortality in stroke patients and is one of the major causes of post-stroke hypoxia[11].

In patients with acute hemispheric stroke, studies using videofluoroscopy have shown that dysphagia and aspiration were more common than shown in studies which used only clinical testing for the diagnosis of dysphagia[90;91]. A study using videofluoroscopy to diagnose dysphagia demonstrated that aspiration was seen up to 50% of patients with an acute stroke[92]. In a similar study Kidd *et al* using videofluoroscopy reported that aspiration was seen in 42% of patients when tested within 72 hours and was related to the presence of dysphagia[89]. A literature review of 107 relevant articles from 1966 to 2005 demonstrated that dysphagia is common problem following acute stroke and the reported incidence varied with the method used, lowest was using cursory screening methods (37% to 45%), higher using clinical testing (50% to 55%) and highest using instrumental testing (64% to 78%)[75]. The literature review also demonstrated that stroke patients with dysphagia had three fold risk of developing pneumonia than patients without dysphagia and even higher, an 11 fold risk of developing pneumonia if dysphagia was associated with aspiration.

Many patients with dysphagia following unilateral hemispheric strokes show some recovery within the first few weeks of the acute event. A study using transcranial magnetic stimulation demonstrated that non dysphagic and persistently dysphagic patients showed

little change in the cortical representation of the pharynx over time, where as dysphagic patients who recovered showed increased representation of muscles of swallowing in the unaffected hemisphere without change in the affected hemisphere[93]. This often preceded the actual recovery of swallowing. This suggests recovery of swallowing may follow remodelling and reorganization of cerebral functions in the undamaged previously non-dominant (swallowing) hemisphere to take over the control of the swallowing process. Patients who remained dysphagic did not show this reorganisation of the non dominant hemisphere. This reorganization is often independent of the recovery of any associated hemiparesis[55]. This recovery of the swallowing process takes place over the next days to weeks.

Studies have reviewed the duration of dysphagia following stroke as it is important in the specialist management of these patients. Dysphagia and aspiration is most severe within the first two weeks following stroke[8;76;89]. It has been demonstrated that a significant number of patients regained their swallow within 14 days and most of the chest infections occurred within the first seven days following stroke[76]. Using bedside swallowing testing, Smithard *et al* demonstrated that though 51% of acute stroke patients had dysphagia and were at risk of aspiration, most the swallowing problems resolved within the first three days following stroke. However, 27% of patients were still at risk of aspiration at the end of the first week and 15 % at the end of one month[9]. Dysphagia persisting for more than three months following stroke was associated with a less favourable outcomes[11]. Further studies have confirmed that dysphagic symptoms resolved within a month in most patients though may persist beyond six months in a small percentage of patients and dysphagia persisting for more than three weeks was associated with less favourable outcome[10;94]. A study using videofluoroscopy have confirmed that dysphagia was most severe during the first two weeks, with the risk of aspiration at its highest, resolved in most patients by the end of two

weeks, and only 8% of patients continued to aspirate after three months[8]. In addition, the study also demonstrated that patients with right hemispheric lesions were more likely to aspirate than patients with left hemispheric lesions[8].

Studies have been done to assess the long term impact of post-stroke dysphagia. A study by Mann *et al* on 128 patients with their first stroke, assessed swallowing function clinically and videofluoroscopically over six month to assess the impact on dysphagia, recovery and the long term prognosis. At presentation, swallowing abnormality was detected in 51% of patients clinically and 64% patients using videofluoroscopy. At six months after the stroke, 87% of 112 survivors had return to their pre-stroke diet. However, clinical evidence of swallowing abnormalities was present in 50% of these patients. Videofluoroscopy performed at 6 months in 67 patients who had a swallowing abnormality at baseline showed penetration occurred in 34% patients and aspiration in another 17 patients. The single independent baseline predictor of chest infection during six month follow-up was delayed or absent swallow reflex (detected by videofluoroscopy) and the single independent predictor of failure to return to normal diet was delayed oral transit time. Independent predictors of the combined outcome events of swallow impairment, chest infection or aspiration at six months were delayed oral transit seen in videofluoroscopy, penetration, age over 70 and male sex[10].

In conclusion, dysphagia is a common problem following acute stroke and seen in both hemispheric and brain stem lesions, though the detection of dysphagia varies depending on the inclusion criteria and the methods used for the diagnosis. As detailed before, videofluoroscopy is only used in clinical situations where the bedside swallowing tests are inconclusive or if there is a strong suspicion of silent aspiration though it provides better results. It is possible that the true incidence of dysphagia and aspiration is higher than

reported above since those studies were performed in patients who could comply with formal swallowing testing and video-fluoroscopic procedures. This excludes a significant proportion of acute stroke patients with large strokes who are unconscious or too drowsy to be assessed by procedures which are commonly used to test dysphagia. Therefore the true incidence of dysphagia may be much higher than shown in many clinical studies. Dysphagia is most severe during the first few weeks following stroke and therefore increased vigilance for early identification and treatment of complications are required at this stage. In addition to the increased vigilance to detect complications, interventions to prevent aspiration and pneumonia should also be carried out at least during these early weeks following stroke.

1.4. Aspiration

As described above, dysphagia due to abnormal lip closure, lingual coordination and delayed or absent swallowing reflex is an important complication following acute stroke and these result in incomplete oral clearance, pharyngeal pooling, regurgitation and aspiration[60].The entry of food or fluid in to the laryngeal vestibule is defined as penetration and the entry of food below the vocal cords is defined as aspiration.

1.4.1. Silent aspiration

Following stroke, though some patients have symptoms of aspiration, in a significant proportion of patients it may not be noticed. If aspiration initiates a cough reflex this is called overt aspiration. Aspiration which occurs without eliciting a cough reflex is called silent aspiration[95]. Aspiration carries a significant risk of pneumonia as the aspirate carries bacteria from the oropharynx in to the lungs[88]. In patients with stroke, the risk of development of pneumonia is seven times greater in patients who aspirate and studies have

shown that incidence of pneumonia in patients who have silent aspiration is six times greater than in patients who could cough on aspiration[96;97]. Videofluoroscopy gives more accurate results than clinical testing in relation to the incidence of silent aspiration following acute stroke. A study by Daniel *et al* in patients with acute stroke demonstrated that 33% had dysphagia when clinically tested, but up to two third (65%) of patients had evidence of silent aspiration which could only be demonstrated by using videofluoroscopy [88]. However, aspiration pneumonia due to silent aspiration is not only confined to patients with acute stroke[88;95]. Patients with various neurological conditions such as Parkinson's disease and motor neurone disease with dysphagia often aspirate silently, and pneumonia is the fourth most frequent cause of death in elderly patients with co-existing neurological diseases[98]. This is due to the weakness and poor coordination of pharyngeal musculature, poor initiation of swallowing and impaired vocal cord motion.

Silent aspiration may result from reduced pharyngeal sensation and from weakness or in-coordination of the pharyngeal musculature[99]. A study using videofluoroscopy demonstrated that patients who have a latency greater than 5 seconds in the swallowing response and in cough on instillation of a citric acid aerosol to the pharynx had a higher incidence of aspiration pneumonia[100]. Prolonged tracheal intubation or tracheostomy are known to desensitize the oropharynx and are associated with a higher incidence of silent aspiration and pneumonia[100]. Repeated exposure of the pharynx to gastric acid due to gastro-oesophageal reflux disease can also reduce pharyngeal sensation, predisposing to silent aspiration[88].

Presence of a weak cough reflex is a predictor of silent aspiration. There are two types of reflex cough[79]. The primary cough reflex, which is also described as the laryngeal cough reflex, occurs at the level of the larynx and is mostly responsible in clearing the upper

airway. The less productive delayed deeper cough is called tracheo-bronchial cough. Various local and central neurological disorders affecting the pharynx can interfere with both cough reflexes and predispose a patient to aspiration[101]. It has been shown that there is a progressive loss of protective swallowing and cough reflexes with age[102]. However, many older people continue to lead active lives without recurrent bouts of pneumonia. This indicates that disease and degenerative changes affecting the central nervous system and neuro-muscular coordination rather than the changes due to age itself predispose an older individual to aspiration and pneumonia[79]. A scintiographic study of older patients with pneumonia showed longer latency in swallowing response in patients with previous basal ganglia infarcts than those without.

The relationship between dysphagia and silent aspiration is incompletely understood. Some patients have severely disordered swallowing, but transport of saliva and food to the stomach proceeds safely, but others who appear to have a safe swallow and no indicators for aspiration at bedside testing will have silent aspiration on video-fluoroscopic examination[95]. Therefore, the possibility of silent aspiration should always be considered in stroke patients with unexplained recurrent pneumonia and these may require more specialised investigations.

1.4.2. Clinical predictors of aspiration

Identification of clinical predictors of aspiration is important to ensure proper management of such patients and to prevent future complications, to plan out further investigations and appropriate feeding methods. Using videofluoroscopy a study demonstrated that half of stroke patients had evidence of aspiration within 24 months following their stroke[103]. Aspiration was more commonly seen in patients with bilateral cranial nerve signs (71%) than in patients with unilateral cortical signs (29%)[104]. Dysphagia was the most common

clinical sign in the patients who aspirated regularly. In another study aspiration was commonly seen in patients with dysphonia, abnormal gag reflex and a weak cough[105]. Also the co-existence of an abnormal gag and an impaired voluntary cough were more predictive of aspiration than each of these symptoms in isolation. Linden and colleagues studied 249 patients with primary neurological problems including stroke and found nine clinical indicators namely, dysphonia, wet phonation, decreased/absent laryngeal excursion, nursed in a recumbent position, wet spontaneous cough, decreased gag reflex, drooling and reduced ability to swallow secretions, harsh phonation and breathy phonation that were significantly associated with aspiration as identified by videofluoroscopy[106].

Only few studies have been done to assess the clinical predictors of aspiration following acute stroke. In a study based on videofluoroscopic examination of patients within 5 days of acute stroke, six clinical indicators were identified to distinguish patients who are at an increased risk of aspiration following acute stroke [77]. Abnormal cough, abnormal gag reflex, dysphonia, dysarthria, voice change and cough after swallow were identified as independent predictors of aspiration. Presence of two or more of these signs further increased the risks of aspiration. The study also identified an abnormal volitional cough and a cough with swallowing were independent predictors of aspiration and presence of two of above will predict the risk of aspiration with 78% accuracy (sensitivity 69.6% and specificity 84.4%). These features were independent so that a patient may demonstrate one feature in isolation without the presence of an additional feature. Another study confirmed that some or all of these features are related to the risk of aspiration either in isolation or of any combination[107]. It has been reported that cough during swallowing and clinical estimates of presence of aspiration are the two most reliable features for predicting aspiration[108] and impaired consciousness and weak voluntary cough were independent predictors of aspiration following stroke[109].

Studies to determine specific neurological predictors of dysphagia and aspiration have not been very successful. Demonstration of a dominant, more important hemisphere for swallowing has been discussed before. Furthermore, some studies have demonstrated that the lesions in the two hemispheres have different swallowing problems, specifically left hemispheric lesions have been associated with oral stage dysfunction and the right hemispheric lesions with pharyngeal stage dysfunction[107;110]. However, not all other studies support these findings[111;112]. A retrospective study of 65 acute stroke patients failed to demonstrate a significant association between dysphagia and aspiration and the size of the lesion or its location. Though described previously, according to this study aphasia was not a predictor of poor swallowing outcome. However, the presence of neuro-cognitive features such as hemispatial neglect and apraxia predicted protracted dysphagia but prospective studies are needed for investigation of these relationships[107]. The need for further research was emphasised by a study in 151 consecutive acute stroke patients which showed that the intensity of dysphagia or aspiration was not predicted by the type of the stroke[113]. The study further demonstrated that non-dominant cortical strokes were associated with dysphagia though there was no association with sub-cortical non-dominant strokes.

In summary, aspiration is common in dysphagic patients and carries a risk of pneumonia. Silent aspiration is particularly important as the patients affected have lost their ability to expectorate the infected material and the aspiration goes unnoticed by the attending clinical staff. Videofluoroscopy provides a higher yield in diagnosing aspiration, especially silent aspiration. Physicians should be aware of signs and symptoms predicting aspiration, and ensure regular dysphagia assessments are conducted and further investigations, such as videofluoroscopy to detect silent aspiration, are considered so that pneumonia is prevented.

1.4.3. Clinical consequences of dysphagia and aspiration

The potential link between fever and stroke was recognised more than 170 years ago in a textbook written by Christian Wilhelm Houfeland. According to his work, one of the most frequent complications following stroke was fever, which occurred in 61% of acute stroke patients[114]. However, it took many years to recognise that such medical complications contributed significantly to the outcome after cerebral ischaemia[115]. It has been reported that up to 95% of patients have at least one relevant medical complication within first three months after stroke and that more than 50% of patients with severe strokes die during hospitalisation due to one or more medical complications[4;116].

Several studies have demonstrated a strong association between dysphagia and pneumonia. In a prospective study in 91 acute stroke patients, Gordon *et al* noted a higher rate of chest infections in dysphagic acute stroke patients than in non-dysphagic stroke patients. Many of these had hemispheric strokes and were classified as severe strokes[76]. Dysphagia has been reported as an independent predictor for stroke severity and was associated with a higher incidence of respiratory problems, longer length of stay, and higher mortality and morbidity[87]. Dysphagia results in aspiration and confirmed aspiration increases the risk of pneumonia by 11 fold[75]. The incidence of lower respiratory tract infection was as high as 68% in stroke patients who aspirated during videofluoroscopy than in non-aspirators(6%) and the use of intravenous fluids without oral intake did not prevent pneumonia in the patients who had persistent silent aspiration[8]. Aspiration contributes to the high incidence of pneumonia in stroke patients, compared to the incidence of pneumonia in age matched non- stroke patients on elderly care wards, which is only 5%[117].

Swallowing problems also lead to dehydration and malnutrition. Malnutrition can increase the risk of infections, gastrointestinal haemorrhage, low albumin levels, oedema and

development of pressure sores. Poor hydration can lead to electrolyte disturbances, paralytic ileus, constipation, vomiting, poor confidence, increased length of stay, and institutionalisation[118]. Poor nutritional state has been correlated with increased mortality after admission with an acute stroke[119].

Mortality is higher in stroke patients who are also dysphagic than in non-dysphagic stroke patients. Dysphagia is an independent predictor of mortality, and subjects who develop aspiration pneumonia have a higher mortality even after adjusting for stroke severity[120]. Odderson *et al* have demonstrated that dysphagia on admission was an independent predictor of mortality and dysphagic patients had a longer length of stay, were less likely to be discharged home and were twice likely to be discharged to a nursing home than non-dysphagic patients [11].

1.4.4. Pulmonary complications of aspiration

Aspiration is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract[121]. Several pulmonary syndromes may occur after aspiration, depending on the amount of aspiration, the nature of the aspirated material, the frequency of aspiration, host factors such as the age, immune status and underlying local or systemic disease processes and the host's response to the aspirated material[122].

Aspiration of stomach contents into the lungs can produce a range of signs and symptoms which include coughing, choking, wheezing, shortness of breath, cyanosis and hypoxaemia and can result in four different outcomes. These are rapid clearance of the aspirated material, or laryngeal obstruction with asphyxia and the risk of death, chemical injury / aspiration pneumonitis caused by the inhalation of sterile acidic gastric contents, and

aspiration pneumonia[123]. Aspiration pneumonitis, which is also referred as Mendelson's syndrome, can recover completely with a brief febrile but uncomplicated course or can progress to a severe respiratory distress and death or development of pneumonia with pyrexia, cough with purulent sputum, coarse lung crackles on auscultation and signs of consolidation in the chest radiograph[124]. This is because even small amounts of gastric acid can lead to chemical injury of pulmonary capillaries and cause exudation of proteinacious fluid which can give rise to bronchospasm, pneumonitis and hypoxia. Secondary infection of the damaged tissues can occur from the onset if gastric contents is colonised by bacteria especially in the presence of a high pH in the stomach or from the organisms aspirated from the oropharynx. Secondary infection is likely even following aspiration of stomach contents with a low pH which prevents the growth of the majority of bacteria[125]. The fourth outcome is aspiration pneumonia and is defined as an infectious process caused by the inhalation of oropharyngeal secretions which are colonized by pathogenic bacteria[122]. Pulmonary aspiration is an important cause of serious illness and death not only in stroke patients also among nursing home residents, elderly people as well as in hospitalised patients with other neurological disorders[126] and will be discussed in detail below.

Approximately 50% of all healthy adults and 70% of patients with depressed conscious level aspirate small amounts of oropharyngeal secretions during sleep[127]. The low bacterial burden in the normal pharyngeal secretions, presence of mainly non virulent commensal organisms, forceful coughing, active cilliary transport and normal immune mechanisms usually result in clearance of this material without serious adverse effects[127]. Any condition that increases the volume or the bacterial load of the aspirate or causes impairment of the defence mechanisms can lead to development of aspiration pneumonia[128]. These conditions include neurological dysphagia, reduced level of consciousness resulting in poor cough reflex and glottic closure, disruption of the gastro-oesophageal junction, or anatomic

abnormalities in the upper gastro intestinal tract[129]. Mechanical disruption of the glottic closure or upper oesophageal sphincter due to tracheostomy, endotracheal intubation, nasogastric feeding and upper gastrointestinal tract endoscopies are associated with an increased risk of aspiration. The risk is also higher in older people because of an increased incidence of dysphagia and poor oral care resulting in oropharyngeal colonisation with potential pathogens, and more frequent gastro-oesophageal reflux[130].

Secretions are less likely to be expectorated in patients with a stroke due to reduced level of consciousness, muscle paresis and poor cough. However, there is no significant reduction in the volume of oropharyngeal secretions and in the presence of reduced pharyngeal sensation and insufficient glottic closure, various quantities of this infected material can enter the respiratory tract[131]. Poor oral hygiene, high inoculation and impaired host defences contribute to the high bacterial content of these secretions. Such episodes of aspiration may be witnessed, produce only subtle signs such as a weak cough, gurgling or wheeze or, more commonly occur silently, which can only be demonstrated by occurrence of oxygen desaturation or other specialised investigations. Patients who aspirate silently without clinical signs of dysphagia or well recognised signs and symptoms of aspiration are at a greater risk of chest infection, as their feeding will not be supervised or restricted and may receive less oropharyngeal care or suction. [8] Even if the aspirate is sterile due to low pH, aspiration of gastric contents can cause acid induced damage leading to atelectasis and necrosis which becomes secondarily infected[123;131].

Knowledge of bacteriology of aspiration pneumonia is important as it determines the choice of antibiotics. The bacterial flora of the oropharynx of a healthy individual mainly consists of facultative Gram positive bacteria, commonly alpha haemolytic streptococci and corynebacterium species[132]. By occupying receptor sites on the oral mucosa they interfere

with the adherence of pathogenic aerobic Gram negative bacilli and by consuming available nutrients and producing substances toxic to them, these commensal bacteria inhibit colonization of the oropharynx by aerobic Gram negative bacilli. Colonisation of the oropharynx by aerobic Gram negative bacilli occurs within few days of hospitalisation and correlates with the severity of the illness.[27]. One study had demonstrated that 37% of moderately ill patients and 73% of severely ill patients carry Gram negative bacilli in their oropharynx[133]. Similar findings are seen in acute stroke patients compared with patients on rehabilitation units who have less colonization [134].

Common organisms involved in aspiration pneumonia in the community overlap with community acquired pneumonia (CAP) and are predominantly Streptococcus pneumoniae and Haemophilus influenzae[135]. Gram negative organisms that colonise the oropharyngeal mucosa are responsible for hospital acquired pneumonia and aspiration pneumonia[6]. Many studies have demonstrated that Enterobacteriaceae, Pseudomonas, Klebsiella and Staphylococcus aureus are the organisms responsible for most of hospital acquired aspiration pneumonias[136]. Factors that increase the risk of colonization and the bacterial load of the oropharynx, and increase the volume of aspirate all raise the risk of aspiration pneumonia[128].

Studies by Moinne *et al* and Torres *et al* have suggested that up to 15% of cases of community acquired pneumonia are due to aspiration[137;138]. There is also a considerable overlap of aspiration pneumonitis and aspiration pneumonia in critically ill patients including patients with acute stroke[6]. Aspiration pneumonia can result when large volumes of gastric contents including food and oropharyngeal secretions are vomited or regurgitated and aspirated, though the lung pathology started as an aspiration pneumonitis[6]. The stomach contents may not have a low pH in patients who are fed via nasogastric tubes, as

the enteral formulae have pH values of 6.6 to7 which can buffer the gastric acid to near neutral level. In addition, injury to pulmonary tissue can be worse if the aspirate contains large concentrations of pepsin and refluxed bile and trypsin from the duodenum. Also the aspirate can carry potentially pathogenic organisms from the oropharynx and the stomach, both of which may have bacterial overgrowth due to the nasogastric feeds. In addition damaged lung tissue can get secondarily infected with oropharyngeal secretions, resulting in aspiration pneumonia.

Diagnosis of aspiration pneumonia is difficult in stroke patients as an episode of witnessed aspiration is essential for firm diagnosis and clinically significant episodes of aspiration may occur silently. However, certain broncho-pulmonary segments are commonly affected by aspiration, and involvement of these segments has been used for the diagnosis of aspiration pneumonia[139]. Therefore pneumonia due to silent aspiration is made when a patient at risk of aspiration has signs of pneumonia and radiological evidence of infiltrates in a broncho-pulmonary segment which is commonly affected by aspiration. In patients who aspirate while in a supine posture, the most common sites of infiltrates will be the posterior segment of the upper lobes and the apical segments of the lower lobes. Infiltrates are commonly seen in the basal segments of the lower lobes in patients who aspirate when upright or in a semi-recumbent position[6]. Radiologically visible infiltrates often occur within several hours of the event and improve over the next few days with treatment. An increase in the shadowing indicates super-infection or retained secretions. However, these radiographic signs are not pathognomonic[140].

Aspiration may be confirmed by the use of invasive investigations such as broncho-alveolar lavage, fibreoptic bronchoscopy, percutaneous needle aspiration and open lung biopsy. These methods are costly, can cause significant patient discomfort, need special

expertise, and can be associated with high complication rates, and are therefore not routinely carried out to diagnose aspiration pneumonia. Scintigraphic studies and continuous oesophageal pH monitoring can also be used to detect silent aspiration[140]. These tests are not done in routine practice partially due to costs and also because the general management and antibiotic therapy is very similar for both types of pneumonia. The usual course of aspiration pneumonia is comparable to that of community acquired pneumonia though there is a higher incidence of cavitations and abscess formation of the lung tissues if there is delay in the treatment[132].

Most studies of aspiration pneumonia do not define specific criteria for diagnosis of aspiration pneumonia and mention only the criteria for diagnosing any pneumonia in the methodology. One review article on aspiration pneumonia suggests the use of following signs and symptoms for the diagnosis of aspiration pneumonia, if they were to develop after a bout vomiting or regurgitation in a patient at risk of aspiration[139].

- Symptoms of development of a chest infection such as new onset cough, wheeze, hypoxaemia and tachypnoea
- Clinical signs such as new inspiratory crackles or bronchial breathing
- Pyrexia
- Leucocytosis
- New pulmonary infiltrates in the gravity dependant lung regions

In summary, aspiration leads to serious pulmonary complications and unless aspiration is witnessed or gastric contents or enteral feeds are detected on tracheal suction, it is difficult to prove that an episode of pneumonia is secondary to aspiration. Specific tests to confirm aspiration or aspiration pneumonia are not done in routine clinical practice, and clinicians have to rely on chest radiographic appearances which are not pathognomonic.

Differentiating aspiration pneumonitis from pneumonia in the critically ill may not be clinically relevant as one follows the other and will be treated with appropriate antibiotics. Considering the high incidence of silent aspiration following stroke, it is possible that many episodes of post-stroke pneumonia might have originated following aspiration, though this is difficult to prove. This may be why many studies have chosen any pneumonia as opposed to aspiration pneumonia as their primary outcome.

1.4.5. Aspiration in critically ill patients including acute stroke patients

It is recognized that a critically ill patient has a higher risk of aspiration and aspiration pneumonia[6]. Ventilator associated pneumonia is the most frequent and serious intensive care unit acquired infection and is associated with a mortality of 20% to 30%. Oropharyngeal dysphagia, reduced pharyngeal sensation and poor cough play a significant role in the development of ventilator associated pneumonia in mechanically ventilated patients such as patients with brain injury, acute stroke, intracranial infection and unconsciousness due to various sedatives and hypnotics. Low GCS due to neurological disease or medications is a well known risk factor for aspiration as patients with a reduced level of consciousness have impaired upper airway protective mechanisms. A recent study has shown that aspiration was higher in patients with GCS of 9 or less or when heavy sedation has been used[141]. In addition various gastro intestinal dysfunctions leading to gastroesophageal reflux, inability to clear the regurgitated material due to dysphagia and aspiration of regurgitated stomach contents mixed with infected oropharyngeal secretions also contribute to the development of ventilator associated pneumonia, which will be described in detail later. Being nursed in a supine position and nasogastric intubation may also increase the gastro-oesophageal regurgitation and aspiration of these patients[142].

Acute neurological injury leads to a cascade of local and systemic metabolic responses leading to a hypercatabolic, hypermetabolic and hyperglycaemic state with altered immune responses and altered gastrointestinal function[143]. Studies in mechanically ventilated, critically ill patients with brain injuries have shown that there is a significant gastric dysfunction and a delay in gastric emptying. A study in 72 critically ill patients using acetoaminophen absorption from the stomach demonstrated a significant delay in gastric emptying and was associated with enteral feed intolerance and gastric colonisation[144]. Patients who were treated with opioid analgesics and narcotics had the most severe delay in gastric emptying. In another study done on a similar patient population using C^{13} octanoic acid feeds and serial breath tests for $C^{13}O_2$ excretion, demonstrated significant delay in gastric emptying following acute brain injury[145]. Early administration of enteric nutrition improves clinical outcomes, reduces infection and other complications. However, maintaining nutrition can be a challenge as nasogastric feeding is still complicated by aspiration and pneumonia as described below.

Various types of gastro intestinal dysmotilities ranging from delayed gastric emptying to gastroparesis have been described in patients who are critically ill. Gastroparesis is commonly seen in critically ill patients and occurs due to a combination of decreased gastric contractility and defective coordination of gastric contraction across the antro-pyloric region[146]. This is a combined effect of increased stress hormones, adrenergic stimulation, vagoparesis and concurrent medication such as anaesthetics and narcotic analgesia[147]. Intra-abdominal surgery, drugs such as morphine, dopamine and propofol, sepsis mediated by interleukin-1 and nitric oxide, hyperglycaemia, hypokalaemia, renal failure and raised intracranial pressure all contribute to gastroparesis. The syndrome of severe gastroparesis and intestinal ileus complicating critical illness is described as gastrointestinal failure. Gastrointestinal failure complicates about 10% of intensive care

admissions and is typically seen within the first few days of a critical illness. It is an independent risk factor for death and is more commonly seen in patients with acute medical and surgical illnesses than in patients following elective surgery [148].

Gastroesophageal reflux is seen in up to 30% of patients who are kept in the supine position[149]. Studies have confirmed that stress hormone adrenalin causes long lasting relaxant effect on the lower oesophageal sphincter favouring gastroesophageal reflux[150]. Gastroesophageal reflux occurs in critically ill patients even in the absence of nasogastric tubes or enteral feeds[150]. Poor gastric emptying and gastroparesis can lead to gastric distension, increase in gastric residual volume, poor closure of the lower oesophageal sphincter and regurgitation of gastric contents, which can lead to aspiration and pneumonia[147].

Upper digestive feeding intolerance (UDFI) is defined as gastroparesis leading to increased residual gastric volume above a given threshold or recurrent vomiting during enteral feeds and is the commonest complication encountered during of nutritional support in critically ill patients [151]. It has been demonstrated that only 35% of critically ill patients tolerated enteral nutrition and 65% of critically ill patients had one or more gastrointestinal complications during their enteral feeds[152;153]. Eighty five percent of these patients had high gastric residual volumes and 75% of these patients had at least one episode of vomiting and 64%of patients showed evidence of gastroesophageal regurgitation[153].

These gastrointestinal dysfunctions interfere with feeding and maintenance of an adequate nutritional input in these patients as feeds have to be interrupted due to vomiting. Most episodes of aspiration are small in volume and may not lead to pneumonia, but the likelihood of pneumonia increases with multiple episodes of aspiration[154]. Therefore, in

2002, the North American Summit on aspiration in critically ill patients issued risk factors for aspiration (table 1.1) and has recommended that all patients on an intensive care unit should be stratified according to the risk of aspiration[25].

Gastric residual volume is commonly measured to assess the risk of aspiration during enteral feeds. However, data are conflicting for what gastric residual volume represents intolerance[155]. Most clinicians use 150 to 200 ml of gastric aspirate as a significant indicator of gastrointestinal motility dysfunction. The common practice of aspirating the stomach to measure gastric residual volume has been criticised by some clinicians as being unreliable and lacking standardisation[156]. Also it fails to differentiate normal gastric secretions from enteral feeds and can result in unnecessary interruptions of the enteral feeding regime. Several more reliable, harmless and sensitive methods such as scintigraphy, paracetamol absorption test, breath test, ultrasound and gastric impedance monitoring are now available[154]. However, refractometry seems to be the most appropriate tool for the regular assessment of gastric volume of the critically ill patient. Several trials have been done to assess the effects of prokinetic agents such as cisapride, erythromycin and metoclopramide to promote gastric emptying but the effect of these medications in prevention of aspiration pneumonia still inconclusive[154].

Table 1-1 Risk factors for aspiration identified but the North American Summit

Risk Factors for aspiration identified by the North American Summit
Major risk factors
Documented previous episodes of aspiration
Decreased level of consciousness
Neuromuscular disease or structural abnormalities of the digestive tract
Endotracheal intubation
Vomiting
Persistently high gastric residual volumes
Supine positioning
Additional risk factors
Presence of a nasogastric tube
Non-continuous or intermittent feeding
Abdominal/thoracic surgery or trauma
Delayed gastric emptying
Poor oral care
Age
Inadequate nursing staff
Large size or diameter of feeding tube
Malpositioned feeding tube
Transport
(Adopted from McClave et al[25])

As described before gastroesophageal reflux is an important cause of aspiration and nosocomial pneumonia in ventilated critically ill patients on an intensive care units. Lower oesophageal sphincter dysfunction has been demonstrated in patients with brain injury. It has been demonstrated that acute head injury causes temporary dysfunction of the lower oesophageal sphincter which improves with neurological recovery. Patients who had a GCS of less than 12 within 72 hours of head injury were assessed for lower oesophageal sphincter dysfunction and tests were repeated at one week. Lower oesophageal sphincter dysfunction was seen in all patients, and the average gastric to oesophageal pressure difference was lower (-0.49mm Hg, range -3.4 to 2.5mm Hg) compared to a normal value of greater than 20 mm Hg. This pressure difference had improved to 13.3mm Hg at the end of the first week and this lower oesophageal sphincter dysfunction contributed to vomiting, aspiration pneumonitis and problems in maintaining enteral feeding[157;158].

The mechanism of gastroesophageal reflux in these patients differs from healthy subjects. Most episodes of gastroesophageal reflux in healthy adults are associated with transient lower oesophageal sphincter relaxation. This phenomenon is not commonly seen in critically ill patients as anaesthesia and sedation inhibits the triggering of the transient lower oesophageal sphincter relaxation [19]. Nind *et al* demonstrated that in critically ill patients the lower oesophageal sphincter pressure was very low or absent. The study was done using oesophageal impedance rather than pH manometry of the oesophagus to detect the reflux episodes. This method is thought to be superior in detecting gastric reflux in nasogastric tube fed patients as the pH may be artificially high due to proton pump inhibitors or the buffering action of the enteral feeds. The study demonstrated that reflux in these patients was due to low or absent basal lower oesophageal sphincter pressure rather than transient lower oesophageal sphincter relaxation. More than two thirds of reflux episodes occurred spontaneously when lower oesophageal sphincter pressure is absent in

these patients. Increased intra abdominal pressure due to straining and coughing induced by suctioning or gastric distension contributed to the rest of the reflux episodes (20-30%). There was also a marked reduction in the activity and peristalsis of the body of the oesophagus[159]. The study also demonstrated that acid reflux occurred in 60% of patients and there were prolonged periods of acid exposure, secondary to impaired clearance following acid reflux. This is partly due to decreased oesophageal motility, secondary to adrenergic stimulation, hypotension and sepsis. Also, this is due to a reduction of chemical neutralization of regurgitated gastric acid in the oesophagus by swallowed salivary bicarbonate, secondary to impaired swallowing and loss of saliva due to suctioning and drooling[160].

Studies in acute stroke patients have shown similar results. A study in 62 acute stroke patients using oesophageal manometry also demonstrated transient upper and lower oesophageal sphincter dysfunction in the first two weeks following acute stroke and dysfunction of both these sphincters resulted in an increased incidence of aspiration and pneumonia[85]. A similar study by Hassett *et al* using oesophageal manometry and 24 hour pH monitoring in recent onset dysphagic stroke patients demonstrated that lower oesophageal sphincter dysfunction was common in this group of patients and led to gastroesophageal reflux and aspiration and patients with minimal gastroesophageal reflux had a higher survival rates and less aspiration pneumonia.[86]. The study also demonstrated that reflux was significantly influenced by the patient's posture and there were significantly more reflux events when patients were nursed either in the right lateral position or the supine position than in left lateral or sitting positions[86]. The observed increase in gastroesophageal reflux and aspiration in the supine position compared to the sitting position has been well documented in previous studies, but an increase in the incidence of

reflux when patients are nursed in the right lateral position has not been documented previously.

Several methods have been used to diagnose the reflux of gastric contents into the pharynx and the lungs in critically ill patients. The glucose oxidase test consists of determination of the glucose concentration in the tracheal secretions after a glucose meal[20]. Demonstration of a blue dye in the tracheal secretions following a test meal has been used in the past[21]. More recently demonstration of gastric enzyme pepsin or of micro beads that were incorporated in a test meal in the tracheal aspirate has been used with greater safety and success. To detect silent aspiration of stomach contents, Clayton *el al* monitored tracheal pH using an electrode which was inserted in to the trachea through the crico-thyroid membrane under a local anaesthetic[161].The study was done in 32 acute stroke patients, 4-19 days after the acute stroke. These patients were considered to be safe to have oral feeds after their swallow was assessed by bedside assessment and videofluoroscopy. The study demonstrated that nine out of thirty two patients showed signs of aspiration following an acidic meal. Though a small study, the results were statistically significant. Also the requirement to use of an invasive technique to diagnose gastro-oesophageal reflux and silent aspiration highlights the difficulties in diagnosing reflux and silent aspiration in stroke patients using conventional methods.

Other studies done in critically ill patients in an intensive care setting have shown that risk of aspiration was significantly higher soon after extubation of a patient[162;163]. Residual effects of sedative drugs, swallowing dysfunction secondary to alteration of upper air way sensitivity, glottic injury and dysfunction of laryngeal musculature have been given as some reasons for this observation[163]. Alterations in swallowing reflexes can occur in patients who have been ventilated for more than 24 hours and may persist for 48 hours.

Keeping such patients nil by mouth for 6 hours and restricting oral intake to a pureed diet for further 48 hours can reduce the risk[162]. Similarly a recent study demonstrated that acute stroke patients who were intubated for neurovascular interventions had a higher incidence of aspiration pneumonia than stoke patients who had the intervention under a local anaesthetic[164]. The study reviewed 136 acute ischaemic stroke patients after endovascular treatment, 83 patients were given a local anaesthetic without intubation and 53 patients were intubated. Aspiration pneumonia was diagnosed in 14% of patients who were not intubated and in 23% of patients who were intubated. After adjusting for age, gender and severity of the neurological deficit, poor outcome at discharge and in-hospital mortality was significantly higher among patients who were intubated (83% versus 55%)

In conclusion, studies in critically ill patients with brain injury have shown that aspiration and pneumonia are major complications and that a reduced level of consciousness was significantly associated with the development of pneumonia. This may be due to an attenuation of pharyngeal protective reflexes, reduced sensation, worsening of the coordination of breathing and swallowing, and cough. In addition, significant dysfunction of the lower oesophageal sphincter, delayed gastric emptying, increased residual gastric volume and enteral feed intolerance have been demonstrated secondary to neurological, hormonal and biochemical changes. These mechanisms predispose critically ill patients to aspiration and pneumonia. It may not be possible to correct the impaired level of consciousness secondary to underlying neurological damage. However, good oropharyngeal care, removal of excessive secretions by suctioning, application of methods to improve lower oesophageal sphincter function and gastric motility combined with vigilance in the detection of feed intolerance could potentially reduce the incidence of pneumonia in this patient group. The next section will review in detail of lower

oesophageal sphincter dysfunction with nasogastric tubes and mechanisms in which nasogastric tubes make reflux and aspiration worse.

1.4.6. Nasogastric tubes as a cause of aspiration and pneumonia

Lower gastroesophageal sphincter

Before the discussion of how nasogastric tubes can cause aspiration, it is important to understand the structure and the mechanisms of the lower gastro-oesophageal sphincter (LES). The lower gastroesophageal sphincter is a physiological entity represented by an asymmetrical muscular thickening at the gastro-oesophageal junction and manometrically identified as a high pressure zone. Anatomically the LES is a 3 to 5 cm long segment of tonically contracted smooth muscle of which 1-2 cm is situated below the diaphragm. This pressure is exerted during resting conditions and is generated by an inward calcium leak with partial depolarisation of the smooth muscles which make up the LES. This leaves the sphincter in a state of tonic contraction preventing reflux from the stomach to the oesophagus[165].

Reflux of gastric content occurs[166]:

i) When the intrinsic LES pressure is primarily and permanently low
ii) Though the LES pressure is normal, it is only exerted on a limited area. e.g.: sphincter is too small
iii) During transient LES relaxation – Spontaneous LES openings unrelated to peristaltic contraction of the body of the oesophagus
iv) During respiratory fluctuation in the LES pressure
v) Increased gastric volume and delayed gastric emptying
vi) Presence of a nasogastric (NG) tube

The LES resting pressure varies from 7-25 mm Hg in relation to intra-gastric pressure and is measured by stationary manometry. The LES competency results from the combined effect of sphincter pressure, overall length of the sphincter and the length of the LES exposed to the positive pressure of the abdomen[167]. The LES is considered defective if any of these mechanical parameters fails and this will lead to gastroesophageal reflux which can be confirmed by 24 hour pH monitoring. LES pressure can be directly affected by intra-abdominal pressure, gastric distension, peptides, hormones, foods and many drugs[168].

The commonest mechanical cause for regurgitation through the LES pressure is inadequate length of its intra abdominal segment or an abnormally short total sphincter area. This will contribute to reflux as a response to the variation in the intra-abdominal pressure. A rise in the intra-gastric pressure beyond the intra abdominal pressure due to gastric dilatation can produce reflux if the LES pressure is low and especially if the intra gastric segment of the sphincter is too short. In addition gastric dilatation reduces the length of the lower oesophageal sphincter are making reflux worse.

The gastroesophageal junction is a specialised segment of the upper gastrointestinal tract designed to prevent reflux of gastric contents into the oesophagus. Two structures, namely the lower oesophageal sphincter and the crural diaphragm act together to generate this high pressure area. Swallowing reduces the lower oesophageal sphincter pressure to match the intra gastric pressure but the protective effect of the oncoming peristaltic wave prevents any reflux during this swallowing induces sphincter relaxation. Prolonged monitoring of the lower oesophageal sphincter pressure has shown that there are episodes of spontaneous sphincter relaxation which occur even in the absence of swallowing. Though this is commoner in patients with reflux oesophagitis, this phenomenon is also seen in normal healthy people. This phenomenon is called transient lower oesophageal sphincter relaxation

(TLESR) and occurs as a result of a balance being created between the intra-oesophageal and intra-gastric pressure, which is also called the common cavity phenomenon. This accounts for 98% of acid reflux episodes in normal subjects. This complex phenomenon is thought be a physiological response triggered by gastric distension. It is not clear whether transient lower oesophageal sphincter relaxation alone is responsible for gastro-oesophageal reflux disease [167].

Recent studies have shown that transient lower oesophageal sphincter relaxation is the main mechanism which is responsible for the gastro-oesophageal reflux. It involves prolonged relaxation of the lower oesophageal sphincter mediated by a vasovagal neural pathway synapsing in the brain stem. This is especially true in the presence of defective oesophageal peristalsis either due to various neurological disorders or prolonged exposure of the oesophageal mucosa to the reflux material. Acid reflux can lead to complications such as oesophagitis, Barrett's oesophagitis and eventually oesophageal carcinoma. Presence of hiatus hernia can further contribute the transient lower oesophageal sphincter relaxation. Drugs such as atropine, baclofen and loxiglumide have been shown to reduce the rate of transient lower oesophageal sphincter relaxation and the number of reflux episodes[168;169].

The lower oesophageal sphincter pressure can also change during respiration. These changes are directly proportionate to the depth of the inspiration and can be abolished by a skeletal muscle paralysing agent. Also intra-crural fibre contraction of the diaphragm during inspiration has been confirmed by crural diaphragmatic EMG and has a protective effect on the gastro-oesophageal reflux[170]. Electromyographic studies have also demonstrated that in delayed gastric emptying, oesophageal dilatation, vomiting or

eructation there is a reduction in the electrical activity of the crural fibres which favours gastro-oesophageal reflux[168;171].

1.4.7. Nasogastric tube feeding and aspiration

Nasogastric tube feeding is an effective and a safe method of providing nutrition in patients who have swallowing difficulties[172]. According to the latest Royal College of Physicians (RCP) guidelines, all stroke patients should have a screening test for their ability to swallow within four hours of admission[1]. The Royal College of Physicians Guidelines also recommend that a formal swallow assessment within the first 24 hours of admission by a speech and language therapist, a specially trained doctor or a nurse using standard tests and a nasogastric tube should be considered if they remain nil by mouth[1]. Patients who have mild to moderate dysphagia are commenced on a diet of modified texture and consistency, and patients with severe dysphagia or patients who are too drowsy to be assessed are kept nil by mouth and commenced on nasogastric feeds[172].

It is easy to presume that in patients who are nil by mouth, nasogastric feeds provide a safer method of providing nutrition without the risks of aspiration and pneumonia. In a study to examine the relationship between the incidence of pneumonia and oropharyngeal protective reflexes in 143 consecutive stroke patients over a period of two years, Nakajob *et al* showed that pneumonia was significantly lower in dysphagic stroke patients who are fed via nasogastric tubes rather than managed only on oral feeds[100]. Patients were grouped as oral feeding without dysphagia, oral feeding with dysphagia, nasogastric feeds with dysphagia and bedridden patients fed via nasogastric tubes. Further analysis of the study showed that reduced oropharyngeal protective reflexes were related to the incidence of pneumonia even in patients who were fed enteraly. Nasogastric tubes were only effective in

preventing pneumonia in mildly or moderately disabled stroke patients with attenuated protective reflexes. Bedridden severe stroke patients with severe dysphagia who were on enteral feeds had the highest incidence of pneumonia.

Though nasogastric tubes are designed to deliver feeds in to the stomach in patients with risks of aspiration and pneumonia, several studies have demonstrated that patients fed via nasogastric tubes continue to be associated with high risk of pneumonia[12;13;173]. Most of the early studies have been done in nursing homes and in patients with dementia. In a retrospective cross-sectional study of key predictors of aspiration pneumonia involving more than ten-thousand patients in nursing homes, Longmore *et al* demonstrated that tube feeding was the third strongest predictor for aspiration pneumonia out of 18 predictors[174]. A systematic review by Finucane *et al* to identify whether nasogastric feeds in patients with advanced dementia prevents aspiration pneumonia, improves survival, reduces the risk of pressure sores and infections or improves function and found no evidence that nasogastric feeds improved any of these important outcomes[175]. The latter review also reported that the risks were substantial and concluded that the practice of tube feeding should be carefully reconsidered in this population[175].

Even in patients with no previous swallowing problems or neurological disease nasogastric feeds have shown to increase the risk of reflux and aspiration. It has been demonstrated that in post-operative patients who needed a nasogastric tube following elective abdominal operations had an increased incidence of post operative pyrexia, atelectasis and pneumonia[140]. A study by Manning *et al* in post operative lower abdominal surgical patients using endoscopically placed lower oesophageal manometers and pH probes to record the pressure and the pH of the lower oesophagus showed that patients who had nasogastric tubes had lower oesophageal sphincter pressures and significantly more

episodes of gastro-oesophageal reflux than patients who did not have nasogastric tubes (a mean of 137 episodes of reflux as opposed to 8 episodes). Also the reflux episodes lasted longer and the drop in pH was greater in patients who had nasogastric tubes[157].

An association between enteral feeds and aspiration pneumonia in ventilated patients has been demonstrated even in older studies. A study by Pingleton *et al* in mid 1980s suggested that the presence of a nasogastric tube predisposed patients to aspiration and that the size of the nasogastric tube, the method of delivery, and the position of the patient also affected the incidence of aspiration pneumonia[176]. In addition work by the same author showed that gastric microbial growth increased after enteral nutrition and that the presence of an antacid or a H2 receptor antagonist favoured microbial colonisation by increasing the pH of the gastric contents[12;17].

Though thought to be a safe method of providing nutrition to a dysphagic or unconscious acute stroke patient, there are several studies that show nasogastric tubes only provide a limited protection against aspiration and pneumonia. Some studies also have demonstrated that dysphagic patients fed via nasogastric tubes have a high incidence of aspiration and pneumonia varying from 13% to 21% [10;76;177]. However, these incidences are low when compared to more recent studies which have demonstrated rates varying from 33% to 68%[178-180]. The relatively lower incidences in these older studies were due to the fact that patients who had an impaired level of consciousness were excluded, those would be expected to be at high risk of aspiration and pneumonia[179]. A study by Dziewas et al demonstrated that pneumonia occurred in 44% of tube fed acute stroke patients[178] and a prospective study by Langdon reported an incidence of pneumonia of 59% in 330 acute ischaemic stroke patients fed via nasogastric feeds who were followed-up for 30 days following stroke[180]. In addition, sub-analysis of data of the 'Turn-mob' program, a

physiotherapy program to reduce post-stroke pneumonia within 14 days following acute stroke, did not prevent pneumonia in the subgroup of patients who were enteraly fed who had a pneumonia incidence of 68.2%[181]. It has also been demonstrated that patients who are fed via nasogastric tubes have a high incidence of pneumonia, if there was associated gastro-oesophageal reflux. In a prospective study Satou et al has shown that 89% of enteraly fed patients developed pneumonia if there was associated reflux, as opposed to 42% if there was no reflux[13].

Table 1-2 Incience of Pneumonia in patients fed via nasogastric tubes

Study	Number of tube fed patients	Ventilated / Intubated	Other uses of nasogastric tube	Incidence of pneumonia
Langdon et al[180]	74	No	No	59%
Cuesy et al[181]	46	No	No	68.2%
Dziewas et al[178]	100	Yes	Gastric drainage during first 24 hours	44%
Hilker et al[177]		Yes	Unclear	Dysphagic patients 54% Ventilated patients 84%
Satou et al[13]	18	No	No	If associated with reflux- 89% If no reflux- 42%

1.4.8. Mechanisms in which nasogastric tubes and feeds predisposes pneumonia

Continued aspiration of pharyngeal secretions

Healthy elderly people produce an average of 0.1 to 0.3 ml/minute of saliva without stimulation and 1.0 to 1.5 ml/minute with stimulation[182]. Colonization of the oropharynx with Gram negative bacteria can occur within a few days of hospital admission, and the contaminated oral secretions can be aspirated causing pneumonia. The presence of a nasogastric tube does not prevent continued aspiration of infected oropharyngeal secretions and this is partly responsible for the high incidence of pneumonia in severely dysphagic patients even if they are managed nil orally and maintained on enteric feeds, especially in the presence of silent aspiration. A study by Dziewas *et al* in one hundred acute stroke patients fed via nasogastric tubes demonstrated that most patients who were on nasogastric feeds acquired pneumonia as early as the second or third day after stroke onset and was thought to be due to increased oropharyngeal secretions, impairment of laryngeal elevation and disruption of upper and lower oesophageal sphincters[178].

A literature review by Gomes *et al* confirmed that aspiration is the most common complication in enterally fed patients and demonstrated that the source of aspiration was accumulated secretions in the pharynx and reflux of gastric contents from the stomach[17]. Continuous presence of a nasogastric tube causing desensitisation of the pharynx making aspiration worse has been suggested[16]. It has been demonstrated that stroke patients in intensive care units who had suction of their sub-glottic space regularly had a lower incidence of pneumonia[183;184]. Also it has been demonstrated that edentulous patients developed less pneumonia in similar situations which may be due to the aspirated secretions containing fewer bacteria[185].

Worsening reflux

Studies have demonstrated that lower oesophageal sphincter dysfunction and reflux is made worse with nasogastric tubes. Scintigraphy studies have clearly demonstrated regurgitation of gastric contents and aspiration in patients who are fed via nasogastric tubes even without underlying neurological dysfunction[186;187]. Reduced lower gastro-oesophageal sphincter tone and gastric distension have been shown to be responsible for this reflux and aspiration[187]. Placement of a nasogastric tube is associated with a reduced gastro-oesophageal sphincter tone in children and development of gastroesophageal reflux[188]. In addition, nasogastric tubes can get displaced, can cause excessive gagging, retching and coughing, all of which can lead to regurgitation of gastric contents, which can result in aspiration[189]. In a patient with reduced upper airway protective reflexes, pharyngeal stimulation by a nasogastric tube can also increase the risk of aspiration by reducing the lower oesophageal sphincter tone[17].

Studies have shown that critically ill patients who are on nasogastric feeds have clinically silent micro-aspiration from the stomach, more frequently than witnessed large volume aspiration[190;191]. Some studies have shown that almost 90% of patients fed via nasogastric tubes had at least one episode of aspiration even though most were clinically silent[141;192]. Some studies have used oesophageal manometry and 24 hour oesophageal pH monitoring to demonstrate lower oesophageal sphincter dysfunction in acute stroke patients who are receiving nasogastric feeds[13;67]. A study by Lucas *et al* using oesophageal manometry demonstrated that that lower oesophageal dysfunction was a significant problem in acute stroke patients and often precludes safe gastric feeding[67]. Oesophageal sphincter pressures were significantly reduced following stroke, with an average lower oesophageal sphincter pressure of 14 mm Hg (normal 29 ± 2.6 mm Hg) and an average upper oesophageal sphincter pressure of 24 mm Hg (normal 47 ± 5.6 mm Hg). In this study feeding

jejunostomies were performed in patients with significantly low lower oesophageal sphincter pressures and the others had feeding gastrostomies. Even with feeding jejunostomies the patient population with lower oesophageal sphincter pressures had a syndrome of increased gastric and biliary secretion with regurgitation which required continued nasogastric suctioning during the first two weeks. Addition of a blue dye into the enteric feeds confirmed that oesophageal aspirates were not regurgitated jejunal feeds but originated from the stomach.

Not all micro-aspirations due to gastric reflux are associated with pneumonia. However, pneumonia occurred more in frequent aspirators, with an incidence four times higher in patients who aspirate gastric contents frequently when compared to the patients who aspirate infrequently. A study by Satou *et al* using 24hour oesophageal pH monitoring demonstrated that 63% of patients who were on nasogastric feeds after an acute MCA infarction had episodes of gastro-oesophageal reflux and two-third of these patients developed aspiration pneumonia. The incidence of aspiration pneumonia was significantly higher in patients who had gastro oesophageal reflux (89.9%) than patients who did not have gastro oesophageal reflux (42%)[13]. This study also showed that patients who had a left hemispheric lesion had significantly more episodes of gastro oesophageal reflux than patients with right-sided cerebral lesions though there was no difference in the pH of the reflux.

In addition to demonstrating sphincter dysfunction and reflux, it is also important to demonstrate gastric contents in the lungs to confirm the gastric source of aspiration. Using an enteral feed formula containing microscopic beads McClave *et al* found that 75% of nasogastrically fed critically ill patients had at least one microscopic aspiration during early course of their illness[25]. Another study to detect the presence of gastric enzyme trypsin in

tracheal secretions found that 320 of 360 critically ill patients who were fed via nasogastric tubes had at least one episode of micro-aspiration. This study also demonstrated that not all micro-aspirations were associated with pneumonia.

It is evident that the increased incidence of aspiration in stroke patients on fed via nasogastric tubes is due to a combination of several inter-related factors namely, loss of anatomical integrity of the lower oesophageal sphincter, gastroparesis, and reflux[17]. Feeding tubes provide no protection from aspiration pneumonia via the gastro-pulmonary route. Presence of pre-existing gastroesophageal dysmotility and hiatus hernia may also increase the risk of aspiration[103;193]. In addition, increase in the frequency of transient lower oesophageal sphincter relaxation has been suggested due to chronic stimulation of the pharynx by the nasogastric tube but further confirmation is needed to support this theory[194]. Desensitisation of the pharyngoglottal adduction reflux due to the presence of the nasogastric tube and an increase in the pharyngeal secretions and changes in the laryngeal elevation due to the presence of a nasogastric tube have been suggested by some researchers but all need further confirmation by larger studies[15;16].

Oropharyngeal colonisation

The bacterial composition of pharyngeal secretions is important as it is the main offending agent that enters the lower respiratory tract to cause aspiration pneumonia. A millilitre of saliva contains one hundred million to one billion bacteria when compared to clear water, which has only hundred to thousand bacteria per millilitre. Though saliva contains a large number of bacteria, most of them are not pathogenic and will not give rise to pneumonia. Gram negative bacteria found in hospitals and nursing homes can lead to colonisation of the oral cavity and pharynx in patients and that can lead to changes in the pharyngeal flora.

Presence of oral or dental disease, antibiotic therapy, systemic illness, reduction of salivary flow, and malnutrition predisposes to such colonisation[17].

The incidence of bacterial colonisation increases with the severity of the underlying disease. It has been demonstrated that colonisation with Gram negative bacteria occurred in 6% of normal,35% of moderately ill, and 73% of severely ill patients[18]. Reduction of salivary flow is an important risk factor and was commonly seen in these patients who are dehydrated and not fed orally. Adherence of micro-organisms to the epithelial cells plays an important role in pharyngeal colonisation. This is affected by multiple host and bacterial factors and increased by malnutrition and severe co-morbidities[195]. All these risk factors are commonly seen in patients with severe strokes who are kept nil by mouth.

The presence of a nasogastric tube itself predisposes to oropharyngeal colonisation, which can be made worse by accompanying poor oral care and being kept by nil by mouth[196;197]. It has also been shown that oral and dental disease, antibiotic therapy, systemic illnesses, malnutrition and reduction of salivary flow increase the incidence of Gram negative bacterial colonisation of the oral and pharyngeal mucosa in patients fed via nasogastric tubes[17;198]. Oropharyngeal mucosal cultures were more frequently positive for Gram negative bacilli (81%) in patients with a nasogastric tube than in patients who are fed by percutaneous gastrostomy (51%). The study also demonstrated that non-dysphagic orally fed controls only had a colonisation rate of 17.5%[22]. Leibovitz *et al* demonstrated that elderly patients with a nasogastric tube for at least 2 weeks develop oropharyngeal colonisation including adherent biofilm formation on the nasogastric tube by Pseudomonas organisms[22]. Also colonisation with Pseudomonas and other Gram negative bacilli was more frequent than in non-dysphagic orally fed controls. These organisms provide a reservoir contributing to aspiration pneumonia.

Gastric colonisation

Presence of a nasogastric tube also increases the incidence of colonisation of gastric contents with Gram negative bacteria[17;199]. Gastric acid prevents growth of bacteria and the contents of the stomach are sterile under normal circumstances. Colonisation of gastric contents with potentially pathogenic organisms can occur when the pH of the stomach is increased by the use of antacids, histamine H2 receptor blockers and proton pump inhibitors[200]. Gastric colonisation by Gram negative bacteria can also occur in patients who receive enteral feeding which neutralises gastric acid, patients with gastroparesis and in small bowel obstruction[17]. Several groups have reported cases of Gram negative pneumonia and bacteraemia in which the organism was also isolated either in the nasogastric feed or from the nasogastric tubing[201]. Reflux of infected gastric contents adds to the bacterial burden of already colonized pharyngeal secretions and aspiration from this pharyngeal pool of secretions is responsible for the high incidence of Gram negative pneumonia seen in these patients.

It has been reported that elderly patients on long-term NG feeds have a significantly higher prevalence of Gram negative bacteria in gastric juices than similar patients who are on oral feeds (73% Vs 13%)[23]. Pseudomonas aeruginosa and Klebsiella pneumoniae were the commonest organisms isolated. The authors also conclude that there was a reduction of stimulated salivary flow in patients who are on long-term NG feeds and there was a significant difference in the concentrations of sodium, amylase, phosphorus and magnesium. In addition, the concentration of uric acid, which is the main non-enzymatic antioxidant of saliva, was significantly lower in patients who received long-term NG feeds which favours bacterial colonisation[23].

Evidence of bacterial migration

In many instances in enterally fed patients, the bacterial contents of the pharynx and the stomach are the same. Though it is possible to differentiate whether the aspirate is gastric or pharyngeal by the assessment of the pH or by the presence of gastric enzymes, it is more difficult by assessing its bacterial content as in many instances the bacterial burden of the pharynx and the stomach are the same. In a study in ITU patients fed via nasogastric tubes, 87% had one or more similar organisms cultured simultaneously from the upper airway and stomach[202]. This is as the nasogastric feeds increases the gastric pH, which favours Gram negative bacterial colonisation of gastric secretions, and bacteria from the stomach can migrate upwards along the tube to colonise the pharynx and vice versa[203]. Segal *et al* studied the bacteriology of gastric juices of 52 patients who were fed via nasogastric tubes to assess the bacteriological burden of the gastric juice. In addition to gastric juice drawn after an overnight fast, cultures were taken from the oropharynx. Out of 107 samples pathogenic bacteria were isolated in 74% of stomach samples and 69% of oropharyngeal samples[24]. Gram negative bacteria and Staphylococcus aureus were the commonest organisms. Proteous species (26%) and Escherichia coli (22%) were the most common isolates from the gastric juices and Proteous species (24%) and pseudomonas species (21%) were the commonest from the oropharynx. Similarity in the composition of the oropharyngeal and gastric flora were observed indicating the passage of pathogenic bacteria in both directions. The gastric pH was higher than normal and this was highly correlated with the isolation of pathogenic bacteria. This support that in addition to the oropharynx, the stomach of the NG fed patients constitutes a reservoir of pathogens with the risk of aspiration pneumonia.

Bio-film formation

Recent studies have shown that oral colonisation of patients with NG tubes has led to development of bio-films on their feeding tubes[204-206]. Initial attachment of bacterial cells on to the surface of the nasogastric tube is followed by their multiplication and the production of an exopolysacharide which lead to biofilm formation. These biofilms are sessile cell communities attached to a surface and to each other, and are usually embedded in various polymeric substances produced by the bacteria[206]. Attachment of bacteria to biotic or abiotic surfaces as biofilms can enhance resistance to environmental stresses and provide protection from various disinfectants. The pH of the medium, nutrient availability and the nature of the abiotic surface can affect biofilm formation[207].

Enterobacter sakazakii is an organism that has been shown to form biofilms on latex, silicon, polycarbonate, glass, stainless steel, and polyvinyl chloride. This organism can cause bacteraemia, sepsis, meningitis and necrotizing enterocolitis[208]. Cronobacter sakazakii, salmonella serovars, and acinetobacter are other bacteria known to form bioflims on enteric feeding tubes. These films occur inside the lumen within 8 -24 hours of the tube being placed. Biofilm can inoculate subsequent feeds, clumps can get detached and be passed to the stomach where they can grow further and cause serious problems in susceptible individuals[205].

In summary, though nasogastric feeding is an easy and an inexpensive way of providing nutrition to stroke patients who are unable to swallow, the nasogastric tube itself predisposes these patients to aspiration and pneumonia by worsening oropharyngeal colonisation, worsening lower oesophageal sphincter dysfunction and reflux. In addition nasogastric feeds promote gastric colonisation of pathogenic bacteria by neutralising gastric acids, trans-migration of bacteria and bio-film formation. Reflux of infected gastric contents adds to the bacterial burden of already colonized pharyngeal secretions. Aspiration

from this infected pharyngeal pool of secretions is responsible for the high incidence of pneumonia observed in these patients. However, many stroke patients have to depend on nasogastric feeds until the swallow improves or a PEG tube is inserted. It is therefore important to investigate methods of reducing the risk of pneumonia in these patients.

1.5. Pneumonia following acute stroke

Following acute stroke, mortality in the first week is mainly due to the initial cerebral injury and the loss of several central regulatory centres. Cerebral oedema secondary to the acute brain injury reaches a peak within the first few days and can lead to raised intracranial pressure, malignant middle cerebral artery syndrome, and uncal or cerebellar coning which can result in a fatal outcome. In patients who survive the initial brain injury, the overall survival and prognosis depend on the occurrence of medical complications[6]. Davenport *et al* demonstrated that 59% of patients who survive acute stroke had medical complications which contributed up to 20% of post-stroke mortality. Nosocomial infections contributed to one third of these medical complications, commonest being pneumonia[4;5]. Urinary tract infection is the second commonest infection following stroke with incidences varying from 6% to27%. However, Urinary tract infections have been shown to have a lesser impact on neurological outcome and mortality than pneumonia[5].

The percentage of patients with an acute stroke surviving the initial neurological injury has improved due to the recent advances in management of hyper-acute stages of stroke and most stroke patients being treated in dedicated acute stroke units or neurological intensive care units [209]. This has lead to an increased in number of critically ill stroke patients surviving long enough to develop major medical complications such as pneumonia and pulmonary embolism. As previously described pneumonia is common following stroke and

significantly contributes to the post-stroke morbidity, mortality, length of stay and poor neurological recovery and outcome[5;10;89]. Therefore prevention of pneumonia is important. In patients who develop pneumonia, early and accurate diagnosis is important, as early initiation of appropriate antibiotics will improve survival. However, early diagnosis of pneumonia can be difficult in stoke patients as signs and symptoms of pneumonia can be masked by neurological dysfunction, old age and stroke associated immunosuppression. This section (1.5) discusses The British Thoracic Society Guidelines for the diagnosis of pneumonia and the effects of stroke on some parameters used for the diagnosis and prediction of pneumonia.

1.5.1. Effects of pneumonia in stroke patients

Studies have demonstrated that post-stroke infection, especially pneumonia is independently associated with poor functional outcome (Modified Rankin Scale > 2) after an ischaemic stroke[5;10;210]. Post-stroke infections were reported in 15% of patients and out of these 88% had a poor outcome at one year. A multicenter retrospective Canadian study demonstrated that development of pneumonia after stroke was associated with increased mortality at 30 days and 1 year, a longer length of stay and dependency at discharge[211]. A study by Kwan *et al* assessing 439 patients found that post-stroke infections can also affect patients admitted with transient ischaemic attacks as well as acute strokes and was associated with poorer short term outcome[212].

A recent systemic review and a meta-analysis on post-stroke infections involving 87 studies which included 137,817 patients showed that there was considerable heterogeneity between studies in infection rates and the criteria for the diagnosis of post-stroke infections. However, the overall pooled infection rate was 30% and rates of pneumonia and urinary tract infection were 10% each. The rate of pneumonia was considerably higher in patients

managed in intensive care units with an incidence of 45%. Studies which specifically evaluated rates of infection in stroke patients reported even a higher incidence of pneumonia, possibly due to the more rigorous methods of detection of pneumonia[213].

In stroke patients with pneumonia poor neurological outcomes are secondary to the resulting hypoxaemia that can affect the neurological recovery of the ischaemic penumbra. Pneumonia can impair neuronal survival within the ischaemic penumbra by causing hypoxia, fever and electrolyte disturbance[214;215]. Fever can increase the cerebral metabolic demands, promote acidosis and can change the permeability of the blood-brain barrier[216;217]. In addition recent studies have demonstrated that activation of the inflammatory cascade due to infection itself play a significant role in causing further damage to an already ischaemic brain[218]. Pro-inflammatory cytokines secondary to infection can up regulate adhesion molecules, recruit and activate leukocytes, promote leukocyte-endothelial interaction and convert local endothelium in the penumbra into a prothrombotic state[219]. Activation and adhesion of leukocytes may also cause disturbances to the microcirculation in the ischaemic brain tissue which can lead to enlargement of the necrotic zone and the ischaemic penumbra[117;196;220]. This activation of the inflammatory cascade is reflected in the peripheral circulation by increased hepatic synthesis of fibrinogen and C-reactive proteins (CRP). Studies assessing inflammatory markers have shown that increased CRP, fibrinogen and chitotriosidase levels (a very sensitive parameter of proliferation of activated macrophages) were significantly associated with worse neurological scores and poor functional outcomes. The entry of Gram negative bacteria into the blood stream can produce lipopolysacharide induced thrombosis through tumour necrosis factor release, activation of the extrinsic pathway, reduction of thrombomodulin and inhibition of the fibrinolytic system[221-223]. All these mechanisms can worsen penumbral

ischaemia resulting in larger infarct volumes, higher mortality and poorer functional outcome.

Pneumonia has been shown to be the commonest cause of death in the post acute phase, highest contributor to the mortality and accounting for nearly one third of all deaths following acute stoke[116;224;225]. A retrospective study on over 14,000 patients demonstrated a threefold increased risk of death among stroke patients who develop pneumonia after adjustment for stroke severity[226]. This association was recognised as early as 1980's and in a large prospective study, Wade *et al* found that 43% of patients with an acute stroke had swallowing difficulties when assessed within the first week and 35-40% of patients with an abnormal swallow following an acute stroke died within six months[227]. Also the aspirators were significantly more disabled than the non aspirators with worse neurological and functional outcomes at three months[89]. Inter-current pneumonia was a predictor of poor functional outcome following a stroke, others been a higher NIHSS score, dysphagia, impaired consciousness, urinary incontinence and raised body temperature on admission[228]. In addition, pneumonia remains the leading cause of death even after discharged from the hospital[120]. Though the incidence varies according to the patient population included and the diagnostic criteria used, aspiration and pneumonia can affect a significant proportion of patients who are dysphagic following acute stroke and contributes significantly to the mortality and morbidity following acute stroke[10].

Post-stroke pneumonia also significantly contributes to the economic burden of post-stroke management. In an American study the cost of hospitalisation of patients with post-stroke pneumonia was more than twenty thousand dollars, which was more than 3 times the cost of managing a patient without pneumonia[229]. Also patients who had post-stroke pneumonia were over 70% more likely to require further care following discharge. According to this

report, the annual cost of stroke associated pneumonia in the United States was more than 459 million dollars[229].

1.5.2. Timing of stroke associated pneumonia (SAP)

Pneumonia and pulmonary embolism have been identified as the leading causes of mortality between the second and fourth week following a stroke in the early 1990s[230]. These complications were attributed to a combination of immobility, reduced level of consciousness, and motor deficits[231]. More recent studies have shown many patients developed pneumonia earlier following their stroke rather than in the second week as shown in previous studies. A study by Hilker *et al* in stroke patients in a neurological intensive care units had shown that 21% of patients fulfilled criteria for the diagnosis of pneumonia and that 58% of these patients had symptoms and signs within the first 48 hours (range from 0 to 6 days)[177]. Further studies done on stroke units have demonstrated that pneumonia is an early complication with nearly half of the pneumonias occurring within two to three days of stroke onset and 70-80% of patients developed pneumonia within first week following stroke[117;178;184;232;233]. It is also possible that a significant number of these very early pneumonias were acquired prior to hospital admission due to aspiration at the onset of stroke, which is also referred as community acquired aspiration pneumonia by some clinicians[6;234].

Many studies do not provide a clear picture of the number of episodes of pneumonia in patients with acute stroke. This may be because they were conducted in Intensive Treatment Unit/Neurology Intensive Care Unit settings where the average length of stay of patients was 6 to 7 days[177]. Persistent swallowing difficulties and aspiration are common within the first two weeks after acute stroke and patients with persistent swallowing problems have a prolonged hospital stay[235;236]. Therefore it is possible that these patients

had recurrent bouts of pneumonia on another unit, which were not included in the data collection or analysis of the original studies.

Other reasons for high incidence of pneumonia in stroke patients

It has been reported that the frequency of infectious complications post-stroke is 23- 65%, significantly higher than the prevalence of hospital acquired infections in other hospital patients which ranges from 6-9%[237]. Eighty-five percent of patients who survive an acute stroke will have various medical complications of which infections account for 23% to 65%, and this is also true for patients in the rehabilitation phase[238]. Prospective studies report even higher incidences of medical complications which vary from 40% to 96% of patients[239]. This suggests that stroke patients are more susceptible to infection and the possibility of an immuno-suppressed state induced by stroke in these patients[240].

There is now a growing body of evidence that in addition to impairment of bulbar reflexes, dysphagia, a reduced level of consciousness and aspiration, central nervous system injury induced immunodepression (SIDS) plays a significant role in the development of post-stroke pneumonia[241;242]. Pneumonia accounts for the majority of these infections, but aspiration alone is not sufficient to explain the high incidence of pneumonia in stoke patients[88]. About 50% of healthy adults aspirate pharyngeal secretions during sleep without major consequences or pneumonia suggesting that there may be an additional immune dysfunction in patients following acute stroke[6]. Experimental and clinical observations have shown that central nervous system injury leads to an immune deregulation which increases the susceptibility to infections and this may explain bacteraemia and frequent pneumonia following even small volumes of oropharyngeal aspiration[241]. In a murine

model, intranasal aspiration of only 200 colony forming units of Streptococcus pneumoniae was sufficient to cause severe pneumonia and bacteraemia if it was preceded by transient middle cerebral artery (MCA) occlusion, but would have needed more than 200,000 units in otherwise normal animals.

It is thought that stroke-induced immunosuppression is due to complex interactions in the hypothalamic pituitary adrenal axis and is mediated by pro-inflammatory cytokines produced by the damaged brain tissue[241]. This results in increased cortisol production, activation of sympathetic nervous system, adrenal medulla and the cholinergic nerve pathway. Cerebral ischaemia triggers a rapid stress response in the hypothalamic pituitary adrenal axis leading to a large increase in corticotrophin and cortisol levels in the blood which is seen within 12 hours of cerebral ischaemia and is initiated by stimulation of the paraventricular nucleus of the hypothalamus to produce a surge of corticotrophin releasing factor. The resulting surge of glucocorticoids from the adrenal cortex suppresses the production of pro-inflammatory mediators and cytokines such as Interleukin-1β, tumour necrosis factor (TNFα), Interleukin -8, nitric oxide, and prostaglandins. It also facilitates the release of anti-inflammatory mediators and cytokines such as Interleukin-4, tumour growth factor-β, and Interleukin -10 and causes lymphocytic apoptosis[243]. This leads to reduced lymphocytic counts, impaired T-cell and natural killer cell activity and reduced mitogen and cytokine production. Severe strokes with larger volumes of infarcted tissue can lead to higher cortisol levels and worse outcomes. Activation of the locus coeruleus and adrenal medulla lead to an increase in catecholamine production which results in a shift from proinflammatory T-1 activation to anti-inflammatory T-2 activation[244]. A catecholamine mediated defect in early lymphocytic activation is thought to be the key factor in the impaired antibacterial immune response after stroke[242]. An associated deficiency of interferon-γ (INFγ) and impaired transfer of T- and natural killer cells can be

observed within 24 hours of an ischaemic stroke. Immuno-suppression following stroke can last for several weeks[242]. It has been demonstrated that infarct size was predictive of post-stroke infections and inversely correlated with admission and post-stroke T-cell counts[245]. Stroke volume was the only independent predictor for lymphopenia and monocyte dysfunction and respiratory infections[246]. Aspiration pneumonia in animals after focal cerebral ischaemia can be prevented by β-adrenoceptor blockage suggesting that immunodepression by sympathetic hyperactivity is a key factor for post-stroke pneumonia. In animal studies, treatment with IFN-γ early after focal cerebral ischaemia has been shown to reduce bacterial burden significantly. In addition IFN-γ deficiency and susceptibility to bacterial infections can be prevented by blocking the sympathetic nervous system, but not the hypothalamic adrenal pituitary axis[247]. Administration of the β-blocker propranolol reduces mortality after MCA occlusion in animal models. These observations suggests that immunodepression by sympathetic hyperactivity is important in the development of post-stroke pneumonia[219]. Targeting brain induced immune-suppression is a theoretically attractive strategy to prevent or minimise the incidence of post-stroke pneumonia. Further research is required for better understanding of the pro-inflammatory and anti-inflammatory cascades that follow an acute stroke. Therapeutic implications remain unclear. Better evaluation of how they translate from animal studies to humans is needed.

1.5.3. Diagnosis of pneumonia

Studies of pneumonia from several countries have used widely diverging definitions and inclusion criteria for the diagnosis of pneumonia. These include a combination of signs, symptoms, and radiological features[135;248;249]. The British Thoracic Society criteria for the diagnosis of pneumonia vary depending on the place of diagnosis and the facilities available e.g. in a primary care setting or in a hospital[250]. For patients seen in general

practice, the British Thoracic Society accepts a diagnosis without the aid of investigations or chest radiographs and relies solely on history and clinical features[250]. The diagnosis of pneumonia in hospital has to be supported by further investigations and a chest radiograph in addition to the physical signs of a chest infection, as it is the gold standard for the diagnosis of pneumonia

1.5.3.1. The diagnosis of pneumonia in the community setting

Studies have demonstrated that clinical signs and symptoms such as pyrexia >38°C, pleuritic chest pain, dyspnoea and tachypnoea in association with new and localizing clinical signs on physical examination of the chest such as dullness on percussion, bronchial breathing and inspiratory crackles provide adequate information for a reliable diagnosis of pneumonia[251;252]. In one study 39% of adults who were treated as lower respiratory tract infection and had new focal signs on chest examination had evidence of pneumonia on the chest radiograph when compared to only 2% of patients who did not have physical signs on chest examination[252].

However, another study in 71 patients demonstrated that the emphasis should be on the duration of symptoms and signs rather than on the combination of respiratory symptoms and signs alone which were of little value in differentiating patients with pneumonia confirmed by a positive chest radiograph from patients who did not have pneumonia[253]. A shorter duration of all these signs (less than 24 hours) had a significant positive predictive value for a clinical diagnosis of pneumonia. Statistical modelling of clinical signs to predict the presence of community acquired pneumonia in 1819 adults attending a hospital out-patient department with acute cough as their only symptom found that only 2.6% such patients had radiographic signs of pneumonia[251]. However, the study also demonstrated that a combination of clinical signs e.g. acute cough, temperature over 37.8°C, raised

respiratory rate (over 25 breaths per minute), sputum production throughout the day, myalgia, night sweats, combined with the absence of rhinorrhoea or sore throat had a sensitivity of 91% and a specificity of 40% for a diagnosis of pneumonia[251]. These studies demonstrate that a combination of good physical examination and interpretation of physical signs is as reliable as a chest radiograph for diagnosing pneumonia. Having more physical signs and considering the duration of symptoms adds to the strength of the diagnosis of pneumonia.

Therefore British Thoracic Society criteria for the diagnosis of community acquired pneumonia in the community have not included the need for a chest radiograph, though fulfilment of all four criteria are required for the diagnosis of pneumonia[250].

I. Symptoms of acute lower respiratory illness, such as cough and at least one other lower respiratory tract symptom such as tachypnoea, defined as a respiratory rate over 25 per minute, purulent sputum, or pleuritic chest pain
II. New focal chest signs on examination, such as dullness on percussion, crackles, or bronchial breathing on auscultation
III. At least one feature to suggest systemic infection (either the symptom complex of sweating, fever, shivers, aches and pains, or presence of a temperature of 38° Celsius or more
IV. No other explanation for the current illness

Although many patients with community acquired pneumonia can be managed in the community without investigations, clinical diagnosis of pneumonia without a chest radiograph can be inaccurate. There is no individual physical sign that is diagnostic of community acquired pneumonia, but the presence of normal vital signs and a normal chest examination make a diagnosis of pneumonia very unlikely[254]. This is further compounded

by inter-observer variability in eliciting and interpretation of physical signs[199;254;255]. In addition presence of co-morbidities such as left ventricular failure, chronic obstructive pulmonary disease and other chronic lung diseases can make interpretation of physical signs difficult. Older patients can commonly present with non-specific symptoms and will have minimal or absent signs of a respiratory illness[256]. Symptomatology can be different in an older person as they can present with non-specific symptoms such as confusion and absence of pyrexia is commoner than in a younger person[135;257]. Therefore a chest radiograph is preferred if such facilities are available.

The British Thoracic Society also has issued a set of guideline for the diagnosis of pneumonia in places where there are facilities to have a chest X-ray[250;258]. These are:

I. Symptoms and signs consistent with an acute lower respiratory tract infection as above (I to IV)
II. Shadowing in the radiograph which is at least segmental and was not known to be previously present and there is no other explanation for that shadow

1.5.4. Problems encountered with the diagnosis of pneumonia in stroke patients

Diagnosis of pneumonia based on clinical features alone can be even more difficult in patients with acute stroke. Due to muscle paralysis, lack of pharyngeal sensation, and reduced cough reflex, well recognised clinical symptoms of a lower respiratory tract infection such as cough and purulent sputum are commonly not observed in patients with large strokes[213]. In clinical practice, purulent sputum is often found only by oropharyngeal suctioning or during chest physiotherapy. In addition, most stroke patients are older and older people often do not manifest recognised signs of infection such as pyrexia and rigors[259]. Also stroke-induced immunodepression may affect a patient's ability to mount a

febrile reaction to infection[260]. Therefore relying on such symptoms alone will delay the diagnosis of pneumonia, especially in the early stages of acute stroke. Also a reduced level of consciousness, receptive dysphasia and muscle paralysis can affect the compliance needed for a good physical examination of the respiratory system. Poor inspiratory effort and the paralysis of the ipsilateral dome of the diaphragm can lead to collapse of the lower lobe, which can interfere with the interpretation of physical signs[261]. Hemiparesis can also involve the muscles of respiration and this leads to reduced voluntary inspiration and chest expansion, which will affect auscultatory signs such as bronchial breathing and inspiratory crackles[262]. Bilateral lower lobe collapse due to poor posture and reduced inspiratory effort can further affect the interpretation of physical signs[263]. Furthermore, co-existing illnesses such as left ventricular failure, fluid overload, chronic obstructive pulmonary disease or pulmonary embolism can produce chest signs that mimic pneumonia[5]. These problems are compounded by inter-observer variability in the interpretation of the signs as well as by the compliance and wakefulness of the patient[255].

Pyrexia of >38°C is a well recognised indicator of an acute infection. It is due to an immune response and subsequent release of proinflammatory cytokines[264]. However, older patients do not always mount a strong inflammatory response to infection and may not exhibit pyrexia[265]. A recent study assessing inflammatory responses in older persons has shown that patients who had microbiologically confirmed infections (pneumonia, UTI and cellulitis) had a mean temperature of 37.6 ± 0.9°C and patients who had probable infection according to International Sepsis Definition Conference (ISDC) criteria only had a mean temperature or 36.5 ± 0.58°C[266].

In stroke patients, interpretation of temperature as a parameter of infection is complex, as cerebral injury itself can increase the body temperature. A temperature >37.5°C is very

common early after stroke, occurring in up to 61% of patients[267]. Pontine haemorrhage is a well known pathology that produces hyperpyrexia[268]. Several studies have shown that large cerebral infarction are associated with increased body temperature and is a poor prognostic sign and a multitude of different inflammatory and biochemical mechanisms for this detrimental effect have been identified[215;269-271]. One study of 390 patients with acute stroke demonstrated that increased body temperature within six hours of admission was independently related to the infarction size, initial stroke severity, mortality and the outcome[270]. For each increment of a single degree Celsius in the body temperature, the relative risk of a poor outcome (measured as death or a low SSS) increased by 2.2 fold. A similar study in 725 consecutive severe acute stroke patients (SSS <25) who had a normal body temperature on admission, the body temperature started to rise 4 to 6 hours after stroke onset and a persistent elevation of temperature for 10 to 12 hours was related to poor outcome[269]. This initial rise in body temperature was not observed in mild to moderate strokes and an initial body temperature less than 37.6°C was not related to stroke severity or stroke outcome. The aetiology of fever after stroke is not always evident and even after a rigorous search the cause of the fever may remain elusive, leading to the assumption of 'central' or neurogenic fever in these patients[272]. Therefore, pyrexia is not a reliable sign for the diagnosis of an acute infection in acute stroke.

Severely ill immobile stroke patients are more likely to have portable chest radiographs rather than departmental radiographs as these patients are too ill to be moved out of the unit[273]. Also many such radiographs are performed in semi-supine or recumbent position rather than as erect postero-anterior view due to patient drowsiness and paralysis[274]. Poor positioning and inability to take in a deep breath and hold for a good inspiratory chest radiograph can affect the identification of radiological signs of pneumonia in the chest radiograph, especially on the lower zones[274]. Another study demonstrated that high

percentage of other diagnostic tests such as chest radiographs were falsely negative due to poor inspiratory effort or falsely positive due to mimics such as lobar collapse and pulmonary infarction[136].

Microbiological diagnosis can be difficult as it may not be possible to obtain a proper sample due to poor cough and contamination from oropharyngeal secretions[6]. It has been reported that 40% of patients in an intensive care setting with pneumonia were not able to expectorate and that the sputum cultures frequently were sterile due to concomitant or previous antibiotic treatment. In addition the results may not be reliable, as sputum may be contaminated by oropharyngeal commensal flora.

1.5.5. The role of microbiological investigations in the diagnosis of pneumonia

According to the International Sepsis Definition Conference (ISDC) 2001, the diagnosis of definite infection requires fulfilment of both clinical and microbiological criteria[275]. Patients with clinical manifestations of infection and radiological evidence of infection without microbiological confirmation are defined as probable infection and patients with clinical features of infection without established microbiological or radiological confirmation are defined as possible infection. As for the diagnosis of pneumonia microbiological confirmation should include isolation of an offending organism either in the blood or sputum cultures or presence of a positive serology.

Establishing a microbiological aetiological cause for pneumonia facilitates identification of resistant organisms and their antibiotic sensitivity pattern which allows narrowing down the spectrum of antibiotic used. This reduces the cost, the threat of antibiotic resistance and side effects such as antibiotic related diarrhoea. The British Thoracic Society guidelines

recommend blood cultures for all patients with suspected pneumonia[276]. Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and Klebsiella can be isolated in blood cultures. A positive culture is a highly specific indicator of microbiological aetiology and is a marker of the severity of the illness[277]. However, many patients with pneumonia do not have associated bacteraemia which are partly due to concomitant administration of antibiotics[277]. The sensitivity of blood cultures in pneumococcal pneumonia is at best only 25% [278]. Interpretation of blood culture results in patients with devices such as a central lines or indwelling catheters should be reviewed in relation to the clinical context. In immuno-competent patients a positive blood culture of a known skin commensal such as Staphylococcus albus is not considered as an aetiological organism for pneumonia, and is more likely to be due to contamination. The common organisms responsible for pneumonia are generally same for the young and the elderly, except for Mycoplasma pneumoniae and legionella infections which are less frequent in the older population and Haemophilus influenzae which is more commonly identified[279;280]. In nursing home residents Gram negative bacilli and anaerobes has been shown to occur more frequently than in matched elderly patients, likely secondary to chronic aspiration[281].

In stroke patients, the specific pathogen is often identified in only 25% of patients, even on tracheal culture or bronchoalveolar lavage[282]. Sputum cultures are most likely to be positive if the sample is purulent. Purulent sputum is defined as secretions of the lungs, bronchi or trachea that have more than 25 neutrophils and less than 10 squamous epithelial cells per low power field (x 100)[283]. Repeated production of purulent sputum over a period of 24 hours is more indicative of onset of infection in the lower respiratory tract rather than a single episode of purulent sputum or change in the colour or character of the sputum. Changes in the character of sputum refer to the colour, consistency, odour and the quantity

of the sputum. Though sputum cultures may identify the causative agent, they have a low sensitivity and specificity for the diagnosis of pneumonia for a number of reasons:

- Inability of patients to produce a good specimen
- Prior treatment with antibiotics
- Delay in transfer and processing of samples (mainly at weekends)
- Difficulties in interpretation secondary to contaminant upper airway respiratory flora which includes potential pathogens such as pneumococci and coliforms[284].

However, many stroke physicians do not depend on microbiological methods for the initial diagnosis and management of pneumonia due to poor yield and delay[285]. This is not uncommon in patients with other illnesses as prospective aetiological studies of non-stroke patients have demonstrated that a microbiological aetiology was not found in 45-60% of patients and, that the yield is even lower in hospitalized patients[278;286].

In many studies of post-stroke pneumonia, Staphylococcus aureus and Gram negative bacteria such as E coli, Klebsiella pneumoniae, enterobacter and Pseudomonas aerugenosa have been the most commonly identified organisms[6;234;287;288]. A study on post-stroke pneumonia on a neuro-intensive care unit demonstrated that Gram negative bacteria were implicated in 40% to 60% of patients and Staphylococcus aureus in 20% - 40% patients[177]. Streptococcal species, which is still the commonly isolated pathogen in community acquired pneumonia, is less commonly found in the sputum cultures of post-stroke patients. This is due to the early colonisation of oropharynx by Gram negative bacilli in these patients and aspiration of this endogenous material frequently being responsible for pneumonia. Irrespective of whether studies were performed on wards or intensive care units, the microbiological pattern was similar in early post-stroke pneumonia and this early

onset pneumonia is sometimes referred to as community acquired aspiration pneumonia[6;232;234].

In summary, the yields of cultures are not very high in post-stroke pneumonia and often no causative organism is isolated. This is partly due to the difficulties of obtaining a good sputum sample secondary to the neurological deficit, poor cough and lowered level of consciousness. Infections caused by anaerobic bacteria require special culture techniques for isolation which are not often carried out by laboratories. Local administrative problems such as delays in the specimen transportation to the laboratories and not processing sputum culture samples during a weekend can affect this yield even further. In addition, culture results which only state the presence of upper respiratory tract flora without identification of the predominant organism do not help establish the diagnosis. Also, some of the suspected pneumonia may have a different aetiology such as lobar collapse or a non infective aspiration pneumonitis due to regurgitated gastric contents which have not yet been infected by pathogenic organisms.

1.5.6. The role biochemical markers for the diagnosis of pneumonia

White blood count, C-reactive proteins, erythrocyte sedimentation rate, and procalcitonin are biochemical markers which are used for the diagnosis of any acute infection including pneumonia. Of these, white blood count and C-reactive proteins are commonly used to diagnose post-stroke pneumonia and will be described in more detail in this section.

White Blood Count

In the general population, including patients with acute stroke, a leucocytosis, white blood count (WBC) of more than 12 x 10^6/ml or leucopenia, a WBC of less than 4 x 10^6/ml, is highly suggestive of a bacterial infection. In a patient with a chest infection a WBC of more

than 15 x 10^6/ml strongly suggests a bacterial infection, but a lower count does not exclude this[289]. A WBC of more than 20 x 10^6/ml is an indicator of the severity of the pneumonia.

Changes in the WBC count have been shown in patients with ischaemic strokes with no infection. An increment in the neutrophil count can occur as early as day one following stroke and is related to the infarct volume, which is more pronounced with large infarcts[246]. The rise is smaller in strokes with low infarct volumes and the neutrophil count reaches the baseline by the fourth day following stroke. Lymphocytopenia is observed in strokes with large infarct volumes and is the basis of stroke-induced immuno-depression, which is discussed in detail in section 1.5.10.

In addition urea, electrolytes and liver function tests can be used to assess the severity of the pneumonia. For an example, a concentration of urea over 7 mmol/l is used as an indication of a severe pneumonia in combination with other symptoms and signs of pneumonia (Confusion, high Urea, Respiratory rate, Blood pressure and Age <65 = CURB65 score)[249]. However, the reliability of these scoring systems have not been assessed acute stroke patients and may be unreliable as indicators such as confusion may directly be related to stroke and high urea secondary to the reduced oral intake due to dysphagia.

C-reactive protein

C-reactive protein (CRP) is an acute phase protein, produced in the liver and has a normal plasma level concentration of less than 10 mg/l. Bacterial infection can rapidly increase CRP levels several-fold within a few hours and the levels may remain elevated until resolution of the active inflammation[290]. However, it is not very specific, as other illnesses such as pulmonary embolism, deep vein thrombosis, myocardial infarction, malignancies,

autoimmune diseases, vasculitidies, trauma and rheumatoid arthritis are associated with an elevated CRP. The main mediator stimulating CRP production is interleukin 6 (IL-6), but other proinflammatory cytokines such as tumour necrosis factors (TNF) and interleukin-1 (IL-1) have been also shown to be responsible.

Increased concentration of the CRP in the plasma is useful for the diagnosis of infection and determining the course of an infection[259]. Studies have demonstrated that high CRP levels within 24 hours of admission are predictive of a bacterial infection and that a fall in the CRP level is usually associated with resolution of the disease[291]. Assay of CRP is fast, readily available and inexpensive. However, the majority of studies of CRP have been done in young patients and in intensive care units. However, sub-analysis of data on various illnesses have shown that mean CRP levels were much higher in elderly patients with septicaemia than previously believed[292;293]. Earlier studies have suggested that CRP response to invasive bacterial infections may be delayed in frail elderly patients[294;295]. It has been suggested that a delayed IL-6 response, the main stimulator for CRP production, and impaired production of pro-inflammatory cytokines are responsible for this poor response of CRP[264;295]. However, more recent studies have shown the usefulness of CRP for the diagnosis of acute infections in an older patient[266;296-298]. A study done in 232 older patients with confirmed infection (pneumonia including aspiration pneumonia 34%, urinary tract infection 21%, cellulitis 27% and exacerbation of chronic obstructive pulmonary disease 7%) demonstrated that a significant elevation of CRP within 24 hours of hospitalisation was predictive of a bacterial infection and a CRP level of 60 mg/l had the best combination of sensitivity, specificity and predictive value though this concentration was lower than previously published[291;297]. Large prospective studies have demonstrated that a high CRP reading within 24 hours of admission to the hospital in older people was highly predictive of an acute infection[266;291].

CRP levels have an important role in the monitoring of patients with pneumonia[299]. The median time for a 50% reduction of CRP level was 3.3 days following treatment and CRP levels which do not fall by 50% within 4 days of initiation of treatment suggest failure of treatment or development of complications such as empyema or antibiotic associated diarrhoea[299]. CRP may also provide a clue to the aetiology of the pneumonia as pneumococcal pneumonia is associated with a higher CRP level than viral or mycoplasma pneumonias [300;301]. An arbitrary cut-off of 100 mg/l has been used as a marker to help distinguish pneumonia from an exacerbation of chronic obstructive pulmonary disease[299].

It has been demonstrated that a raised CRP level on admission is a more sensitive marker for the presence of pneumonia than a raised WBC count or an increased temperature and that the majority of patients with pneumonia on admission had a CRP over 50 mg/l[300]. Further analysis demonstrated that 75% of patients with pneumonia had a CRP of over 100 mg/l and that CRP levels were higher in patients who did not receive antibiotics prior to admission[300]. Some studies have demonstrated that a cut-off value of 40 mg/l was sufficient in older patients with bacterial infections and a CRP level of 60 mg/l provided the optimal combination of sensitivity, specificity, and predictability for an underlying infection rather than a non-infective aetiology[264;266]. Another study demonstrated that a cut-off value for sepsis should be 80 mg/l irrespective of the age of the patient[302].

There is emerging evidence on the peripheral inflammatory response following stroke. In a prospective study in 36 patients with acute ischaemic stroke Emsley *et al* showed that the CRP levels were elevated on admission (4 mg/l), relative to age matched controls (2 mg/l) ($p = 0.01$)[220]. The greatest elevation was observed at 5-7 days from stroke onset (18 mg/l) ($p < 0.001$). Similar results have been demonstrated in other studies and high CRP levels

within first week have shown to be associated with unfavourable outcomes, recurrence of stroke and other cardiovascular events[303;304]. This very early increase in the inflammatory markers may either be induced by stroke itself, or may indicate a pre-existing inflammatory condition which may have contributed to the development of stroke. A prospective study in 51 acute stroke patients demonstrated that an increased level of CRP on the day of admission was associated with an ongoing infection and resulted in poor neurological outcomes[218]. However, the study concluded that the infection was acquired prior to stroke onset and the resulting inflammatory process predisposed these patients to have a stroke rather than infection was acquired following stroke.

1.5.7. The role of the chest radiograph in the diagnosis of pneumonia

New infiltrates detected in the chest x-ray concomitant with signs and symptoms of a chest infection have been the key requirement for the diagnosis of hospital acquired pneumonia. Many studies of pneumonia use chest radiograph as a prerequisite for diagnosis of pneumonia. However, there have been questions about the reliability of the chest radiographs if done too early in suspected pneumonia cases. Studies have demonstrated that the initial chest x-ray lacked sensitivity and in suspected community acquired pneumonia chest radiograph may not demonstrate any parenchymal change in up to 21% of patients[273;305]. In addition more than half of the patients who had a negative chest radiograph on admission went on to develop radiographic infiltrates within 48 hours[273]. Another study demonstrated that a chest radiograph was not always necessary for the diagnosis of pneumonia as combined cough, purulent sputum, fever, tachycardia, tachypnoea and abnormal chest signs had a sensitivity of 95% and specificity of 56% of predicting pneumonia[306]. The study also suggested that chest radiographs were unnecessary

in patients with acute respiratory symptoms, if their vital signs and physical examination finding are within normal limits.

Even in hospitalised patients, chest radiographs done too early lack sensitivity in diagnosing pneumonia as a review of chest radiographs on hospitalised patients with final clinical diagnosis of pneumonia found that in one third of patients the initial radiograph had no evidence of pneumonia[305]. In this study, though many clinical characteristics were similar between patients who were radiologically asymptomatic, those with symptomatic chest radiographs on admission were older (73 years versus 68 years) and had greater pneumonia specific severity illness scores. Both groups had similar rates of positive sputum and blood cultures. However, microbiology was different as streptococcus pneumonia was more common in patients with chest x-ray confirmed pneumonia than in the patients who had normal chest radiographs, in whom other streptococcus species and Gram negative bacilli were more frequent. In-hospital mortality was similar in both groups. This study concluded that patients who were admitted with signs and symptoms of pneumonia with no confirmation in the chest radiographs had serious lower respiratory tract infections with substantial rates of bacteraemia and mortality. It has been suggested that absence of radiographic findings should not supersede clinical judgement and empirical treatment[305].

Though the lower lobes are affected commonly regardless of the aetiology, there are no characteristic radiographic features to predict the likely pathogen[258]. However, certain radiographic appearances are more likely to be associated with particular organisms such as pneumonia caused by Staphylococcus aureus is more likely to present with multi-lobar shadowing, cavitation, pneumatoceles and spontaneous pneumothorax. Also Klebsiella pneumonia commonly affects the upper lobes (especially on the right), and may be associated with a bulging interlobar fissure and abscess formation with cavitation[307;308].

Homogenous shadowing is less commonly seen in mycoplasma pneumonia. Multifocal involvement and pleural effusion at presentation are more likely due to bacteraemic pneumococcal pneumonia than with non bacteraemic pneumococcal pneumonia.

Hospital acquired pneumonia is defined as pneumonia which occurs after 48 hours of hospitalisation. Criteria for diagnosis of hospital acquired pneumonia may vary according to the healthcare system and country. The United States Centre for Disease Control criteria for hospital acquired pneumonia requires the presence of radiological changes in two or more serial chest radiographs with at least one of new or progressive and persistent infiltrate, consolidation, cavitation or pneumatocele. In patients without underlying pulmonary or cardiac diseases such as chronic obstructive pulmonary disease, respiratory distress syndrome, broncho-pulmonary dysplasia and pulmonary oedema, one definite chest radiograph is acceptable if the clinical and microbiological criteria for the diagnosis of pneumonia are fulfilled[309].

In patients with pre-existing pulmonary or cardiac disease non-infective conditions such as pulmonary oedema, pulmonary embolism and congestive cardiac failure may simulate signs of pneumonia. In the presence of such medical conditions, serial chest radiographs are required to distinguish these non-infective conditions from an infective pathology. It has been suggested that a comparison of radiographs at diagnosis, three days before diagnosis and days two and seven after diagnosis of pneumonia should be done if available. Clinical features of pneumonia have a rapid onset and progression but radiological findings do resolve more slowly and may persist for several weeks. In addition a rapid radiological improvement suggests a non-infective process such as atelectasis or congestive cardiac failure rather than pneumonia[309].

There are many radiological terms describing the radiographic changes of pneumonia such as “air space disease”,” patchy areas of increased density”, and “focal opacification”. In addition some radiological reports do not use the term pneumonia. However, in the appropriate clinical setting such descriptive terms are considered as positive radiological findings for the diagnosis of pneumonia[309].

In critically ill patients with extended hospital stay there may be multiple episodes of hospital acquired pneumonia. For the diagnosis of recurrent hospital acquired pneumonia, evidence of the initial infection, a combination of new signs and symptoms and new radiological evidence are required. Identification of a new pathogen or a change in the pathogen alone is not adequate for diagnosis of a new episode of pneumonia[309].

Radiological resolution frequently lags behind clinical improvement, especially following bacteraemic pneumococcal pneumonia and legionella pneumonia. It has been demonstrated that complete resolution of chest radiographic changes was seen at 2 weeks in 51% of cases, by 4 weeks in 64%, and in 73% in 6 weeks. Radiological resolution is slower in older persons, in patients with multi-lobar involvement, in smokers, and in hospitalised patients rather than patients in the community[258].Radiological deterioration following admission to a hospital is more common in older patients and in staphylococcal pneumonia[307]. Radiological changes of pneumonia caused by atypical pathogens improve faster than when the pneumonia is caused by other bacterial organisms[310]. A multivariate analysis showed only age and multi-lobular involvements were independently related to the rate of radiological resolution[258].

Studies of the role of CT chest scans for the diagnosis of pneumonia are limited. One study has shown CT scans improve the accuracy of the diagnosis of community-acquired

pneumonia when compared with chest x-ray alone[311]. Also CT scans are more sensitive and can be used in subjects where the diagnosis is in doubt[312]. However, in usual hospital practice CT scanning has a limited role as an investigative tool due to the cost, availability, time required and use of radiation.

1.5.8. Risk factors and clinical predictors of pneumonia

In view of the high morbidity and mortality associated with aspiration and pneumonia, physicians need to identify stroke patients who are at risk of pneumonia and provide intensive preventative interventions to such patients. Until recently most of the studies of risk factors for pneumonia were performed in patients managed on intensive care units, in which stroke patients only formed a small proportion of the patient population.

Risk factors for post-stroke pneumonia

A depressed level of consciousness, tube feeding, immobility, endotracheal intubation, mechanical ventilation, stroke location, reduced pharyngeal sensation, and abnormal voluntary cough were all positively correlated with risk of aspiration in videofluoroscopic studies[77;313;313]. However, there have been only few studies prior to the last two decades that reviewed the association of these variables with the development of pneumonia. A study on 103 patients with head injury demonstrated that the incidence of microbiologically proven pneumonia was 21% and the risk factors for the development of pneumonia were presence of a nasogastric tube, continuous enteral feeds, mechanical ventilation more than a day, use of H2 receptor blockers, use of intense sedation, muscle relaxants, use of barbiturates and corticosteroids, intubation, craniotomy, and positive end expiratory pressure ventilation[314]. However, the mean age of these patients was 41 years and considering other patient criteria and the therapeutic interventions received, these patients

were significantly different to patients managed on stroke units who will have a different risk factor profile.

Studies new and old have identified that poor oral health and the presence of oral pathogens as risk factors for pneumonia following acute stroke [76;232 315;316]. In a retrospective study in 378 consecutive stroke patients, Langmore *et al* has suggested a stage model for predicting aspiration pneumonia, which included dependence of oral care, reduction in salivary flow (due to reduced production and medication), altered oral flora, increased concentration of bacteria in saliva and aspiration[317]. The study also demonstrated that patients who had a history of chronic obstructive airway disease had a higher risk of post-stroke pneumonia and patients with diabetes and hypertension developed pneumonia early in their post-stroke period[317].

Table 1.3 shows various clinical predictors for post-stroke pneumonia which have been identified by some recent studies. Many have identified stroke severity (clinical and/or radiological assessment), dysphagia, unsafe water swallowing test, old age, a reduced level of consciousness, and mechanical ventilation as highly predictive of pneumonia. In a landmark study on stroke patients managed in a neuro-intensive care unit, Hilker *et al* demonstrated that a reduced GCS on admission (<8/15), a large neurological deficit, presence of dysphagia endotracheal intubation, and mechanical ventilation were significant risk factors for stroke associated pneumonia[177]. The risk of pneumonia was highest in the acute stage and in patients with non lacunar strokes in the middle cerebral artery territory. The study also demonstrated that posterior circulation strokes and multifocal infarctions in various vascular territories also had a higher incidence of pneumonia due to a cumulative effect on swallowing reflex, bulbar palsy and aspiration.

Predictors of post-stroke pneumonia

Pre-existing abnormalities in the chest radiograph was also a predictor of stroke associated pneumonia as it was demonstrated in an earlier study[318]. These may be an indicator of silent aspiration, increased susceptibility of the lung to infection or of early pneumonia[177;318]. A more recent prospective study in 236 acute stroke patients on a neurological intensive care unit demonstrated more detailed independent predictors for stroke associated pneumonia which included dysphagia, a NIHSS score 10 or more, non-lacunar basal ganglia infarction, and any other infection present on admission. These risk factors could predict stroke associated pneumonia with 76% sensitivity and 88% specificity. In addition, the study also demonstrated that patients with lacunar infarctions had significantly lower risk of developing pneumonia and patients with a reduced level of consciousness and vomiting did not respond well to the initial course of antibiotics[233].

In one of the first studies of predictors for post-stroke pneumonia conducted on a stroke unit, Dziewas *et al* demonstrated that a decreased level of consciousness and the presence of severe facial palsy were independent predictors for post-stroke pneumonia[178]. A high NIHSS score on admission was an independent predictor of a poor outcome according to this study. A decreased level of consciousness has also been identified as a risk factor for aspiration and pneumonia in patients with other non-stroke neurological disorders as it is associated with a reduction of protective reflexes and impairment of the coordination between breathing and swallowing[127]. In contrast, the association of severe facial palsy and aspiration is stroke specific and may reflect the effects of co-existing weakness and incordination of the tongue and the oropharyngeal musculature.

A prospective trial of predictors of pneumonia in acute stroke patients which included 412 patients with ischaemic and haemorrhagic strokes demonstrated that age over 65 years, an

abbreviated mental test (AMT) score of less than 8, dysarthria or dysphonia, a modified Rankin scale score of four or more and failure of the water swallow test were major predictors of post-stroke pneumonia. The presence of two or more of these risk factors predicted pneumonia with 91% sensitivity and 76% specificity[319]. However, the study did not demonstrate the presence of chronic obstructive pulmonary disease, reduced salivary flow or multiple medications as predictors for development of pneumonia, which is in contrary to common consensus[319]. This study has been criticised as abbreviated mental test is not performed routinely in stroke patients and may be unreliable soon after a stroke.

Scoring systems for prediction of stroke associated pneumonia

Several scoring systems have been introduced to formally predict the risk of pneumonia in stroke patients. In a retrospective study, Chumbler et al reviewed data of 1363 stroke patients admitted to several regional hospitals between 1998 and 2003 to formulate and validate a scoring system for predicting stroke associated pneumonia[320]. Points were assigned scored for an abnormal swallow test and a history of pneumonia (4 points), the NIHSS score (3 points), patients being found face down at the time of stroke onset (3 points), and age over 70 years (2 points). A 3-level classification system was created denoting a low, median and a high risk of pneumonia. The rate of pneumonia was 2% for the low risk group, 4% for the medium risk group and 23% for the high risk group[320]. Recently, a simpler 10 point scoring system was introduced to predict the risk of post-stroke pneumonia. After reviewing data on 15,335 patients and using multivariable regression analysis, independent predictors of pneumonia were translated into a point scoring system, the A(2)DS(2) score. The points are scored as: Age over 75 year = 1, Atrial fibrillation = 1, dysphagia = 2, male Sex = 1, stroke severity, NIHSS 0-4 = 0, 5-15 = 3, above 16 = 5. The risk of pneumonia varied between 0.3% in patients with a score of 0 and 39.4% in patients with a score of 10[321]. Prediction and calibration properties were

reproduced in the validation cohort consisting of over 45000 patients with ischaemic strokes.

Table 1-3 Clinical Predictors of Pneumonia in stroke patients

Author	Clinical predictors
Langmore et al 1998[317]	• comorbidities such as hypertension and diabetes • chronic obstructive airway disease • multiple cerebral infarctions • aspiration on videofluoroscopic studies
Hilker et al 2003 [177]	• a reduced GCS on admission (<8/15) • a large neurological deficit • endotracheal intubation • mechanical ventilation • presence of dysphagia • non lacunar strokes in the middle cerebral artery territory • posterior circulation strokes • multifocal infarctions in various vascular territories
Dziewas et al 2004[178]	• a decreased level of consciousness • a high NIHSS score • presence of severe facial palsy
Sellars et al 2007[319]	• age >65 years • a low abbreviated mental test score <8 • dysarthria or dysphonia • a modified Rankin scale score of four or more • failure of the swallow test • stroke severity (total anterior circulation stroke) • initial NIHSS score more than 6 • a lower serum albumin level
Walter et al 2007[233]	• age >73 years • impaired vigilance • dysphagia, NIHSS >10 • non-lacunar basal ganglia infarction • any other infection present on admission • combined brain stem and cerebellar infarctions • infarctions affecting >66% of the middle cerebral artery territory • hemispheric infarctions exceeding middle cerebral artery territory • mechanical ventilation • cardio-embolic strokes

1.5.9. Methods used in clinical trials to establish the diagnosis of pneumonia in stroke patients

Criteria for any patient group

There are several standard criteria for the diagnosis of pneumonia relevant to any patient group. The BTS guidelines for the diagnosis of pneumonia were discussed earlier. The criteria of the US Centre for Disease Control and Prevention (CDC) for the diagnosis of pneumonia are another standard criteria which has been commonly used[322]. According to these guidelines at least one of the first (A) and one from the latter (B) criteria should be fulfilled in addition to new onset pulmonary infiltrates on the chest radiograph to make a definite diagnosis of pneumonia is made.

A) Abnormal respiratory examination- new onset crackles, signs of consolidation
B) Investigations to suggest an ongoing infection- positive microbiological cultures from the blood or lower respiratory tract, leucocytosis and elevation of inflammatory markers

Criteria used in stroke research

Owing to the complexity of the signs and symptoms of pneumonia in stroke patients and to problems related to biochemical and microbiological investigations, different studies have included various combinations of signs, symptoms and laboratory reports for the diagnosis of pneumonia. After reviewing the literature on stroke associated pneumonia from 1985 to 2010, it was apparent that many studies did not adhere to standard criteria for the diagnosis of pneumonia and that the diagnostic methods differed between studies. Also most of the studies of stroke associated pneumonia were undertaken in patients in an intensive care setting and a significant proportion of patients were intubated and ventilated. However,

most studies included new development of inflammatory shadowing on the chest radiograph as an essential criterion for the diagnosis.

Few stroke studies have used criteria of the US Centre for Disease Control and Prevention (CDC) with some modifications for the diagnosis of pneumonia. Some studies have used another set of standardized criteria, commonly referred as MANN'S criteria for the diagnosis of pneumonia. These require three or more of the following characteristics to be fulfilled: temperature over 38°C, productive cough with purulent sputum, abnormal respiratory examination, abnormal chest radiographs findings, arterial hypoxia, and isolation of a relevant pathogen on the Gram stain or by culture[10]. Patients who do not fulfil these criteria, but where a clinical diagnosis was made by the attending physician, these patients were considered to have a suspected pneumonia[319 10].

Table 1.4 lists details of various diagnostic criteria used by various authors for the diagnosis of stroke associated pneumonia. Many studies have considered varying combinations of tachypnoea (respiratory rate >22/min), tachycardia, inspiratory crackles and bronchial breathing as abnormal respiratory examination. Hypoxia has been defined as pO_2 <70 mm Hg or oxygen saturation <94% by many authors. The temperature requirement was higher in older studies (38°C) though more recent studies only required temperatures of 37.5 – 37.8°C. Many studies had a total WBC >11 x 10^6/ml or <4 x 10^6/ml as abnormal though some required higher a value as 12 x 10^6/ml. Presence of leucocytosis or a microbiological diagnosis was not always required and CRP as an inflammatory marker was used only in few studies. A positive chest radiograph was a requirement in many studies.

However, in some studies the diagnosis of pneumonia was vague and non-standardised and some had not defined or described pneumonia and the clinical diagnosis of the attending clinicians were taken from case notes retrospectively[27;319;323]. Even in a landmark study on oral selective decontamination by Gosney *et al*, the diagnosis of pneumonia was made by the clinical-care team, usually when patients were commenced on antibiotics.

Diagnosis of aspiration pneumonia

Development of pneumonia following a witnessed aspiration was considered as aspiration pneumonia in many studies. Some studies diagnosed aspiration if enteral formula was suctioned from oropharyngeal secretions. Most studies described above had broader diagnoses such as stroke associated pneumonia or ventilator associated pneumonia rather than trying to identify aspiration pneumonia as a separate entity. It may be that in stroke patients and patients in an ITU on whom most of the studies were done, silent aspiration is commoner than witnessed aspiration. Radiological evidence of infiltrates in a characteristic broncho-pulmonary segment which is known to be affected by aspiration could have been used for the diagnosis of aspiration. However, no study had done the necessary radiographs to view these segments or reviewed the existing radiographs in such detail. Also the reported frequency of aspiration in enterally fed patients depended on how aspiration was clinically defined (either silent or symptomatic) and the method of diagnosis of aspiration (Pepsin Analysis, radionuclide tagged feeds).

In summary, studies had varying diagnostic criteria and did not have a gold standard for the diagnosis of pneumonia. A positive chest radiograph was a requirement in many studies and the validity of some components such as purulent sputum, cough and fever were doubtful.

Table 1-4 Criteria for the Diagnosis of Pneumonia

Author	Diagnostic criteria
US Centres for Disease Control and Prevention (CDC) 2004[322]	At least one of: • abnormal respiratory examination • pulmonary infiltrates on the chest radiograph And, at least one of: • productive cough with purulent sputum • positive microbiological cultures from the lower respiratory tract • leucocytosis • increased CRP levels
"Mann" criteria Mann and Hankey 1999[10]	Three of the following criteria • fever >38°C • productive cough • abnormal respiratory examination [respiratory rate >22 per minute/crackles or bronchial breathing/arterial hypoxia (pO_2 <70 mm Hg or oxygen saturation <94% or PaO2 <9.3kPa)], • tachycardia • abnormal chest radiograph • culture of a relevant pathogen
Kammersgaard et al 2001[324]	At least 2 of: • fever >37.5°C • total leucocytes >9000 /ml • positive chest radiograph • positive results from microbiological analysis
Kwan and Hand et al 2007[212]	• presence of relevant clinical symptoms and/or signs (example purulent cough, unilateral inspiratory crackles, bronchial breath sounds) with at least one of: • fever >37.5°C • leucocytosis • a positive chest radiograph
Vogelgesang et al 2008[325]	• Presence of clinical signs • CRP >50 mg/l • procalcitonin >0.5 ng/ml
Chamorro et al 2005 Urra et al 2009[241;245]	• temperature >37.5°C in two determinations • temperature >37.8°C on one occasion in patients with suggestive symptoms (example: cough, dyspnoea, pleuritic pain) • total white cell count 11,000 /ml or <4,000 /ml • pulmonary infiltrates on the chest radiograph • positive results from microbiological analysis
Schwarz et al 2008[29]	• new infiltrates in chest radiographs plus at least one of:

	• fever >38°C • total white cell >12,000 /ml or <3,000 /ml • purulent tracheal secretions
Tanzi et al 2011[326]	• clinical signs or symptoms (fever and/or productive cough and consolidation on chest radiograph) • positive Gram stain/culture

1.6. Prevention of pneumonia in stroke patients

Prevention of pneumonia is important for the general wellbeing of an older person and even more following stroke as it will reduce mortality, morbidity and length of hospital stay. As an individual becomes older, the incidence of pneumonia increases and this is associated with a rise in mortality[327]. Changes in host defences such as reduced IgG and lymphopenia, co-existing illnesses, concurrent medication that can affect swallowing and respiratory secretions, changes in the oral bacterial flora secondary to the use of dentures and poor oral care, and age related changes to the swallowing mechanism have been shown to be responsible for the high incidence[328;329]. In this section, the methods to prevent post-stroke pneumonia have been discussed under two headings. Initial general review of non-phramacological measures of pneumonia prevention is followed by a more detailed review on drug therapies which have been used to prevent pneumonia following stroke. As my research project is on metoclopramide a detailed review of literature, following steps which would be undertaken for a systematic review, was conducted on drug therapies which have been used to prevent post-stoke pneumonia.

1.6.1. General measures

1.6.1.1. Vaccination

Vaccination against Influenza given once a year has been shown to reduce influenza, viral pneumonia and secondary bacterial pneumonia in people over the age of 65 years[330]. It has been shown to reduce the number of febrile days and all other respiratory conditions associated with influenza[331]. There is also evidence that polyvalent pneumococcal vaccine reduces the incidence of pneumococcal pneumonia in older people and in patients who have other risk factors such as COPD[332]. This vaccination is now recommended for all

adults over the age of 70 years[333]. While there is no specific evidence of its effect in patients with stroke, in vaccination of a wide range of older people will reduce pneumonia risk in vaccinated patients who subsequently develop a stroke.

1.6.1.2. Oral hygiene

Aspiration of colonised oropharyngeal secretions is an important risk factor for development of aspiration pneumonia in an older person[334]. Studies have shown that older patients receiving good oral care had a lower incidence of pneumonia than patients who did not have oral care and reduced oropharyngeal colonisation and inflammation [335]. In addition, poor denture care has been shown to promote bacterial growth in oropharyngeal secretions with an increased incidence of aspiration pneumonia, and nursing home residents who received intensive oral care had a lower incidence of pneumonia than residents who had usual oral care[185;336;337]. The importance of good oral care is not limited to nursing home residents; a study in patients on intensive care units which included all ages demonstrated that regular dental plaque decontamination reduced dental plaque growth and incidence of pneumonia when compared to standard care[338]. Therefore, good regular oral care and denture care is important to reduce the incidence of pneumonia.

1.6.1.3. General clinical care

The gastro-intestinal tract is a potential source of Gram negative bacteria which can give rise to pneumonia[339]. Inappropriate use of antibiotics or antibiotic prophylaxis can promote colonization with drug resistant organisms or select a resistant strain in the oropharynx which can be aspirated [339]. In addition, antibiotic induced vomiting may increase the risk of aspiration. Elevation of gastric pH due to antacids and proton pump inhibitors increases the risk of bacterial overgrowth in the stomach[176;202;340]. Thus, having strict antibiotic policies,

avoidance of unjustified antibiotic treatment and of proton pump inhibitors could potentially reduce the risk of pneumonia.

Though there is a progressive reduction of the swallowing reflex and pharyngeal sensation with age[341;342] it is not associated with an increased risk of aspiration as there is no significant impairment in laryngeal protective mechanisms or in the cough reflex with age[343]. However, the use of sedatives and narcotics has been shown to depress the cough reflex in older people, especially during sleep[127]. Thus, avoidance of such medications or limitation of their use will reduce the risk of aspiration during sleep[127].

Regular hand washing and use of barrier techniques to prevent cross-infection have been recognised as important methods in the prevention of nosocomial infections[344;345]. Appropriate handling of mechanical feeding devices, respiratory devices, suction apparatus and maintenance of a safe distance between patients' beds also reduces cross infection in hospital patients including those with a stroke[346].

1.6.1.4. Assessment of swallowing and risks of aspiration

The importance of a formal dysphagia screening protocol in the reduction of pneumonia was demonstrated in a study on 2532 acute stroke patients[316]. The study concluded that the risk of pneumonia was significantly higher at sites with no formal dysphagia screening and that a formal dysphagia protocol should be offered to all stroke patients regardless of stroke severity[316]. There are several ways of diagnosing dysphagia and the risk of aspiration which include bedside swallow assessment, assessment of oxygen saturation while swallowing and more specialised tests such as videofluoroscopy and fibreoptic endoscopic evaluation of swallowing, [347].

The bedside swallowing assessment is the commonly used swallow test following stroke as this test will provide adequate information regarding the presence and the severity of swallowing disturbances and the way the nutrition should be managed. Routine assessment is started with oropharyngeal examination. Patients are observed for presence and severity of facial asymmetry, facial weakness, extent of drooling, and pooling of saliva. This is followed by observing the type of speech and non speech movements of the mandible, lips, tongue, palate and the pharynx. The ability to produce a volitional cough is assessed and the nature of the voice and the severity of the dysphonia are noted. Assessments of dysarthria also include evaluation of articulatory precision, fluency and intelligibility. It has been reported that a weak voluntary cough, wet voice, cough on swallow, a prolonged swallow or a combination of these are highly predictive of aspiration[347].

Several forms of bedside swallowing assessment tests have been used to evaluate patients with an acute stroke. A common method of predicting aspiration is by the assessment of the difficulties in drinking measured small volumes of water as the bedside assessment of dysphagia[76;87;348]. Smithard et al used 5 ml aliquots followed by a larger volume (60 ml), observing for dribbling, cough, dysphonia, laryngeal elevation, and the time to finish the drink[109].A combination of all these signs were significantly predictive of aspiration and logistic regression identified that a reduced conscious level and a weak voluntary cough were significant independent predictors of aspiration. A study compared 302 swallowing assessments with aspiration on videofluoroscopy demonstrated that patients who coughed after swallowing or developed a hoarse voice or a wet voice had the highest risk of aspiration[349]. In the above mentioned study, the time and the number of swallows required to drink 150 ml of water, cough, delayed swallow, and dysphonia also indicated a problem with swallowing and risk of aspiration. Elicitation of the gag reflex is not routinely performed in clinical practice as it has been demonstrated that up to 30% young adults and

44% of healthy older adults have unilateral or bilateral absent gag reflexes[350]. While impairment of the gag reflex and reduced laryngo-pharyngeal sensation are associated with swallowing difficulties, some studies have shown that they are less predictive of aspiration than the presence of a weak cough or dysphonia[95;109]. In addition elicitation of the 'gag' reflex causes significant discomfort to the patient.

Videofluoroscopy (modified barium swallow) is the gold standard of swallowing assessment and risks of aspiration in patients with dysphagia and most studies have been correlated with detection of aspiration on videofluoroscopy[351]. Videofluoroscopy consists of video recording of a patient's swallowing mechanism during swallowing a given volume of barium paste starting with 3 ml and increased in volume if no adverse effects such as aspiration are noted. The patient stands or sits at 45 to 90 degrees while consuming barium impregnated liquids of different consistencies and the swallowing is imaged in lateral and antero-posterior projections. It is a dynamic study where the therapists can examine the anatomical structures and function of the oral and pharyngeal phases of swallowing and test potential compensatory techniques[351;352].

Royal College of Physicians of London Guidelines of stroke care recommend bedside swallow assessment within first 24 hours of acute stroke[1]. However, the most valid protocol is yet to be determined and may be irrelevant as different centres already have established screening tools[316]. A commonly used method is the ability to swallow different volumes of water as described in Smithard's study. This is due to the test being safe, easily repeated and straightforward to perform. Any doubt about a patient's ability to swallow safely will usually result in nil by mouth and referred to a speech and language therapist[353]. Asymptomatic patients will be placed on normal diet and fluids but will be observed during mealtimes and respiratory status monitored[79;88].

1.6.1.5. Control of gastroesophageal reflux

Gastric reflux is not uncommon in older people[354]. It has been estimated that more than one third of the older population have symptoms of gastroesophageal reflux, at least intermittently[355]. Aspiration of large volumes of acidic gastric contents gives rise to lung damage and aspiration pneumonitis (Mendelson's syndrome)[356]. Even aspiration of small amounts of gastric fluid can damage the tracheo-bronchial mucosa and lung epithelium though it may not clinically manifest as aspiration pneumonitis or pneumonia[357]. This damage is worse when the aspirate is acidic, but epithelial damage can also be due to the pepsin content and the low osmolality of the aspirate. Damaged lung tissue can get secondarily infected causing pneumonia[202;340]. Gastric reflux occurring over longer periods can result in interstitial pulmonary fibrosis[358]. Thus treatment of gastro-oesophageal reflux disease should reduce the incidence of pneumonia. Elevation of the head end of the bed and use of prokinetic medications such as cisapride and metoclopramide can reduce gastro oesophageal reflux [359]. Surgical procedures such as fundoplication have been performed with varying success rates in patients with intractable gastro-oesophageal reflux disease not responding to medical treatment but are not recommended in first few weeks after stroke[360].

1.6.1.6. Turn-mob program

This was a study which examined the effect of passive mobilisation in bed following acute stroke[181]. It was a randomised control trial to assess the efficacy of regular turning and passive mobilisation of acute stroke patients, carried out by a relative who received specific training in the technique from a physiotherapist compared to routine patient care[181]. There were 223 participants within 48 hours of acute stroke, predominantly partial anterior

circulation strokes (88%), with a mean NIHSS score of 12-14 (52%). Patients with haemorrhagic strokes and who were ventilated were excluded. The mobilisation program was carried out every 6 hours for 3 consecutive days. The program consisted of passive mobilisation of the 4 limbs through each segments' entire range of motion, sustaining for 10 seconds, every 6 hours. In addition to the passive movements those patients were turned to left and right lateral recumbent position every two hours. Follow-up was for 14 days post-discharge and signs and symptoms of pneumonia were the primary endpoint. The study had firmly defined criteria for the diagnosis of pneumonia which included a chest radiograph. The study demonstrated that there was a 61% of reduction in the episode of pneumonia in patients who were treated with turn-mob passive exercises as opposed to patients only receiving standard care (Control group 26.8% vs. turn-mob group 12.6%). However, the predominant stroke type was PACS (89%), 30% had a NIHSS of 2 to 7 and 41% had a NIHSS of 8 to 13, which shows the majority of patients who were recruited were either mild or moderate strokes. Only 20% of patients had an impaired swallow (which was assessed by the gag reflex) and enterally fed patients only formed 20% of the patient population. The program did not prevent pneumonia in nasogastrically fed group as 68.2% of these patients developed pneumonia.

1.6.1.7. Secondary prevention of cerebrovascular disease

Dementia and atherosclerotic cerebrovascular disease have been shown to be more closely associated with aspiration pneumonia than with any other neurological disorder in old age[361]. Patients with multiple lacunar infarcts have been shown to have a significant delay in the swallowing response and a reduction in the frequency of swallowing during sleep[362]. The risk of aspiration is highest during sleep as both the cough reflex and spontaneous cough are reduced during sleep in these patients with chronic cerebrovascular disease[363]. Silent cerebral infarcts are commoner than expected with incidences ranging from 23% to

51%[364;365]. Patients with silent cerebral infarctions, i.e. patients with radiologically demonstrable infarcts without any neurological impairment have a higher incidence of pneumonia than patients with no silent infarctions[366]. The incidence is higher in patients with cerebral infarctions deep in the brain, especially in basal ganglia region than in the cortex[361;366]. Therefore, primary and secondary stroke prevention by appropriate use of anti-platelet agents, statins and anticoagulant therapy not only prevent further strokes but also reduce the risks of aspiration and pneumonia following stroke.

1.6.2. Review of literature on drug therapies to reduce pneumonia in acute stroke patients

Introduction

Background review of literature done for this thesis showed that there was a paucity of research into prevention of pneumonia following acute stroke other than assessment and management of dysphagia. In addition, there was only limited evidence on drug treatment for prevention of pneumonia following stroke. As this could be a sample error, it was decided to conduct a detailed literature review on the interventions that are available to prevent post-stroke pneumonia following guidelines of a formal systematic review. The aim was to establish what evidence was available on this topic as a systematic review is considered as the strongest evidence available for a particular clinical question.

Systematic reviews are reviews of primary studies that have an explicit statement of aims and objectives of the review with methods that are pre-planned[367]. Such reviews which have a strict design and include a comprehensive, reproducible search of all available evidence which can be critically appraised to provide a critical summary of all available evidence addressing a particular issue. In addition, completion of such a review was

thought to be important to address the perceived lack of research in this field, and to support the work in this thesis.

1.6.2.1. Methods

The literature review as in any systematic review began with the identification of a clinical problem[368]. The clinical question at the heart of this review was 'Drug therapies that are used to prevent pneumonia in patients following acute stroke'. A review protocol was then designed, studies were searched and the relevant studies were selected and appraised for quality. Data were collected from these selected studies, findings were synthesised and were summarised and a final report was written. Khan *et al* had produced a framework to perform a systematic review and the literature review for this thesis was conducted according to this step-by-step staged framework [368].

Step 1- framing the question

Step 2- identifying relevant work

Step 3- assessing the quality of studies

Step 4- summarizing the evidence

Step 5- interpreting the findings

A systematic review requires two reviewers to be involved in the process of review of articles to minimise selection bias. The review of literature for the thesis was carried out only by one reviewer (the researcher) due to unavailability of a second review and due to time pressures. However, every effort was taken to minimise bias and to include all relevant articles in the literature review and not to overlook relevant articles.

1.6.2.2. Identification of the clinical question

The clinical question that needed a literature review for this thesis was 'are there any drug therapies that can be used to prevent pneumonia in patients following acute stroke'. To be included in the review, trials had to meet the following inclusion and exclusion criteria.

1.6.2.3. Inclusion criteria

Selection of papers

- Published clinical trials
- Tested a drug therapy for prevention of post-stroke pneumonia

Selection of studies

- Studies which included participants aged 18 years or over
- Participants with a diagnosis of stroke
- Describe a pharmacological intervention
- Describe and define the intervention clearly
- Describe pneumonia clearly

1.6.2.4. Exclusion criteria

- Studies that reviewed the effect of diagnosis and management of post-stroke pneumonia
- Interventions which included non-drug interventions such as electrical or magnetic stimulation
- Animal studies
- Publications prior to 1980

- Interventions which used medications which are not listed in BNF
- Studies which included less than 10 participants

No paper was excluded on the basis of language or the community it came from. Review papers and editorials were excluded from search results.

1.6.2.5. Identifying relevant work

Search strategies and selection of relevant studies

Embase and Medline databases were searched using Medical Subject Headings (MeSH) terms stroke, pneumonia and prevention with the logical operator 'AND', covering the period from January 1980 to January 2013. The search was not restricted to the type of article to capture as many as relevant publications during the initial search. However, the search was restricted to adults (over the age of 18 years) and to human studies. Duplicates were excluded from the results after combining both databases. Also to capture as many relevant publications as possible, a general search of the internet was performed using Google and Google Scholar Search Engines and a hand searching of various medical journals was performed. Following completion of the searches, preliminary screening of retrieved articles was carried out to exclude irrelevant studies. Titles from all electronic hits were reviewed online and potentially relevant titles were downloaded and saved in a separate folder. These included editorials, review articles, guidelines, letters and case reports.

In addition to the literature search, relevant articles obtained via the internet (Google) search were included. The first stage of screening was completed based on the study titles and by immediately excluding those outside the topic and the ones which did not fulfil the inclusion criteria or had exclusion criteria. Publications which were considered not to be relevant were also excluded. Examples of irrelevant papers included pneumonia in

coronary heart disease, prevention in pneumonia in older people, pneumonia as a complication of dysphagia and general preventive strategies of stroke. All abstracts of the titles pertaining to stroke and pneumonia were considered as potentially relevant and were downloaded and saved in another folder for the second stage of review.

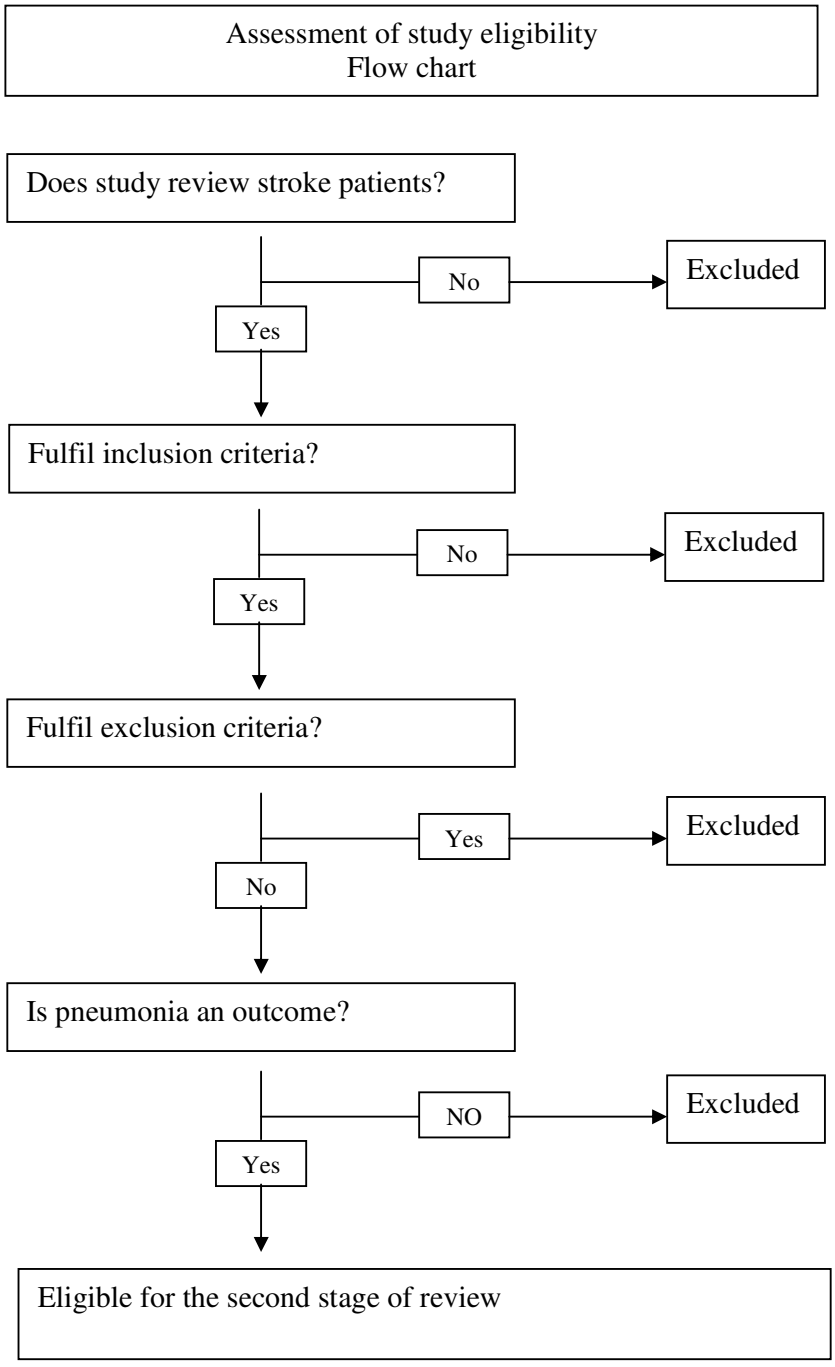


Figure 1-1 - Study Eligibility Flow Chart

Search History:
1. MEDLINE; pneumonia.ti,ab; 74087 results.
2. MEDLINE; exp PNEUMONIA/; 69708 results.
3. MEDLINE; stroke.ti,ab; 128486 results.
4. MEDLINE; exp STROKE/; 75162 results.
5. MEDLINE; prevent*.ti,ab; 865677 results.
6. MEDLINE; exp PREVENTION/; 1394 results.
7. MEDLINE; 1 OR 2; 106929 results.
8. MEDLINE; 3 OR 4; 154922 results.
9. MEDLINE; 5 OR 6; 866021 results.
10. MEDLINE; 7 AND 8 AND 9; 181 results.
11. EMBASE; pneumonia.ti,ab; 93123 results.
12. EMBASE; exp PNEUMONIA/; 171982 results.
13. EMBASE; stroke.ti,ab; 178238 results.
14. EMBASE; exp STROKE/; 49175 results.
15. EMBASE; prevent*.ti,ab; 1052773 results.
16. EMBASE; exp PREVENTION/; 13120 results.
17. EMBASE; 11 OR 12; 194724 results.
18. EMBASE; 13 OR 14; 197779 results.
19. EMBASE; 15 OR 16; 1056409 results.
20. EMBASE; 17 AND 18 AND 19; 455 results.
21. EMBASE; 20 [Limit to: (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 204 results.
22. MEDLINE; 10 [Limit to: (Human Age Groups All Adult 19 plus years)]; 123 results.
23. EMBASE,MEDLINE; Duplicate filtered:
    [20 [Limit to: (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]],
    [10 [Limit to: (Human Age Groups All Adult 19 plus years)]]; **327 results.**
    257 unique results (70 duplicates)

Figure 1-2 - Search History

The second stage of the review was based on study abstracts of these publications saved to identify further articles which were not relevant, and these were also excluded. Articles on predictors or risks of post-stroke pneumonia and secondary effects of pneumonia in stroke patients were excluded. Also studies of prevention of pneumonia by assessment and management of dysphagia and studies of post-stroke medical complications which included pneumonia were excluded. Any study based upon low patient numbers (<10) was excluded to prevent inclusion of case studies or reports as they may contain untested opinions. Also, studies using non-specified medications or drugs which were not included British National Formulary were excluded. After the second stage of sifting was complete, full texts of all relevant papers were downloaded, printed and reviewed by the researcher.

Assessing study quality

Assessment of quality of studies is an important component of a systematic review. The strength of evidence assessed is mainly to measure the appropriateness of the study design to answer the specific research question[368]. The randomised controlled trial design is normally the most appropriate source of evidence for judging the effectiveness of individual or group interventions[369]. Multiple quality checklists and numerical scales from 4- 55 have been identified to assess the quality of a study[370]. However, The Cochrane Handbook for Systematic Reviews of Interventions highlights that methodological assessment using a scoring system can be fraught with difficulty[371]. Therefore methodological quality assessment of studies were conducted using guidelines recommended by 'Methods for development of NICE public health guidance, March 2006)[369]. The data collection form, 'Methodology checklist for RCT' (appendix 2), as recommended by NICE was used to enter study details and every effort was done to be unbiased with the quality assessment as there was no second reviewer. The following indicators were recorded in the review of overall quality of the trials.

- method of randomisation
- concealment
- blinding of participants
- blinding of care providers to the intervention group
- blinding of outcome assessor
- reliability and validity of outcome measures used
- potential confounding factors
- statistical analysis

Randomisation allows fair and equal allocation of participants to each treatment group. It also seeks to ensure statistical comparability of treatment groups[372]. The process of concealment ensures that participants and the researcher have no knowledge of impending allocation and correct randomisation relies upon appropriate concealment[373]. Without concealment there is a risk of the process of randomisation being inappropriately influenced. Unblinded studies are prone to bias, which would either exaggerate or underestimate the 'true' effect of an intervention. In addition, if participants are not blinded, the knowledge of their group allocation may impact upon their assessment of outcome of any intervention they receive. Assessment of confounding factors is important as these can influence the effect of the intervention. In a randomised study, confounding factors are expected to be roughly equally distributed between groups[368].

Final quality assessment of the studies were conducted using guidelines recommended by 'Methods for development of NICE public health guidance, March 2006[369]. Each study was categorised by study type (type 1-4) and quality graded using a code, '++', '+' or '-', based on the extent to which the potential source of bias has been minimised (Appendix 3)[369]. Later the scores of study design and quality were combined.

Assessment of heterogeneity in systematic review

Variability of the studies which were pooled together in a systematic review is defined as heterogeneity. Variability of the outcomes utilised, interventions explored and participants included is defined as clinical heterogeneity and variability in study design or quality is defined as methodological heterogeneity[371]. Variability in the evaluation of treatment effects of the studies is defined as statistical heterogeneity. For the purpose of the systematic review performed for this thesis, clinical heterogeneity was based upon the characteristics of populations, interventions and outcomes. Methodological heterogeneity was based upon study design and quality. There was no intention to exclude any study from the review based upon a poor review of methodological quality. Also a sub-group analysis and a meta-analysis of the studies were not planned as a part of the systematic review for the thesis.

1.6.2.6. Data extraction and evidence tables

Prior to beginning data extraction, each article was reviewed for the type of study, country of origin, year of publication, number of patients, primary and secondary outcomes, type and the duration of the intervention and the incidence of pneumonia, as given in the table 1.5.

Table 1-5 - Information extracted from selected studies on interventions

Year of publication	Type of study
Primary outcomes	Secondary outcomes
Number of patients	Intervention used
Duration of intervention	Complications
Inclusion criteria	Nasogastric feeds

Data extraction was conducted using data extraction sheets as recommended by 'Methods for development of NICE public health guidance, March 2006[369]. As there was no second reviewer, data extraction was done by the researcher and every effort was made to be unbiased during this process. Completed methodology check lists (Appendix 2) and data extraction sheets (Appendix 4) were used to produce evidence tables. This was to identify similarities and differences between selected studies including study population, intervention used and outcome measures. After the data extraction, the publications were reviewed to find out different types of drug therapies used and group them according the class of drug therapy.

1.6.3. Results

The first search used the terms stroke, pneumonia and prevention produced 123 results in Medline and 204 results in Embase from 1980 to 2013 (table 1.6).

Table 1-6 - Databases, Search Terms and Hits Used for the Review

Database	Search Terms	Results
MEDLINE	Pneumonia	106929
	Prevention	866021
	Stroke	154922
	Pneumonia + Prevention + Stroke	181
	Pneumonia + Prevention + Stroke (limited to humans, Adult over18)	123
EMBASE	Pneumonia	194724
	Prevention	1056409
	Stroke	197779
	Pneumonia + Prevention + Stroke	455
	Pneumonia + Prevention + Stroke (limited to humans, Adult over18)	204
	Total results	327
	Unique results (after duplicates filtered out)	257

Of these 70 were duplicate results, therefore there were 257 unique hits. All titles of these articles were reviewed by the researcher and 202 were excluded as they were not relevant to the search e.g. studies related to pneumonia in other medical conditions as they did not review any aspect of prevention of pneumonia in stroke patients. This left 55 papers in total for the second stage of review (abstracts), which reviewed various aspects of stroke-related pneumonia. Of these 16 were excluded as they reviewed the impact of formal assessment of dysphagia in prevention of stroke-associated pneumonia. Five more studies were excluded as they were on predictors of risk factors for pneumonia. Twelve studies were excluded as they reviewed post-stroke complications and pneumonia was one of those complications. Studied which reviewed the effect of pneumonia on stroke patients were

also excluded (n = 6). There were also two studies on prevention of pneumonia in post-stroke patients using traditional Chinese medications and they were excluded as review only considered medications listed in the BNF. Two studies were excluded as they had less than 10 patients in the studies. Two were excluded as they were letters to the editors discussing individual opinions. Though the study showed a significant reduction in post-stroke pneumonia, the physiotherapy study 'turn-mob program' was excluded as it did not use any medication. The remaining 9 studies could be divided into three major subgroups of drug therapies used to prevent post-stroke pneumonia as use of ACE inhibitors, use of prophylactic antibiotics, and the rest grouped as miscellaneous. Though they did not appear in the original search, three additional papers, one on oral decontamination in post-stroke patients[27], one on Cochrane collaboration meta-analysis on preventative antibiotics[374] and another meta-analysis on ACE inhibitors[375] were included in the review, making a total of 12 articles. These three additional articles were identified by the researcher from the Google search. Though all articles on ACE inhibitors were in chronic stroke rather than acute stroke, they were retained in view of their clinical significance.

Full articles of all 12 abstracts were obtained and were critically reviewed. The systematic review identified two studies of ACE inhibitors and one meta-analysis on ACE inhibitors. The two articles on ACE inhibitors were excluded as they also appeared in the meta-analysis. The extra article on ACE inhibitors which did not appear in the original search but which was added later was excluded, partly as it included patients other than stroke and the subset of trials which were in stroke patients were included in the meta-analysis on ACE inhibitors which appeared in the original search. The Cochrane collaboration on meta-analysis of preventative antibiotic therapy was excluded as four of the total of five studies which were included in the meta-analysis had already appeared in my literature search and the other article by De Falco[376] did not specify the age of its participants, which was a pre-

requisite to be included in the literature search. One study was excluded as it reviewed the effect of prior treatment with statin on the incidence of pneumonia. One article was excluded as it was a review article. Of the four articles on preventative antibiotics, one article reviewed the effect of preventative antibiotics on the neurological recovery and did not state the infection rates. However, this study was not excluded from the review as it was felt that the effect of antibiotics on the rate of infections would have affected the neurological recovery of the participants and the authors were to be contacted regarding the rates of pneumonia of that study. This gave a total of 6 articles for the literature review (figure 1.3)

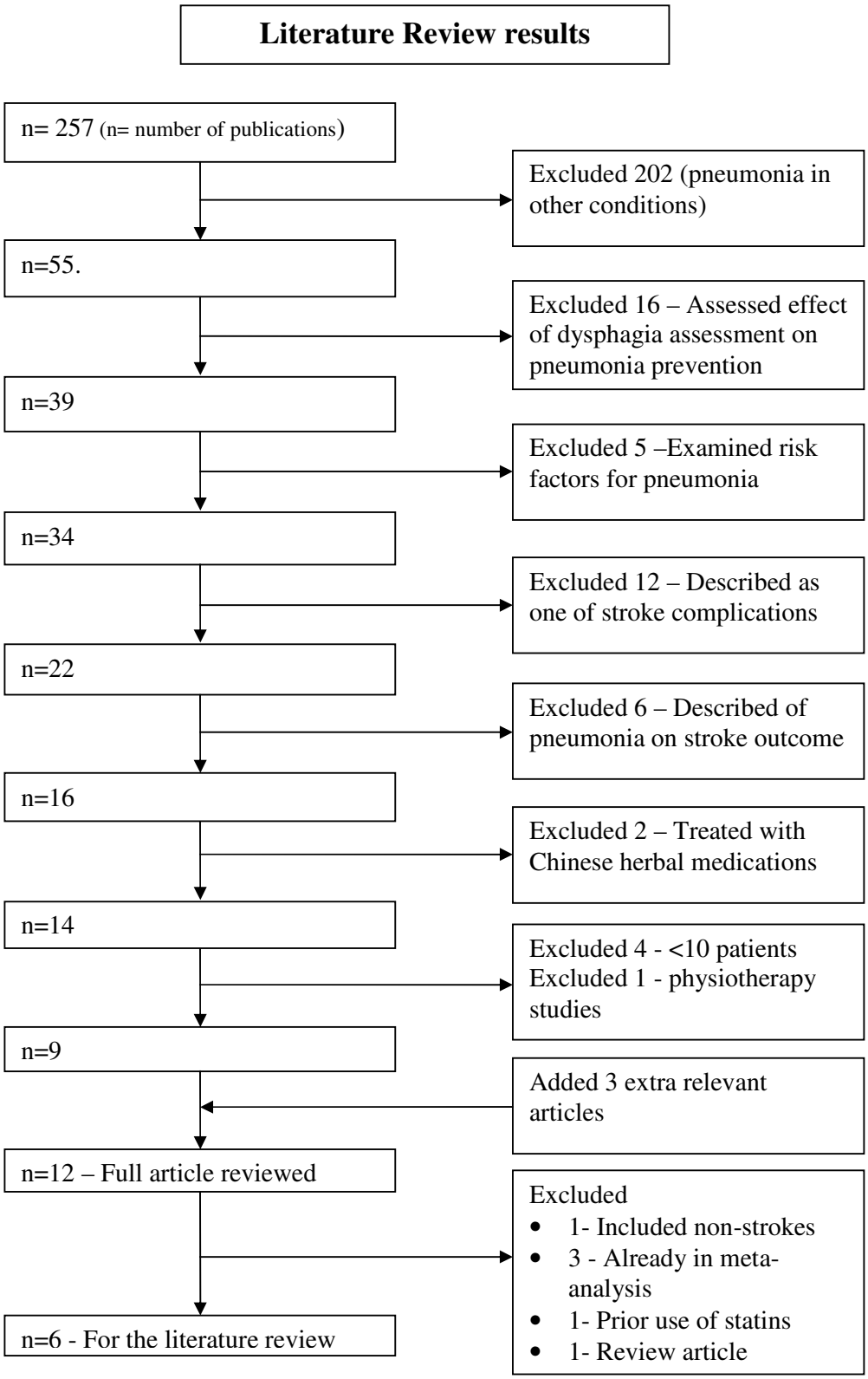


Figure 1-3- Process of Literature Review Results

Table 1-7 Summary of Assessment of Methodological Quality

Name of the study	MISS	PANTHERIS	ESPIAS	Minocycline treatment in acute stroke	Selective oral decontamination study
Agents used	Mezlocillin + sulbactam	Moxifloxacin	Levofloxacin	Minocycline	Polymyxin E, Colistin, Amphotericin
Power calculation	Not done	Performed	Performed	Performed	Under powered
Randomisation method	Computer generated number sheet	Computer generated adaptive randomisation	Computer generated number sheet	Randomisation according to the patient's hospital identity number	Computer generated
Concealment	Numbered sealed envelope	Clear concealment	Opening a sealed envelope	Unclear	Yes
Blinding of patients	Treatment team not blinded	Yes	Yes	No	Yes
Blinding of interventional procedures	Un-blinded	Yes	Yes	No	Yes
Blinding of outcome assessors	Yes	Yes	Yes	Yes	Yes
Follow-up and exclusions	Maximum 10 days. Well defined exclusion at the start of the trial	6 months follow-up for survival and neurological recovery	3 months follow-up for survival and neurological recovery	3 months follow-up for survival and neurological recovery	Follow-up 3 weeks
Exclusion after randomisation	No	Yes	No	No	No
Selective reporting and other survey of bias	None noted	ICH excluded, exclusion of patients with poor prognosis following randomisation. PP analysis instead of ITT used to assess the pneumonia	None noted	None noted	None noted
Reliability of outcome measures used	Well defined outcome measures	Well defined outcome measures	Well defined outcome measures	Well defined outcome measures	Well defined outcome measures
Statistical analysis performed	Standard statistical methods used. (Chi-square, Mann-Whitney Rank test)	Standard statistical methods used. ITT and PP analysis	Standard statistical methods used. ITT and ANCOVA adjusted baseline for CRP & WBC	Standard statistical methods used. ITT and PP analysis	Standard statistical methods used.

ESPIAS - Early Systemic Prophylaxis of Infection After Stroke study, PANTHERIS - Preventive ANtibacterial THERapy in acute Ischemic Stroke, MISS - The Mannheim Infection in Stroke Study ICH – inter-cerebral haemorrhage, PP – per-protocol, ITT – Intention-to-treat, ANCOVA – analysis-of-covariance, CRP, C-reactive protein, WBC white cell count,

1.6.3.1. Assessment of methodological quality

Of the six articles included in the systematic review, five articles (four articles on preventative antibiotics and one article on selective oral decontamination) and one meta-analysis on the use of ACE-inhibitors were assessed for their methodological quality. The assessment revealed a few methodological weaknesses in the literature reviewed which are described below and are summarised in table 1.7.

Power calculation

Only three studies included details of power calculation to determine an appropriate sample size[28;377;378].

Method of randomisation

All five studies were randomised controlled studies and four used computer-generated randomisation methods. One study used the patients' hospital identity number to generate a randomisation sequence[378].

Concealment

Apart from one study[378], the rest reported concealment via a codes sealed in envelops.

Blinding

Three studies were double-blind controlled studies[27;28;377] and the other two only had outcome assessors blinded[29;378].

Selective reporting and other sources of bias

Apart from the PANTHERIS study using *per-protocol* (PP) analysis to demonstrate a significant reduction in the incidence of pneumonia no other source of bias was identified. As all the studies were randomised controlled studies, confounding factors were expected to be roughly equally distributed between the two groups. This was confirmed by assessing participants' baseline criteria in all five studies.

Statistical tests employed

All five studies used standard parametric and non-parametric methods, when appropriate, during data analysis.

Homogeneity

There was no homogeneity in respect of interventions, participants, and outcome measures which made pooling of data were impossible. However, the next sections will discuss each category individually, highlighting their clinical messages and limitations.

The necessary assessment of the type of evidence and the quality appraisal has been shown in table 1.8.

Table 1-8 Summary Table for Type and Quality of Evidence for Studies

Post-stroke pneumonia prevention by angiotensin-converting enzymes inhibitors: results of a meta-analysis (included 5 studies)	1^{++}
MISS - The Mannheim infection in stroke study	1^{+}
PANTHERIS - Preventive antibacterial therapy in acute ischemic stroke	1^{-}
ESPIAS - Early systemic prophylaxis of infection after stroke study	1^{+}
Minocycline treatment in acute stroke	1^{+}
Selective oral decontamination study	1^{+}

1.6.3.2. Data extraction and evidence tables

The articles were divided into three categories of primary treatment choice as

- use of ACE inhibitors
- use of prophylactic antibiotics
- use of selective oral decontamination

Relevant data from data extraction sheets were entered into evidence tables for each of the primary treatment choice categories, as difficulties in combining the interventions and the outcomes of each category into one table.

1.6.4. Preventative antibiotics

Four studies were identified which evaluated preventative antibiotics in patients following acute stroke[28;29;377;378]. All four trials were randomised controlled studies and two had a double blind design. Allocation concealment was insufficient in the study which used minocycline[378]. Three of the studies described ineligibility withdrawals after the randomisation in accordance with trial criteria or due to inability to complete the treatment protocol. One study did not describe the withdrawals[29]. In this study, patients with a life expectancy of less than 90 days were excluded, therefore the overall mortality rate was 0%. Lampl's study excluded patients with dysphagia and other three studies did not report on the incidence of dysphagic patients.

Of four studies involving 426 patients in total, two studies were double blind and both used fluoroquinolones (levofloxacin, moxifloxacin)[28;377], the third study used minocycline[378] and the fourth used a combination of a beta-lactam antibiotic with a beta-lactamase inhibitor[29]. More details are given in the table 1.9. In all studies antibiotic therapies were started within 24 hours of stroke onset and Lampl *et al's* study required the presence of symptoms for at

least 6 hours. The duration of antibiotic treatment varied between 3 to 5 days. Most patients (93%) had ischaemic strokes as only the ESPIAS study included cerebral haemorrhages. Stroke severity was based on the NIHSS in 3 studies and varied from greater than 4 to greater than 11. Lampl *et al*'s study used the modified Rankin Scale to assess the disability associated with stroke.

The primary outcome was infection rate in two studies[28;377] and the proportion of patients with fever in one study[29] though the rate of infection was measured as a secondary outcome. The fourth study (n = 151), which used minocycline measured NIHSS and modified Rankin Scale as the primary outcome and did not measure the rate of infection[378]. Of three studies which reported infection rate, two studies specified the type of infection and Chamorro's study did not specify the type of infection. The definition of an infection varied significantly between studies. One study used the official criteria of the US centre for Disease Control and Prevention, however, with significant modifications[28]. Secondary outcomes were scores of modified Rankin Scale, NIHSS and Barthel Index and survival. The infections that were observed were mostly pneumonia (n = 61) and urinary tract infections (n = 21). The infection rate in the placebo group was 38.1% (53 of 139 patients) and 23.5% (32 of 136 patients) in the patients who received an antibiotic. The studies which recorded infection rates (n = 275) demonstrated that in adults with acute stroke preventative antibiotics reduced the incidence of infection. The number needed to treat to prevent infection was 7 and to prevent death was 83. Mortality varied from 0% to 7%, and there was no significant reduction in the mortality in the patients who had antibiotics. Nearly 5% of patients (10 out of 210) who had antibiotics died compared to 6% (13 out of 216) of patients who had a placebo. However, when comparing the incidence of pneumonia there appeared to be no benefit, as in three studies the pneumonia rates were not given[29;378] and in the other (Harms et al) the reduction was not statistically significant. No major side-

effects or harm were observed other than that one patient who was treated with mezlocillin plus sulbactam developed exanthema and another patient developed elevated liver enzymes[29].

Table 1-9 - Studies of Preventative Antibiotics

Study (reference)	Antibiotic	Year of publication	Number of patients (Antibiotic/Placebo)	Type of study
Chamorrow et al (ESPIAS)[377]	Levofloxacin/ Placebo	2005	67/69	RCT
Lampl et al[378]	Minocycline/ Control	2007	74/77	RCT
Harms et al (PANTHERIS) [28]	Moxifloxacin /Placebo	2008	39/40	RCT
Schwarts et al (MISS)[29]	Mezlocillin plus Sulbactam/ control	2008	30/30	RCT

(A – antibiotics, P – placebo, RCT – Randomised controlled trial, ESPIAS - Early Systemic Prophylaxis of Infection After Stroke study, PANTHERIS - Preventive ANtibacterial THERapy in acute Ischemic Stroke, MISS - The Mannheim Infection in Stroke Study)

Table 1-10 Studies of Preventative Antibiotics Outcome

Study (reference)	1^0 outcome	2^0 outcome	Duration of intervention	Infection rate A vs P n/N (%)	Pneumonia A vs P n/N (%)
Chamorrow et al (ESPIAS)[377]	Rate of infection at one week post-stroke	Neurological outcome and mortality at day 90	3 days	12/66 (18) vs. 11/64 (17) p=0.7	Not stated
Lampl et al[378]	NIHSS, MRS and Barthel score at 90 days		5 days	Not stated	Not stated
Harms et al (PANTHERIS) [28]	Infection within 11 days	Neurological outcome, mortality	5 days	6/39(15) vs. 13/40(33) p=0.1	3/39 (7.7) vs. 8/40 (20) P=0.2
Schwarts et al (MISS)[29]	Changes in body temperature	Rate of infection at day 10	4 days	15/30(50) vs. 27/30 (90) p= 0.002	Not stated

(NIHSS – National Institute of Health stroke scale, MRS – modified Rankin scale, ESPIAS - Early Systemic Prophylaxis of Infection After Stroke study, PANTHERIS - Preventive ANtibacterial THERapy in acute Ischemic Stroke, MISS - The Mannheim Infection in Stroke Study, A – Antibiotic group, P – placebo group)

1.6.5. ACE inhibitors

Details of the meta-analysis on post-stroke pneumonia prevention by ACE inhibitors were reviewed[379]. Details on the studies which were included in the meta-analysis are given in the table 1.11. There were a total of 8,693 patients from three RCTs and two cohort studies, 4940 were Asians and 3753 were non Asians (Europeans and Australians). There were total of 473 episodes of pneumonia in the total group. The sample size varied from 394 to 6105 post-stroke patients. The control group had other antihypertensives, such as angiotensin receptor blockers, beta-blockers, calcium channel blockers, and in the study by Ohkubo *et al* a placebo. Two studies were retrospective[380;381] and others were prospective[26;382;383].

The incidence of pneumonia in the control groups ranged from 4.7 to 17.9%. All studies showed a preventative effect of ACE inhibitors compared with the control groups. The overall combined relative risk following administration of ACE inhibitors compared to control was 0.61 (95%CI 0.51-0.75, P <0.001). When the analysis was restricted to the Asian population (after excluding 3753 Caucasian patients from Ohkubo's study), the relative risk was estimated at 0.42 (95%CI 0.32-0.56, P <0.001). Apart from Ohkubo's study, other four studies only were on Japanese patients. Review of these four studies showed that the preventative effect of ACE inhibitors were greater in the Japanese patients than the other Asian patients, with a relative risk of 0.38 (95%CI 0.27-0.54, p <0.001)[26;380;381;383]. The estimated number needed to treat (NNT) for all five studies was 34.3 (95%CI 25.9-50.6) range (9.3-113.6) and was 20.4 (95%CI 16.3-27.4) where only data from the Asian patients were analysed.

Table 1-11 - Studies of ACE Inhibitors

Study (year of publication) (reference)	Patients	Number of patients	Patient number (ACEI/ Placebo)	Type of study	Duration of intervention (years)	Elderly (>65 years)	Rate of pneumonia (ACEI) Event / Total n/N (%)	Rate of pneumonia (control) Event/total n/N (%)
Sekizawa et al (1998)[383]	HT and history of stroke	440	127/313	RCT	2	yes	9/127 (7%)	56/313 (18%)
Arai et al (2000)[381]	HT and history of stroke	394	208/186	Retrospective cohort study	4	yes	8/208 (4%)	15/186 (8%)
Arai et al (2001)[380]	HT and history of stroke	404	209/195	Retrospective cohort study	2	yes	10/209 (5%)	23/195 (12%)
Ohkubo et al (2004)[382]	HT and history of stroke or TIA	6,105 (all) 2,352 (Asian)	3.051/ 3,054 (all) 1,176/ 1,176 (Asian)	RCT	3.9	no	All 117/3,051 (4%) Asian 26/1,176 (2%)	All 144/3,054 (5%) Asian 48/1,176 (4%)
Arai et al (2005)[26]	HT and history of stroke	1,350	430/920	RCT	3	yes	12/430 (3%)	79/920 (9%)

(ACEI- Angiotensin Converting Enzyme Inhibitors, HT- Hypertension, RCT- Randomised Control Trial)

1.6.6. Selective oral decontamination

One study was identified which assessed the effect of selective oropharyngeal decontamination (SDD) in acute stroke patients[27]. The aim of the study was to determine the levels of colonisation of pathogenic aerobic Gram-negative bacteria (AGNB) in acute stroke patients and the effect of SDD on oral flora and its effect on post-stroke pneumonia and mortality. It was a prospective single blinded randomised controlled trial and the patients (n = 203) were randomised to receive either SDD with oralbase gel containing a combination of antibiotics (colistin, polymyxin and amphotericin) or placebo applied topically to the oral mucous membranes four times a day. The study included patients with both safe and unsafe swallow and the treatment continued for two weeks for patients with a safe swallow and three weeks for patients with unsafe swallowing. Twenty patients died and 19 withdrew, therefore full follow-up was obtained in 164 patients. The primary endpoint of the trial was the rate of AGNB carriage and the study demonstrated that SDD significantly reduced the AGNB carriage following acute stroke ($p = 0.03$). The incidence of pneumonia was a secondary outcome and the treatment group had significantly less number of pneumonia, eight in total and seven (87%) in the placebo group and one in the treatment group (13%) which was statistically significant ($p = 0.03$).

1.6.7. Discussion

Introduction

This literature review demonstrated that there is only limited evidence on the use of medical treatments for the prevention of pneumonia in patients following acute stroke. Out of what initially appeared to be a large number of citations only six research articles (including one meta-analysis of five trials) fit the required criteria. The level of heterogeneity was such that pooling of data was impossible and separate descriptions of

each group were provided instead. The systematic review did not identify any clear evidence for medications that can reduce pneumonia in acute stroke patients who are fed via nasogastric tubes.

ACE inhibitors

Substance P is a neurotransmitter that plays a pivotal role in the swallowing reflex and acts via neurokinin receptors[384]. An extensive plexus of nerves which contain substance P has been demonstrated in the upper airway epithelium which synapses with glossopharyngeal and vagal endings[385]. A reduction in substance P levels by capsaicin desensitization or by blockage of neurokinin receptors has been shown to reduce cough and swallowing reflexes induced by various stimuli [386;387]. In addition, inhibition of substance P centrally with direct antagonists or dopamine antagonists interrupts swallow[388]. It has been demonstrated that patients with aspiration pneumonia have lower levels of substance P in their respiratory epithelium[384]. Thus, medication that increases substance P levels in the upper airway should stimulate the cough reflex by its stimulatory action on the glossopharyngeal and vagus nerves[387]. Substance P is degradated by the enzyme angiotensin converting enzyme[388]. It has been demonstrated that the use of an ACE inhibitor increases substance P levels in the upper respiratory tract and increases the sensitivity of the cough reflex and is thought to be responsible for dry cough, which is a common side effect of ACE inhibitor treatment[389;390].

Though large numbers of studies have demonstrated that the use of ACE inhibitors reduced the incidence of pneumonia in older patients, patients with cardiac illness and in diabetes, the systematic review identified only few studies that assessed the effect of ACE inhibitors in patients following stroke. Even these studies were conducted on chronic stroke patients rather than acute stroke patients, with the follow-up periods up-to 4 years. The beneficial

effect of ACE inhibitors in reducing pneumonia following stroke was more significant in the Asian population than European Caucasian population[26;382]. These findings are similar to the findings of the meta-analysis by Caldeira et al in patients with various diseases such as congestive cardiac failure, diabetes and stroke which demonstrated that though ACE inhibitors significantly reduced the risk of pneumonia in all patients the odds reduction was significantly higher in Asian patients (57% vs. 12%, $p < 0.001$)[375]. Studies of the effect of ACE inhibitors on pneumonia in non-stroke Asian population have demonstrated conflicting results as a study by Arai et al on 576 patients with no previous strokes did demonstrate a reduction in pneumonia with ACE inhibitors[391], a study by Terammoto et al on a similar patient group failed to demonstrate a similar beneficial effect[392]. However, in patients with a history of stroke, all studies have demonstrated that ACE inhibitors significantly reduced the incidence of pneumonia in the Asian population. This was further confirmed by the sub-analysis of the PROGRESS trial data which demonstrated that ACE inhibitors (perindopril) significantly reduced the risk of pneumonia of Asian ethnicity with no significant effect on non-Asian participants[382]. The mechanism by which ACE inhibitors reduce incidence of pneumonia has been discussed in the previous section. Genetic differences in ACE polymorphism between non-Asian and Asian population have been suggested as a possible explanation for this difference in protective effect observed in the Asian population[393]. Polymorphism I/I and I/D, which are more prevalent in Asian population was responsible for the protective effect seen in the post-hoc analysis in PROGRESS trial, where as the D/D polymorphism particularly common in white population was less protective. Though the genetic evidence is equivocal, the reduced protective effect may explain the increased levels of serum ACE inhibitors were still associated with high levels of kinin catabolism in patients with the D/D polymorphism[394].

Even in Asian population the best effects of ACE inhibitors were seen in patients with a stroke, which can be explained the mechanism of action of ACE inhibitors. ACE inhibitors through the inactivation of substance P and increasing kinins levels in the upper airways improve upper airway reflexes such as swallowing and cough[395]. However, when consider the in swallowing mechanism in an older individual, it is clear that older people have their cough and swallow reflexes intact unless complicated by other concurrent illnesses[396;397]. Addition of an ACE inhibitor to a such person will not have any obvious beneficial effect on the incidence of pneumonia as they still have intact upper airway protective mechanisms despite the other changes associated with old age. However, following stroke even patients with a normal cough reflex aspirate small volumes of saliva, especially during sleep, increasing the risk of aspiration pneumonia ten-fold[391]. Therefore when an older person suffers a stroke, treatment with ACE inhibitors improve or restore these defences by inactivating substance P, thereby exerting a protective effect on risk of aspiration and pneumonia.

Preventative antibiotics

Though the collective data demonstrated that preventative antibiotics did reduce the incidence of post-stroke infections, individual review of each paper showed widely differing outcomes. Though all studies did not report on the incidence of pneumonia, sub-analysis of the available data did not demonstrate that the use of antibiotics prevented post-stroke pneumonia. One study (ESPIAS) was terminated prematurely as the rate of infection was similar in patients in both groups. Selection bias was implicated, as some studies included patients with less severe strokes and some studies excluded patients with an estimated life expectancy of less than 90 days following recruitment. This selected patients with less severe strokes, as reflected in low mortality rates, and this might have overestimated the effects of the antibiotics. Also withdrawal of some patients after

randomization on the grounds of ineligibility may have been influenced by the knowledge of outcome, which would again favour the antibiotic regimen. This selection of patients would have been responsible for the low mortality seen in these trials, ranging from 0% – 7%, far less than the average mortality following acute stroke. Though in the per-protocol analysis (which was highlighted in the results of the trial) showed a significant reduction in pneumonia in the PANTHERIS study, but the intention to treat analysis did not show such reduction. Also, the antibiotics used in two studies (ESPIAS and PANTHERIS) are not commonly used on stroke wards now, as the use of quinolones has been associated with a high incidence of Clostridium difficile infection[398]. In addition the problem of inducing drug resistance should be considered in use of prophylactic antibiotic treatment.

One trial used minocycline for its potential neuroprotective effects as it has several anti-inflammatory effects, reduces microglial activation, inhibits apoptotic cell death and has a favourable effect on experimental animal stroke studies[399]. However, it has inadequate microbiological cover for the predominant organisms responsible for post-stroke pneumonia. Of other antibiotics ceftriaxone appears to be more promising as a prophylactic antibiotic in view of its neuroprotective effects[400]. This beta-lactum antibiotic reduced mortality and neurological deficits in rat models, as it improves neuronal survival within the penumbra and has shown to up-regulate of neurotrophics in the peri-infarct zone[401]. It also has a broader antibacterial spectrum which is effective against many organisms responsible for post-stroke pneumonia[398]. These observed effect warrant further evaluation of preventative antibiotics. However, to study these effects the trials should have standardised definition of pneumonia and review clinical and functional outcomes such as Modified Rankin Scale (mRS) and length of stay.

Miscellaneous group

The principle of the oral selective decontamination is that colonisation of oropharynx with aerobic Gram-negative bacteria- AGNB is common following acute stroke and reduction in the colonisation will result in a reduction of pneumonias caused by aspiration of infective oropharyngeal secretions[6;283]. Though in the study on SDD, pneumonia was not the primary outcome, it demonstrated that SDD significantly reduced the incidence of pneumonia in post-stroke patients. However, the incidence of pneumonia was significantly lower in both groups than in many previous studies (5%). Also, there were no formal criteria for the diagnosis of the pneumonia which was obtained by examining the case notes for evidence of probable pneumonia. The three antibiotics which were used as SDD are no longer available in the NHS.

1.6.8. Conclusion

In spite of a high incidence of pneumonia following stroke and its contribution towards post-stroke mortality and morbidity, my reading of the evidence is that there is a significant lack of research into medical interventions to prevent stroke related pneumonia. It may be partly due to stroke patients being included into the same trials on prevention of pneumonia with mixed participants such as older people, nursing home residents and patients with other common medical conditions such as diabetes and chronic heart disease. Historically, not recognising stroke as a specific disease entity and branding stroke along with elderly care research or chronic central nervous system diseases may be partly responsible in the lack of research into acute stroke.

There is emerging evidence from one recent meta-analysis including five clinical studies that ACE inhibitors significantly reduce pneumonia, but this evidence is restricted to

patients with chronic stroke. Results from antibiotic studies are conflicting. A much larger study (Stroke INF, n = 1200) is still recruiting and may resolve this issue[402]. More research is also needed in relation to safety of prophylactic antibiotics and to establish whether pneumonia is delayed rather than prevented, and to determine if broader spectrum antibiotics are more effective in treatment. The potential risk of development of bacterial resistance is a major disadvantage of preventative antibiotics. Potential benefits of the use of antibiotics should be weighed with the problems such as selecting out resistant strains, antibiotic related side effects such as Clostridium difficile infection and general induction of resistant microbial strains[403].

More research is needed on antibiotics with neuro-protective effects and methods to prevent antibiotic resistance when used regularly on a stroke ward. Most importantly, none of the studies have specifically targeted patients fed via nasogastric tubes, in whom the incidence of pneumonia is several-fold higher than in other stroke patients. Further research is needed into prevention of pneumonia in stroke patients, especially in severe strokes and in patients fed via nasogastric tubes. Although promising, at least in theory, there is no study of the use of antiemetic agents in the prevention of post-stroke pneumonia.

1.7. Interventions to reduce pneumonia in patients fed via nasogastric tubes

Aspiration pneumonia has always been a significant clinical problem in critically ill dysphagic patients and is associated with increased use of antibiotics, longer time on mechanical ventilation, increased length of hospital stay and high mortality. Pneumonia continues to occur even if oral feeding is not attempted and the patients are fed via nasogastric tubes due to aspiration of oropharyngeal secretions and regurgitated gastric

contents. In addition to the approaches to prevention of pneumonia which was described in the previous section, these patients who are fed via nasogastric tubes require further preventative measures to reduce pneumonia related to the nasogastric tube. Various methods including changes in body posture, selective oropharyngeal decontamination, post pyloric feeding, and subglottic suctioning have been tried with varying success. As the thesis focuses on the prevention of aspiration and pneumonia in stroke patients who are fed via nasogastric tubes, interventions to reduce the incidence of aspiration and pneumonia in patients receiving nasogastric feeds will be discussed in detail in this section.

1.7.1. Body posture

Studies have shown that risk factors for pneumonia, such as gastro-oesophageal reflux and aspiration in the critical ill intensive care patients who are fed via nasogastric tubes, can be reduced by managing them in a semi-recumbent position (elevation of the head end of the bed by 30°-45°). In ventilated patients who are receiving nasogastric feeds, supine posture has been shown to increase the risk of gastric aspiration and pneumonia when compared to patients who are nursed in the semi-recumbent position and the risk was dependent on the length of time the patient was kept in the supine posture[404;405]. In a prospective study involving 86 critically ill intensive-care patients, microbiologically confirmed aspiration pneumonia occurred in 23% of patients who were managed in supine position while receiving nasogastric feeds when compared to only 5% of patients who were managed in a semi-recumbent position [406].

Some studies have shown that the benefit of a semi-recumbent posture was not always observed in the presence of nasogastric feeds. These studies have concluded that nasogastric tube was an independent risk factor for gastro-oesophageal reflux irrespective of body posture[404;407]. However, semi-recumbent posture was still beneficial as there were

fewer episodes of reflux, aspiration and pneumonia though it was not statistically significant. In a large, prospective study involving critically ill ventilated patients using radioactive technetium (Tc^{99}) labelled feeds, it was demonstrated that irrespective of the body posture radioactivity was detected in the oropharyngeal contents within first five hours of commencement of nasogastric feeds. This indicates the continued occurrence of gastro-oesophageal reflux even when patients were maintained in the semi-recumbent posture. However, the radioactivity of the endobronchial secretions was more in patients who were managed in the supine position[407].

This available evidence led to the clinical acceptance that elevation of the head end to 45 degrees or more is a simple and a safe method of reducing aspiration pneumonia with no extra cost. Aspiration still can occur when transferring patients between units or while having investigations, as during these procedures patients are usually placed in a recumbent position. This may be at least partly responsible for the findings of a study by Rowat *et al*, which demonstrated that stroke patients were most likely to be hypoxic in the scanners or during ward to ward transfers[408].

1.7.2. Nasogastric feeding regime

Nasogastric feeds are administered either continuously over 10 to 12 hours or as intermittent bolus feeds every 2 to 3 hours, with the volume of each bolus being about 250 ml. Most studies of nasogastric feeding regime were done in critically ill intensive-care patients and it has been shown that high volumes of feed per session in intermittent feeding can lead to larger residual gastric volumes, gastric distension, enteral feeding intolerance, and increased gastro-oesophageal reflux[409;410]. These studies also demonstrated that more patients developed aspiration pneumonia when fed using intermittent bolus feeds than on continuous feeds. In studies involving enterally fed elderly patients, intermittent large bolus feeds were less well tolerated and were associated with diarrhoea[411;412]. In addition, patients

on continuous feeds achieved their nutritional goals faster and had fewer episodes of chest infection irrespective of age and the severity of stroke [411].

Continuous feeds have their own limitations such as patients being attached to feeding tubes longer, which interferes with patients' mobilisation and therapy input and the tendency to raise the gastric pH facilitating gastric colonization of Gram negative bacteria, which increase the risk of pneumonia[413]. However, the study also demonstrated that though the gastric pH was lower in patients receiving intermittent feeds, the rate of ventilator associated pneumonia was similar in both groups[413].

It has been recommended that nasogastric feeds should be started at a slower rate usually 25 ml/hour and gradually build-up to the required rate (usually 100 ml/hour) over a period of 48 to 72 hours[414;415]. Studies done in intensive care patients recommend that the volume of the residual gastric content should be monitored and evidence of abdominal distension (by regular measurement of abdominal girth) should be observed over the first few days of commencing nasogastric feeds. If the residual gastric content is more than 200 ml or if the patient has significant abdominal distension, the rate of the feed should be reduced and the build up of the rate should be done at a slower rate[414;415]. Some frail older patients may not tolerate a rate of 100 ml/hour, thus such patients should have a lower rate of 75 ml/hour and may need longer feeding sessions to achieve the prescribed feeding regime[415]. Feeding should preferentially be done during morning and afternoons rather than overnight as a semi-recumbent posture may be difficult and uncomfortable to maintain and observations for complications such as regurgitation and vomiting are missed in a darkened ward[415]. Intermittent bolus feeds should be started at a 200 ml bolus administered over an hour and advancing the volume to reach the target feed volume with a limited number of feeds,

which is usually 3 to 4 times a day[415]. Thus initially there may be 5 to 8 bolus feeds to achieve the required nutritional intake.

On the assumption that liquid feeds support gastro-oesophageal reflux, trials have been done to assess the effect of semi-solidification of nutrients. A study involving 14 stroke patients who were on PEG feeds, twenty four hour oesophageal multichannel intra-luminal impedance and pH was measured during and after feeding with semi-solidified and liquid feeds respectively. Though a small study, it demonstrated that semi-solidification of nutrients did not appear to be effective in preventing gastro-oesophageal reflux caused by liquid PEG feeds[416].

Studies in adults comparing continuous versus bolus feeds as a means to reduce the incidence of pneumonia have been mainly conducted on intensive care units though the recommendations may be applicable to patients with acute stroke. The evidence available so far suggest that continuous feeds are better tolerated by patients and associated with a lower incidence of pneumonia than bolus feeds. As opposed to intubated, ventilated intensive care patients, patients on stroke units will be mobilised early following stroke will have more inter-departmental transfers and practical difficulties of maintaining semi-recumbent position throughout the time period of continuous nasogastric feeds. In addition, bolus feeds are more physiological as they stimulate more distal colonic motor suppression and promote water resorption[415]. Therefore more studies are needed on nasogastric feeding regimes and body posture during enteral feeds in patients managed on stroke units.

1.7.3. Size of nasogastric tube

As nasogastric tubes interfere with the function of the lower oesophageal sphincter, it can be assumed that nasogastric tubes with a larger diameter can induce sphincter dysfunction and reflux more than a fine bore tube. Several studies have been conducted to assess this possibility. However, the results contradict each other as described below. A randomised controlled trial in mechanically ventilated, critically ill patients demonstrated that there was no increased incidence of gastro oesophageal reflux or aspiration pneumonia in patients who were fed using fine bore 8F nasogastric tubes when compared to a similar group of patients who did not have nasogastric feeds. However, patients who had their feeds through 16F nasogastric tubes had significantly higher incidence of reflux and pneumonia than patients who were fed using fine bore nasogastric tubes[417]. A study done in children with continuous oesophageal pH monitoring to detect lower oesophageal sphincter dysfunction and reflux concluded that the size of the NG tube was a significant risk factor predisposing the child to gastro oesophageal reflux and that nasogastric tubes with a larger diameter increased the gastro oesophageal reflux and interfered with clearance of the acid from the oesophagus[418]. However, a study in adult intubated and ventilated patients with head injury failed to demonstrate that small-bore (2.85mm diameter) nasogastric tubes were associated with less gastro-oesophageal reflux and micro aspiration following a radio-active technetium colloid meal, when compared to patients with medium–bore nasogastric tubes (6mm)[419]. Another study in ventilated adults showed similar results and demonstrated that there was any significant difference in the episodes of reflux in patients who were fed using small bore (8F) tubes than large bore (14F) tubes[420]. In a large study Metheny *et al* demonstrated that monitoring of the residual volume to evaluate gastric emptying, prevention of mal-position of the feeding tube and avoidance of supine posture during feeding were more important than the size and site of the tube placement[421] Therefore in clinical practice nasogastric tubes of medium size are used (8-10F) as smaller tubes are

easily obstructed by feeds and medication and larger tubes can cause undue discomfort to patients and can lead to nasal and oesophageal ulceration[420]. The main indications for the use of large-bore tube are the need for repeated gastric aspiration or need for administration of highly viscus drugs or feeds via the nasogastric tube[415].

1.7.4. Gastric pH management

As higher gastric pH is associated with gastric colonisation and an increased incidence of pneumonia, studies have been performed to assess the effect of alteration of gastric pH and bacterial colonization. A multi-centre, double blind randomized study in ventilated patients who were given either nasogastric feeds of a pH of 6.5 or an acidic nasogastric feed with a pH of 3.5 (achieved by adding hydrochloric acid) demonstrated that there was a significant reduction of gastric colonization in the group who received acidic feeds and a non significant reduction in the incidence of the pneumonia[422]. However, patients who were on an acidic formula had a higher residual gastric volume, more interruption to their feeds and higher mortality when compared to the control group. This was secondary to acidaemia and upper gastrointestinal haemorrhage which obscured any potential benefit from a reduction in the incidence of pneumonia. In addition there was no difference in the duration of mechanical ventilation, length of the ITU stay or usage of antibiotics[422].

Studies have also assessed the association of agents which increase gastric pH to prevent gastric ulceration, with gastric colonization and ventilator associated pneumonia in patients fed via nasogastric tubes. A multi-centre randomized placebo controlled trial including 1200 patients showed that there was no significant difference in ventilator associated pneumonia, upper gastrointestinal haemorrhage, length of ITU stay or mortality between two groups of patients who were treated with either sucralfate, a gastro protective agent

that does not alter the gastric pH, or intravenous ranitidine[423]. However, a meta-analysis of eight randomized trials comparing ranitidine and sucralfate has shown that there is a significant increase in the incidence of ventilator related pneumonia in patients who are treated with ranitidine[424].

The use of proton pump inhibitors also increase the gastric pH and has been linked to an increased risk of community acquired pneumonia[425-427]. An association between the use of proton pump inhibitors and an increased risk of pneumonia has been demonstrated in critically ill ventilated patients[428;429]. Studies comparing the incidence of pneumonia in enterally fed patients treated with either H-2 receptor blockers or proton pump inhibitors have been inconclusive. A study in 887 patients who had cardiothoracic surgery and had either ranitidine or a proton pump inhibitor (pantoprazole) as stress ulcer prophylaxis demonstrated that the use of pantoprazole was associated with a higher incidence of ventilator associated pneumonia than ranitidine[425]. However, another large study, in a similar patient group failed to show such association.

The available evidence suggests that increasing the gastric pH is associated with an increase in the incidence of pneumonia as it promotes gastric colonisation of Gram negative bacteria. Avoiding unnecessary medications for gastric acid suppression has been agreed as a part of various guidelines and care bundles in the prevention of pneumonia in ventilated and enterally fed patients[429;430]. However, reducing the gastric pH by acidification of feeds though reduced the incidence of pneumonia was associated with harmful side effects and increased mortality.

1.7.5. Control of subglottic secretions

Aspiration of pooled oropharyngeal and sub-glottic secretions which are colonized by bacteria is a major cause for aspiration pneumonia in dysphagic patients[6]. Aspiration of colonised tracheal secretions above an inflated endotracheal tube cuff which is also referred as the "pool of death" by some authors is a common cause pneumonia[151]. Usual clinical practice is suctioning of pooled secretions as required, usually performed following clinical examinations by medical and physiotherapy staff. Few studies have been conducted to compare the incidence of pneumonia in critically ill patients with continuous subglottic suctioning as opposed to intermittent suctioning of oropharynx when required. A randomised controlled study in 155 patients compared continuous aspiration using a specialized endotracheal tube to standard care demonstrated a significant reduction in the number of Gram positive cocci and Haemophilus influenza organisms in their sputum[184]. In addition there was a significant delay in the onset of pneumonia, which was 12 days in patients with continuous suction compared to 5 -9 days in patients who only had standard care[184]. However, there was no difference in the number of ITU days or in mortality. Two further studies confirmed that there was a lower incidence of ventilator associated pneumonia in patients who received continuous sub-glottic suction[431;432]. A recent meta-analysis has shown that continuous subglottic suction reduces ventilator associated pneumonia in high risk patients and is cost effective. However, there was no significant benefit on the duration of ventilation, length of hospital stay or on mortality[433]. Though a promising concept in stroke patients with severe dysphagia, no studies have been to assess its efficacy following acute stroke.

1.7.6. Avoidance of sedatives

A depressed level of consciousness worsens a patient's swallowing problems[127]. In addition to this narcotics also delay gastric emptying and increase the risk of gastroesophageal reflux and aspiration. Meissner *et al* demonstrated that intragastric naloxone (which antagonises antiperistaltic effects while preserving analgesia) in patients who are on continuous fentanyl infusion improved gastric emptying and reduced the incidence of pneumonia[434]. Therefore it is important to use sedatives sparingly or not at all whenever possible in patients who are critically ill. Daily sedation interruption and assessment for readiness to wean are strategies carried out to reduce pneumonia in critically ill ventilated patients who are fed via nasogastric tubes[435].

1.7.7. Site of delivery of feeds

It can be argued that as lower oesophageal sphincter dysfunction, reflux and gastric stasis cause significant problems when feeds are delivered to the stomach, a more distal site for tube placement should reduce the incidence of these complications and pneumonia. However, several randomized studies have demonstrated that the incidence of aspiration pneumonia is similar in patients who have a nasogastric tube and patients with tubes placed in the duodenum (post pyloric tubes) and in the small bowel[25;422 187]. Three meta-analyses of these studies of gastric feeds versus small bowel feeds have come to conflicting results[436;437]. The first meta-analysis demonstrated that there was a significant reduction in pneumonia with small bowel feeds when compared to gastric feeds, though there was no reduction in mortality. The study recommended that patients with a history of reflux and aspiration or a medical condition resulting in delayed gastric emptying should have their feeds delivered to the jejunum rather than to the stomach[436]. However, another meta-analysis by Marik *et al* failed to show such an advantage[437]. It is unclear why post pyloric

feeds do not show a clear advantage over gastric feeds, but may be related to technical differences between the studies, such as definition of pneumonia, location of feeding tube port and the use of concurrent gastric decompression. Also enteral feeding directly into the small bowel may paradoxically inhibit gastric emptying through a feedback mechanism called the "ileal break" and causes an increase in the incidence of reflux and aspiration[438]. To counteract this ileal break some centres routinely use concurrent gastric decompression in patients who are receiving post pyloric feeds.

It has been suggested that small bowel feeding should be considered when patients are intolerant of gastric feeding, especially when aspiration is detected[439] and enteral feeds should be commenced using small bowel tubes if there is a high risk of gastric intolerance[440]. However, this procedure is not widely feasible as it requires personnel with special training[440]. The North American Summit recommends post pyloric feeds in patients who have two or more risk factors for aspiration and the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends jejunal feeding tubes for patients at high risk of aspiration[151].

Although the PEG tube is a more effective way of feeding, better tolerated by the patient, and has a lower incidence of displacement, there is no difference in the incidence of aspiration pneumonia when compared to nasogastric tubes[236]. A study which reviewed 69 patients with gastrostomies and 86 patients with jejunostomies found no difference in the rate of pulmonary aspiration or other pulmonary complications[149]. Another study by Metheny *et al* to assess the effects of site of the feeding tube on aspiration failed to demonstrate any preferred feeding site[154]. Therefore, the site of the enteral feeding tube does not alter the incidence of pneumonia.

1.7.8. Oral and selective digestive bacterial decontamination

As the bacterial content of oropharyngeal secretions significantly contributes to aspiration pneumonia, several studies have assessed the efficacy of oral and selective digestive bacterial decontamination (SDD) for the reduction of pneumonia and mortality in ventilated patients who are fed nasogastric tubes[27;441;442]. The full form of SDD has four components, an oral gel containing a combination of antimicrobial drugs applied to the oral cavity four times a day, a liquid suspension containing the same antimicrobial administered via a nasogastric tube, a three day course of intravenous antibiotics and, fourthly, strict infection control measures[441]. The intention is eradication of Gram negative bacilli from the oropharynx while preserving the normal bacterial flora.

Studies have looked at various combinations such as oral and gastrointestinal decontamination with or without intravenous antibiotics, oral decontamination alone and gastrointestinal decontamination alone. Most of the studies were done in critically ill patients in intensive care units. The antibiotic used, criteria for diagnosis of pneumonia and the type of patient population varied but selective digestive decontamination significantly reduced the incidence of pneumonia and was independent of the choice of antibiotics [442;442]. The majority of studies which used oral decontamination alone also showed a significant reduction in the incidence of pneumonia though there was no reduction in mortality, duration of the mechanical ventilation or length of stay in the intensive care units. In the trials which also used intravenous antibiotics, development of bacterial resistance was a significant concern[414].

Not many studies have assessed the efficacy of oral decontamination on stroke patients. In a randomised controlled double blind trial, Gosney *et al* studied the effect of SDD using a gel containing 2% colistin, 2% polymyxin and 2% amphotericin B, applied three times a

day for 3 weeks in stroke patients with poor swallow and for 2 weeks in patients with a normal swallow[27]. This is the first study using the SDD in acute stroke patients. The primary outcome was the level of oral colonization and isolation of Gram negative bacteria (AGNB) and secondary outcomes were effects of selective digestive decontamination on the incidence of pneumonia, mortality and morbidity. It had already been shown that the AGNB colonize the oropharynx of a stroke patient soon after hospital admission and one study has demonstrated that the change of oral flora occurred as early as 24 hours following hospitalisation[27]. Colonisation correlates with the severity of the illness, with an incidence of 37% in moderately ill and 79% in seriously ill patients with similar incidence in acute stroke patients[133;287]. Mostly these AGNB are Echserichia coli and enterobacter [287]. Gosney's study demonstrated a similar pathogenic spectrum as shown in previous studies and the sputum cultures confirmed that these bacteria were implicated in the documented episodes of aspiration pneumonia. The study also showed a high level of carriage and colonisation in patients within the first three weeks following their stroke, which was in keeping with previous studies[287]. The study confirmed that SDD can eradicate AGNB from the oral cavity of acute stroke patients. Oral decontamination also reduced documented episodes of pneumonia, though this result may not be reliable as there were no clear guidelines for the diagnosis of pneumonia. Also the incidence of pneumonia was much lower than many other studies conducted in post-stroke patients. In addition the mortality remained unchanged and re-colonisation of the oropharynx occurred after discontinuation of SDD treatment. The Royal College of Physicians Stroke Guidelines now recommend routine application of antibacterial oral gel in stroke patients who are fed via nasogastric tubes[1].

1.7.9. Avoiding malpositioned nasogastric tubes

Any nasogastric tube where the distal end is not in the stomach is called a malpositioned tube. Malpositioned nasogastric tubes can occur due to faulty insertion or tube migration back into the oesophagus following a bout of retching or vomiting or due to restlessness or agitation of the patient. A malpositioned nasogastric tube can have its distal end in the trachea or in either bronchus, but more commonly in the right bronchus due to its alignment with the trachea.

Feeding through misplaced tubes can occur if its position is not checked prior to each feed. The position of the distal end of the tube should be confirmed before commencement of each feed as the tube can migrate proximally or distally in the gastrointestinal tract either due to being regurgitated back to the oesophagus or being carried into the duodenum by gastric peristalsis. A tube may be pulled out by a confused patient or may be accidently dislodged during patient care or movements. A recent study in 201 critically ill patients, 25 episodes of proximal displacement of nasogastric tubes were reported over three days and patients with displacement had a higher incidence of aspiration and pneumonia[443].

Observing the external length of the nasogastric tube can provide some indication of such displacement but this is not a reliable indicator as the distal tip can spontaneously enter the oesophagus and remain coiled in the oesophagus without altering its external length. Previously an auscultatory method was used to confirm the position of the nasogastric tube, with the assumption that gurgling sounds when air is insufflated through the nasogastric tube confirmed that the distal end of the nasogastric tube was within the stomach (Woosh test). This test is no longer carried out as concerns have been raised over it safety and reliability. Measuring and confirming an acidic pH of the aspirate is reliable. However, use of neutral enteral feeds and proton pump inhibitors can result in higher pH values of the

aspirate thus limiting its value. Also it may be difficult to obtain an aspirate in some patients. In these difficult clinical situations a chest radiograph becomes the only reliable method of confirming the position of the nasogastric tube[444]. Reliance on chest x-ray or assessment of the pH of the nasogastric aspirate to confirm the tube position has reduced the incidence of pneumonia due to administration of enteral formula into the lungs via malpositioned tubes. Radiography remains the gold standard for confirming tube placement, and in many institutions it is mandatory before a nasogastric tube is used for feeding especially when the tube requires stylets for insertion[445]. Recently there have been several safety guidelines regarding the confirmation of the position of the nasogastric tube to avoid aspiration and pneumonia secondary to malposition[446].

1.7.10. Reduction of Bronchorrhea

Stroke-induced excessive bronchial secretions can occur, particularly in brain stem strokes[447]. Methods to reduce bronchorrhea have described and a few recent studies report the effect on the incidence of pneumonia. In a study of 19 patients with bronchorrhea showed that all had brain stem strokes with 55% affecting the dorsal lateral medulla. Increased bronchial secretions were mediated via the parasympathetic nervous system, and copious amounts of secretions developed within three days after stroke onset and persisted for up to two months[448]. Use of anti-cholinergic medications reduced the volume of secretions and patient discomfort, the need for regular expectoration or oropharyngeal suctioning, episodes of aspiration pneumonia and the number of courses of antibiotics[448]. A case report on two patients showed that trans-dermal scopolamine reduced increased salivation and possibly aspiration after an acute stroke. However, treatment with scopalamine was associated with significant side effects[449].

1.7.11. Regular measurements of gastric residual volumes

Measurement of gastric residual volumes (GRV) has been used to assess the risk of aspiration in enterally fed patients. A large GRV indicates intolerance to feeds, as well as symptoms such as vomiting and aspiration, which should prompt either a reduction in the infusion rate or cessation of feeding. However, threshold GRV values that mark increased risk of enteral feed intolerance are not universally agreed and therefore vary widely among hospitals. An excessively low threshold will lead to frequent and unnecessary discontinuation of feeds which will interfere with provision of the necessary nutrition. Chang *et al* defined enteral feed intolerance as a GRV of greater than 150 ml on two consecutive measurements done every 4 hours or a single GRV of greater than 500 ml. In this study 46% of the patients had enteral feed intolerance with an increased incidence of pneumonia and mortality. However, a study done by McClave *et al* found no difference in aspiration with a GRV of 200 ml compared to a GRV of 400 ml, as a threshold above which nasogastric feeding should be withheld. The study also demonstrated that an increased GRV had a low sensitivity for diagnosing the risk of aspiration[25]. This demonstrates inconsistency between studies of the importance of the GRV as a predictor of risk of aspiration.

Gastric residual volume measurement also has several technical issues that interfere with its accuracy. A small diameter feeding tube may collapse with suction, and withdrawal of gastric contents with a syringe may not empty the stomach completely. Aspiration also varies with the location of the ports of the tube, location of the distal end in the stomach and the position of the patient. In addition the volume of the aspirate may not only be gastric secretions but also could contain nasogastric feeds. Thus, it has been recommended that GRV measurements should be combined with clinical assessment of enteral feed

intolerance such as auscultation of bowel sounds and assessment of abdominal distension[450]. As mentioned in a previous section, several guidelines exist on how to diagnose GRV. The North American Summit recommended feeds to be withheld if the GRV is greater than 500 ml and careful bedside evaluation to be carried out if GRV is between 200 to 500 ml. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines state that feeding should be withheld if residual volumes exceed 200 ml in two successive assessments[25].

1.7.12. Cranial and pharyngeal electrical stimulation

Because brainstem swallowing centres have bilateral cortical innervation, measures that use electrical stimulation to enhance cortical input of the unaffected sensori-motor cortex could potentially expedite the takeover of the swallowing centre of the unaffected hemisphere, which might in turn enhance the recovery of dysphagia. Kumar *et al* studied the effect of non invasive brain stimulation on improvement of stroke related dysphagia. In this pilot study 14 patients with subacute unilateral hemispheric infarctions were randomised to have anodal transcranial direct current stimulation (tDCS) or to sham stimulation of the sensori-motor cortical representation of swallowing on the unaffected hemisphere over five consecutive days. Severity of the dysphagia was measured using a validated swallowing scale, the Dysphagia Outcome and Severity Scale. Patients who received anodal tDCS gained 2-6 points of improvement on the Dysphagia Outcome and Severity Scale compared to the control group who only had a 1.25 point improvement. Recent studies have examined the role of pharyngeal electrical stimulation in expediting the recovery of swallow after acute stroke[451-453]. The hypothesis is that electrical stimulation of the pharynx will generate sensory impulses reaching both dominant and non-dominant swallowing centres in motor cortices which will enhance the takeover of the swallowing function by

the undamaged non-dominant swallowing centre[454]. Initial studies were done in healthy subjects who had 1Hz repetitive transcranial magnetic stimulation to induce a unilateral virtual lesion in the pharyngeal motor cortex followed by active or control (sham) pharyngeal electrical stimulation. Motor evoked potentials and swallow accuracy were recorded before and after the virtual lesions to assess the response to the pharyngeal electrical stimulation. Following this study, fifty acute stroke patients with dysphagia underwent pharyngeal electrical stimulation to assess its efficacy on swallow. The primary end point was the reduction of aspiration two weeks post intervention. The study showed that pharyngeal electrical stimulation for 3 days improved airway protection, reduced aspiration, improved feeding status and shortened hospital stay[455]. Both these types of electrical stimulation studies need further investigation in a larger number of patients prior to be used as routine treatment for dysphagia[456].

Paced glottic closure with a subcutaneously implanted stimulator linked to the ipsilateral recurrent laryngeal nerve using perineural electrodes has been tried to reduce aspiration on persistent aspirators following acute stroke. In a small study including five patients, Broniatowski *et al* showed that paced vocal cord adduction significantly reduced the incidence of aspiration and pneumonia. Again though promising, these new interventions need further research on larger number of patients[457].

In summary, though a number of interventions have been tried to reduce the incidence of pneumonia in enterally fed patients though only a few measures have shown consistent positive results. However, most were conducted in patients who were on intensive care units, in which acute stroke patients only form a small percentage. Only few studies included stroke patients managed on stroke units. Though some of the recommendations of

these ITU studies may be applicable to stroke patients as both stroke patients on stroke units and ITU patients share dysphagia, reduced protective reflexes, nasogastric feeding, and gastro oesophageal sphincter dysfunction. However, they also differ in several ways as ITU patients tend to be younger, have more comorbidities and have various contributory factors that would favour gastroparesis and reflux than patients managed on stroke units. They are almost invariably intubated and ventilated; both would increase the gastro-oesophageal reflux and aspiration. Disease profiles of ITU patients also differ as the majority of these patients are post-operative, have several major illnesses, and many have multi-organ failure. In addition these patients receive various medications such as anaesthesia, dopamine, narcotics and neuromuscular blocking agents, which affect the motility of the gastro-intestinal tract, gastric perfusion, residual gastric volume and gastro-oesophageal reflux. This is worsened by the autonomic response and increased stress hormones associated with stress and pain. Also these patients are intensely observed and commonly receive one-to-one nursing care. In contrast to ventilated paralysed patients in an ITU, patients with an acute stroke are older, have stroke as the main illness and are less intensely monitored. They can be restless and agitated, are able to use the non-paralysed arm to pull out the nasogastric tube, sometimes several times a day, especially during the first few days of their illness. Passing a nasogastric tube through an already colonised oropharynx several times can introduce bacteria into the stomach along the nasogastric tube. Furthermore, vomiting induced by pharyngeal irritation, restlessness and agitation favours aspiration, especially if the patients are not observed intensely.

Maintaining appropriate position during feeds, ACE inhibitors and selective oral decontamination have shown to reduce the incidence of pneumonia following stroke. Maintaining the body posture at 30 degrees or more is now standard practice during nasogastric feeds. The Royal College of Physicians (RCP) stroke guidelines recommend an

ACE inhibitor as one of the first line antihypertensive in stroke patients unless contraindicated. These also enhance cough and reduce pneumonia as an additional effect. Liquid preparations are available for patients who have dysphagia or fed via nasogastric tubes. The most recent RCP guidelines also recommend chlorhexidine oral gel as standard practice for all stroke patients who remain nil by mouth. Data on prophylactic antibiotics are inconclusive and this treatment should not be used unless new studies provide strong evidence. A considerable amount of safety precautions are now being carried out to confirm the position of nasogastric tube to prevent feeding using a nasogastric tubes which is wrongly positioned. However, aspiration and pneumonia still remains a significant cause of mortality and morbidity in stroke patients who are fed via nasogastric tubes suggesting that further research and new interventions are necessary to prevent this serious medical complication in stroke patient, who depend on enteral feeds for their nutrition.

1.7.13. Prokinetic Agents

Prokinetic agents are drugs that improve gastric emptying by promoting forward gastric peristalsis. They also reduce the residual gastric volume and gastric stasis and this leads to a reduction of gastro-oesophageal regurgitation[458]. Prokinetic agents have been extensively researched in diabetic gastroparesis and reflux oesophagitis and have shown to reduce symptoms by promoting gastric emptying[459]. It has been demonstrated that prokinetic agents also improve gastric emptying in enterally fed patients and the North American Summit recommends the use of prokinetic agents in patients on enteral feeds, who have more than two major risk factors for aspiration[25]. Prokinetic agents which have been researched include cisapride, erythromycin, domperidone and metoclopramide[460]. Studies of the efficacy of prokinetic agents mainly relate to critically ill ITU patients, and patient numbers are small[461;462]. The effects of each individual agent on the gastrointestinal tract are described below.

Cisapride

Cisapride is a prokinetic agent which improves upper gastric motility by direct action on gastric serotonin $5HT_4$ receptors and indirectly as a parasympathomimetic. Stimulation of serotonin receptors leads to a release of acetylcholine in the autonomic nervous system in the upper gastrointestinal tract. It also increases the muscle tone in the lower oesophageal sphincter and improves gastric motility. However, cisapride has now been withdrawn due to life threatening side effects such prolongation of the QT interval and predisposition to cardiac arrhythmias[463].

Erythromycin

Erythromycin increases gastric motility by acting on the motilin receptors of the upper gastrointestinal tract which stimulates contraction of the gut and gall bladder and triggers a phase of migrating myoelectric complexes[464]. It also increases lower oesophageal sphincter tone and oesophageal peristalsis. Erythromycin improves gastric motility in diabetic gastroparesis, in patients following partial gastrectomy, after vagotomy and in chronic intestinal pseudo-obstruction[465]. Side effects of erythromycin are nausea, vomiting, stomach cramps and the development of antibiotic resistance, which could be a major problem in patients who are prone to recurrent pneumonia[398]. Erythromycin also associated with an increased risk of sudden cardiac death especially when given with medications that inhibit the effect of the cytochrome p-450 3A enzyme[466].

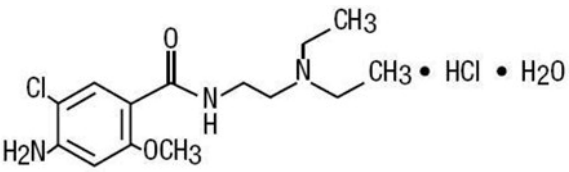
Several studies of erythromycin in enterally fed critically ill patients demonstrated that they improve gastric emptying though the effect lasts only for a short period[464;467]. In a study of 40 critically ill enterally fed ventilated patients Reignier *et al* showed that erythromycin 250 mg 6 hourly for 5 days improved gastric emptying, which was measured by regular

aspiration of the residual gastric volume, led to a higher return rate to successful enteral nutrition[468]. This improvement in emptying was only seen in the first few days and no significant difference in residual gastric volumes on the 4th and 5th days. A smaller study in critically ill mechanically ventilated patients intolerant to nasogastric feeds (indicated by a residual volume >250 ml when feeding was administered at a rate of 40 ml/hour) also showed a transient improvement of the residual gastric volume one hour after infusion of 200 mg erythromycin [469]. A study in critically ill enterally fed ventilated patients with head injuries and gastric feed intolerance (defined as a residual volume >150 ml) demonstrated a more sustained improvement in gastric motility and that also enhanced early nutritional intake with erythromycin[470]. Therefore the evidence suggests that erythromycin transiently improves gastric motility in enterally fed critically ill patients and may therefore reduce the risk of gastro oesophageal reflux and aspiration.

Metoclopramide

Metoclopramide is one of the most commonly used anti-emetics in clinical practice. It is cheap and has relatively few side effects. Metoclopramide has similar prokinetic actions as erythromycin, but carries no risk of antibiotic associated complications. It has a better safety profile than the agents discussed before and was therefore selected as the prokinetic agent for the MAPS study. Mechanism of action, pharmacokinetics and adverse effects of metoclopramide are discussed in section 1.8.

1.8. Metoclopramide



$C_{14}H_{22}ClN_3O_2 \bullet HCl \bullet H_2O$ MW 354.27

Figure 1-4 Metoclopramide molecular structure

Metoclopramide is a commonly used antiemetic in clinical practice. It has a central action on the chemoreceptor trigger zone and a peripheral action on the upper gastro-intestinal tract. It improves gastric motility by blocking gastro-inhibitory dopaminergic D2 receptors in the upper gastrointestinal tract[30]. It is also a mixed 5-HT3 receptor antagonist and a 5-HT4 receptor agonist. Its central mechanism of action closely resembles the antiemetic effect of phenothiazines by its direct antagonist effect on the D2 receptors in the chemoreceptor trigger zone in the brain stem. The chemoreceptor trigger zone is located close to the area postrema on the floor of the fourth ventricle in the medulla. It receives input from blood borne hormones and drugs and is connected to the vomiting centre where it initiates vomiting. The chemoreceptor trigger zone is situated outside the blood brain barrier, and this is reason why drugs such as dopamine which do not enter the central nervous system produce nausea. At higher doses 5-HT3 antagonist activity also contribute to the anti-emetic effect of metoclopramide.

However, the main action of metoclopramide as a prokinetic agent is due to its dopamine D2 receptor blocking effect on the gastro intestinal tract. Dopamine acting via D2 receptors has a direct relaxant effect on the upper gastro-intestinal tract, mainly the lower oesophageal sphincter, fundus and the antrum. Dopamine also inhibits the release of prokinetic acetylcholine from the cholinergic neurones of the myenteric plexus by

activating pre-junctional D2 receptors which indirectly inhibit upper gastro-intestinal muscle activity[471]. Metoclopramide by antagonising the inhibitory effects of dopamine on pre-synaptic and post-synaptic D2 receptors, increases the lower oesophageal sphincter pressure, gastric tone and gastric antral contractility. It also improves antro-duodenal coordination and peristalsis of the stomach and duodenum[30]. In addition metoclopramide sensitises the gut to the stimulatory effects of acetylcholine and increases pre-synaptic excitatory 5- HT4 receptor activity, both of which improves forward peristalsis[30]. It therefore accelerates gastric emptying, reduce gastric stasis and decrease post-prandial fundal relaxation via its multiple actions. Metoclopramide also reduces gastro oesophageal reflux due to increased LES tone[30]. Prokinetic properties of metoclopramide are limited to the proximal gastro-intestinal tract.

1.8.1. Pharmacokinetics and metabolism

Metoclopramide undergoes first pass hepatic metabolism and is partially metabolised by the cytochrome P450 (CYP) system which exhibits significant individual variation [472]. Oral bioavailability ranges from 30% to 100% and 20% to 30% of the drug is excreted unchanged in the urine. Impaired clearance of metoclopramide is seen in patients with renal insufficiency and cirrhosis. Individual variations in the genotypes and phenotypes of the CYP system affect the drug level and may increase the risk of complications such as tardive dyskinaesia in low metabolisors. Metoclopramide is also a competitive inhibitor of the P450 enzyme similar to neuroleptic agents such as haloperidol, chlorpromazine and risperidone. Concomitant use of metoclopramide with neuroleptic agents may increase the bioavailability of each drug which increases the risk of side effects. Metoclopramide is available as tablets, as a liquid preparation, and an orally absorbed sublingual preparation. An intranasal formulation is also available and has the advantage of rapid onset of action and circumvention of the first pass hepatic metabolism. Subcutaneous and intravenous

injections have been shown to improve symptoms in patients with more refractory symptoms.

Metoclopramide is effective as a short-term treatment of gastroparesis, but a meta-analysis of long-term metoclopramide therapy showed no consistent benefit on gastric motility after one month[473]. However, this was mainly based on small and uncontrolled open label studies. Another study demonstrated that gastric emptying transiently improved with metoclopramide and returned to baseline in spite of continued treatment after one month[474]. Nevertheless, symptomatic improvement of gastroparesis continued beyond this suggesting this may not only be due to the pro-motility effect, but also due to its antiemetic effect and normalization of gastric slow wave dysrhythmia[475].

Metoclopramide is widely used as a treatment of gastroparesis, especially in diabetes[458]. Currently it is the only drug which is approved by the Unites States Food and Drug Administration (US FDA) for the treatment of gastroparesis[25]. The use of metoclopramide in critically ill patients in ITU who have gastroparesis has been investigated. A double-blind study in 40 patients, who were enterally fed after coronary artery bypass surgery using paracetamol absorption test, showed that a single dose of intravenous metoclopramide effectively improved gastric emptying[476]. Another the study has demonstrated that although metoclopramide had a prokinetic effect on stomach it did not have any effect on the gall bladder[477].

As both cisapride and metoclopramide promote gastric emptying in critically ill patients, studies have been done to compare cisapride and metoclopramide for facilitating gastric emptying and improving tolerance to nasogastric feeding using gastric residual volumes and gastric emptying times[478]. Studies concluded that though both cisapride and

metoclopramide enhanced gastric emptying and improved tolerance to enteral feeds, metoclopramide provided a quicker onset of action and reduced gastric residual volume to a greater extent than cisapride[478;479].

1.8.2. Adverse effects

Most of the side-effects from metoclopramide result from its ability to cross the blood-brain barrier[480]. The British National Formulary cites extrapyramidal effects especially acute dystonic reactions as the most frequent side-effect[398]. Dystonic reactions can occur in 0.2-6% of patients and increases with higher doses[481]. These can be spasmodic and sustained involuntary muscle contractions resulting in twisting, repetitive movements or abnormal postures. It can present as torticollis, facial spasm, oculogyric crisis, trismus, and opisthotonis. These adverse effects are seen mainly in children and young females, though it has been reported in older females. Dystonic reactions usually occur within first 24 – 48 hours after initiation of therapy and are fully reversible within 24 hours following discontinuation of the metoclopramide with no long lasting effects[482].

Other extrapyramidal reactions include akathisia, a subjective feeling of inner restlessness and objective findings of motor restlessness[483]. This is mainly seen with intravenous administration, especially with rapid administration[484]. Prolonged therapy can result in Parkinsonian-like symptoms including tremor, rigidity and bradykinesia[482]. These symptoms resolve within 2-3 months of discontinuation of metoclopramide. Occasionally tardive dyskinesia, characterised by involuntary movements of the face, tongue or extremities, can be a side effect of use of long-term use of metoclopramide[482]. The incidence can vary from 1 to 15% after usage of metoclopramide for more than three months and may not reverse even after discontinuation of the medication.

In addition drowsiness, lethargy and fatigue are reported by 10% of patients and metoclopramide can worsen underlying depression. Blockade of central D2 receptors can also cause hyperprolactinaemia[485]. Other side-effects include restlessness, diarrhoea, neuroleptic malignant syndrome, rashes, pruritus, oedema, and rarely methaemoglobinaemia. Most of these side-effects are fully reversible with discontinuation of metclopramide.

1.8.3. Trials done to assess the efficacy of metoclopramide in the prevention of aspiration and pneumonia in patients who are fed via nasogastric tubes.

While there are good reasons to hypothesize that metoclopramide could reduce aspiration and pneumonia in acute stroke patients who are fed via nasogastric tubes, an extensive literature search in databases such as Medline, Mednet, Cochrane library and CINAHL did not reveal any clinical trials to support the use of metoclopramide in this patient group. The search reviewed articles from 1960 to 2010 and the key word which were used are stroke, aspiration, pneumonia, nasogastric feeds, enteral feeds, gastro oesophageal reflux and metoclopramide. There were studies using metoclopramide to reduce the intolerance of enteral nutrition therapy in critically ill traumatic brain injury patients and patients in intensive care units. However, the studies reviewed only the actions of metoclopramide on residual gastric volumes and improvement on achieving nasogastric feed targets rather than its effect on aspiration and pneumonia[155;486;487].

The closest was a study by Yavagal *et al* to assess the effect of metoclopramide in the prevention of pneumonia in critically ill patients receiving nasogastric feeds in an intensive care unit (ICU)[488]. It was a randomised controlled trial of 305 consecutive patients admitted to the ICU who required nasogastric feeding within 24 hours of admission to the unit. Metoclopramide was administered via the nasogastric tube, at a dose of 10 mg every eight hourly. A total of 174 patients received the placebo and 131 patients received

metoclopramide. The patient population was predominantly post-operative, many following intra-abdominal surgery and the average age was 35. The majority had endotracheal intubation, tracheostomy and mechanical ventilation. The study showed that metoclopramide did not decrease the rate of pneumonia nor had any effect on the mortality. However, there was a statistically significant ($p = 0.006$) delay of 1.5 days in the development of pneumonia in the treatment group. The study population of this study was significantly different to an average patient on a stroke unit as these patients were younger, had more co-morbidity and have various contributory factors that would favour gastroparesis and reflux such as intubation and mechanical ventilation. Therefore it is possible that patients managed on a stroke ward may have different outcomes when treated with metoclopramide. Also the study did not encounter any major side-effects of metoclopramide. Therefore a study to test the effect of metoclopramide on the incidence of aspiration and pneumonia in acute stroke patients fed via nasogastric tubes can be justified.

1.9. Summary of the evidence

Stroke is the third leading cause of mortality in England and Wales. In patients who survive the initial cerebral injury medical complications, such as aspiration pneumonia, pulmonary embolism, and urinary tract infections are the most likely causes of death. Amongst these pneumonia is the most common and the leading cause of increased length of stay, poor neurological outcome, morbidity and mortality. Pneumonia also affects the nutritional state, as recurrent aspiration can result in interruption of feeds, which further compromises recovery. Therefore, an intervention that reduces aspiration and pneumonia would be expected to improve recovery, mortality and long term clinical outcome in patients with acute stroke.

Dysphagia following acute stroke is common with an incidence up to 70%. Aspiration and pneumonia are common complications of dysphagia with incidence ranging of 25% to 55%. Aspiration can cause pneumonia either by aspiration of oropharyngeal secretions colonized by pathogenic bacteria. Severely dysphagic patients or patients who are too drowsy are kept nil by mouth and fed via nasogastric tubes to avoid aspiration. However, nasogastric feeding itself is still associated with a significant risk of aspiration and high incidence of pneumonia. Several studies have demonstrated that nasogastric feeds increases the risk of pneumonia by more than six fold.

Oropharyngeal pooling, re-colonisation of oropharyngeal mucosa by pathogenic Gram negative bacteria and micro aspiration of oropharyngeal secretions are recognised contributors towards the development of post-stroke pneumonia and will continue in spite of presence of a nasogastric tube. In addition, there is a significant reduction in lower oesophageal sphincter tone and gastric motility following stroke. This is partly due to the initial neurological injury and partly secondary to circulating stress hormones following acute stroke. These result in reduced peristalsis of the stomach, gastroparesis, increased gastric volumes, gastro-oesophageal sphincter dysfunction and gastro-oesophageal reflux. Regurgitation of stomach contents to an already dysfunctional pharynx and micro-aspiration of this material also significantly contribute to the development of post-stroke pneumonia. In addition, the presence of a nasogastric tube through the lower oesophageal sphincter has been shown to further impair sphincter function and worsen regurgitation.

Regurgitated gastric contents are a significant cause of pneumonia in patients fed via nasogastric tubes. It can be argued that this micro-aspiration should not cause pneumonia as the gastric acid usually prevents growth of bacteria. However, acidic gastric aspirates can damage the lung tissue which is then at risk of being secondarily infected. More

commonly, patients who are fed via nasogastric tubes have a higher gastric pH due to the neutralisation of gastric acid by the feeds. This promotes colonisation of the gastric contents with potentially pathogenic organisms such as Gram negative bacteria and Staphylococcus aureus. Analysis of the bacterial composition of the oropharynx and the gastric contents in patients who are fed via nasogastric tubes indicates passage of pathogenic bacteria in both directions. Biofilm formation on the nasogastric tube has also been suggested as a factor.

Several interventions to reduce aspiration and pneumonia in stroke patients have been tested. These include maintaining appropriate posture during feeds, acidification of stomach contents, selective gastro-intestinal decontamination, intermittent versus bolus feeds and preventative antibiotics. Apart from the maintenance of body posture at 30 degrees and selective oropharyngeal decontamination, none have demonstrated a reduction in the incidence of pneumonia in post-stroke patients fed via nasogastric tubes.

After reviewing the mechanisms responsible for gastro- oesophageal dysfunction and aspiration following stroke, it can be postulated that an agent that improves forward gastric peristalsis, and increases gastro-oesophageal sphincter tone could reduce reflux and aspiration. Metoclopramide is a commonly used prokinetic agent which acts on the dopamine D2 receptors in the upper gastrointestinal tract and antagonises the inhibitory effects of dopamine on the upper gastrointestinal tract. Therefore metoclopramide can increase the lower oesophageal sphincter pressure, gastric tone and gastric antral contractility. All these mechanisms accelerate gastric emptying, reduce gastric stasis, increase lower oesophageal sphincter tone and reduce gastro-oesophageal reflux. The rationale behind the MAPS trial is that metoclopramide would reduce reflux and aspiration of stomach contents into the respiratory tract and therefore would reduce the incidence of

pneumonia in acute stroke patients. The only study that tested the effect of metoclopramide in patients receiving nasogastric feeds was done on an ITU and demonstrated that metoclopramide significantly delayed the onset of pneumonia. As there was some beneficial effect, it is justified to test the effect of metoclopramide in patients with acute strokes who are fed via nasogastric tubes. In addition, as stroke patients are older it is possible that many of these already have gastro-oesophageal reflux which would be made worse by the stroke and a nasogastric tube. Also as they did not encounter any significant side effects when used in the recommended doses, it gives the reassurance of the safety of metoclopramide when used in this patient population. Therefore MAPS study was designed to test the efficacy of metoclopramide in reducing aspiration and pneumonia in acute stroke patients who are fed via nasogastric tubes.

Chapter 2 Aims and Structure of the thesis

Aims of this study:

- To test whether metoclopramide can reduce aspiration and pneumonia in acute stroke patients who are fed via nasogastric tubes in a randomised control trial
- To conduct a secondary analysis of data collected for the diagnosis of pneumonia as part of the study above, to identify early predictors of post-stroke pneumonia

Hypotheses to be tested:

- Regular treatment with the prokinetic agent metoclopramide prevents aspiration, pneumonia and hypoxia in stroke patients fed via nasogastric tubes
- An increased respiratory rate and a drop in oxygen saturations are good predictors of pneumonia in acute stroke patients
- A raised CRP level can be used as a biochemical marker for early diagnosis of pneumonia in acute stroke patients

Chapter structure

- The effect of metoclopramide on the incidence of pneumonia in stroke patients who are fed via nasogastric tubes: the MAPS study (chapter 3)
- Secondary analysis of data from the MAPS study relating to signs and symptoms of pneumonia for the early diagnosis of post-stroke pneumonia (chapter 4)
- A general discussion and conclusion (chapter 5)

These studies will add to the limited body of knowledge on prevention of pneumonia in stroke patients fed via nasogastric tubes and early predictors of post-stroke pneumonia.

Chapter 3 MAPS study

Abstract - Does Metoclopramide reduce Pneumonia in acute Stroke Patients fed via nasogastric tubes? (MAPS study)

Introduction: Aspiration and pneumonia is a common problem in dysphagic patients fed via nasogastric tubes**.** This is partly due to continued aspiration of infected oropharyngeal secretion and partly due to aspiration of refluxed gastric contents, secondary to lower oesophageal sphincter dysfunction, gastroparesis, and regurgitation which follows acute stroke. Metoclopramide, a dopamine-2 receptor antagonist of the upper gastrointestinal tract increases lower oesophageal sphincter tone, improves gastric contractions, and forward peristalsis of the stomach. In theory it should reduce reflux, therefore aspiration and pneumonia in this patient population. The aims of the study were to assess whether regular treatment with metoclopramide reduces the incidence of pneumonia in acute stroke patients fed via nasogastric tubes.

Methods: This is a double-blind randomised controlled trial. Patients within 7 days of admission with an acute stroke who needed nasogastric feeds and did not have signs of pneumonia were randomized to 10 mg metoclopramide or placebo three times daily via the nasogastric tube for 21 days or until nasogastric feeds were discontinued. Participants were examined daily for clinical evidence of pneumonia. A diagnosis of pneumonia was made when a patient had clinical signs of pneumonia, high inflammatory markers, and new radiological features of chest infection using radiography.

Results: Sixty patients (mean age 78 years, 22 males, mean NIHSS 19) were randomized (metoclopramide n = 30, placebo n = 30). Pneumonia was diagnosed in 26/30 and 08/30 in

placebo group and treatment group respectively ($p < 0.001$). The rate of aspiration, lowest oxygen saturation, highest C-reactive protein, highest white blood cell count, and NIHSS score were also significantly lower in the metoclopramide group. The study could not show any statistical difference in mortality between the two groups.

Conclusion: This study has shown metoclopramide to improve clinical outcomes in patients fed via NGT. The findings of this study should be confirmed in a larger study.

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3.1. Introduction

As already described, pneumonia is common in acute stroke patients who are fed via nasogastric tubes and any intervention that can prevent pneumonia will contribute to better patient recovery and survival. In this chapter, the design and the results of the effect of metoclopramide on the incidence of pneumonia in acute stroke patients who have rely on nasogastric feeds for their survival will be reported.

3.2. Methodology

3.2.1. Study design and setting

This was a randomized, double-blind placebo-controlled clinical trial which was conducted in the Acute Stroke Unit of University Hospital of North Staffordshire, Stoke-on-Trent. This is a 32 bed unit which has 16 male and 16 female beds. Patients are admitted to the unit via the Accident and Emergency Department, the Emergency Assessment Unit, the Medical Receiving Area and via other wards. About 900-1000 acute stroke patients are admitted per annum to the University Hospital of North Staffordshire Hospital, and of these admissions over 90% are admitted directly to the stroke unit.

3.2.2. Recruitment

All acute stroke patients admitted to the Acute Stroke Unit were eligible for recruitment. All these patients initially presented to the Accident and Emergency Department with sudden onset of focal neurology which was suggestive of an acute stroke. The majority of these patients were identified in the community by the paramedics and brought to the Accident and Emergency Department as a medical emergency. All patients with a suspected stroke were assessed by an experienced doctor to establish a clinical diagnosis of

a stroke. Patients with clinical signs and symptoms of acute stroke underwent an urgent CT scan of the brain within four hours of presenting. A combination of signs and symptoms and CT scan findings was used to formally diagnose acute strokes and the aetiology. All patients whose clinical features confirmed by neuro-imaging were transferred to the Stroke Unit. Non-stroke diagnoses such as subdural haemorrhages and cerebral tumours which would have presented with similar neurological signs were identified after the review of CT images and were referred to appropriate specialities.

Bedside swallowing assessment according to unit policies was performed in all patients. Patients who fail the swallowing test or remained too drowsy to be tested were kept nil by mouth and nasogastric feeds were considered, unless the patient was moribund and feeding was not considered appropriate. Patients on the stroke unit who required a nasogastric tube for feeding were eligible for enrolment in the MAPS trial. All patients who needed a nasogastric tube were reviewed by the researcher as possible recruits for the MAPS study. This included a complete physical examination and review of their case notes. Patients who had already been diagnosed as having a lower respiratory tract infection or pneumonia or who had other exclusion criteria were excluded from recruitment. As the unit provided a seven day acute stroke service and the researcher worked seven days a week during the trial period (apart from holidays), most of the acute stroke patients could be reviewed for the suitability for the MAPS study on the day of admission to the stroke unit. Patients with advanced malignancy or patients who were commenced on the Liverpool care pathway for dying on admission due to severe strokes with multiple co-morbidities were not recruited as they would not live long enough to the completion of the trial. In patients with a severe stroke (NIHSS >30), recruitment was not considered if the patient's family had a strong opinion that the patient should only have symptomatic/palliative treatment due to either patient's previous wishes or as a collective family decision. Such patients were not

considered to have active treatment such as nasogastric feeds or antibiotics. Recruitment of other brain pathologies such as brain tumours and brain abscesses which can mimic vascular strokes due to their focal neurological signs was averted as all patients were scanned on admission.

During the period of research application process for the MAPS trial, metoclopramide was widely used in clinical practice as an antiemetic and a prokinetic agent in many disease conditions and there was no time limit on its usage. For the MAPS trial metoclopramide was used for these therapeutic effects over a period of three weeks. Therefore an authorisation was obtained from the Medicine and Healthcare products Regulatory Agency (MHRA) for the MAPS trial as a phase 4 clinical trial. The study was approved by the by the North Staffordshire Local Ethics Committee on 26th July 2007 and the North Staffordshire Research and Development Consortium granted permission for the research to be conducted on 10th August 2007 (REC reference number is 07/Q2604/41).

3.2.3. Inclusion criteria

All adult patients admitted to the Acute Stroke Unit were considered for enrolment into the study if they required placement of a nasogastric tube for enteral feeding and if they could be recruited either before or within 48 hours of insertion of the nasogastric tube, no longer than a week had passed since the stroke,

3.2.4. Exclusion criteria

- Patients who had a nasogastric tube in place for more than two days
- More than seven days following the stroke
- Patients with signs and symptoms of a chest infection before recruitment

- Patients with a known oesophageal stricture or a carcinoma which would interfere with the insertion of a nasogastric tube
- Patients with terminal illnesses such as advanced malignancies
- Patients on concurrent dopaminergic drugs
- Patients with a history of neurodegenerative condition which should affect swallowing e.g. Parkinson's disease and motor neurone disease
- Patients who had presented as strokes, but later were diagnosed to have a non stroke pathology (e.g. brain tumour) were excluded retrospectively
- Pregnancy
- Patients recruited to another study
- Patients where a decision not to treat actively had been made either due to poor chances of survival due to severity of the stroke or because of the patient's prior expressed wishes
- Known contraindications for the use of metoclopramide: Gastro-intestinal obstruction, perforation or haemorrhage; recent gastro-intestinal surgery; phaeochromocytoma; breast-feeding[398]

3.2.5. Consent

Patients and their next of kin were approached for the recruitment to the trial. Consent was sought from the patients if they were competent to give fully informed consent. For incompetent patients assent was sought from the next of kin. Consent was obtained at the earliest possible time if trial inclusion criteria were met. The principles of informed consent in the current edition of declaration of Helsinki were used as guidance[489]. Information was given about the aim, objectives intervention, possible side effects, planned observations and follow up procedures of the study. Information was provided verbally and in writing,

using clear and understandable language. Oral explanations were given if further information was needed. Adequate time and opportunity was given to read and ask questions before signing the consent form. In competent patients who had difficulties in signing due to right upper limb weakness a partial signature or some written sign on the consent paper was accepted. Such signatures were always witnessed by an independent member of staff. The consent form was dated and kept with the patient's notes. A second copy was kept in the research file. After consent or assent was obtained patients were randomised to the trial and an entry was made in the patient's case notes documenting recruitment to the trial.

3.2.6. Randomisation

Patients were given an identification recruitment number sequentially from one. Sixty patients were randomised by the lead of the research network who was independent from the study. This randomisation was done by numbered cards at a ratio of 1:1, metoclopramide: placebo. Sixty identical cards numbered 1 – 60 were placed in a cardboard box for the intended sixty patients. The stroke research network member who was independent from the study pulled out 30 cards out of the box. They were allocated to metoclopramide 10 mg and the remaining 30 cards were allocated to placebo. The randomisation was done in the presence of three independent witnesses and the researcher had no part in the randomisation process. Each card, with the randomisation number and the treatment option was placed in identically numbered, sealed opaque envelopes. In addition, the randomisation number and the treatment options were written in a confidential log, which was also sealed and was only was opened at the end of the trial when the trial was unblinded. All sixty envelopes were kept in a locked cabinet in a secure room to which the researcher had no access. After recruiting a patient the researcher informed the research office of the recruitment and the patient's details. A member of staff in the office then

released the numbered opaque envelope with the patient's recruitment number written outside and the treatment instruction (metoclopramide 10 mg TDS or placebo) inside. In addition the patient's details and the recruitment number were recorded in a separate log in the research office.

3.2.7. Blinding

This study was conducted as a double blind trial. The trial treatment was prescribed on the patient's prescription chart by the researcher, as "Metoclopramide trial drug (metoclopramide 10 mg or placebo) per nasogastric tube TDS as detailed in the trial envelope (trial number 07/Q2604/41). The sealed randomisation envelope was taken by the researcher from the research office following randomisation and handed to the nurse in charge on the acute stroke unit. The nurse in charge opened the envelope after confirming with another senior nurse or a doctor that it was sealed at the time of handing over. The envelopes with the treatment instruction were kept in the locked drug trolley. The drug trolley is always kept locked or when opened is observed by the nurse responsible for the drug round. The researcher had no access to the drug trolley or its keys. The nurse who does the drug round administered metoclopramide or placebo as instructed in the envelope, sign the prescription chart to confirm the drug administration and returned the envelope back to the drug trolley. Recruitment of a patient to the MAPS study was added on to the daily nurses hand-over sheet to ensure all nurses would be aware of the recruitment and the need to administer a trial drug according to the instructions in the sealed envelop in the drug trolley. Neither the patient nor the researcher knew which treatment was administered to the patient. Once the treatment period was complete the envelope was sealed and returned to the research office by a senior staff nurse of the unit.

The nurse administering the study drug was not blinded to the treatment options. However, the research team and the rest of the team who were involved in the patients' care were blinded to the treatment options. Most of the nursed on the stroke unit are experienced nurses and are fully aware of the importance of blinding process of a double blinded randomised control trial. However, there was potential for inadvertent unmasking of treatment allocation, especially when requesting medication from the pharmacy and when the treatment chart monitoring was done by the ward pharmacist. Therefore to overcome this potential problem and possible bias, independent assessors were used for interpretation of chest radiographs and for the diagnosis of pneumonia.

3.2.8. Intervention

Patients were randomized to one of two groups:

1) The intervention group: colourless metoclopramide syrup 10 mg tds (08:00, 15:00, and 21:00) via the nasogastric tube for 3 weeks or until discontinuation of nasogastric feeding
2) The control group: normal saline 10 ml via nasogastric tube tds (08:00, 15:00, and 21:00) for 3 weeks or until discontinuation of nasogastric feeding

The dose of metoclopramide used in this study is the standard recommended dose according to the British National Formulary[398]. Colourless metoclopramide syrup was supplied by the Hospital Pharmacy Department free of charge as a good will gesture to support this student project. Following randomisation a nasogastric tube was inserted by Acute Stroke Unit staff if the tube was not already present, according to Stroke Unit protocol. Insertion of a nasogastric tube and its maintenance was not part of the trial.

Other than the above mentioned treatment, a daily examination for pneumonia and the weekly observations done for three weeks which have been detailed later in the chapter, no other intervention was done as a part of the trial. All other management and care related to nasogastric tubes, type of nasogastric feeds, volume of feeds, safety issues regarding nasogastric tube placement and dietician review were done as routine patient care. All patients received standard stroke care according to Royal College of Physicians guidelines and local guidelines which included early mobilisation, daily physiotherapy and occupational therapy assessment, chest physiotherapy as required, regular attention to positioning and turning, and oropharyngeal suctioning, as required. None of the above mentioned care standards were altered for the purpose of the trial. Treatment of pneumonia or any other infection was according to the standard antibiotic policy of the hospital.

3.2.9. Care of nasogastric feeding and post-stroke care received by MAPS participants

At the University Hospital of North Staffordshire, bedside swallowing assessment (Level 1 swallowing test) in post-stroke patients was performed similar to method described by Smithard (described in section 1.6.1.4), as it is safe, easily repeated and straightforward to perform[109]. Patients who are comatose or too drowsy to be assessed for the safety of their swallow and patients who are identified as being at high risk of aspiration by bedside swallowing tests were kept nil by mouth and a flexible polyurethane nasogastric tube, with an inner diameter of 10 mm unless otherwise indicated (Medicina NG tubes, Medicina, Bolton, United Kingdom) was inserted by a doctor or a senior staff nurse. The same type of nasogastric tube was used in all patients. After initial placement correct position of the tube was confirmed by a chest X-ray or by pH testing (pH testing strips, Medicina, Bolton, United Kingdom) as per the nasogastric feeding protocol. (appendix14) All patients were positioned in semi-reclined position throughout the nasogastric feeds and three hours after the feed. Being on nasogastric feeds did not preclude patients from being sat out or

receiving therapy input. Nasogastric feeds were not interrupted during therapy sessions. Nasogastric feeds which were continuous rather than bolus feeds, were commenced in the morning after the patients were washed to reduce the effect of changes of body posture on aspiration and as general patient's care is easier in this position. Feeding overnight was not routinely carried out as patients cannot be observed for feed-related complications. The amount and type of nasogastric feeds was calculated by a dietician according to the patient's nutritional requirements and other parameters such as serum electrolytes, presence of lactose intolerance, renal function and the severity of hypo-albuminaemia[415]. Patients who were fed via nasogastric tubes were managed closer to the nurses' station so that they could be observed for complications such as vomiting and displacement of the nasogastric tube. When necessary, soft mittens were applied after consent from the next of kin to restless patients to prevent patients pulling at their nasogastric tubes. Reinsertion of a nasogastric tube when displaced, confirmation of the position before each feed and application of mittens to prevent a restless patient pulling out the tube were part of routine patient care on the ward (appendix 14). Patients' other medications were continued as routine care.

If a patient developed aspiration pneumonia antibiotics were commenced according to local guidelines. The initial choice was co-amoxiclav and clarithromycin if the pneumonia occurred within 48 hours of admission. This was changed to Tazocin (piperacillin/tazobactam) if there was no clinical improvement as determined by clinical examination and laboratory investigations. A pneumonia which occurred more than 48 hours after admission was treated initially with Tazocin. Metronidazole was added to the antibiotic regime routinely to cover anaerobic bacteria. Patients who were allergic to penicillin were treated with clarithromycin as the first line antibiotic and aztreonam if there was a poor response. Sputum was sent for culture and sensitivities, and antibiotics were

changed according to sensitivities. Most sputum samples were obtained during chest physiotherapy or oropharyngeal suctioning. Regular chest physiotherapy and suctioning of the upper airways was done as required. Nasogastric feeds were continued uninterrupted during episodes of pneumonia, as long as the correct placement of the tube was confirmed.

Use of other anti-emetics, ACE inhibitors and catheters

If an antiemetic was needed for clinical reasons, only non-prokinetic agents were used in trial patients and were prescribed in the 'as required' section of the prescription chart. This is again part of routine patient care. Cyclizine 50 mg, three times a day was the alternative antiemetic used in these patients. If a patient required a prokinetic agent for clinical reasons, the trial code was to be broken, and treatment was to be given as clinically indicated. However, such need did not arise during the trial. The use of other antiemetics was recorded during the trial. ACE inhibitors were the preferred antihypertensive agent if there were no contraindications as they have shown to improve mortality in stroke patients. Erythromycin is an antibiotic which has prokinetic properties and the plan was to use an alternative antibiotic for infections needing a Gram positive cover. However, there was no indication for the use of erythromycin on the patients as hospital guidelines had recommended the use of clarithromycin in the treatment of pneumonia.

The unit adhere a "minimal catheter" policy, and urinary incontinence was managed with incontinence pads rather than by indwelling catheters to reduce urinary tract infections. However, in the presence of signs and symptoms of an infection, possibilities of a non-respiratory tract infection was always considered and investigated by careful inspection of the cannula sites, urine dipsticks and mid stream urine culture examinations.

3.2.10. Assessments

Patients were assessed at baseline and then at weekly intervals for 3 weeks.

Baseline assessment

- Demographic details (e.g. age, gender)
- Date of stroke
- Date of admission
- Date of recruitment
- Date of commencement of nasogastric feeds
- Body weight
- Level of consciousness (Glasgow Coma Scale [GCS]) at recruitment
- Presence of other medical conditions - atrial fibrillation, hypertension, diabetes mellitus, heart failure (by history, examination or on more than 20 mg frusemide or equivalent per day), ischaemic heart disease (history of angina or myocardial infarction or treatment with nitrates or nicorandil)
- Previous lung disease – e.g. chronic obstructive pulmonary disease or asthma (by history or from list of drugs), other chronic lung problem (e.g. pulmonary fibrosis, thoracoplasty, pneumoconiosis)
- Oxygen saturation on admission to the Acute Stroke Unit and at enrolment (Milolta 3i pulse oximeter, Minolta Radiometric Instruments Operations, Osaka, Japan)
- Clinical stroke syndrome (Oxfordshire Community Stroke Project [OCSP] stroke classification categories: total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke and posterior circulation stroke (POCS)[37]
- Full neurological examination and assessment of stroke severity (National Institute of Health Stroke Scale [NIHSS])[490]
- Results of the CT scan of the brain (infarct, haemorrhage, normal, non specific changes)

- Medications on admission (see below)
- Current use of antibiotics and the reasons for its usage. Use of antibiotics at the time of recruitment were recorded as it could have an impact on the patients' susceptibility to pneumonia and possible side effects such as Clostridium difficile
- Baseline inflammatory markers e.g. WBC, CRP, ESR

Only medications which were thought to be of relevance to the trial were recorded. Cardiovascular medications recorded included diuretics, digoxin, antihypertensives and antianginals as they were indicative of cardiovascular co-morbidity. Angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers were listed separately as they have been shown to improve swallowing and reduce the incidence of pneumonia, and will be required in secondary analysis of results. Proton pump inhibitor intake was recorded as this affects the pH of gastric secretions and promotes bacterial colonisation of the stomach. In addition, the presence of medications which affect the respiratory system, such as bronchodilators, medications with anti-cholinergic actions [antidepressants, bladder stabilizing agents, tranquillizers, antihistamines] and sedatives [hypnotics, tranquillizers, antihistamines] was recorded.

3.2.11. Follow-up

The maximum period of patient followed up was 3 weeks. All patients were examined daily for the presence of pneumonia until they were enteraly fed and were on the trial medication. In addition, detailed assessments were made at the end of week 1, 2 and 3. Permanent removal of the nasogastric tube for whatever reason (swallowing improvement or withdrawal of treatment), transfer out of the Acute Stroke Unit to another unit, or completion of the 3 weeks in the study were considered as the end of the trial as for trial medication administration and daily clinical examination. However, even if the nasogastric

feeds were discontinued before the end of third week, all patients had a weekly review for presence of pneumonia. This weekly review also included a case-note review to record any diagnosis of pneumonia made by the clinical team managing the patient. In addition all formal reports of chest radiographs and inflammatory marker levels were recorded of these patients.

Week 1 and 2 assessment:

- Five minute pulse oximetry in the morning at rest
- Routine observation – pulse, blood pressure and temperature
- Lowest oxygen saturation for the week
- Highest temperature for the week
- Number of antibiotics
- Need for ACE inhibitors
- Antiemetics used outside the trial
- Neurological status- NIHSS

Final (week 3) assessment:

- As for week 1 and 2 oxygen saturation for 5 minutes, pulse and blood pressure
- Date of the removal of nasogastric tube (if removed before the end of 21 days)
- Reason for removal of the nasogastric tube (patient no longer requires nasogastric feeds as swallowing has improved, PEG tube insertion and treatment withdrawal)
- Insertion of a non-standard nasogastric tube (yes/no, size if yes___)
- Number of episodes of pneumonia over 3 weeks (as detailed in 3.2.1)
- Number of episodes of witnessed aspirations over 3 weeks
- Number of days oxygen was given
- Number of days on NG feeds during the 3 weeks

- Number of days nasogastric feeds interrupted or without NG feeds during the 3 weeks
- Number of nasogastric tubes reinserted during the trial period
- Body weight
- Lowest oxygen saturation during the 3 weeks
- Number of different antibiotics given during the 3 weeks
- Number of days of antibiotic treatment during the 3 weeks
- Highest temperature during the 3 weeks
- Highest WBC count during the 3 weeks
- Highest CRP level during 3 weeks
- Weekly NIHSS score
- Number of days with an urinary catheter
- Co-existing other infections e.g. UTI
- Treatment with angiotensin converting enzyme inhibitors (yes/no)
- Treatment with erythromycin (yes/no)
- Use of non-trial antiemetics (yes/no)

End of trial assessment:

All the details as above and the documentation of the final outcome were made at end of the third week or when the nasogastric feeding was discontinued, which ever was earlier. Four end of trial outcomes were recorded:

- nasogastric tube was removed as swallowing improved
- referred for a PEG tube insertion
- nasogastric tube removed due to withdrawal of treatment/palliation or commencement of the Liverpool care pathway for the dying
- transferred out of the stroke unit

Oxygen saturations were assessed for the MAPS trial by pulse oximetry. On weekly assessments the researcher monitored oxygen saturations over five minutes in the morning on room air using a pulse oximeter (Minolta 3i). While there are several other causes for the development of hypoxia than aspiration, it is assumed that these other causes (development of heart failure, pulmonary emboli, hypostatic pneumonia) will be equally distributed between the two groups, and the differences are therefore an indicator of treatment effect (e.g. prevention of aspiration), especially if they did not develop all the criteria for the diagnosis of pneumonia. Oxygen saturations are assessed every six hourly on the stroke unit on a daily basis for the first 72 hours and later according to clinical need. However, these results were difficult to interpret, as some of the readings were done in patients while being treated with oxygen. Longer (overnight) pulse oximetry was also considered, but was considered as technically not feasible and again would be affected by oxygen treatment in some patients. Weekly assessments over 5 minutes on air were therefore was the feasible option for the purposes of this study.

3.2.12. Outcomes

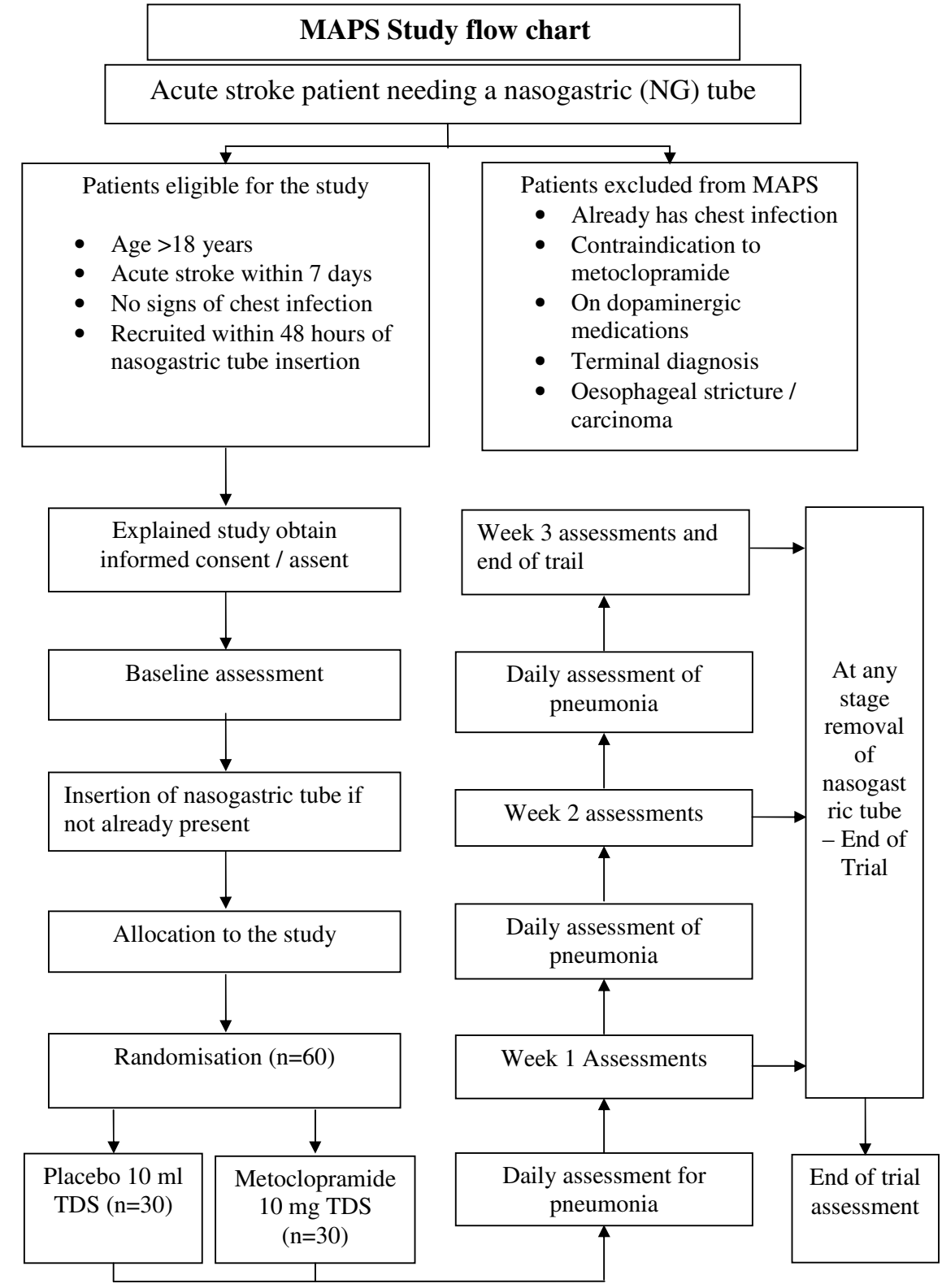
Primary outcomes

- The number of diagnosed episodes of pneumonia (any) as detailed in section 3.2.1.

Secondary outcomes

- The number of episodes of witnessed aspiration
- The number of antibiotic days
- The number of different antibiotics prescribed
- The highest CRP and WBC levels
- End of trial outcomes
- The lowest oxygen saturation

Figure 3-1 – MAPS Patient Flow Chart



3.2.13. Diagnosis of pneumonia for the MAPS Trial

The diagnosis of pneumonia in this study was based on a combination of clinical findings, laboratory results and radiological features. The British Thoracic Society (BTS) recommendations for the diagnosing pneumonia with few additions were used for the diagnosis of pneumonia[250]. Quantification of tachypnoea as a respiratory rate above 25/min and hypoxia as oxygen saturation less than 90% on room air were added on to the symptoms and changes in the white blood cell count and elevated inflammatory markers were added on to the systemic features. These modifications were added following the recommendations made by the local ethics committee. The rest of the criteria remained unaltered. Therefore diagnosis of pneumonia for the MAPS trial was made following if the patient fulfilled at least one of each four criteria listed below.

1) Symptoms of an acute lower respiratory tract illness (at least one of – cough, Respiratory rate over 25 per minute, sputum production or presence of hypoxia with oxygen saturation less than 90% on room air).
2) New focal chest signs on examination (new inspiratory crackles, bronchial breathing or signs of consolidation).
3) At least one systemic feature – fever over 38°C, shivers, rigors, leucocytosis (>11000 /ml) or leucopenia (<3000 /ml) or elevated inflammatory markers e.g. CRP
4) Radiological shadowing which includes at least in one segment and was not known to be previously present.

Each patient in the study was examined once a day, including weekends, by the researcher and this included a comprehensive examination of the respiratory system as detailed below.

i) Baseline observations - pulse, blood pressure, oxygen saturation, temperature and respiratory rate

ii) Chest examination – percussion for dullness, auscultation for bronchial breathing and inspiratory crackles

iii) Need for suctioning due to increased respiratory secretions and the presence of purulent sputum was noted

A CRP level above a cut-off level of 30 mg/l was considered as elevated. Clinical suspicion of pneumonia was defined as either the presence of two or more signs such as hypoxia with an oxygen saturation of less than 90% or a drop in the saturation of more than 3%, a respiratory rate of more than 25 per minute, a rise in of temperature more than 38°C and new chest signs on auscultation. Productive cough with purulent sputum or the presence of purulent sputum during chest physiotherapy or during oropharyngeal suctioning was also considered as a sign of a chest infection. Changes in oxygenation were assessed by pulse oximetry. In addition, evidence supporting a diagnosis of pneumonia was taken from the medical notes if the diagnosis had already been made by another doctor. In all patients who were recruited to the trial, another doctor on the ward was asked to examine the patient to confirm chest signs if the researcher found any abnormal signs. This was usually a medical registrar attached to the Stroke Unit. A chest radiograph and a blood test for CRP and a full blood count were requested as part of routine clinical care in all patients with suspected pneumonia if they had localising chest signs on examination. Even without localising chest signs, if the clinical suspicion of pneumonia was high, these investigations were requested, which is the usual ward practice for the early diagnosis of pneumonia. If there was purulent sputum a sample was sent to the microbiology laboratory for culture and sensitivities. The final diagnosis of pneumonia was made by an independent senior doctor after reviewing the symptoms, physical signs, blood results and the chest radiograph. This was usually the stroke consultant responsible for the management of the patient. As for the trial purposes, the diagnosis of pneumonia was recorded only after consultant confirmation. Patients who

had clinical signs of pneumonia without new infiltrates in the chest radiograph were classified as having a probable pneumonia and patients who had a clinical diagnosis of pneumonia with new infiltrates in the chest radiograph were classified as having a definite pneumonia. For this study aspiration pneumonia was diagnosed if the patient developed pneumonia according to the modified BTS criteria following an observed or suspected episode of vomiting or aspiration. Aspiration was diagnosed either if aspiration was witnessed by ward staff or if nasogastric feed was noticed in the respiratory secretions on suctioning or during chest physiotherapy.

The lowest oxygen saturations were documented on air prior to administration of oxygen. If the patient was already on oxygen, observation charts were used to obtain saturations on air prior to the commencement on oxygen therapy. This was mainly in patients who had low oxygen saturations at night and when oxygen treatment was commenced prior to the ward team review of the patient on the morning ward rounds. Such patients' oxygen therapy was not discontinued to record of the lowest oxygen saturations for the purpose of the trial, as it was thought unethical and may cause undue distress or deterioration of the patient's condition. The lowest oxygen saturation while on oxygen was not recorded as the concentration of oxygen treatment varied and all were adjusted to maintain saturations above 94%. However, if there were episodes where the patient was without oxygen due to being restless and accidently removing the oxygen therapy device, these opportunities were used as soon as possible to record the oxygen saturation on air.

All episodes of pneumonia were treated with intravenous antibiotics according to the local guidelines. Initial treatment was intravenous co-amoxiclav 1.2 g three times a day and clarithromycin 500 mg twice a day if the pneumonia was within few days of hospital admission and did not fulfil the criteria for severe pneumonia. If the onset of pneumonia

was more than a few days after admission or the patient had signs of a severe pneumonia the choice of antibiotic was intravenous Tazocin, as this was the first line of antibiotic for severe hospital acquired pneumonia according to the hospital guidelines. As silent aspiration plays a significant role in most stroke associated pneumonias, metronidazole was commonly added to the antibiotic combination. If there was a poor response to the initial antibiotic combination, which was suggested by a poor clinical response and the absence of a fall or a continuing rise of the inflammatory markers, antibiotics were changed according to advice of a consultant microbiologist. Poor response to co-amoxiclav and clarithromycin was commonly encountered and the second line of antibiotics was either Tazocin or meropenem. Aztreonam or levofloxacin were used in patients who were allergic to penicillin. Patients were examined daily and the examination findings were recorded in the patient's case notes. These measures were done as part of routine clinical practice. A C-reactive protein reading over 30 mg/l was considered as significantly elevated for the MAPS trial. This figure was obtained by review of previous research papers [264;266]. A white cell count (WBC) over 11 x 10^6/ml was considered as elevated. The response to the antibiotics was defined as normalisation of the WBC and a 50% or more reduction of the CRP value from its highest within five days of starting antibiotics, together with the normalisation of the body temperature, a reduction of chest signs, a reduction in the colour and volume of sputum and the ability to wean off the supplementary oxygen therapy, if used, to maintain oxygen saturations above 94% on air. This is again was standard clinical practice on the unit.

As for the research, data were recorded in separate data sheets allocated to each patient, in addition to entries made in the case notes. Baseline observations, inflammatory markers (if available) and chest signs were recorded in data sheets for all patients on recruitment and on day 4, 7, day 14 and day 21. If the end of the trial was earlier than the day 21, these

observations were recorded on that day. If there were no positive chest signs it was noted as chest was clear in the trial log. If a diagnosis of pneumonia was made, all physical signs were recorded on the day of diagnosis and at the end of the course of antibiotics were recorded in the patients' research data sheet. In addition the vital signs and chest signs on the day prior to the pneumonia were taken from the case notes and from the observation charts and were recorded in the research data sheets. All CRP and white cell counts done during the trial period irrespective of presence of pneumonia were recorded in the data sheets.

3.2.14. Plans for drop-outs and missing data

Patients who would withdraw consent / assent, intervention needed to be discontinued due to side-effects and patients who would be transferred out to another unit were the possible drop-outs. Non-compliance was not expected as the trial medication was administered regularly by the nursing staff. Data and outcome measures of patients who had to be withdrawn from the trial due to withdrawal of consent / assent or due to side-effects were to be included in the final analysis until the day of withdrawal from the trial. All relevant data and outcome measures of patients who were transferred out from the stroke unit were to be used in the analysis from the recruitment to the point of transfer. In addition, local hospitals were to be contacted on the 21st day from recruitment to assess whether the patients were alive and whether they still required enteral feeds. These details were to be included in the final analysis. However, details of further episodes of pneumonia, courses of antibiotics and their neurological status were not to be included in the final analysis as trial intervention and observations end at the point of transfer. Patients with no outcomes were not expected as the outcomes were assessed in a dichotomised yes/no response for the presence of pneumonia and aspiration. Every effort was made to minimise missing data.

However, if there were missing data, retrospective case note review was planned to obtain such data.

3.2.15. Statistical methods

Data entry and analyses were conducted in SPSS 21 (Armonk, NY: IBM Corporation) and Stata 13 (College Station, TX: StataCorp). The efficacy of metoclopramide in reducing post-stroke pneumonia was investigated using the intention-to-treat approach. Intention-to-treat analysis was chosen as it provides an unbiased comparison of the two study populations and to avoid effects of drop-outs. Though poor compliance was not expected in the MAPS trial, using intention-to-treat analysis does not require observation of compliance status or incorporation of compliance into the analysis. Normally distributed interval data were described using means and standard deviations, non-normal data or ordinal data were described using medians and inter-quartile ranges, and nominal data were expressed as percentages.

Initially the treatment group and the placebo groups were compared for baseline demographics, neurological scores, CT findings, previous illnesses and previous lung pathologies to assess for baseline imbalances between the two groups. Later the two groups were compared in relation to the outcome variables such as episodes of pneumonia, episodes of aspiration, highest WBC and CRP, the number of different antibiotics prescribed, number of days of antibiotic treatment, NIHSS scores at the end of the trial period and the lowest oxygen saturations. Three final outcome variables namely nasogastric tube removal as improvement of swallowing, referral for insertion of a PEG tube, and withdrawal of treatment as terminally ill, were compared between the two groups.

During statistical analysis outcomes were adjusted for age and baseline NIHSS score, as pre-specified covariates. Missing values were imputed through multiple imputation, on a 'missing at random' assumption, using ten imputed datasets. The primary outcome – number of episodes of pneumonia – was compared between groups using a Poisson regression model, with estimates reported as rate ratios (RRs). A similar analysis was applied to the number of aspirations, but owing to zero-inflation a negative binomial regression model was applied to the number of days of antibiotic treatment. Mortality and final clinical outcome were analysed using binary and multinomial logistic regression, respectively, with estimates reported as odds ratios (ORs). Follow-up NIHSS scores and lowest oxygen saturation values were analysed using analysis of covariance and reported as mean differences. Highest WBC and highest CRP did not satisfy the distributional assumptions of analysis of covariance and therefore were first log-transformed; these estimates were expressed as fold changes.

A sensitivity analysis was performed for all outcomes by calculating unadjusted estimates. Statistical significance was set at $p \leq 0.05$ (two-tailed) and 95% confidence intervals were calculated for estimates of treatment effect.

3.2.16. Sample size

No previous study has been performed to assess the efficacy and safety of metoclopramide to prevent pneumonia in stroke patients fed via NGTs. The MAPS trial was done as a pilot study of testing metoclopramide for the prevention of aspiration and pneumonia in acute stroke patients who are fed using nasogastric tubes. The previous studies which used metoclopramide were conducted in patients managed on intensive care units and as described before they constitute a very different patient population than acute stroke patients who are managed on stroke units. Therefore the findings of these studies could not

have been taken for a formal sample size calculation for the MAPS study. Therefore the MAPS study was designed as a pilot study and was intended to assess the feasibility, safety, the potential efficacy of metoclopramide procedural issues and make basic estimates of effect size if findings indicate that it is worth while going onto a full study. If procedures were shown to be good and valid the findings of the pilot study will be used to inform and work up a full trial. Data of this study will be used to estimate the sample size for the major trial.

As this was a pilot study no formal study size calculation was undertaken. The size of the study was determined by time constraints and feasibility. UHNS admits approximately 900 patients to the stroke unit per year. About 10% of these patients need nasogastric feeding. Not all fit the inclusion criteria or would be willing to consent to be included into a clinical trial. Many were expected to be excluded because of pneumonia on admission or before insertion of a nasogastric tube. Also recruitment to other trials prevented some patients being recruited to the MAPS trial. Therefore, recruitment of 1-2 patients per month was thought to be feasible. The research project was expected to be carried out over two years and it was considered that enrolment of 60 subjects was a feasible target. This was set as the sample size.

3.2.17. Ethical considerations

The study was conducted according to the Medical Research Council guidelines for good clinical practice in clinical trials and the declaration of Helsinki[489]. The research was conducted in compliance with national and local regulations. The research was approved by the Local Research Ethics Committee and the North Staffordshire Research and Development Consortium. The scientific design and conduct of the study was guided by the Research Governance Framework for Health and Social Care.

3.2.18. Data protection

Data collection for all patients was done by the researcher. The research supervisor and research staff within the stroke unit supported the researcher in the data entry and analysis. Data collection forms containing personally identifiable data were kept in a locked cabinet, which was located in the local research office which had a coded lock. For data entry on to computerized databases and analysis, personally identifiable data were converted to an alphanumerical code using a specific code number for each participant. The principal investigator, members of the stroke unit research staff, statisticians and supervisors at Keele University had access to the anonymised data.

Data were stored on a password protected office computer and a password protected portable computer. One back up copy was made of all data which was kept in a locked cupboard on the acute stroke unit. Anonymised data may be made available to other researchers for meta-analysis and publication in media such as the Cochrane Database. Data records and files will be destroyed after 15 years of storage.

3.3. MAPS trial Results

3.3.1. Recruitment

The MAPS trial was conducted over a period of three years, from October 2008 to September 2011. During this period 2932 acute stroke patients were admitted to the Acute Stroke Unit and recorded in the Stroke Register. Out of these admissions, 296 patients needed a nasogastric tube for a period of at least 24 hours. A significant number of these patients (n = 202) already had signs of lower respiratory tract infection or pneumonia and were not eligible for recruitment to the MAPS trial. Thirty-four patients were excluded due to other exclusion criteria, inability to obtain consent or due to recruitment to another clinical trial. A total of 60 patients were recruited to the MAPS trial and the data of all 60

patients were used in the analysis. Written informed consent was obtained in 14 patients, and assent from the next of kin in 46 patients. As the plan was to use intention-to-treat analysis, data of all participants were included in analysis. Of the 60 patients who were recruited, there were no patients who had to be withdrawn from the trial due to later withdrawal of consent or assent. Also there were no patients who needed to be withdrawn due to later identification of an exclusion criterion or due to a non-stroke diagnosis which was not apparent at recruitment. All participants had outcome measures and adhered to the study protocol. There were no participants who had to be withdrawn from the trial due to development of side-effects to the intervention. However, there were two patients who were transferred out of the stroke unit to a peripheral hospital during the trial period while they were on nasogastric feeds. The data of these patients until they were transferred out of our unit were utilised in the analysis. Both patients were transferred out during their third week of the trial (one each from the treatment group and the placebo group) and enquiries made from the hospitals they were transferred to confirmed that both patients were alive and had PEG tubes inserted in the fourth week after the stroke. Apart from the lowest oxygen saturations, there were no missing data in any of the primary or secondary outcome measurements.

All patients were admitted on the same day of their stroke (table 3.1). Five patients were recruited to the MAPS trial on the day of their admission and four of them were in the placebo group. In both groups, 44 patients (73%) were recruited within 48 hours of admission. The majority of patients were recruited prior to the insertion of the nasogastric tube, which was usually within the first 48 hours of admission to the ward. The mean time duration from admission to randomisation to the MAPS trial for all patients was 2 days. All patients who were recruited were randomised to the treatment or to the placebo arm within 30 minutes of recruitment.

3.3.2. Baseline characteristics

Baseline characteristics of the groups are given in table 3.2. The mean age of the subjects was 78 years and subjects were predominantly female (63%). Though six patients (10%) did not have any significant co-morbidity, most patients had one to three comorbidities on admission. The common comorbidities were hypertension (66%), diabetes (30%) and atrial fibrillation (61%). Atrial fibrillation was known in 31 patients on admission and six more patients were diagnosed as having atrial fibrillation during the trial period. Twenty-one patients (35%) had a history of ischaemic heart disease and nine patients (15%) had congestive cardiac failure. There were ten patients (16%) with a history of previous lung disease, namely bronchial asthma (n=2), chronic obstructive pulmonary disease (n=7) and pulmonary fibrosis (n=1). Fifty-three patients (88%) had a normal baseline chest radiograph on admission, emphysematous lung fields in five patients and pulmonary congestion in two patients.

Nine patients (15%) were not on any medication prior to admission. Common medications on admission were diuretics (48%), proton pump inhibitors (45%) and digoxin (30%). Eighteen patients (30%) were on an ACE inhibitor (Nine patients in each group), nine (15%) were on beta-blockers, 15 patients (25%) were on other antihypertensives, seven patients (12%) were on anti-anginal medication and five (9%) were taking regular salbutamol and ipratropium inhalers prior to admission. Five patients were on oral anticoagulants for atrial fibrillation. Apart from one patient who was on penicillin for suspected sub-acute bacterial endocarditis no other patient was on antibiotics at the time of recruitment. There was no difference in the medication on admission between the two groups. Acute stroke treatment was similar in both groups. Nine patients (15%) had therapeutic intravenous thrombolysis on admission, five (8%) in the placebo group and four (7%) in the treatment group.

The mean Glasgow coma scale of 12 was in both groups. Both groups had high mean NIHSS scores, 20 in the treatment group and 19 in the placebo group 19, which suggests that most had severe strokes with significant disability. The majority of patients had severe strokes with a total anterior circulation syndrome in 51 (83%) patients the majority of patients 56 (94%) had ischaemic strokes. Baseline CRP levels were available in 49 patients (81%), baseline WBC was available in all 60 patients (100%) and the baseline albumin was available in 45 patients (75%). As ESR is not a commonly done baseline investigation, it was available only in 20 patients (33%). The mean WBC of the treatment and placebo groups were within the normal range and the differences were statistically not significant.

The mean time from admission to insertion of a nasogastric tube for all patients was two days. Most patients had their nasogastric tube inserted within 48 hours of admission, 26 patients (86%) from the treatment group and 23 (76%) from the placebo group. Two patients from the placebo group had their nasogastric tube inserted within 24 hours of admission. In summary, there was no statistical difference in the baseline characteristics between the two groups and the two groups were well matched for baseline clinical characteristics. Also they did not have evidence of an early or ongoing pneumonia on admission.

Follow-up period

One patient had treatment withdrawal within the first week. All other 59 participants were enteraly fed during the first week and had daily clinical examinations according to the study protocol. During the second week nine more participants had their treatment withdrawal and by the end of 2 weeks 31 participants were still fed via nasogastric tubes (66% of the total number of participants). The 31 participants who were still enteraly fed by the end of two weeks continued to have daily clinical examinations. Each remaining 20

(34%) participants who were not fed enteraly and therefore not on the trial medication were reviewed at the end of two weeks for presence of pneumonia and a full case-note review for the diagnosis of pneumonia was performed. By the end of three weeks only 33% of participants were enteraly fed and they received full three weeks of daily clinical examination. All other participants who were alive (other than the two who were transferred out) had their three weekly reviews for the presence of pneumonia and a full case-note review. Telephone enquiries were made to the local hospitals for the possible diagnosis of pneumonia for the two patients who were transferred to peripheral hospitals. This ensured that all participants (n=60) were reviewed for the diagnosis of pneumonia (primary outcome) during the entire length of study period, which was three weeks.

3.3.3. Main outcomes

3.3.3.1. Episodes of pneumonia

Thirty-four patients (57%) had at least one episode of pneumonia, 26 patients (76%) in the placebo group and 8 (24%) in the treatment group. The mean number of episodes of pneumonia was 1.33 in the control group and 0.27 in the metoclopramide group. From the Poisson regression, this represented an RR of 3.241 ($p < 0.001$, 95% CI 1.76- 5.96) (table 3.3). All 8 patients who had pneumonia in the treatment group and thirteen patients in the placebo group had only one episode of pneumonia. However, thirteen patients (40%) in the placebo group had two episodes of pneumonia. There were no patients who had more than two episodes of pneumonia during the trial period.

In the MAPS study only 14 episodes of pneumonia (30% of all pneumonias) were confirmed by a positive sputum culture. Eleven of these microbiologically confirmed pneumonias were in the placebo group and three episodes were in the treatment group. The

organisms isolated were Staphylococcus aureus (n = 4) and Gram negative bacilli such as Klebsiella (n = 4), E. coli (n = 2), Proteus (n = 1), Citrobacter (n = 1) and Seratia (n = 1).

3.3.3.2. Time to pneumonia

The time from admission to the onset of pneumonia and the time from insertion of the nasogastric tube to the diagnosis of pneumonia were reviewed. The mean time from admission to the stroke unit to the diagnosis of pneumonia was 4 days for all patients, was 4 days for the placebo group and 6 days for the treatment group. The onset of pneumonia was delayed by two days in the treatment group (p = 0.006).

3.3.3.3. Witnessed aspirations

There were 17 patients (28%) who had at least one episode of witnessed aspiration (Table 3.3). Of forty-three patients who had no witnessed aspirations, 29 (67%) were in the treatment group and 14 (33%) were in the placebo group. The patients in the placebo group had a mean of 0.73 episodes of aspiration, compared to a mean of 0.03 in the metoclopramide group (RR = 20.54; p = 0.003). The mean time from nasogastric tube insertion to the first episode of aspiration was 5 days for all patients. The mean time for aspiration was 5 days in the placebo group and 9 days in the treatment group.

Of 17 patients who aspirated, one was in the treatment group and had only one episode of aspiration. Of 16 in the placebo group, 5 (29%) had not more than one episode of witnessed aspiration and nine patients (53%) had not more than two episodes of aspiration. Two patients had multiple episodes of aspiration of which details of first three episodes were recorded. There were total of 30 episodes of witnessed aspirations. Thirteen episodes occurred while the patient was in the supine position, 15 episodes occurred when maintained at 30 degrees inclination and two episodes were associated with spontaneous

vomiting while the patients were sat out of bed (Table 3.4 and 3.5). Most aspirations occurred while on nasogastric feeds or within two hours of completion nasogastric feeds. Nine episodes of aspiration occurred when patients were being transferred to the radiology department and 13 episodes occurred when the patients were being turned. All patients received oro-pharyngeal suction and chest physiotherapy as soon as the aspiration was noted. Seven episodes resulted in aspiration pneumonia. During the other ten episodes patients were already on treatment for pneumonia. However, the aspirations caused further clinical deterioration in these patients and led to a change of the antibiotic regime to a stronger antibiotic and the addition of metronidazole.

3.3.3.4. The number of antibiotic days and the number of antibiotics

There were a total of 296 antibiotic days for all patients during the trial period (treatment group was 68 and the placebo group 228 days). Patients in the placebo group also had a higher mean number of days on antibiotic treatment (7.57) than those in the metoclopramide group (2.27); this represented an RR of 3.94 ($p < 0.001$). The average number of different antibiotics types used in the treatment group was 0.7 per patient 2.6 per patient in the placebo group (table 3.6).

3.3.3.5. WBC and C-reactive protein

All white cell counts and C-reactive protein results from recruitment to the end of the trial were reviewed to obtain the highest levels, rather than recording the CRP and white cell counts according to a specified date (table 3.6). The mean of the highest white cell count for the total group was 15.0 x 10^6/ml and the highest C-reactive protein for the total group was 79.4 mg/l. There was a statistically significant reduction in the two inflammatory parameters in the treatment group compared to the control group. The mean for the highest white cell count in the treatment group was 12.2 x 10^6/ml, lower than the placebo group

16.8 x 10^6/ml (p = 0.004). The treatment group had a lower mean CRP value at 61.1 mg/l than the placebo group at 97.7 mg/l (p = 0.045).

3.3.3.6. Trial termination

The mean time from the stroke to the end of the trial, which was either the removal of the nasogastric tube or completion of 21 days which ever was shorter (which constitute the end of trial drug administration), was 14 days for all sixty patients and from the insertion of nasogastric tube to the end of the trial was 12 days, though all patients who were alive (n=50) had their second and third week review for the presence of pneumonia. The mean time from the stroke to the end of the trial was 15 days for the placebo group and 13 days for the treatment group. Seventeen patients (28%) spent the full three weeks in the trial with nasogastric feeds and trial medication, while being cared by the Acute Stroke Unit. Of these 11 patients were in the placebo group and 6 were in the treatment group. Two patients who were transferred out of the unit in the 3rd week of the trial were referred to have a PEG tube inserted in the local hospitals they had been transferred to. This makes a total of 19 patients (31%) who were on nasogastric feeds at the end of 21 days.

Three defined end of trial outcomes were removal of nasogastric tube due to improvement of swallow, referral for PEG and treatment withdrawal. Thirty-one patients (52%) had their nasogastric tubes removed as their swallowing improved during the trial period of three weeks (table 3.6). Significantly more patients in the treatment group (66%) had their nasogastric tube removed than in the placebo group (53%) due to improvement of their swallow improved (p = 0.006, RR = 1.817, 95% CI 1.07-3.1). The type of diet they were commenced and the consistency of fluid when they were commenced on oral feeds were not recorded. Of patients who remained at UHNS, seventeen patients (28%) were referred to have a PEG tube inserted as there was no improvement of their swallow. Two patients,

one from each group were transferred to another hospital during their 3rd week of the study period. Both had nasogastric tubes as there was no swallow and both had been referred to have a PEG after transfer. Therefore nineteen patients (32%) were referred for PEG, 7 (23%) from the treatment group and 12 (40%) from the placebo group. There were more patients who required PEG tubes in the placebo group, however, the difference was not statistically significant (p-value = 0.17). Patients who continued nasogastric feeds for more than the 3 weeks after the trial period were not assessed for further development of pneumonia or aspiration in accordance with the study protocol.

Ten patients (17%), three (10%) from the treatment group and seven (23%) from the placebo group, had their nasogastric tube removed as they were considered for treatment withdrawal and palliation. Though there were more treatment withdrawals in the placebo group this was not statistically significant (p = 0.17) Poor response to treatment, neurological complications of the stroke such as malignant middle cerebral artery syndrome, extension of the stroke, and severe pneumonia with poor response to antibiotics were the most frequent reasons for treatment withdrawal. Consideration of poor quality of life even if there was a chance of survival was another reason for treatment withdrawal in patients with large strokes with multiple co-morbidities who were expected to require institutionalised care with PEG feeds. Such decisions were made after regular multi-disciplinary meetings and discussions with next of kin and other close family members. The initial phase of the treatment withdrawal included removal of the nasogastric tube and agreement not to further escalate medical treatment or to prescribe further courses of antibiotics. Trial-related observations were terminated once the nasogastric tube was removed as per protocol. Patients at the end of their lives were referred to the hospital palliative care team for supportive treatment or for the commencement of the Liverpool

Care pathway for the dying. There were no unexpected deaths in patients who were on the MAPS study during the time of the clinical trial.

3.3.3.7. Oxygen saturations

Of all available oxygen saturation readings the lowest saturation on air during the trial period was recorded for analysis. However, the lowest oxygen saturations were not available in all 60 patients. The commonest reason for this missing data was that some patients had commenced oxygen therapy at the time of the assessment for the trial and the lowest oxygen saturations on air were not documented by the attending staff prior to the commencement of oxygen therapy. This was mainly seen in patients who had oxygen treatment commenced at night (n = 7). Misplacement of patients' observation charts (n = 4) was another contributory factor. Retrospective case-notes review did not provide any further information on these missing lowest oxygen saturations. Out of 49 patients who had the lowest saturation recorded, the mean lowest oxygen saturation on air was 89.2% mm Hg. The mean of the lowest oxygen saturation on air was available in 27 patients (90%) in the placebo group and was 85.1% mm Hg (Table 3.6). There were 22 patients (73) in the treatment group who lowest oxygen saturation readings and they had a mean of 93.9%, which was significantly higher than in the placebo group ($p < 0.001$).

3.3.3.8. Neurological scores

In the treatment group, the mean NIHSS score improved from 20 to 16 at the end of the first week (Table 3.8). After this initial improvement the NIHSS score remained almost unchanged for patients in the treatment group. In the placebo group the initial mean NIHSS score of 19 remained almost unchanged for the first two weeks and deteriorated to 22 at the end of the third week. The differences of the NIHSS scores in the treatment group vs. the

placebo group were 4 at the end of week 1, 3 at the end of week 2 and 6 at the end of week 3 ($p = 0.008$).

3.3.3.9. Recovery of swallow

All patients in the treatment group and 29 patients (96%) in the placebo group needed nasogastric feeds during the first week of the trial. From there onwards there were more patients leaving the trial in the treatment group due to improvement of their swallow. At the end of two weeks 13 patients (43%) of patients in the treatment group and 18 patients (60%) in the control group were on nasogastric feeds, and at the end of three weeks the remaining patients were 7 (23%) and 12 (40%) for treatment and placebo groups respectively.

3.3.3.10. Other bacterial infections

The commonest non-respiratory infection encountered during the trial period was urinary tract infection. There were six patients with culture positive urinary tract infections, four (13%) in the treatment group and two (7%) in the placebo group. Four urine infections were due to Escherichia coli, one due to a Klebsiella species and the other due to a Proteus species. All infections were treated according to sensitivities with either trimethoprim or co-amoxiclav for a total of five days. One patient in the treatment group had lower limb cellulitis and was treated with intravenous benzyl penicillin for 5 days.

3.3.3.11. The use of ACE inhibitors and of other antiemetic agents

Nine patients in each group were on ACE inhibitors on admission. One patient in the treatment group and seven patients in the placebo group were commenced on ACE inhibitors during the trial period. Therefore there were more patients on an ACE inhibitor in the placebo group. Ten patients (33%) in the placebo group and two patients (7%) in the

treatment group needed another anti-emetic at least once during the trial period. Cyclizine 50 mg was the antiemetic used and majority of patients who had cyclizine were in the placebo group.

3.3.3.12. Thirty Day Mortality

Though formal trial observations ended at 21 days following recruitment, retrospective case-notes review was done to record thirty day mortality for all patients who were on the trial. Forty patients (66%) were alive at that point as ten more patients had died following the end of the trial. Though statistically not significant, there were more survivors in the treatment group (treatment group 22 patients and placebo group 18 patients $p = 0.2$). Pneumonia was recorded as either the immediate cause of death or a contributory cause of death in the death certificates in all ten patients who died following the end of the trial.

3.3.4. Summary of results

The two groups were well matched in the demographic data, stroke type and severity, co-morbidities and previous lung pathologies. There was a significant reduction in the incidence of pneumonia in the patients who were treated with metoclopramide. Also in patients who developed pneumonia this occurred significant delayed in the treatment group than in the control group. In keeping with a reduction in the incidence of pneumonia, the treatment group also had a lower number of antibiotic days and significantly lower levels of inflammatory markers. There were also significantly fewer witnessed aspirations in the treatment group than in control group and oxygen saturations were higher.

Patients who had metoclopramide also had significant neurological recovery at the end of 3 weeks and had more patients not needing nasogastric feeds due to resuming oral feeds. There was a weak trend towards more survivors in the treatment group at the end of three

weeks and there were fewer patients who required a PEG tube insertion though both were not statistically significant. The reduction of the incidence of pneumonia in the treatment group was not influenced by the use of concomitant medication such as ACE inhibitors or antiemetic as they were more used in the placebo group.

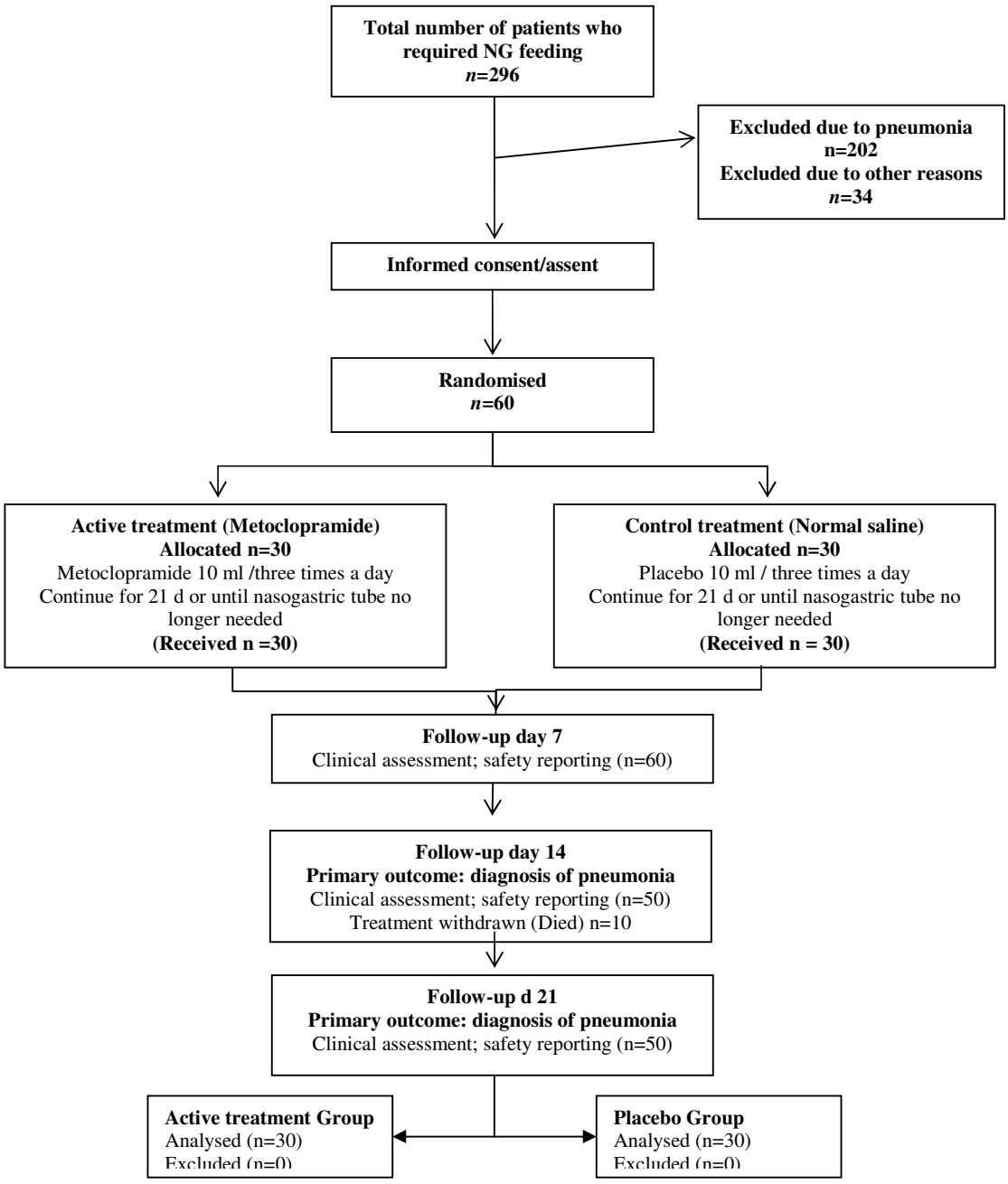


Figure 3-2 - Flow of patients

Table 3-1- Time from Admission to NGT Placement and Recruitment

		Treatment Group n = 30 (%)	Placebo Group n = 30 (%)
Admission to fist nasogastric tube (days)	0	0/30 (0)	2/30 (7)
	1	17/30 (57)	11/30 (36)
	2	9/30 (30)	10/30 (33)
	3	3/30 (10)	5/30(17)
	4	0/30 (0)	2/30 (7)
	5	1/30 (3)	0/30 (0)
	Mean (SD)	2.0 (1.0)	2.0 (1.0)
	Range	1.0 to 5.0	0.0 to 4.0
Admission to randomization (days)	0	1/30 (3)	4/30 (14)
	1	12/30 (40)	8/30 (26)
	2	9/30 (30)	10/30 (33)
	3	5/30 (17)	5/30 (17)
	4	2/30(7)	3/30 (10)
	5	0/30 (0)	0/30 (0)
	6	1/30 (3)	0/30 (0)
	Mean (SD)	2.0 (1.0)	2.0 (1.0)
	Range	0.0 to 6.0	0.0 to 4.0

Table 3-2 – Baseline characteristics

		Treatment Group n = 30 (%)	Placebo Group n = 30 (%)	p-value[1]
Age (years)	Range	55 to 91	46 to 95	
	Mean (SD)	76.9 (± 6.3)	79.2 (± 10.8)	0.19
Gender	Male	11/30 (37)	11/30 (37)	
	Female	19/30 (63)	19/30 (63)	1.00
Number of comorbidities	0	3/30 (10)	3/30 (10)	
	1	5/30 (17)	4/30 (14)	
	2	7/30 (23)	12/30 (40)	
	3	11/30 (37)	6/30 (20)	
	=>4	4/30 (13)	5/30 (17)	
Diabetes		07 (23)	10 (33)	0.4
Hypertension		18 (60)	22 (73)	0.3
Atrial fibrillation		20 (66)	17 (57)	0.4
Lung pathology	0	27/30 (90)	23/30 (77)	
	1	3/30(10)	6/30 (20)	
	2	0/30 (0)	1/30 (3)	
Baseline chest radiograph	Normal	28/30 (93)	25/30 (87)	0.3
	Abnormal	2/30 (7)	5/30 (17)	
Number of different drugs	0	4/30 (14)	5/30 (17)	
	1	5/30(17)	10/30 (33)	
	2	7/30 (23)	5/30 (17)	
	3	8/30 (27)	6/30 (20)	
	=>4	6/30 (20)	4/30 (13)	
NIHSS	Range	11.0 to 31.0	5.0 to 30.0	0.4
	Mean	19.9 ± 6.0	18.6 ± 6.7	
GCS	Range	8.0 to 15.0	6.0 to 15.0	0.4
	Mean	12.1 ± 2.5	12.1 ± 2.8	
CT diagnosis	Infarction	29/30 (97)	27/30 (90)	0.3
	Haemorrhage	1/30 (3)	3/30 (10)	
Type of stroke	TACS	27/30 (90)	24/30 (80)	0.3
	PACS	2/30 (7)	3/30 (10)	
	POCS	1/30 (3)	3/30 (10)	
CRP (mg/l)	Mean (SD)	13.6 (14.7)	11.2 (8.1)	0.5
ESR (mm/h)	Mean (SD)	15.4 (13.7)	19.3 (13.5)	0.5
Albumin (mg/l)	Mean (SD)	37.9 (4.3)	36.7 (4.0)	0.3
WBC (10^3/l)	Mean (SD)	9.5 (2.5)	9.9 (3.8)	0.6

([1]By Student's *t* test two-tailed, NIHSS - National Institute of Health Stroke Scale, GCS - Glasgow Coma Scale, CT- Computerised Tomograghic, TACS – Total Anterior Circulation Syndrome, PACS – Partial Anterior Circulation Syndrome, LACS – Lacunar Syndrome, PoCS – Posterior Circulation Syndrome, CRP- C Reactive Protein, ESR - Erythrocyte Sedimentation rate, WBC- White Blood Cells)

Table 3-3 - Episodes of Pneumonia and Aspiration

	Number of Episodes n	Treatment Group n = 30 n (%)	Placebo Group n = 30 n (%)	Total n = 60 n (%)	p-value[1]
Pneumonia	1 or more	8 (27)	26 (87)	34 (57)	
	0	22 (73)	4 (13)	26 (43)	
Number of patients with pneumonia	0	22 (73)	4 (14)	26 (43)	
	1	8 (26)	13 (43)	21 (35)	
	2	0 (0)	13 (43)	13 (22)	<0.001
No of patients with aspiration	0	29 (97)	14 (47)	43 (72)	
	1	1 (3)	5 (17)	6 (10)	
	2	0 (0)	9 (30)	9 (15)	
	3	0 (0)	2 (7)	2 (4)	<0.001

(1By student's t-test two-tailed, PEG – Percutaneous Endoscopic Gastrostomy)

Table 3-4 - Details of each Episodes of Witnessed Aspirations

	Number of Patients	Position			Presence of Nasogastric Tube	Pneumonia
		Supine	30 Degrees	Seated		
Treatment Group						
1st episode	1	1	0	0	1	0
2nd episode	0	0	0	0	0	0
3rd episode	0	0	0	0	0	0
Total episodes	1	1	0	0	1	0
Placebo Group						
1st episode	16	6	10	0	15	12
2nd episode	11	4	5	2	11	5
3rd episode	2	2	0	0	2	1
Total episodes	29	12	15	2	28	18

Table 3-5 - Positions Associated with Aspiration

	1st episode	2nd episode	3rd episode	Total (%)
Activity				
Turning	7	6	0	13 (43)
Transfers	7	2	0	9 (30)
None	3	3	2	8 (27)
Position				
Supine	7	4	2	13 (43)
30 degrees	10	5	0	15 (50)
Seated	0	2	0	2 (7)

Table 3-6 - Highest Inflammatory Markers, Antibiotic Days during 3 Weeks of Study and End of Trial Outcomes

		Treatment Group n = 30	Placebo Group n = 30	Total n = 60	p-value[1]
Highest WBC (10^6/ml)	Range	3.2 to 23.5	4.1 to 41.0	3.2 to 41.0	
	Mean (SD)	12.2 (3.9)	16.8 (7.6)	15.0 (6.0)	0.004
Highest CRP (mg/l)	Range	0.4 to 258.0	3.5 to 307.0	0.4 to 307.0	
	Mean (SD)	60.1 (62.2)	97.7 (79.3)	78.9 (73.2)	0.045
Lowest Oxygen Saturation	Number of patients n(%)	22 (73)	27 (90)	49 (82)	
	Range	89.0% to 97.0%	68.0% to 94.0%	68.0% to 97.0%	
	Mean	93.8% (2.3)	85.2% (5.4)	89.0% (6.1)	<0.001
Antibiotic treatment (days)	Range	0.0 to 12.0	0.0 to 16.0	0.0 to 16.0	
	Mean	2.3	7.7	5.0	<0.001
End of trial outcomes	Nasogastric tube removed -swallow improved	20 (67)	11 (36)	31(52)	0.02
	Referred for PEG	7 (23)	12 (40)	19 (32)	0.17
	Nasogastric tube removed treatment withdrawn	3 (10)	7 (23)	10 (17)	0.17

([1]By student's t-test two-tailed, CRP- C-Reactive Protein, WBC - White Blood Cells)

Table 3-7 - Time lag between the Admission and First Pneumonia / Aspiration

		Treatment Group n = 30	Placebo Group n =30	Whole Group n = 60	p-value[1]
Time from admission to first pneumonia (days)	Number[2]	8	26	34	
	Mean (SD)	6.0 (4.0)	4.0 (2.0)	4.0 (3.0)	
	Range	3.0 to 14.0	2.0 to 9.0	2.0 to 14.0	0.05
Time from Nasogastric tube insertion to pneumonia (days)	Mean (SD)	4.0 (3.0)	2.0 (1.0)	3.0 (2.0)	
	Range	2.0 to 9.0	1.0 to 6.0	1.0 to 9.0	0.006
Admission to first aspiration (days)	Mean (SD)	11.0	7.0 (6.0)	7.0 (6.0)	
	Total	1	16	17	
Nasogastric tube to aspiration (days)	Mean (SD)	6.0	5.0 (3.0)	5.0 (3.0)	
Recruitment to end of trial (days)	Mean	13.0	15.0	14.0	
Number of patients who completed 3 weeks of the trial		7.0	12.0	19.0	

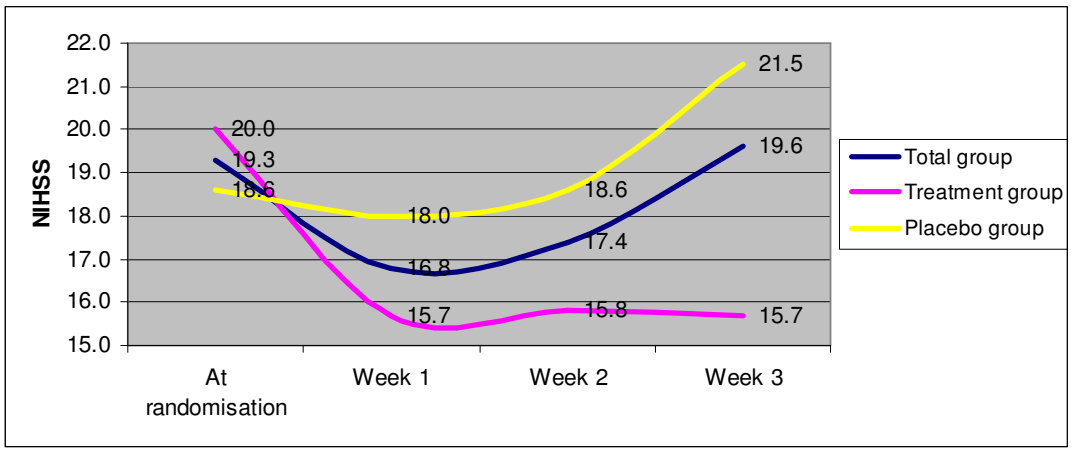
([1]By student's t-test two-tailed, [2]Number of patients with pneumonia (n))

Table 3-8 Changes in Neurological Deficit (NIHSS) over the Trial Period

	Admission		Week 1		Week 2		Week 3	
	number n (%)	Mean (range)	number	Mean (range)	number	Mean (range)	number	Mean (range)
Total Group n = 60	59 (98)	19.3 (5.0 – 31.0)	58	16.8 (2.0 – 34.0)	31	17.4 (4.0 – 32.0)	17	19.6 (4.0-32.0)
Treatment Group n = 30	29 (97)	20.0 (11.0– 31.0)	29	15.7 (6.0 – 33.0)	13	15.8 (4.0 – 25.0)	6	15.7 (8.0 – 24.0)
Placebo Group n = 30	30 (100)	18.6 (5.0 – 30.0)	29	18.0 (2.0 - 34.0)	18	18.6 (4.0 - 32.0)	11	21.5 (4.0 - 30.0)

(NIHSS – National Institute of Health Stroke Scale)

Figure 3-3 Changes in NIHSS



(NIHSS – National Institute of Health Stroke Scale)

3.4. Discussion

3.4.1. Effect of metoclopramide on pneumonia

The MAPS study findings suggest that metoclopramide reduces the incidence of pneumonia in acute stroke patients who are fed via NGT. This is the first randomised controlled study of metoclopramide in patients with acute stroke fed via nasogastric tubes and was designed as a pilot study with no sample size calculation. While this outcome is statistically highly significant, the study size was relatively small (n=60) and a false positive result cannot be excluded. In keeping with the observed reduction in the incidence of pneumonia, the treatment group also required fewer days of antibiotics, had lower levels of inflammatory markers, and were less hypoxic. There were fewer deaths in the metoclopramide group than in the placebo group, but this effect was not statistically significant. The results of MAPS have also shown that recruitment in the sub-acute stage of stroke is feasible and that regular administration of metoclopramide for a maximum of 21 days is safe in this patient group.

3.4.2. Timing of Pneumonia

MAPS study also demonstrated that most pneumonia occurred within the first week following stroke. Also of 296 patients who required a nasogastric tube, almost two thirds of patients were excluded as they already had signs and symptoms of pneumonia. This is in-keeping with previous studies that have demonstrated that post-stroke pneumonia is an early complication and most occurred within the first week of following stroke[178]. Of 34 episodes of initial pneumonias, almost all occurred within the first week following stroke and of all 47episodes of pneumonia seen during the trial, 76% occurred within the first week. Also pneumonia was seen as an early complication following nasogastric tube

insertion, with a mean duration of three days to pneumonia following nasogastric tube insertion. This emphasises the fact that these patients need maximising all protective measures against pneumonia at least during their first week following acute stroke.

The maximum number of episodes of pneumonia was two over the study period. There were no patients who had three or more episodes of pneumonia, a problem which is not uncommon in day-to-day clinical practice. The trial period was three weeks and most episodes of pneumonia were treated with courses of antibiotics lasting for 7-10 days thus limiting the episodes of pneumonia to a maximum of two. However, the review of causes of 30 day mortality showed that all deaths between the end of the trial and day 30 were in patients who were still enteraly fed and was due to recurrence of hospital acquired pneumonia. Also during second and third weekly reviews of patients who were not on nasogastric feeds, none of them had any further episodes of pneumonia. This shows that pneumonia is not only an early complication of stroke but also continues to be a significant problem as long as the patients are fed via nasogastric tubes. There were equal numbers of patients from each group in the ten deaths which occurred between completion of the treatment period and 30 days. This demonstrates that the mortality in the treatment group increased when they stopped receiving metoclopramide. It is possible that the withdrawal of the protective effect of metoclopramide in patients who were in the treatment group was responsible for equalising this incidence of pneumonia and mortality between the two groups.

3.4.3. Matching of the two groups

The two groups of the study were well matched for demographic data and co-morbidities, especially vascular comorbidities such as hypertension and diabetes. Most of the participants had few comorbidities with 83% having less than three other diagnoses. Incidences of hypertension and diabetes in the MAPS study were very similar to the

incidences seen in previous studies of post-stroke pneumonia. A significant proportion of participants were in atrial fibrillation, making a cardiac source of the emboli a likely cause for the stroke. This would also explain the high incidence of total anterior circulation strokes observed in this patient group as cardiac emboli are larger than platelet emboli and result in large areas of cerebral ischaemia[491]. In addition, most of the patients with atrial fibrillation were not anticoagulated at the time of admission. This may be partly due to the fact that recruitment to the trial was done before the widespread education campaigns for the detection and treatment of atrial fibrillation was conducted locally.

The two groups were well matched for previous lung pathologies and baseline chest radiograph findings in this study. Previous lung pathologies were reviewed as people with chronic respiratory disease are prone to recurrent respiratory tract infections. As Stoke-on-Trent is a former industrial and mining area, it was expected a significant number of patients would have chronic lung disease. However, the majority (80%) of participants did not have previous respiratory disease, and the baseline chest radiograph was normal in most subjects. It is possible that patients with chronic lung disease also to have a higher incidence of smoking and other co-morbidities and may not have survived to an older age in which stroke is more common.

The two groups were also similar in their neurological burden on admission as measured by GCS and NIHSS scores. The predominant CT diagnosis in both groups was cerebral infarction and there were only four patients (7%) with cerebral haemorrhage. The incidence of cerebral haemorrhage in the MAPS study is less than incidences demonstrated in some previous studies of post-stroke pneumonia[5;67;377], though several other studies excluded patients with cerebral haemorrhages from their study[28;180;378]. The reasons for reduced incidence of haemorrhages were partly due to those patients with small cerebral

haemorrhages not requiring nasogastric feeds and the patients with large intra cerebral haemorrhages had aspiration pneumonia on admission, secondary to associated vomiting with an intra cranial bleed. Also many patients with large cerebral haemorrhages had been commenced on the Liverpool care pathway for dying or decision made for no further active treatment other than palliation prior to admission to the Stroke Unit. Such decisions were made after recognising such large intra cerebral haemorrhages were incompatible with survival.

Most patients requiring nasogastric feeds usually have large strokes which involve a significant part of the cerebral hemisphere[228]. This was reflected in the MAPS study. The majority of participants (85%) had signs and symptoms of a total anterior circulation stroke, which was reflected in high NIHSS scores on admission. When compared to many previous studies MAPS study had more patients with total anterior circulation syndrome strokes[5;29;161;377;378]. None of the participants had lacunar strokes as such patients tend to have relatively minor non-disabling strokes, and low NIHSS scores and therefore rarely require nasogastric feeds[226]. Patients with low NIHSS scores (5 – 10) in the MAPS study were those with posterior circulation strokes. This group had significant impairment of their swallowing mechanism as lesions in the brain stem frequently involve the swallowing centre often sparing the more peripheral long tracts[35]. Therefore patients with posterior circulation strokes can have relatively mild weakness with severe swallowing problems. Also some neurological deficits in posterior circulation strokes, such as cranial nerve palsies, are not scored in the NIHSS scoring system resulting in a low NIHSS score in spite of significant signs and symptoms.

Therefore participants of the MAPS study were well matched and were not very different from patients recruited to other stroke related clinical trials.

3.5. Effect of metoclopramide on other outcomes

3.5.1. Aspiration

There was a significant reduction ($p < 0.001$) in the incidence of vomiting and aspiration in the treatment group. Out of 17 patients who had witnessed aspiration, 16 were in the placebo group. Most episodes of vomiting resulted in aspiration pneumonia and significant disruption to the feeding regime. As a potent antiemetic the reduction of episodes of vomiting in the treatment group can be explained, which was partly responsible for the reduction in the incidence of pneumonia in this patient group. Most episodes of vomiting and aspiration occurred when the patients were being washed or turned in bed. In addition, transfers of patients for various investigations were associated with vomiting and aspiration. It has been demonstrated that supine posture was more associated with aspiration in patients who are fed via nasogastric tubes than a semi-reclined posture. However, it is common practice to maintain patients in supine posture during washing and transfer, which might have contributed to this observed association of vomiting during patient transfer and personal care. These findings can be related to a study by Rowat *et al* on changes of oxygen saturations following acute stroke, in which patients had their lowest oxygen saturations in the CT scanner or during transfer between units[408]. These findings may also be secondary to either overt or silent aspiration during these procedures. Therefore it is advisable to complete washing and personal care of patients prior to connecting them to nasogastric feeds and to avoid transfer while being connected to or soon after nasogastric feeds. It is best to delay transfers if possible, two hours after completion of feeds, which will allow time for adequate gastric emptying.

It was also interesting to observe that patients continued to vomit and aspirate even when they were maintained at a semi-reclined position of 30^0 during their nasogastric feeds. Few

previous studies have shown that semi-reclined position was still associated with reflux and aspiration in the presence of a nasogastric tube. These results suggest that stroke patients may require a higher inclination than used in previous studies, possibly 45^0 or more during nasogastric feeds. This is further confirmed as there were only two episodes of vomiting and aspiration when patients were sat out during their feeds.

3.5.2. Treatment withdrawal

There were ten patients who had their nasogastric feeds discontinued as all active treatment was withdrawn to be commenced on the Liverpool Care Pathway for dying. Decision to withdraw treatment was made due to a combination of extension of stroke, worsening neurology and poor response to optimal medical management. There were less number of patients who had their treatment withdrawn in the treatment group and at the end of the third week more patients were alive in the treatment group though it was not statistically significant.

3.5.3. Resumption of oral feeds and neurological recovery

There was statistically significant number of patients who had their swallow improved to resume oral feeds so that their nasogastric feeds could be discontinued in the treatment group. There was also a significant reduction in the number of patients who required a percutaneous endoscopic gastrostomy tube insertion in the treatment group though it was not statistically significant.

As for the neurological recovery, both groups showed an improvement in their neurological scores during the first week. This is the neurological recovery which can be expected within the first week of an uncomplicated stroke, secondary to the reduction in cerebral

oedema and improvement of the penumbral circulation. However, the treatment group appeared to have a better neurological recovery which was apparent from the first week of the trial. In addition, the patients in the placebo group demonstrated a further deterioration of their neurological status during the third week, which was demonstrated by worsening of the NIHSS scores.

Studies have shown that presence of a nasogastric tube for a longer time was associated with recurrent episodes of aspiration and pneumonia[17;151]. The effects of persistent activation of the inflammatory cascade secondary to pneumonia on the penumbral micro-circulation may have contributed to this observed impaired neurological recovery of the patients in the placebo group[223]. In addition, pneumonia is a leading cause for post-stroke hypoxia and persistent hypoxia will delay the recovery of the ischaemic penumbra [214;215;217]. Being relatively free of pneumonia made patients in the treatment group less hypoxic which was confirmed by the significant difference in the lowest recorded oxygen saturations in the two groups. It can be postulated that better oxygen saturations and reduced inflammatory activity contributed to the better neurological recovery including an early recovery of swallow in patients who were treated with metoclopramide.

3.5.4. Other infections

The MAPS study also demonstrated that there was a statistically significant difference in the white blood cell count and the CRP levels between the treatment and the placebo group. This confirms that some form of an infection or an inflammatory process was more prevalent in the placebo group following acute stroke. With the fulfilment of criteria for pneumonia during the periods of increased inflammatory response, it is safe to assume that these changes were due to the higher incidence of pneumonia in the placebo group. None of the participants had infected venflon sites. One patient in the treatment group had an

unrelated lower limb cellulitis. Urinary tract infection was diagnosed in six patients (10%) in the total group of which four were in the treatment group. The incidence of urinary tract infection following acute stroke varies between 6-27%, older studies and studies done in ITUs reporting higher incidences[4;492-494]. Many stroke patients were catheterised in the past and many ITU patients are still commonly are catheterised, which is responsible to this high incidence of urinary infections[494]. The low incidence of urinary tract infections observed in the MAPS trial compared to other trials reflect the catheter policy of the stroke unit which minimises the use of urinary catheters to promote continence following stroke.

3.6. General discussion

3.6.1. Metoclopramide

Metoclopramide is a commonly used prokinetic agent, which acts on the dopamine D2 receptors in the upper gastrointestinal tract[30]. Metoclopramide antagonises the inhibitory effects of dopamine on the gastric contractility and sensitise the upper gastrointestinal tract to the stimulatory effects of acetylcholine[471]. By these actions metoclopramide increases the lower oesophageal sphincter pressure, gastric tone and gastric antral contractility therefore, accelerates gastric emptying, increases lower oesophageal sphincter tone, and reduce gastric stasis and gastro-oesophageal reflux[495].

There are no other studies of the effect of metoclopramide in post-stroke patients fed via nasogastric tubes. The only trial that used metoclopramide three times daily in patients fed via nasogastric tubes failed to demonstrate a reduction of the incidence of pneumonia, mortality or length of stay with metoclopramide[488]. Nevertheless, the onset of pneumonia was delayed by nearly two days in the treatment group which was statistically significant and likely to be clinically relevant in acute care. The latter study had several major

differences to the MAPS study. The mean age of the study population was 36 years, younger than most stroke patients. It was conducted on an intensive care unit, and the patient population was not comparable including critically ill patients with head injuries, post-operative patients, and patients with a mixture of acute neurological conditions including acute stroke. The paper does not state the proportion of acute stroke patients who were included in the trial, but of 305 participants 71 (25%) were post-operative patients. In addition, 136 patients (45%) were intubated and mechanically ventilated and 58 patients (19%) needed a tracheostomy, all of which predisposes patients to aspiration by depressing pharyngeal reflexes and compromising protective laryngeal reflexes[163]. Raised intra-gastric pressure during ventilation increases gastro-oesophageal reflux and patients receiving mechanical ventilation have shown to have a high incidence of nosocomial pneumonia, especially if they are fed via nasogastric tubes[177]. In addition, critically ill patients managed in an intensive care unit are exposed to other factors that affect gastro-intestinal motility and absorptive function[129]. These include opioids, dopamine and catecholamines. Furthermore autonomic effects of pain, stress and trauma further impairs gastro-intestinal function. Hypotension and the vasoconstrictor effects of stress hormones can lead to gastric hypoperfusion[129]. All these additional factors in critically ill patients might have affected the desired effects of metoclopramide in reducing reflux and pneumonia. This has been further confirmed by a study using another prokinetic agent cisapride on gastric emptying in critically ill patients fed via nasogastric tubes. The study demonstrated that there was significant day to day variation in gastric motility despite therapeutic plasma levels of the drug and the effect on gastric emptying was not consistent secondary to mechanical ventilation and the use of other medication such as narcotics and inotrops[496].

When compared to the study by Yavagal et al, the patient population of the MAPS trial were much older (average age of 77 years) and only had an acute stroke as their critical

illness[488]. None of them had endotracheal intubation or tracheostomy and no patient received mechanical ventilation. Similarly none of the MAPS participants were post operative and none received any opioids, dopamine or catecholamine infusions which could affect peristalsis. Thus the patient population of the MAPS study was very much different from Yavagal's study and the difference in the two patient populations may explain the difference in the results of the two trials. Also our patients represent many patients who are usually managed on an acute stroke unit. However, though Yavagal et al failed to demonstrate any reduction in pneumonia in patients who were treated with metoclopramide, their study demonstrated that metoclopramide significantly delayed the onset of pneumonia by 1.5 days[488]. Similarly the MAPS study also demonstrated that there was a 2 day delay in the development of pneumonia in the patients who received metoclopramide which was also statistically significant. As pneumonia is an early complication following acute stroke and there were significant number of patients who only required nasogastric feeds for the first week following stroke, these few extra days of protection may be all what these patients need to be free of pneumonia. Therefore it was justified to test the effect of metoclopramide on acute stroke patients who were fed via nasogastric tubes.

3.6.2. Rationale for duration of treatment, treatment regime and type of pneumonia

Metoclopramide was given for a period of three weeks. Practicalities of following up patients for a longer period than this were the main reason to limit the duration of the study for three weeks. Also, dysphagia would have resolved in a significant proportion of patients by the end of the second week following acute stroke, and that patients with persistent dysphagia would have had a percutaneous endoscopic gastrostomy by this time, therefore significantly reducing the number of patients likely to benefit at this stage[497]. Furthermore, studies have shown that there is a reduction of efficacy of metoclopramide after four weeks

when administered regularly[473]. Most importantly, the maximum incidence of pneumonia is seen within the first two weeks following acute stroke and it was thought that was the time these patients need interventions to prevent episodes of regurgitation, aspiration and pneumonia[117;177;184]. Also by limiting the use of metoclopramide to three weeks would prevent more serious and potentially irreversible extra-pyramidal side-effects such as tardive dyskinesia, which are associated with long-term usage of metoclopramide.

It has been demonstrated that higher doses of prokinetic agents can achieve optimal effect in critically ill patients[496]. These doses may overcome the gastro-intestinal dysfunction caused by drugs, decreased gastric perfusion and the autonomic effects of stress and pain, commonly seen in the critically ill[496]. However, higher doses of prokinetic agents may not be safe in critically ill patients as doses of metoclopramide 40 mg per day or higher can produce drowsiness, extra-pyramidal reactions and restlessness due to central nervous system toxicity[481]. These side effects may occur at a lower dose in patients with impaired renal function, which is not uncommon in critically ill patients[498]. Therefore the recommended regular dose according to the BNF, which is 10 mg/tds was used in the MAPS trial[398;498].

3.6.3. Choice of outcome assessment

There were several reasons for having any pneumonia rather than aspiration pneumonia as the primary outcome. The diagnosis of aspiration pneumonia has always been based on a combination of clinical suspicion or observed aspirations, new physical signs and new infiltrates in chest radiograph of dependant lung region following such aspiration[139]. The medical literature does not give any better way of clinical diagnosis of aspiration pneumonia. Many clinical studies reported using various combinations of criteria for the diagnosis of pneumonia but none clearly defined a set of criteria for the diagnosis of

aspiration pneumonia. In addition up to 50% of aspiration in stroke patients can be silent, and therefore confirmed pneumonia without overt signs of aspiration may still be caused by aspiration[88]. Also, patients who have the most depressed cough reflex are those most at risk of silent aspiration and these are the patients who would be kept nil by mouth and fed via nasogastric tubes[17]. Therefore, it can be assumed that stroke associated pneumonia in a significant number of patients with large strokes started as aspiration pneumonia. Patients in this study were not observed constantly for aspiration and the trial did not include interventions such as tracheal pH monitoring or other measurements to diagnose aspiration. Therefore aspiration pneumonia was not chosen as the primary outcome, because the high prevalence of silent aspiration may have lead to under diagnosis, making this an unreliable indicator of the efficacy of trial intervention. Thus, number of episodes of any pneumonia was chosen as the primary outcome and number of episode of aspiration pneumonia was chosen as a secondary outcome. It was assumed that patients with other causes of hypoxia and lung shadowing will be equally distributed between the intervention and control group. Therefore any difference in additional chest signs, radiological changes and hypoxia should be due to the intervention.

3.6.4. Dopamine and swallow

Dopamine agonists increase substance P levels and both dopamine D1 and D2 antagonists decrease substance P levels[499]. The basal ganglia are involved in dopamine metabolism in the brain and patients with basal ganglia infarcts have an impaired dopamine metabolism[500]. It has been suggested that reduced dopamine levels secondary to basal ganglia involvement lead to a reduction in substance P levels in the glossopharyngeal and vagus nerves resulting in an impairment of swallow and cough reflexes, with an increased the risk of aspiration and pneumonia. It has been demonstrated that patients with basal ganglion infarctions have a higher incidence of pneumonia than patients with hemispheric

strokes or strokes in other locations and this is thought to be due to reduced dopamine metabolism, therefore reduced the substance P levels in the glossopharyngeal and vagal sensory nerves[366]. In addition, bilateral basal ganglion strokes are associated with delayed triggering of the swallowing reflex, multiple episodes of pneumonia and increased mortality[500]. Replacement of dopamine corrects these abnormalities and it has been demonstrated that intravenous infusion of levodopa in patients who had basal ganglia infarcts improved of their swallowing reflex[501;502].

It is interesting to see how a dopamine antagonist could reduce the incidence of pneumonia in post-stroke patients who are fed via nasogastric tubes as a dopamine antagonist may be expected to delay the recovery of swallow and worsen aspiration. Conversely, recent studies done in patients with Parkinson's disease have shown that treating Parkinson's with dopaminergic medication did not achieve the improvement in swallowing as anticipated though there was a constant improvement in the rest of the motor function[503]. The swallowing abnormalities persisted after administration of drugs, either with or without dopaminergic activity[504]. These new findings cast a doubt on the importance of dopamine in the recovery of swallow. In acute strokes the facilitation of cerebral plasticity to take over the swallowing function by the non-dominant swallowing centre may be more important in the recovery of dysphagia. Having less inflammatory activity and better oxygen levels would have helped the recovery of the penumbra, improved of cortical plasticity and take over the swallow by the non-dominant swallow centres in the undamaged hemisphere.

In addition, the peripheral action of dopamine on the gastrointestinal tract is predominantly inhibitory, leading to poor lower oesophageal sphincter tone and gastroparesis[505]. It is very likely that this peripheral action of dopamine on the gastrointestinal tract was responsible

for the reduction of pneumonia in the patient group who were treated with metoclopramide. In addition, the action of metoclopramide on the chemoreceptor trigger zone and the vomiting centre did reduce the episodes of vomiting and aspiration which was partly responsible for the reduction in aspiration and pneumonia.

3.6.5. Other factors might have affected the results

Another possible reason for the metoclopramide in the reduction of pneumonia in our patient group is that the possibility of these patients might have had pre-existing gastro-oesophageal dysfunction. Most stroke patients are older and it has been shown that older people have a higher incidence of gastro-oesophageal reflux diseases including hiatus hernia. Nearly half of our patients were on a proton pump inhibitor or an antacid at the time of recruitment, which further indicate the possibility of peptic ulcer disease or reflux. Metoclopramide as a commonly used anti-reflux medication reduced the reflux the patients in the treatment group if they already had hiatus hernia or gastro-oesophageal reflux disease. A nasogastric tube would have caused further disruption of the gastro-oesophageal sphincter dysfunction in patients who already had gastro-oesophageal reflux disease, which may explain the very high incidence of pneumonia in the placebo group. However, none of our patients had a diagnosis of gastroesophageal reflux disease at randomisation nor were investigated for such disease prior to admission. None of the patients were investigated for gastro-oesophageal reflux disease following randomisation as it was not in the study protocol.

It is possible that D2 receptor blockade of metoclopramide might have had an immuno-modulating effect which may have contributed towards the reduction in the incidence of pneumonia. Significant percentage of normal healthy subjects aspirate during sleep with no adverse effects[127;506]. It has been demonstrated that stroke patients have a higher incidence

of pneumonia than age matched patients on an elderly care ward[507]. This is partly secondary to stroke-induced immunosuppression making them more susceptible to infections, in which stress hormones play a significant role. Beta blockers have been demonstrated to reduce the impact of stroke-induced immunosuppression[260]. Further research is needed to assess the peripheral action of dopamine, which is a stress hormone, as a mediator of stroke-induced immunosuppression.

3.6.6. Adverse Effects

The well known side-effects of metoclopramide are extra pyramidal dysfunctions including dystonic reactions, oculogyric crisis and tardive dyskinesia[398]. There have been recent concerns of these central nervous system side-effects in the long term use of metoclopramide and drug safety authorities such as Medicines and Healthcare products Regulatory Agency (MHRA) have issued restrictions on long term regular use of metoclopramide[508]. Participants of the MAPS study were observed regularly for the development of extrapyramidal side-effects. However, none of the patients participated in the MAPS study manifested any major side-effects of metoclopramide during their treatment period. In addition, the previously mentioned Yavagal *et al*'s study on metoclopramide also did not report on any serious side-effects of metoclopramide[488]. Literature states that these side-effects are more likely to be associated with high doses, intravenous administration and prolonged usage. Dystonic reactions including oculogyric crises, are most likely to occur within a few days of treatment, and are more common in young patients, though they have also been reported in older females[398;481]. In addition, dystonic reactions are easily recognised and completely reversed on discontinuation of metoclopramide with no long lasting damage. Drug-induced Parkinsonism and tardive dyskinesia are associated with long-tem drug usage, usually more than three months. Tardive dyskinesia is most common in older females and may not be reversible with

withdrawal of metoclopramide[482]. Other side-effects such as confusion, diarrhoea, cardiac arrhythmias and hyperprolactinaemia are fully reversible with discontinuation of metoclopramide. As only 30 patients were exposed to active treatment with metoclopramide in the MAPS study, we cannot exclude that such effects could occur in larger cohorts. It is possible that limiting the maximum dose to 10mg three times a day was safe and did not produce toxic drug levels that would have produced early dystonic reactions and limiting the usage of metoclopramide for a maximum of 3 weeks prevented manifestation of side-effects associated with its long-term use. In addition, longer courses of metoclopramide may not be needed in stroke patients who are fed via nasogastric tubes as they need maximum protection during the first two weeks when the incidence of pneumonia is at its peak. Also most patients will regain their swallow by the end of two weeks. The participants of the MAPS study represent the average patient population of a stroke unit. Our findings suggest that metoclopramide in the doses and duration used in the MAPS trial appears to be safely used in this patient population. A much larger study is needed to exclude rare side effects. When balancing the potential fatal complication of pneumonia against potentially reversible side-effects in short-term usage, time-limited use of metoclopramide under close clinical supervision on the stroke unit is a reasonable option.

The MAPS study has also shown that testing the effects of metoclopramide in this patient population was feasible, as it was possible to obtain consent, randomize, and to complete observations, investigations, and follow-up of participants without major impediment, and as there was a good adherence to the allocated treatment. However, 80% of patients who had NGTs were not eligible for recruitment, mainly because they already has signs of pneumonia. Early recruitment within few hours of admission in patients who are likely to

need NGT feeding (severe stokes, reduced level of consciousness) would allow a higher proportion of potentially eligible patients to be recruited.

Our study has limitations. No formal sample size calculation was performed. While the reduction in pneumonia was highly significant statistically the sample is not large enough to exclude a false positive result (type 1 error) with confidence. The study was not fully blinded, as the nurse dispensing the treatment was aware of the allocation. This could have introduced bias, but as the nurses were not involved in recruitment or assessment of patients this risk is considered low. Also to counter-act this possible source of bias, independent assessors were used to interpret chest radiographs and for the diagnosis pneumonia. A larger randomized controlled fully blinded study is needed to confirm the reduction of pneumonia and to determine whether metoclopramide affects mortality and long-term handicap. These have been discussed in detail in chapter 5.

3.7. Conclusion

In conclusion, metoclopramide in the doses of 10 mg administered every eight hours appear to reduce the incidence of pneumonia in acute stroke patients who are fed via nasogastric tubes. In patients who had pneumonia, metoclopramide delayed the onset of pneumonia by two days. The MAPS study has also shown that testing the effects of metoclopramide in this patient population was feasible and metoclopramide was well tolerated. In addition to the observed reduction in pneumonia, patients were less hypoxic, needed fewer types of antibiotics and had fewer antibiotic days. They also had less episodes of witnessed aspiration. At the end of the third week though statistically not significant, fewer patients required a PEG tube insertion and there were more survivors in

patients who received metoclopramide. A trial with larger patient number and full blinding is needed to confirm the findings of the MAPS study.

Chapter 4 Diagnosis of pneumonia

Abstract - Diagnosis of pneumonia in acute stroke patients

Introduction: The diagnosis of pneumonia following stroke is difficult as patients do not manifest well recognised signs and symptoms of a respiratory illness.

Method: Signs and symptoms of 47 radiologically confirmed episodes of pneumonia in patients with severe acute stroke (mean age 77, mean NIHSS 17) were reviewed to establish the most consistent signs of post-stroke pneumonia. In addition, baseline and all available CRP and WBC values of the first pneumonia (n = 34) were reviewed to compare the performance of white cell count (WBC) and C-reactive protein (CRP) as diagnostic markers of post-stroke pneumonia

Results: 70% of pneumonias occurred within the first week following stroke. The most common symptoms were tachypnoea 45/47 (95%) and a drop in oxygen saturation <90% on air 44/47 (93%). Cough, purulent sputum, and temperature >38°C were observed in 28 (59%), 25(53%) and 15(32%) episodes respectively. The highest mean temperature with pneumonia was 37.7°C. The commonest physical sign was new onset unilateral coarse crackles (97%). Signs of consolidation and bronchial breathing were elicited in 25 (53%) and in 3 (6%) episodes respectively. 14 (30%) pneumonias had positive sputum cultures.

The highest CRP levels (mean±SD) were 35.5±32.4 mg/l for patients with no pneumonia and 120.3±89.6 mg/l for patients with pneumonia ($p < 0.001$). The highest WBC (mean±SD) was 11.1±3.1/ml for the no pneumonia group and 15.7±5.7/ml for the pneumonia group ($p < 0.001$). The highest CRP levels were observed within 24 hours of

pneumonia. CRP alone had a predictive power (R^2) of 0.50; adding WBC only improved this by 4% (predictive power of CRP and WBC combination 0.54, WBC alone 0.25). On ROC analysis, the area under the curve was 0.86 for CRP and 0.77 for WBC. A CRP cut-off of 40 mg/l had sensitivity 0.69, specificity 0.84; a cut-off value of 65 mg/l had sensitivity 0.61, specificity 0.96 for diagnosing post-stroke pneumonia. For every 1 mg/l increment of CRP, the risk of pneumonia increased by 0.5% (OR = 1.05).

Conclusion: Pneumonia is an early complication following acute stroke but is not usually associated with well recognised signs and symptoms of pneumonia. A drop in oxygen saturation, tachypnoea, and coarse inspiratory crackles were the most consistent clinical signs and though nonspecific should alert the attending physicians of impending pneumonia. A positive sputum culture is not common. CRP appears to have a better predictive power than a raised WBC for early diagnosis of post-stroke pneumonia. A cut-off value of CRP 40 mg/l had the best combination of sensitivity and specificity.

4.1. Introduction

The diagnosis of pneumonia is based on clinical, biochemical and microbiological parameters[258]. In addition a chest radiograph is recommended by many guidelines[258;275]. However, diagnosis of pneumonia in stroke patients, especially in those with a severe stroke can be difficult as the recognised signs and symptoms of infections such as pyrexia, rigors and leucocytosis are not always manifested in this patient group[259]. In addition a reduced level of consciousness, impaired voluntary inspiration on the affected side, reduced pharyngeal sensation and an impaired cough reflex can make signs and symptoms of a chest infection difficult to detect[213;261]. The systemic inflammatory response may be muted and interpretation of chest radiographs can be difficult due to a multitude of reasons such as older age, hemiparesis, co-existing other illness and stroke-induced immunosuppression[242]. However, early diagnosis of pneumonia is important to allow initiation of treatment and to prevent complications and associated mortality. In this chapter, secondary analysis of all available data on clinical signs, symptoms and inflammatory markers for the diagnosis of pneumonia will be performed to identify predictors for an early diagnosis of on-going post-stroke pneumonia, which will help in early decision making and therapeutic intervention.

4.2. Aim of the study

The aim of the study is to find out early predictors of post-stroke pneumonia by secondary analysis of data collected in the MAPS trial.

4.3. Hypotheses to test

- Increased respiratory rate and a drop in oxygen saturation are good predictors of pneumonia in acute stroke patients
- A raised CRP level can be used as a biochemical marker for early prediction of pneumonia in acute stroke patients

4.4. Methodology

A brief outline on diagnosis of pneumonia is given here as this has been discussed in detail in the methodology section in chapter 4. As a part of routine clinical practice all patients were examined daily for signs and symptoms of pneumonia as detailed below.

iv) Baseline observations pulse, blood pressure, oxygen saturations, temperature and respiratory rate.

v) Chest examination – percussion for dullness, auscultation for type of breath sounds including bronchial breathing and additional sounds such as inspiratory crackles.

vi) Need for suctioning due to cough or increased respiratory secretions and the presence of purulent sputum was noted.

If clinical symptoms and signs were suggestive of pneumonia a chest radiograph was requested and blood was taken for inflammatory markers. If there was purulent sputum a sample was sent to the microbiology laboratory for culture and sensitivities. Daily examination findings were recorded in patient's case notes. These measures are done as part of routine clinical practice.

As for the research, data were collected on separate data sheets allocated to each patient. Baseline observations, inflammatory markers (if available) and chest signs were recorded in all patients on recruitment and on day 7, day 14 and day 21. If the end of the trial was earlier than day 21, these observations were recorded on that day. If there were no positive chest signs it was noted as 'chest was clear' in the trial log. If a diagnosis of pneumonia was made, all physical signs were recorded on the day of diagnosis and at the end of the course of antibiotics in the patients' research data sheet. In addition the vital signs and chest signs on the day prior to the pneumonia were reviewed from the case notes and the observation charts and were recorded in the research data sheets. All available CRP and WBC counts performed during the trial period irrespective of presence of pneumonia were recorded in the data sheets.

Early indicators of stroke associated pneumonia

Data on the day of the diagnosis of pneumonia were analysed to identify early signs and symptoms of post-stroke pneumonia. Further statistical analysis of increased respiratory rate, a drop in the oxygen saturations and the highest values of CRP and WBC were carried out to see their predictive power, sensitivity and specificity for the diagnosis of pneumonia. Also further analysis of CRP levels was done to determine a cut-off level that would be sensitive and specific for the diagnosis of post-stroke pneumonia. All patients had C-reactive protein and white cell counts measured on arrival to the Acute Stroke Unit or at least within 48 hours of admission and if there was a suspicion of pneumonia. Also a patient with a diagnosis of pneumonia had several measurements of inflammatory markers to see the response to antibiotics or the need to change antibiotics. Thus patients with pneumonia had several C-reactive protein and white cell count measurements during the trial period, and all of the readings taken on these variables were used in the analysis. Erythrocyte sedimentation rate (ESR) was not regularly measured, as samples were often

rejected by the laboratory for unknown reasons or not being processed due to undisclosed reasons. Therefore available ESR readings were not used in the initial analysis.

Measurement of CRP and WBC was mainly performed in patients with a clinical suspicion of pneumonia. Therefore patients who did not have pneumonia did not have many data on inflammatory markers. However, there were more data on inflammatory markers during the first week following stroke, even in patients who did not have pneumonia. As most of the pneumonia episodes occurred within the first week following stroke and as there were more data in both groups, only the first episodes of pneumonia were chosen for the analysis. The data were grouped as event (pneumonia) / no event. The values of the day of the diagnosis of pneumonia, or the closest, were considered for analysis for the participants who had pneumonia. The mean of the available measurements of relevant values during the first week were included in the analysis in patients who did not have pneumonia. Only the CRP and WBC of first 34 episodes of pneumonia were chosen for the analysis as most of these episodes occurred within the first week of the stroke where there were more data in patients who did not have pneumonia. Also the parameters for the diagnosis of second pneumonia would have been affected by the longer hospital stay of these patients, such as possibility of appearance of other medical complications, previous course of antibiotics and the possibility of the general condition of the patient could have deteriorated following a longer hospital stay. Though clinically and biochemically highly suggestive of a new episode of pneumonia, there was no way to prove that the initial pneumonia had fully resolved by the time of the onset of new symptoms related to the second episode of pneumonia.

In the first stage of analysis, diagnostic markers of pneumonia were identified by entering candidate predictors in a multivariable logistic regression model. The variables included as predictors in the model were: crepitus, O_2 saturation, temperature, respiratory rate, C-

reactive protein (CRP), white blood count (WBC). The diagnostic markers were identified in terms of their significance as predictors in the logistic regression model, but also evaluated in terms of their predictive strength; this was indicated by their contribution to the goodness-of-fit of the model, as expressed by the Nagelkerke pseudo-R^2 statistic.

The second stage of analysis focused on any diagnostic markers identified in the first stage that were numeric variables. Receiving operating characteristics (ROC) methods were used to identify appropriate diagnostic thresholds on these variables in terms of sensitivity and specificity. The area under the ROC curve (AUC) indicates the accuracy with which the scale can be used to classify or diagnose. An AUC statistic of one indicates that the scale has the greatest possible sensitivity and specificity whilst zero denotes the worst possible sensitivity and specificity. An intermediate value of 0.5 indicates that the scale classification is no more accurate than guessing. The Youden index was also calculated for each observed point on the scale. This statistic expresses, on a 0–1 scale, the maximum difference between sensitivity and 1–specificity (i.e. between the true positive rate and the false positive rate) for a given cut-off score, and can thereby identify the cut-off that simultaneously maximizes both sensitivity and specificity.

4.5. Results of diagnosis of pneumonia

4.5.1. Signs and symptoms of pneumonia

During the MAPS study there were 47 episodes of radiologically confirmed pneumonia (table 4.1). Thirty-four patients had only one episode of pneumonia and 13 patients had two episodes of pneumonia during the trial period. Most patients (97%) had the first pneumonia during the first week following commencement of nasogastric feeds. Details of signs and

symptoms of pneumonia are shown in table 4.1. All these signs and symptoms of pneumonia were the signs that were present on the first day of the diagnosis. The most commonly encountered symptom was tachypnoea, which was observed in 45 episodes (95%) of pneumonia. A drop in oxygen saturation less than 90% on air was seen in 44 episodes (93%). Cough and purulent sputum were seen in 28 episodes (59%) and 25 episodes (53%) of pneumonia respectively. An increased temperature more than 38°C was seen only in 15 episodes (32%) and chills and rigors were only observed in one occasion. The mean of the highest temperature associated with pneumonia was 37.7°C. The commonest physical sign on chest examination was new-onset crackles and 46 episodes (97%) of pneumonia had coarse inspiratory crackles. The crackles which were recognised as a sign of infection were of new onset, coarse and unilateral or asymmetrically distributed on the lower lung fields. Signs of consolidation such as dullness to percussion, reduced air entry and aegophony were seen only on 25 episodes (53%). Bronchial breathing was detected only on three occasions. Positive sputum cultures were only found in 14 episodes of pneumonia (30% of all pneumonias). The commonest organisms identified were Staphylococcus aureus (n = 4) and Gram negative bacilli such as Klebsiella (n = 4), E. coli (n=2), Proteus (n = 1), Citrobacter (n = 1) and Serratia (n = 1).

In the MAPS study all 47 episodes of pneumonia were confirmed by new radiological changes on the chest radiograph. Most of the patients had several chest radiographs during the first week after nasogastric tube insertion to confirm the position of the nasogastric tube, a procedure done routinely if no aspirate can be obtained or if the pH of the aspirate is not acidic. This gave the researcher the opportunity to review and compare several chest radiographs in making the diagnosis of pneumonia. The most consistent inflammatory marker for the diagnosis of pneumonia was an increase in C-reactive protein levels over 30 mg/l, which was seen in 41 episodes of pneumonia (87%). Also the elevation of CRP level

was an early indicator of pneumonia as in most episodes of pneumonia the elevation occurred within the first 24 hours of the diagnosis of pneumonia. An elevated white cell count was observed in 38 episodes of pneumonia (80%). A rise of the white cell count was also seen within the first 24 hours and resolved after successful treatment of pneumonia.

4.5.2. Early indicators of stroke associated pneumonia

In the first stage of data analysis, many of the clinical variables (crepitus, O_2 saturation, respiratory rate) exhibited 'complete separation' with no overlap in values of the predictor variable between the two outcome categories ('pneumonia' and 'no pneumonia'). This was because there were no patients in the non-pneumonia group documented tachypnoea, hypoxia or new onset unilateral chest signs. This precluded these variables from being tested statistically in the logistic regression model, but also confirmed their association with the diagnosis of pneumonia. CRP and WBC were, however, testable. The odds ratios for CRP and WBC were 1.046 (95% CI 1.019, 1.073; p = .001) and 1.247 (95% CI 1.060, 1.468; p = .008), respectively. Thus, an increase of one mg/l CRP or one unit WBC increases the likelihood of pneumonia by approximately 0.5% and 25%, respectively (the magnitude of the odds ratios cannot be compared, as there a different numbers of points on the two scales). If each predictor is analysed separately, the Nagelkerke R^2 value for CRP is .506, compared to .232 for WBC, suggesting that CRP is a stronger predictor of pneumonia. If analysed together, the addition of WBC to CRP increases the R^2 only modestly – from .501 to .546, suggesting that information on WBC adds little additional diagnostic information to that derived from CRP.

4.5.2.1. Cut-off values

CRP and WBC were taken forward to the second stage of data analysis. A cut-off value for CRP was reviewed using receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) indicates the accuracy with which the scale can be used to classify or diagnose. An AUC statistic of one indicates that the scale has the greatest sensitivity and specificity whilst zero denotes the worst possible sensitivity and specificity. An intermediate value of 0.5 indicates that the scale classification is no more accurate than guessing and the closer the value is to 1, the more accurately it can predict sensitivity and specificity. From the ROC analysis, the AUC for CRP was 0.86 (95% CI 0.79, 0.95) and the AUC for WBC 0.77 (95% CI 0.64, 0.90) which demonstrates that CRP is a more accurate diagnostic marker than WBC (figure 5.1). Table 4 shows the sensitivity, specificity and the Youden index for observed values of CRP. The highest Youden index observed for CRP was 0.57, which corresponded to three cut-offs: ≥25.6 mg/l (sensitivity, 0.85; specificity 0.72), ≥36.5 mg/l (sensitivity, 0.73; specificity, 0.84), ≥64.7 mg/l (sensitivity, 0.61; specificity, 0.96). The choice of the optimum diagnostic cut-off for CRP will therefore depend on the relative weight given to sensitivity and specificity; if sensitivity is prioritized, ≥25.6 is the optimum cut-off. Table 5 shows values of sensitivity, specificity and the Youden index for WBC. The highest Youden index observed for WBC was 0.65, which corresponded to a cut-off of ≥11.53 (sensitivity, 0.73; specificity 0.92).

Cut-off values for specific CRP values are given below.

Cutoff	Sensitivity	Specificity
36.5 mg/l	0.727	0.840
45.0 mg/l	0.697	0.840
50.0 mg/l	0.667	0.840
59.4 mg/l	0.606	0.920

Cut-off values for specific WBC values were calculated and are given below.

Cutoff	Sensitivity	Specificity
10.0	.788	.720
11.0	.727	.840
12.0	.667	.920
13.0	.485	.960
14.0	.364	.960
15.0	.333	1.000

4.5.3. Summary of results

The most commonly encountered symptoms were tachypnoea and a drop in oxygen saturation, which were seen in almost all pneumonias. Cough and purulent sputum were only observed in half and an increased temperature more than 38°C was only seen in one-third of pneumonias. The commonest physical sign was new onset crackles and was present in almost all pneumonias.

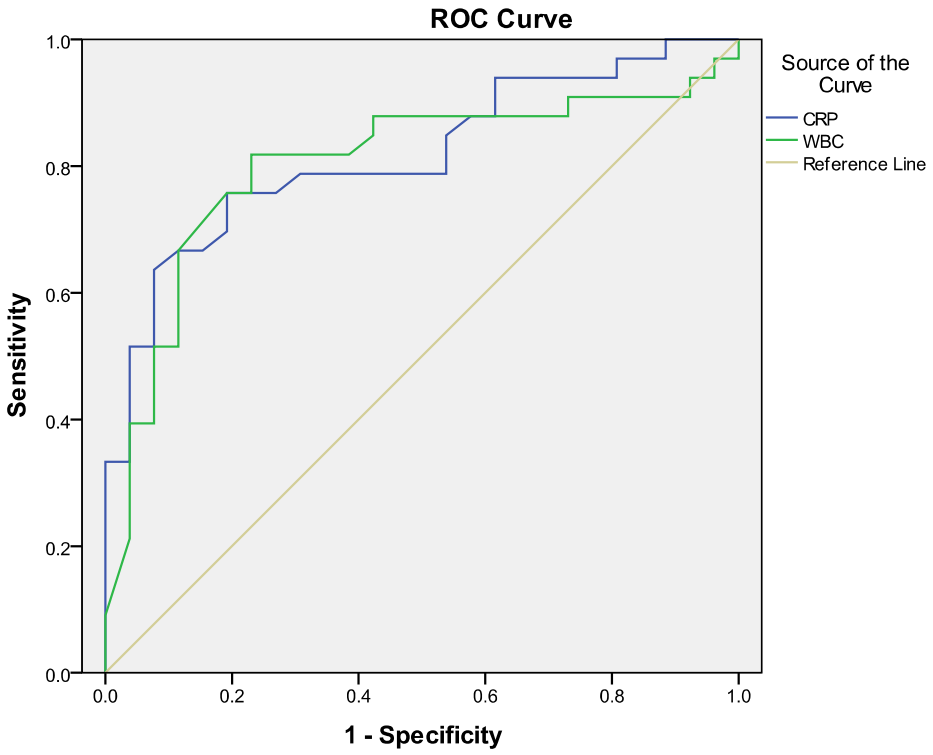
Results also suggest that if one had the choice of using CRP or WBC, CRP would be the best to use. If both were available both parameters can be used. However, the improvement of predictive power was quite small (about 5%), and also it would be much more complex to produce a clinical rule of thumb using the two variables rather than just one.

Table 4-1 Signs and Symptoms of Pneumonia (episode and frequencies)

	First episode n = 34 (%)	Second episode n = 13 (%)	Total n = 47 (%)
Signs and symptoms			
Respiratory rate >25/m	32 (94)	13 (100)	45 (96)
Oxygen saturations <90%	31 (91)	13 (100)	44 (94)
Cough	22 (65)	6 (46)	28 (60)
Purulent sputum	19 (56)	6 (46)	25 (53)
Temperature >38°C	12 (35)	3 (23)	15 (32)
Chill and rigors	1 (3)	0 (0)	1 (2)
Chest examination			
Inspiratory crackles	33 (97)	13 (100)	46 (98)
Sign of consolidation	18 (54)	7 (54)	25 (53)
Bronchial breathing	3 (9)	0 (0)	3 (6)
Investigations			
CRP > 30 mg/l	30 (88)	11 (85)	41 (87)
WBC >11	29 (85)	9 (69)	38 (81)
ESR > 20 mm/hour	5 (15)	1 (8)	6 (13)
WBC <3	1 (3)	0 (0)	1 (2)

(CRP-C Reactive Protein, ESR–Erythrocyte Sedimentation Rate, WBC-White Blood Cells)

Figure 4-1 Receiver operating characteristic (ROC) curves of CRP and WBC



Diagonal segments are produced by ties.

CRP – C reactive proteine, WBC – White blood cells

4.6. Discussion

4.6.1. Clinical signs and Symptoms for diagnosis of pneumonia

The diagnosis of post-stroke pneumonia can be difficult as stroke patients do not manifest well known signs and symptoms of respiratory illness[76;177]. However, early diagnosis is important to enable timely initiation of antibiotic treatment and to prevent complications and associated mortality. According to our findings increased respiratory rate and a fall in oxygen saturation were the most common symptoms of stroke-associated pneumonia. The most consistent physical sign on examination of the chest was inspiratory crackles. However, these signs are very nonspecific and can be present in many respiratory diseases such as lung collapse, pulmonary embolism or bronchospasm. Tachypnoea and drop in oxygen saturation to less than 90% on air with new onset inspiratory crackles should alert the attending physician of possible pneumonia, which would warrant careful examination for further signs of consolidation and initiation of investigations such as inflammatory markers and a chest radiograph. This is especially true as our results demonstrated that other well-known symptoms such as high temperature, cough, and purulent sputum were less often observed in post-stroke pneumonia. Also other known signs of pneumonia were less commonly encountered in the study population. Poor patient compliance, difficulty in maintaining an optimal positioning to auscultate all over the lung bases and poor inspiratory efforts of the patient may have contributed to this reduced level of identification of consolidation and bronchial breathing.

Older people do not commonly manifest high temperatures with acute infection, and this is also well documented following acute stroke[266]. These findings are reflected in our study as only fifteen episodes of confirmed pneumonia had a temperature of above 38°C. Our stroke patients were older, average age was 78 years and as previous studies have shown, did not

manifest temperature above 38°C. It is also possible that stroke-induced immunosuppression could have played a role in the muted temperature response. However, the majority of patients had a temperature above 37.5°C with pneumonia. Thus it is important to be vigilant of an impending infection with a rise of temperature of 37.5°C or more rather than expecting higher temperature spikes. However, if patients mount an immune response with a rise in temperature, it is a significant sign of acute infection as it has been demonstrated that in an older person, for every single degree of rise in temperature (in Celsius), the risk of infection was increased by almost four-fold[266].

It has been demonstrated that large strokes are associated with an initial rise of temperature, which was a poor prognostic sign[267]. Patients in our trial had large strokes reflected by an average NIHSS score of 18. However, an initial rise in the temperature was not observed in participants. This may be because after the initial record of temperature on admission it was not recorded for the following 6 to 24 hours, the time for the organisation of investigations and transfer of patients from the Emergency Department to the Acute Stroke Unit. Even in the Acute Stroke Unit, unless required, frequent temperature recording more than three times a day is not carried out as standard practice. Therefore this initial rise in temperature could have been missed. It is also possible that patients who had a high temperature weren't approached to participate in the study as the temperature rise was considered as a sign of possible early infection.

4.6.2. Laboratory Tests

In this study only 14 episodes (30%) of pneumonia had a positive microbiological diagnosis, all from the first episode of pneumonia. Bacteria isolated from these sputum cultures were similar to those in other studies performed in patients with acute stroke.

Sputum cultures from the second episodes of pneumonia did not produce any significant bacterial growth, possibly because all these patients had already had a long course of antibiotics for their first pneumonia, which may have selected out a strain that is not commonly tested in laboratories including anaerobes, or simply because the presence of antibiotics hindered any bacterial growth in cultures[213]. Though an elevated WBC count with neutrophilia is commonly observed in bacterial infections, a similar response was not expected in our patient group as the leukocyte response is not always present in an older person and would have been affected by stroke induce immunosuppression. However, most of our patients in the MAPS study did have an adequate WBC response to pneumonia, which settled with the resolution of pneumonia.

4.6.3. Predictors of Pneumonia

Diagnosis of post-stroke pneumonia cannot be delayed, as commencement of antibiotics as soon as possible is necessary for a better recovery and to avoid complications. As described before, well recognised signs and symptoms are frequently absent in stroke patients and, as demonstrated in the study, commonly observed signs and symptoms such as an increased respiratory rate and hypoxia can occur in other respiratory illnesses. Departmental chest radiographs can be difficult to organise, are commonly done as portable, and may be of poor quality. Many portable chest radiographs are done towards the end of the day due to organisational difficulties and may not be reviewed by experienced physicians until next the day which will further delay the commencement of appropriate antibiotics. However, in clinically suspected post-stroke pneumonia, having most recent CRP and WBC will provide adequate justification for early initiation antibiotics without relying on chest radiographs.

The study demonstrated that CRP and WBC values were highly predictive of pneumonia. CRP appears to have a better predictive power and adding WBC did not significantly improve the predictive power of the model. Also it appears that CRP of 36.5 mg/l has the best cut-off value for sensitivity and specificity for the diagnosis of stroke associated pneumonia. As a practically workable, easy to remember cut-off value, CRP of 40 mg/l can be recommended to be used for the diagnosis of post-stroke pneumonia. This is less than cut-off values observed in some studies performed on older people with pneumonia and some studies have suggested cut-off values high as 60 – 80 mg/l[264;266;509]. Stroke-induced immunosuppression may have played a role in this lower cut-off value observed in stroke patients. Therefore a modest rise of CRP should alert attending physicians of impending pneumonia in acute stroke patients.

As CRP is as good as or a better predictor of pneumonia and adding the WBC gives no significant improvement to its predictability, the diagnosis of post-stroke pneumonia can be achieved by fewer blood samples. This is especially important in patients with difficult or limited venous access due to long hospital stay, multiple venepunctures, venous sclerosis and hypoalbuminaemic oedema. The commonest set of investigations on an enterally fed patient is urea and electrolytes, done as a single biochemical sample, which is required for the adjustment of feeds and the intravenous fluids. CRP being a biochemical investigation can be assessed from the same sample unlike WBC, which is analysed as a haematological sample, therefore needing an extra blood sample. Therefore having CRP as the predictor will reduce patient discomfort, limit the required blood samples and reduce cost.

It can be argued that WBC and CRP are nonspecific indicators of any infection and the findings of the study may not reflect true changes which may occur with pneumonia. However, as described in chapter 4, the incidence of other infections was low in this patient

group. Also the data on all available CRP and WBC measurements were incorporated in the analysis, including data on patients who had other infections. Therefore it can be argued that the findings of the analysis are a true reflection of changes seen in post-stroke pneumonia. These findings need to be validated in a separate sample of stroke patients, which will be done along with the second stage of the MAPS study.

4.6.4. Incidence and the timing of pneumonia

In the MAPS study the overall incidence of pneumonia was 56%. However, compared to the intervention group, the incidence of pneumonia was much higher at 87% in the non-intervention group. This is a higher incidence of pneumonia than quoted in older studies, though recent studies that have reviewed patients fed via nasogastric tubes reported around 70% incidence of pneumonia[180;181]. The incidence varied according to the type of patients included, criteria for diagnosis and the place of the study. Most of these studies included all stroke patients admitted during a defined time period irrespective of the severity of the neurological deficits and dysphagia. Many studies included mild strokes that are less likely to be at risk of developing aspiration and pneumonia. Some older studies excluded stroke patients who were semiconscious or unconscious, the subgroup of patients who have the highest risk of aspiration and pneumonia. Our patient population had severe strokes with an average NIHSS of 19 and had no swallow reflex, thus needed nasogastric feeds to sustain life. This is the type of post-stroke patient who would have the maximum risk of developing pneumonia. A recent study demonstrated that 88 to 91% of enterally fed stroke patients developed aspiration pneumonia in the presence of a nasogastric tube[13]. Sub-analysis of the turn-mob study demonstrated that nearly 70% of patients who were fed via nasogastric tubes had pneumonia. Therefore more detailed studies to look into the incidence of pneumonia in stroke patients who are fed via nasogastric tubes are required. In the MAPS study the patients who did not have metoclopramide to improve gastric reflux

and motility had a similar incidence, which was significantly corrected by administration of metoclopramide three times a day.

This study showed that the average time from the acute stroke to the onset of pneumonia was 4 days and the average time from insertion of a nasogastric tube to the onset of pneumonia was 3 days. This is in keeping with many studies done before which demonstrated that pneumonia is an early complication of a post-stroke patient[89;177]. Of 56% of all patients with pneumonia, the majority (64%) had only one episode of pneumonia. In addition non-resolving or recurrent pneumonia contributed significantly to the mortality of the stroke patients who were fed via nasogastric tubes.

4.7. Summary

In summary, an increase in the respiratory rate more than 25 breaths per minute, a fall in oxygen saturations less than 90% on air and new onset inspiratory crackles were the most commonly observed signs and were highly predictive of the onset of pneumonia. Well recognised symptoms of a chest infection such as cough, purulent sputum, and pyrexia were less commonly observed. Isolation of an organism from sputum samples was not common. As for the investigations, elevation of CRP and WBC were highly predictive of pneumonia and CRP had the highest predictive value. A CRP level of 40 mg/l can be taken as the cut-off level for the diagnosis of pneumonia. This is particularly important in stroke patients as stroke itself can increase the serum CRP levels.

Chapter 5 General conclusion, limitations and scope for future trials

5.1. General summary

The focus of this study was to identify methods to prevent aspiration and pneumonia in stroke patients who are fed via nasogastric tubes. The literature review identified that pneumonia is common after acute stroke and it contributes significantly to the post-stroke mortality and morbidity[5;6]. In addition, it is evident that pneumonia is directly related to dysphagia and aspiration that follows stroke and severely dysphagic patients have to rely on nasogastric feeds for their survival. Similarly, evidence suggest that nasogastric tubes are associated with a high incidence of pneumonia, due to continued aspiration of infected oropharyngeal secretions and to gastro-oesophageal dysfunction that follows stroke[13;17]. These include gastro-oesophageal sphincter dysfunction, gastric stasis and reflux, which are made worse by the presence of a nasogastric tube[12;13;17]. The mechanisms of how nasogastric feeds cause this refluxed gastric contents to be infected was reviewed. In addition it was argued how a prokinetic agent would counter-act these mechanisms and reduce reflux, therefore aspiration and pneumonia in stroke patients who are fed via nasogastric tubes.

The systematic review of available literature undertaken for this study has demonstrated that there is a paucity of research into prevention of pneumonia in acute stroke patients and that there were no studies that specifically addressed prevention of pneumonia in stroke patients fed via nasogastric tubes. The MAPS study has demonstrated that metoclopramide at a dose of 10 mg administered every eight hours significantly reduced the incidence of pneumonia in acute stroke patients who are fed via nasogastric tubes. In addition, this study has provided evidence that stroke patients do not regularly manifest several well known diagnostic criteria for the diagnosis of pneumonia but that an increase in the respiratory rate

<25 breaths per minute, a fall in the oxygen saturation <90% on air and new onset of inspiratory crackles were the most commonly observed signs and were highly predictive of pneumonia.

5.1.2. MAPS study

The specific objective of the MAPS study was to test the effect of prokinetic agent metoclopramide on the incidence of pneumonia in acute stroke patients who are fed via nasogastric tubes. Metoclopramide was specifically chosen as it is a commonly used prokinetic agent and has a dual action, namely a central action to reduce vomiting and a peripheral prokinetic action on the upper gastrointestinal tract[472]. It has fewer serious side-effects than other prokinetic agents especially in short-term use, side-effects are easily recognised, and most are easily reversed by discontinuing the medication[481].

This is the first randomized controlled study of metoclopramide in patients with acute stroke fed via nasogastric tubes. Conducted as a pilot study, results of MAPS have shown that recruitment in the sub-acute stage of stroke is feasible and that regular administration of metoclopramide for a maximum of 21 days is safe in this patient group. Study findings suggest that metoclopramide reduces the incidence of pneumonia in acute stroke patients who are fed via NGT. Being a potent prokinetic, metoclopramide very likely reduced the contribution of infected gastric reflux and aspiration towards the development of pneumonia following stroke. Also as an antiemetic, metoclopramide reduced vomiting and aspiration in this patient group. In keeping with the observed reduction in pneumonia, the treatment group had less number of antibiotics and antibiotics days, had lower inflammatory marker levels and were less hypoxic. In addition to the reduction in the incidence of pneumonia, the onset of pneumonia was delayed by two days which was in

keeping with previous research[488]. There were more survivors in the metoclopramide group at 30 days though it was not statistically significant.

Patients who were treated with metoclopramide appear to have a better neurological recovery at the end of 3 weeks and more patients could discontinue nasogastric tubes as they resumed oral feeds. Neurological recovery following stroke depends on recovery of ischaemic and injured tissue in the penumbra and taking over of various functions by non-dominant cortical centres[55;510]. Inflammatory activity and hypoxia worsen the penumbral ischaemia and delay its recovery secondary to activation of tumour necrosis factor and macrophages and the resultant changes in the micro-vasculature[511]. Having less inflammatory activity and better oxygen levels due less pneumonia might have helped the recovery of the penumbra, facilitated cortical plasticity to take over the swallow by the non-dominant swallow centre in the undamaged hemisphere. This may explain the observed better neurological recovery and early recovery of swallow in patients who were treated with metoclopramide.

There have been recent concerns of the central nervous system side effects of metoclopramide with long-term treatment[508]. Extra-pyramidal movements including dystonia reactions, well known side effects of metoclopramide, were not encountered during the MAPS study. Dystonic reactions are more commonly seen in younger patients, higher doses and others such as drug-induced Parkinsonism and Tardive dyskinesia on prolong treatment[481]. Patients in the MAPS study were much older, doses were according to the recommendations of British National formulary and the maximum treatment duration was 3 weeks which was not long enough for side-effects such as Tardive dyskinesia to manifest. Pneumonia is an early complication following acute stroke and many patients would have had recovered their swallow within first two weeks following stroke[112]. This

makes the need for metoclopramide mainly during the first few weeks following stroke, which is not long enough for more permanent adverse effects to occur. Also acute dystonic reactions, the anticipated side-effects during early days of treatment are easily identified, and are completely reversed on discontinuation of metoclopramide[481]. Therefore when comparing with the risk of pneumonia, a potentially fatal complication following acute stroke to the risk of developing a potentially reversible set of extrapyramidal side effects, the use of metoclopramide under adequate supervision during the first few weeks following stroke can be justified, if these patients have to rely on nasogastric tubes for their feeds and medication.

5.1.3. Diagnosis of pneumonia

Review of the literature showed that the diagnosis of pneumonia in post-stroke patients is difficult as they do not manifest well recognised signs and symptoms of a respiratory illness[213;262]. The objective of the secondary analysis of the data collected for the diagnosis of pneumonia was to find reliable criteria for the early diagnosis of post-stroke pneumonia. Three types of parameters are commonly used for the diagnosis of pneumonia, which are clinical, laboratorial, and radiological parameters[250]. Though various combinations of clinical signs, inflammatory markers, and microbiological data have been used for the diagnosis of pneumonia, new infiltrates in the chest radiograph is an essential criterion for the diagnosis of pneumonia according to most standard guidelines[81;322]. However, relying on a chest radiograph to diagnose pneumonia in a bed bound stroke patient can be difficult[274]. This may delay the diagnosis of pneumonia and the initiation of antibiotics, which in turn will delay recovery and increase pneumonia related complications[250]. Therefore early diagnosis of pneumonia is paramount in the management of pneumonia.

In my clinical practice, I have observed that an increased respiratory rate and a fall in the oxygen saturations were common and preceded the development of chest signs and radiological changes of pneumonia in post-stroke patients. Also I have identified CRP as a reliable parameter for the diagnosis and monitoring the progress of pneumonia. Therefore I hypothesised that an increased respiratory rate and a fall in the oxygen saturations were reliable early predictors and CRP is a good biochemical marker for the diagnosis of post-stroke pneumonia. As a part of the MAPS study, data on the signs and symptoms of the radiologically confirmed episodes of pneumonia were recorded in detail. In view of the difficulties in the early diagnosis of post-stroke pneumonia, the signs, symptoms and results of inflammatory markers of all episodes of pneumonia were analysed to identify reliable criteria for the early diagnosis of pneumonia in stroke patients and they were tested for the reliability and the predictability.

The thesis demonstrated that pneumonia is an early complication following stroke and an increase in the respiratory rate more than 25 breaths per minute, a fall in oxygen saturations less than 90% on air and new onset inspiratory crackles were the most commonly observed signs and were highly predictive of pneumonia. Well recognised symptoms of a respiratory infection such as cough and purulent sputum were not observed in one third of patients and pyrexia was not observed in two thirds of patients. A positive microbiological culture was not common and was observed in 25% of pneumonias. As for biochemical investigations, elevation of CRP and WBC were highly predictive of pneumonia and CRP had the highest predictive value. A CRP level of 40 mg/l has been shown to be the cut-off level for the diagnosis of pneumonia.

5.2. Limitations

5.2.1. The MAPS trial

A total of 60 patients make the MAPS trial a relatively small research project. Also a sample size power calculation was not performed as this was done as a pilot project as there were no previous publications on the use of metoclopramide in acute stroke patients. While the reduction in pneumonia was highly significant statistically the sample is not large enough to exclude a false positive result with confidence. In addition, the trial was conducted only on one stroke unit. Therefore it is possible that local practice of this unit might have had an effect on the results, which may have been different if conducted on a unit that had different treatment criteria for treating acute stroke patients fed via nasogastric tubes. Management of post-stroke patients and management of nasogastric feeds on our unit are based on National Institute of Clinical Excellence guidelines and Royal College of Physicians guidelines and are carried out by a well trained multi-disciplinary team. However, some practices of acute stroke care may differ in other stroke units, depending on resources and facilities available. As for an example, principles of early mobilisation and having physiotherapy and occupational therapy services on the ward throughout the day until 9pm, seven days a week which is available in our stroke unit may not be available on other units. Having less urinary catheterisations made the incidence of urinary tract infections low in the MAPS study participants. However, urinary tract infections will be more common in units where patients are frequently catheterised and will have an effect on criteria for the diagnosis of pneumonia.

Effects of local population on the trial results should be considered. Other than few (n = 3) Asian patients, most of the participants were local people from Stoke-on-Trent who were white Caucasian in their ethnicity. There were no Afro-Caribbean or Oriental patients in

the trial. Effects of ethnicity on the metabolism of ACE inhibitors and its effect on reducing pneumonia have been discussed before. Though unlikely, it cannot be excluded that people who live in Stoke-on-Trent have a higher incidence of gastro-oesophageal reflux, which makes the effect of metoclopramide in reducing reflux, aspiration and pneumonia very significant. However, lack of a good ethnic mix is not uncommon in many previous studies[5;29;161;377;378].

5.2.1.1. Researcher bias

The trial was designed to minimise researcher bias. Allocation of the treatment options for the intended 60 participants was done prior to the commencement of the trial and these codes were kept in a locked safe in the research facility. This process was performed by an independent team working for the West Midlands research network and the researcher had no part in this. Following randomisation of a patient and production of the consent or the assent from, the sealed envelope of the treatment option for that randomisation number was released from the office. All details of randomisation numbers and patient's details were kept in another register in the same office to which the researcher had no access.

The study was not fully blinded, as the nurse dispensing the treatment was aware of the allocation. This could have introduced bias, as a doctor working on the same stroke unit, one can argue that the principle researcher had the opportunity to know the treatment options of the participants. Also there was potential for inadvertent unmasking of treatment allocation especially when requesting medication from the pharmacy and treatment chart monitoring was done by the ward pharmacist. This could have biased the diagnosis of pneumonia. This bias would have been prevented by having similar looking metoclopramide and placebo rather than using 10 ml of saline as the placebo. Various steps were undertaken to ensure blinding of the study. Allocation bias was minimised by

randomisation of all intended treatment options prior to the commencement of the study and sealed envelopes containing the treatment options being retained in an independent research office until their release after recruitment of a participant. After release, envelopes containing the treatment options were always kept in the locked drug cabinet which was handled only by qualified nurses. Treatment was prescribed as MAPS trial drug metoclopramide 10 ml or normal saline 10 ml on the drug chart thus doctors handling the drug chart could not know which arm of the trial the patient was recruited into. The confirmation of chest signs was made by at least two other independent assessors, either consultants or registrars, who would examine the patient prior to making a clinical diagnosis of a lower respiratory infection or pneumonia. The final diagnosis of pneumonia was made by the consultant who was responsible for the patients' overall care. Most of the time there were several entries of physical signs and diagnosis of pneumonia in case notes by on-call doctors who were even not aware of the study. The key feature for the diagnosis of definite pneumonia, the chest radiograph, was reported by independent doctors in the radiology department as a part of routine clinical practice. Inflammatory markers were handled by the University Hospital of North Staffordshire pathology laboratory as part of ward practice, and the lab personnel were not aware of this research project.

All of these ensured that there was minimal bias when the clinical findings, chest radiograph findings and laboratory test results were considered for the diagnosis of pneumonia. During the period of the MAPS trial there were more than 10 other on-going clinical trials on the stroke unit. All patients received standard medical and stroke care according to local guidelines and NICE guidelines in management of stroke patients. This ensured the uniformity of treatment of patients on clinical trials and all received the standard stroke care irrespective of being recruited to a trial and whether the patient were on a trial drug or on a placebo.

5.2.1.2. Exclusion risks

Almost two-thirds of patients who required nasogastric feeds were excluded from the MAPS study due to the presence of pneumonia. This is partly due to the presence of pneumonia on admission or development of pneumonia while a decision was being made for nasogastric feeds, which was two days in MAPS trial. These patients would have been the most vulnerable for the development of pneumonia, in whom the effect of metoclopramide was not tested.

5.2.1.3. Follow-up period and functional out-comes

A longer follow-up period on neurological recovery and functional recovery would have added strength to the findings of the trial. Longer follow up was not planed due to practical difficulties in follow-up of these patients. However, the neurological recovery of the patients who were treated with metoclopramide at the end of three weeks was suggestive of a good clinical outcome. Details of functional recovery, using modified Rankin score or Barthel score would have added strength to the findings of the trial.

Procedures such as measurements of gastric residual volume at regular intervals to demonstrate gastroparesis or oesophageal manometry or pH measurements to demonstrate gastro-oesophageal dysfunction in two groups would have added strength to the findings of the trial and would have been useful in making further recommendations. These were not planned due to lack of resources, funding and time.

5.2.2. Diagnosis of pneumonia

The main limitation was that this was performed as a retrospective analysis of data which were collected for the MAPS trial. Therefore the data collection was done according to a protocol intended for the MAPS trial rather than for a trial that was intended to identify criteria for the diagnosis of post-stroke pneumonia. This resulted in laboratory

investigations being performed only with the clinical suspicion of pneumonia and not performed according to a specific protocol at regular intervals. As the patients with no pneumonia did not require regular laboratory tests, there were less data on inflammatory markers in this patient group, though all had baseline and day 7 inflammatory marker levels. Availability of inflammatory marker levels at regular intervals would have provided a better comparison between the two groups. Even in patients with pneumonia, inflammatory markers were not done at regular intervals after the diagnosis of pneumonia. This prevented detailed analysis of these markers to assess their response to antibiotic treatment. Lack of laboratory data was also evident in the second episodes of pneumonia, therefore had to be excluded from the analysis. A well-defined prospective study will overcome this short-coming.

The predictors for the diagnosis of post-stroke pneumonia have not been validated in another post-stroke population. Also the predictors were tested only on a specific cohort of stroke patients (patients with severe strokes who were fed via nasogastric tubes), therefore the findings may not be applicable to the whole stroke population. However severe strokes, especially patients who are fed via nasogastric tubes have the highest incidence of pneumonia and it is in this cohort of patients the diagnosis of pneumonia is particularly difficult due lack of well known signs and symptoms of pneumonia. At any given time on a stroke unit, there are several patients who depend on enteral feeds and the predictors demonstrated in this thesis will help a clinician in the early diagnosis of pneumonia in this patient cohort. However, a prospective study on unselected stroke patients with non-stroke controls will provide predictors which can be generalised to all stroke patients according to the stroke severity.

5.3. Possible further trials for the future

5.3.1. MAPS study as a larger, multi-centre study

Planning the MAPS study as a multi-centre study with a larger number of participants will strengthen the findings of the study. Also having identical looking trial drug and the placebo in similar looking vials would strengthen the blindness of the study. Nearly two-thirds of patients who required nasogastric tubes could not be recruited to the MAPS study as these patients developed pneumonia within 24 hours of admission to the hospital. Having different inclusion criteria to recruit patients within few hours of admission, with the assumption of that these patients will need nasogastric feeds will allow more participants to be recruited, especially the most vulnerable for the development of pneumonia. This decision can be either based on clinical assessment of severity of stroke (e.g. NIHSS >10) or size of the infarct on the CT scan, as patients with large strokes frequently require nasogastric feeds. If such a patient with a large stroke, would fail the water swallow test or remain too drowsy to be assessed can be reviewed as a potential participant to the MAPS trial, if they could be recruited within 12 hours of admission to the hospital. With such early recruitment many of the participants will not have a nasogastric tube at the time of recruitment and metoclopramide can be administered intravenously until insertion of a nasogastric tube is performed. In view of MHRA concerns of extra-pyramidal side effects of long-term metoclopramide treatment, the duration of intervention can be limited to two weeks as this is the time period where post-stroke pneumonia is prevalent. In addition, dysphagia in the majority of patients would have resolved by the end of this period. Exclusion criteria can remain as in the MAPS pilot study and British Thoracic Guidelines for the diagnosis of pneumonia can be used in the larger study.

The diagnosis of any post-stroke infection may be affected by clinical practices and policies of other stroke units. The use of urinary catheters and venflon care may vary

between units, which will affect the incidences of urinary tract infections and venflon related infections. A low threshold to diagnose urinary tract infections and the use of antibiotics for such infections potentially can affect the clinical manifestations and the diagnosis of pneumonia. Therefore having another primary outcome such as mortality or length of stay, in addition to the episodes of pneumonia will strengthen the findings of the study. Secondary outcomes and the weekly follow-up plans can remain as in the pilot study. A longer follow-up which includes mortality, neurological and functional recovery (mRS) will also strengthen the findings of the study.

The findings of the MAPS pilot study can be used to calculate the sample size for the intended larger study. The incidence of pneumonia was 27% and 87% in the treatment group and the placebo groups respectively. The incidence of pneumonia in the placebo group is higher than other post-stroke pneumonia studies and the possible reasons have been discussed before. Other studies have shown an incidence of 44% for post-stoke pneumonia in acute stroke patients who are fed via nasogastric tubes. Therefore for the proposed multi-centre study 44% is preferred as the expected rate of pneumonia in the control group rather than the 87% seen in the pilot study. The expected incidence of pneumonia in the intervention group can be taken from the MAPS pilot study (27%), which will be a 40% reduction in the incidence of pneumonia by the use of the intervention. As patients are recruited within the first 12 hours, some patients will not require longer-term tube feeding as some patients may have rapid improvement of dysphagia within 24 -48 hours of admission. To account for this, the study size has to be increased by 20% and a further 10% to be added to account for loss of follow up and withdrawals. To achieve 80% power with a significance level (alpha) of <0.05 and 1:1 randomization, a study size of 298 participants are required for the planned multi-centre study.

5.3.2. Other possible future studies

Oral decontamination has been shown to reduce the incidence of pneumonia in stroke patients as significant amount of bacteria are transmitted from the infected oropharynx. A combination of anti-reflux medication and oral decontamination may prove to be even more effective than using each intervention separately. Though had shown promising results in animal studies, evidence for regular use of prophylactic antibiotics in acute stroke in humans is still lacking. It may be due to the many causative factors for pneumonia such as oropharyngeal colonisation, gastro-oesophageal dysfunction and reflux, and silent aspiration still continues despite the treatment with systemic antibiotics. A new randomised control trial with varying combinations of oral decontaminants, metoclopramide and intravenous antibiotics can be piloted and may prove very successful in the reduction of post-stroke pneumonia.

Bolus feeds have been investigated by few researchers to reduce the incidence of pneumonia in patients who are fed via nasogastric tubes. Some physicians prefer bolus feeds as they are more physiological than continuous feeds and patients can be better observed during the feeds are in progress. Main problems of bolus feeds were increased residual gastric volume, discomfort and possible worsening regurgitation. However, a study can be designed to assess the efficacy of bolus feeds used along with metoclopramide, which would increase forward peristalsis of the stomach and reduce the residual volume and regurgitation, therefore be more effective than used alone.

Not many studies have been performed to understand the reasons that lead to poor nutritional status in post-stroke patients who are fed via nasogastric tubes. Effect of a stroke on the small intestine has been less researched, when compared to research performed to assess the effects of stroke on the upper gastro-intestinal tract. Possibilities of poor

digestion, pancreatic failure and poor absorption are possibilities. Any of the research planned to assess the incidence of pneumonia in stroke patients fed via nasogastric tubes can be combined with a sub-project that will review the adequacy of a formally calculated nasogastric feeds on patients' nutritional state. In addition, a randomised control trial on regular supplementation of pancreatic enzyme preparation Creon can be combined to one of the future research projects designed in stroke patients fed via nasogastric tubes to assess possible pancreatic dysfunction following acute stroke.

5.4. Conclusion

The MAPS study suggests that time-limited prophylactic use of metoclopramide in patients fed via NGT is well tolerated and has the potential to reduce the rate of pneumonia and improve other clinical outcomes in acute stroke patients fed via NGTs. These findings need to be confirmed in larger, multicentre, randomized and blinded trials. If confirmed the findings could lead to a new approach to the prevention of pneumonia in stroke patients fed via NGTs.

In addition, the work done for the thesis also demonstrated that stroke patients do not regularly manifest several well known clinical signs and symptoms of a chest infection. An increase in the respiratory rate, a fall in the oxygen saturation and new onset inspiratory crackles were the most commonly observed signs and were highly predictive of pneumonia. As for investigations, elevation of both CRP and WBC were highly predictive of pneumonia but CRP appears to have the highest predictive value. For every single point in increase in the CRP levels there was a 0.5% rise in the predictability of pneumonia. A CRP level of 40 mg/l had the best sensitivity and specificity as the cut-off level for the diagnosis of post-stroke pneumonia.

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Appendices

Appendix 1: Stroke syndromes

Oxfordshire Community Stroke Project Classification (OCSP)

Total Anterior Circulation Stroke (TAC)	All of • Hemiplegia contralateral to the cerebral lesion, usually with ipsilateral hemisensory loss • Hemianopia contralateral to cerebral lesion • New disturbance of higher cerebral function (dysphasia, visuospatial)
Lacunar Stroke (LAC)	• Pathological definition • Occlusion of a single deep (LS) perforating artery • 5% can be due to haemorrhage • Occurs at strategic sites • More likely seen on MRI than CT scan • Classical lacunar syndromes correlated with relevant lacunes at autopsy
Partial Anterior Circulation Stroke (PAC)	Any of • Motor / sensory deficit + hemianopia • Motor/sensory deficit + new higher cerebral dysfunction • New higher cerebral dysfunction + hemianopia • New higher cerebral dysfunction alone • A pure motor/sensory deficit less extensive than for LAC (eg. confined to one limb, or to face and hand but not to whole arm)
Posterior Circulation Stroke (POC)	Any of • Ipsilateral cranial nerve palsy (single / multiple) with contralateral motor and/or sensory deficit • Bilateral motor and/or sensory deficit • Disorder of conjugate eye movement (horizontal/vertical) • Cerebellar dysfunction without ipsilateral long tract sign • Isolated hemianopia or cortical blindness Other signs include Horner's sign, nystagmus, dysarthria, hearing loss, etc
Code last letter as follows:	
(S) (I) (H)	Syndrome: Indeterminate pathogenesis, prior to imaging (e.g. TACS) Infarct (e.g., TACI) Haemorrhage (e.g., TACH)

Appendix 2: Methodology checklist: randomised controlled trials

A.2 Methodology checklist: randomised controlled trials

Study identification *Include author, title, reference, year of publication*			
Guideline topic:		**Key question no:**	
Checklist completed by:			
SECTION 1: INTERNAL VALIDITY			
In a well-conducted RCT study:		**In this study this criterion is: (*Circle one option for each question)***	
1.1	The study addresses an appropriate and clearly focused question.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.2	The assignment of subjects to intervention groups is randomised.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.3	An adequate concealment method is used.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.4	Subjects and investigators are kept 'blind' about intervention allocation.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.5	The intervention and control groups are similar at the start of the trial.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.6	The only difference between groups is the intervention under investigation.	Well covered Adequately addressed	Not addressed Not reported Not applicable
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable
1.8	What percentage of the individuals or clusters recruited into each intervention arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Well covered Adequately addressed Poorly addressed	Not addressed Not reported Not applicable

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code ++, + or –*	
2.2	If coded as + or – what is the likely direction in which bias might affect the study results?	
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	

Appendix 3: Type and quality of evidence for studies on the efficacy of interventions

Adapted from the Scottish Intercollegiate Guidelines Network (2001); for further information, see further reading.

Type and quality of evidence	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a high risk of bias
2^{++}	High quality systematic reviews of these types of studies, or individual, non-RCTs, case-control studies, cohort studies, CBA studies, ITS, and correlation studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well conducted non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a high risk – or chance – of confounding bias, and a significant risk that the relationship is not causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus
NB: for policy interventions, then CBA can be awarded level 1 evidence.	

PHIAC or the PDG is responsible for endorsing the final levels ascribed to the body of evidence.

Appendix 4: Data Extraction form

Description of the comparator(s):

Method/mode of delivery (for example, peer education):

Providers/deliverers of the intervention:

Length, duration and intensity of the intervention:

Time to follow-up (average/median):

How many (n, %) participants completed the intervention?

For non-completers, were the reasons for non-completion described?

Outcomes[3]:
Health promotion outcomes:
- Health literacy ☐
- Social action and influence ☐
- Healthy policy changes ☐
- Other ☐
  - Describe:
- Were baseline measurements of outcomes assessed? Yes ☐ No ☐

Intermediate outcomes:
- Lifestyle changes ☐

[3] Adapted from Nutbeam's model (1998).

- Social action and influence ☐
- Healthy policy changes ☐
- Other ☐
  - Describe:
- Were baseline measurements of outcomes assessed? Yes ☐ No ☐

Health and Social outcome measure(s):
- Mortality ☐
- Morbidity ☐
- Quality of life ☐
- Other ☐
  - Describe:
- Were baseline measurements of outcomes assessed? Yes ☐ No ☐

Were the outcome measure(s) validated? Yes ☐ No ☐ Not clear ☐
If yes, how?

Analyses:
Data collection methods used:

Describe methods used (intention to treat, descriptive statistics, qualitative analysis etc):

Unit of analysis:
Individual ☐ Group ☐ Organisation/institution ☐
Community/environment ☐ Policy/socio-political ☐
Other (describe) ☐

Power

Was a power calculation presented? Yes ☐ No ☐

If yes, describe:

Was the study powered to detect an effect if one exists?

Yes ☐ No ☐ Not clear ☐

Any other process details:

Results:

Briefly describe the results for each of the main outcomes, paying particular attention to issues relating to health inequalities and cost effectiveness:

Are there any key criticisms of the conclusions drawn by the author's?

Does the paper address or offer any evidence of effect in the following groups? If so, please ensure that evidence is presented in results above.

Children and young people	Yes ☐	No ☐	Not clear ☐
Older people	Yes ☐	No ☐	Not clear ☐
Gender	Yes ☐	No ☐	Not clear ☐
Black and minority ethnic groups	Yes ☐	No ☐	Not clear ☐
Lower socio-economic status	Yes ☐	No ☐	Not clear ☐

Other (please specify):

Does the paper demonstrate any evidence of harms or adverse effects associated with the intervention?

Do the authors identify any strengths and/or weaknesses of the evidence presented?

In your opinion, are the results generalisable to the UK?

Yes ☐ No ☐ Not clear ☐

Why:

Do the authors identify any evidence gaps or make any recommendations for further research?

Is there any data on cost-effectiveness presented?

Are there policy implications of the work?

Are there effective practice implications of the work?

Pass to other reviewer for second opinion?

Comment:

Appendix 5: GCS Score

GLASGOW COMA SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Activity Score

EYE OPENING

None	1 = Even to supra-orbital pressure
To pain	2 = Pain from sternum/limb/supra-orbital pressure
To speech	3 = Non-specific response, not necessarily to command
Spontaneous	4 = Eyes open, not necessarily aware

_____

MOTOR RESPONSE

None	1 = to any pain; limbs remain flaccid
Extension	2 = Shoulder adducted and shoulder and forearm internally rotated
Flexor response posture	3 = Withdrawal response or assumption of hemiplegic
Withdrawal	4 = Arm withdraws to pain, shoulder abducts
Localizes pain	5 = Arm attempts to remove supra-orbital/chest pressure
Obeys commands	6 = Follows simple commands

_____

VERBAL RESPONSE

None	1 = No verbalization of any type
Incomprehensible	2 = Moans/groans, no speech
Inappropri ate	3 = Intelligible, no sustained sentences
Confused	4 = Converses but confused, disoriented
Oriented	5 = Converses and oriented

_____

TOTAL (3–15):

_____

Appendix 6: NIHSS score

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Category	Score/Description		Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials	Date/Time Initials
1a. **Level of Consciousness** (Alert, drowsy, etc.)	0 = Alert 1 = Drowsy 2 = Stuporous 3 = Coma						
1b. **LOC Questions** (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect						
1c. **LOC Commands** (Open/close eyes, make fist/let go)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect						
2. **Best Gaze** (Eyes open - patient follows examiner's finger or face)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation						
3. **Visual Fields** (Introduce visual stimulus/threat to pt's visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)						
4. **Facial Paresis** (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete						
5a. **Motor Arm - Left** 5b. **Motor Arm - Right** (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
6a. **Motor Leg - Left** 6b. **Motor Leg - Right** (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can't resist gravity 3 = No effort against gravity 4 = No movement X = Untestable (Joint fusion or limb amp)	Left					
		Right					
7. **Limb Ataxia** (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs						
8. **Sensory** (Pin prick to face, arm, trunk, and leg - compare side to side)	0 = Normal 1 = Partial loss 2 = Severe loss						
9. **Best Language** (Name item, describe a picture and read sentences)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute						
10. **Dysarthria** (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Near to unintelligable or worse X = Intubated or other physical barrier						
11. **Extinction and Inattention** (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect						
	TOTAL SCORE						

INITIAL	SIGNATURE	INITIAL	SIGNATURE	INITIAL	SIGNATURE

189387 1004

Source: J Neurosci Nurs © 2006 American Association of Neuroscience Nurses

Appendix 7: Research and Development approval letter

North Staffordshire Research and Development Consortium NHS

DEPARTMENT OF RESEARCH AND DEVELOPMENT
Medical Research Unit
Thornburrow Drive
Hartshill
Stoke-on-Trent
ST4 7QB
Telephone: 01782 554334
Fax: 01782 412236

Email: darren.clement@uhns.nhs.uk
katie.roebuck@uhns.nhs.uk

Ref: DC/kr

10th August 2007

Dr Anushka Warusevitane
Staff Grade Physician in Elderly Care
North Staffordshire Combned Healthcare NHS Trust
Springfield Unit
Stoke on Trent
Staffordshire
ST4 6QG

Dear Dr Warusevitane,

Re: Investigation into Does Metoclopramide reduce aspiration, pneumonia and hypoxia in acute stroke patients who are fed by nasogastric tubes

I can confirm that the above project has been approved by the Research & Development Department. The details of the project will be entered on to the R&D database and will be included with our next submission to the National Research Register.

I note that this research project has been approved by the North Staffordshire Local Research Ethics Committee (07/Q2604/41).

If you need any further advice or guidance please do not hesitate to contact us.

Yours sincerely,

Darren Clement
R&D Manager - North Staffordshire NHS R&D Consortium

Appendix 8: Ethic Committee approval letter

NHS

National Research Ethics Service
North Staffordshire Local Research Ethics Committee
Mellor House
Corporation Street
Stafford
Staffordshire
ST16 3SR

Telephone: 01785 252233 ext 5941

30 July 2008

Dr. Anushka Warusevitane
Staff Grade Physician in Elderly Care
North Staffordshire Combined Healthcare NHS Trust
Spingfield Unit
Stoke on Trent
Staffordshire
ST4 6QG

Dear Dr. Warusevitane

Full title of study: **Does Metoclopramide reduce aspiration, pneumonia and hypoxia in acute stroke patients who are fed by nasogastric tubes. (Pilot Study)**

REC reference number: **07/Q2604/41**

This study was given a favourable ethical opinion by the Committee on 26 July 2007.

It is a condition of approval by the Research Ethics Committee that the Chief Investigator should submit a progress report for the study 12 months after the date on which the favourable opinion was given, and then annually thereafter. To date, the Committee has not yet received the annual progress report for the study, which was due on 31 July 2008. It would be appreciated if you could complete and submit the report by no later than 1 September 2008.

Guidance on progress reports and a copy of the standard NRES progress report form is available at http:// www.nres.npsa.nhs.uk/applicants/after-ethical-review/progress-reports

There is also guidance on declaring the end of the study at http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/endofproject

[Failure to submit progress reports may lead to a suspension of the favourable ethical opinion for the study.]

REC reference number **07/Q2604/41** **Please quote this number on all correspondence**

Yours sincerely

Janet Clarke

Janet Clarke
Assistant Coordinator

E-mail: janet.clarke@ssh-tr.nhs.uk

Cc Dr D Clements, R&D Manager, UHNS

This Research Ethics Committee is an advisory committee to West Midlands Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within

Appendix 9: Patient Information Sheet

Patient information sheet
The metoclopramide aspiration study

A randomised controlled study of the effect of metoclopramide in reducing aspiration, pneumonia and hypoxia of patients who are fed by nasogastric tubes after an acute stroke (pilot study)

I am doctor attached to the Acute Stroke Unit, intending to do the above research project as a part of my MSc in Geriatric Medicine. This research is to assess whether the drug called metoclopramide will reduce the incidence of aspiration and pneumonia in stroke patients who are receiving nasogastric feeds.

I you are interested in helping us with our research, it is important to that you understand not only why the research is being done, but also what it would involve. Therefore could you please take time to read this information sheet carefully, and if you wish discuss it with others, before deciding whether or not you would like to participate in this study. If any information is unclear or if you would like more information please contact Dr. A Warusevitane or Dr. C Roffe (contact details can be found at the end of this form). Do take time to decide whether you wish to take part. If you do not want to take part in this study, we would like to assure you that your current medical care will not be compromised in anyway and we would like to thank you for giving us a bit of your time.

Introduction to the study
Patients who have had a stroke often lose the ability to swallow. If this happens feeding by mouth is not safe because of the risk of choking on food and drinks. Artificial nutrition via a feeding tube often has to be given for a period of time to prevent starvation. Pneumonia is a common complication of tube feeding. One of the major causes of pneumonia in this patient group is the entry of stomach contents in to the lungs (aspiration). This happens when food in the stomach is pushed back (regurgitated) in to the oesophagus (gullet). This is due to a combination of delayed emptying of stomach contents into the small bowel and malfunction of the valve which prevents stomach contents entering into the gullet.

Metoclopramide is a drug which is commonly used in clinical practice to prevent and treat sickness and vomiting. It accelerates the passage of stomach contents into the gut and improves function of the lower oesophageal sphincter, the valve which prevents leakage of stomach contents into the gullet. Because of this it might be useful in preventing pneumonia in stroke patients with feeding tubes. Some doctors use metoclopramide for this purpose, but there is no evidence form clinical studies in stroke patients to show that it is effective. The purpose of this study is to examine whether metoclopramide prevents pneumonia due to regurgitation of stomach contents in stroke patients fed via feeding tubes.

What are the side effects of the drug?
Metoclopramide is commonly used by doctors in routine clinical practice to prevent vomiting. Side effects of this drug are rare. Rarely this drug can cause involuntary movements mainly affecting the muscles of the head and neck (dystonic reactions). These usually occur within the first few days after starting metoclopramide, are easily recognised, and usually settle within 24 hours of stopping the drug. If the movements are distressing they can also be aborted by an injection of procyclidine. There is no long term harm done to the patient by these dystonic reactions or the medication which is given to reverse it.

Other, less frequent side effects of metoclopramide listed in the British National Formulary are: drowsiness, diarrhoea, depression, itching, rashes and swelling of the feet. Hyperprolactinaemia (increased blood levels of a hormone called prolactin) and tardive dyskinesia (involuntary movements of the mouth and tongue) can occur after prolonged use (several months). These are only very rarely encountered in routine clinical practice. Each patient is will be observed for adverse effects, and the drug will be discontinued if such adverse effects develop. If you or your relatives become in any way concerned do not hesitate to contact the ward doctor. (tel.01782 552257)

Why are we telling you this now?
We are inviting you to join this study to find out whether metoclopramide prevent pneumonia in tube fed stroke patients. You have been chosen because you have had a stroke affecting your swallowing and therefore need to be fed via a tube.

Do I have to take part?
Participation in this clinical trial is entirely voluntary and you are not obliged to support this clinical trial. If you do decide to take part you will be given this information sheet to keep and will be requested to sign a consent form. Even if you decide to take part you are still free to withdraw at any time without giving any reason. This will not affect the standard of care you would receive.

What will happen if I take part?
If agree to take part in the study you will be asked to sign a consent form. The researcher will then asks you questions about your health, examine you and record baseline information about you and your stroke. You will then be given metoclopramide 10 mg three times a day via the feeding tube or a matching dummy treatment (placebo) for three weeks or until the feeding tube is removed. Whether you are given metoclopramide or placebo will be chosen randomly by using a pack of sealed envelopes, prepared before the commencement of the trial. The treatment allocation is determined by chance (random) and neither you nor the researcher will know which of the two treatments you are given. This type of a trial is called a randomised controlled trial. This is done to reduce the bias of interpretation of your progress by the researcher.

You will be examined five times a week for the next 3 weeks to check for signs of pneumonia and recovery from the stroke. If you develop symptoms of a chest infection (such as cough or a high temperature) this will be reported to the doctor looking after you who will arrange further investigations and treatment. If clinically indicated a blood sample will be taken to confirm the diagnosis of a new infection. You may also have a chest x-ray to see whether you have developed radiological evidence of a chest infection. All this is routine clinical practice for any patient in this situation but for this trial the results of your tests will also be recorded in the research file. Treatment of any chest infection will be according to the hospital guidelines.

The trial ends 3 weeks after the insertion of the feeding tube. On the last day of the trial your health, the level of you recovery, and test results from your clinical notes will be reviewed and recorded in the trial file.

What are the possible advantages and disadvantages of taking part in this research?
You will not directly benefit from this study yourself, however your participation may help others who, in the future find themselves in the same position as you are in now. As mentioned above, acute dystonic reactions could be a rare side effect. This is reversible and there will be no long term or permanent problems or side effects.

What happens if something goes wrong?
If you are harmed by taking part in this research project, there are no special compensation agreements. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you have to pay for it. Regardless of this if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service Complaints Mechanism may help you.

Will my taking part in this study be confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will not have your name, date of birth or address, so that you cannot be identified from that information. If you agree your GP will be notified of your participation in the trial.

What happens to the results of the research study?
The results of the study will be presented at scientific meetings and published in medical or scientific journals as well as in literature relevant to stroke patients and their carers. The findings may affect the way future stroke patients would be treated and may be included in clinical guidelines for stroke management. You will not be identified in any of these reports or publications. You can obtain a copy of the results by contacting me or my supervisor directly (the addresses are given at the end of this page).

And finally….
We would now like to thank you having taken the time to enquire about our study. If you have any further questions please contact us and we will be happy to answer all your questions. Further information on research studies can also be obtained from the Patient Advocacy Liaison Services (PALS), tel: 01782 552814, 01782 552317. If we have answered all your questions and you want to support this study you will now need to sign the consent from. If however, you have decided not to participate, we would like to thank you for taking the time to find out about this study.

Thank you.
Contact for further information

Dr. Anushka Warusevitane.
Ward 84, City General Hospital
Newcastle Road
Stoke on Trent ST4 6QG.
Tel: 01782 552257

Dr. Christine Roffe
Springfield Unit,
City General Hospital.
Stoke on Trent ST4 6QG.
Tel: 01782 552313.

Appendix 10: Consent form

Version 04
20/06/2007

CONSENT FORM

Title of the project: Does Metoclopramide reduce the incidence of aspiration, pneumonia and hypoxia in acute stroke patients who are fed by nasogastric tubes (pilot study).

Name of the researches: Dr. Anushka Warusevitane, Dr. C. Roffe

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible members of the research team or by members of the data monitoring committee. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐

_____	_____	_____
Name of the patient	Date	Signature
_____	_____	_____
Name of person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 11: Assent Form

Version 04
20/06/2007

ASSENT FORM

Title of the project: Does Metoclopramide reduce the incidence of aspiration, pneumonia and hypoxia in acute stroke patients who are fed by nasogastric tubes (pilot study).

Name of the researches: Dr. Anushka Warusevitane, Dr. C. Roffe

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my relative's participation is voluntary and that he/she is free to withdraw at any time, without giving any reason, without his/her medical care or legal rights being affected. ☐
3. I understand that sections of any of my relative's medical notes may be looked at by responsible members of the research team or by members of the data monitoring committee. I give permission for these individuals to have access to my relative's records. ☐
4. I agree my relative ……., to take part in the above study. ☐

_____	_____	_____
Name of the relative	Date	Signature
_____	_____	_____
Name of person taking consent (If different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix 12: MAPS trial data collection form

Hospital ID Sticker or

Name:

Sex: Male/Female

DOB: DD MM YYYY

Unit No/Hiss NO:

Metoclopramide preventing Aspiration and Pneumonia in acute Stroke (MAPS) trial
Data collection Form

Eligibility for trial inclusion

Admitted to the Stoke Unit	☐ Yes	☐ No
<7 days from admission	☐ Yes	☐ No

Please proceed if both answered as Yes

Pre existing pneumonia	☐ Yes	☐ No
Patient with a terminal illness	☐ Yes	☐ No
Brain tumour or metastases presenting as stroke	☐ Yes	☐ No
Known oesophageal stricture or carcinoma	☐ Yes	☐ No
>24 hours form the nasogastric tube insertion	☐ Yes	☐ No

Please proceed to the next section if all answered as No

Baseline criteria

Date of stroke DD MM YYYY

Date of admission:

GCS on admission: E V M At randomisation: E V M

Date of first NG insertion:

Type of Stroke:

☐ LACS ☐ TACS ☐ PACS ☐ POCS ☐ Unclassifiable

CT diagnosis

☐ Cerebral infarct ☐ Intracerebral h'age ☐ Small V disease ☐ SHD

☐ SAH ☐ Not done ☐ Other

Past medical history

☐ DM ☐ Htn ☐ AF ☐ IHD ☐ CCF

Previous lung disease

☐ Athsma ☐ COPD ☐ Pulmonary Fibrosis

☐ Pneumoconiosis ☐ Other

Medication:

☐ Diuretics ☐ ACEI ☐ Inhalers ☐ Nebs ☐ Digoxin

☐ PPI ☐ Other antiHtn ☐ antianginal

Baseline CXR

☐ Normal ☐ Lung Congesion ☐ Emphysematous ☐ Fibrosis

☐ Effusion ☐ Consolidation ☐ Other

Baseline inflammatory markers

CRP ☐ ESR ☐ WBC ☐ Albumin ☐

Already on antibiotics

☐ Yes ☐ No

If yes Antibiotic: ☐

Reason: ☐

Randomisation

Randomisation No: ☐

☐ Consent ☐ Assent

Date & time of randomisation: ☐ DD MM YYYY

☐ HH:MM

Trial Medication group:

☐ Medicine A ☐ Medicine B

	Date	Time	O2 sat	RR	HR	BP	Temp	Weight
Admission								
Randomisation								
1st week assessment								
2nd week assessment								
3rd week assessment								

Weekly assessment:

	First week assessment	Second week assessment	Third week assessment
O_2 saturation at 10 am			
On oxygen	Yes / No …….%	Yes / No …….....%	Yes / No ……%
If on oxygen – Sats on room air			
Lowest BP			
Highest BP			
Highest temperature			
No of days with NG feed			
No of doses of trial drug			
Days NG interrupted			
Problems with confirming			
No NG tube			
Etc.			
Course of antibiotics	Yes / No	Yes / No	Yes / No
Type			
Days up to now			
Presumed diagnosis			
New medications			
ACEI			
Other antiemetics			
Erythromycin			
GCS	E M V	E M V	E M V
NIHSS score			
Inflammatory markers			
CRP			
ESR			
WBC			

Witnessed aspiration

	1st episode	2nd episode	3rd episode
Date			
Time			
Body posture			
Presence of NG feeds			
Intervention			
Suction only			
Suction and antibiotics			
Stop feeding			
Outcome			
No change			
Pneumonia			
Feed discontinued for >24h			
Death			

Diagnosis of Pneumonia

	1st episode	2nd episode	3rd episode
Date			
Symptoms of acute LRTI			
Cough			
Purulent Sputum			
RR >25/m			
O_2 Sats <90%			
New focal chest signs			
Inspiratory crackles			
Bronchial breathing			
Signs of consolidation			
Systemic features of inflammation			
Fever >38° C			
Chills and/or rigors			
WBC >11			
WBC <3			
CRP			
ESR			
Radiological evidence (at least one segment not known to be previously present)			
Diagnosis			
Definite pneumonia			
Probable pneumonia			

Presence of at least one criterion from each category will establish the diagnosis of pneumonia. Presence of at least one criterion from three categories will make a diagnosis of possible pneumonia.

CXR in episode one

☐ No change ☐ Incresed lung markings ☐ Inflammatory shadowings

☐ Effusion ☐ Other ☐ Consolidation

Side.....
Lobe .....
Segment .....

CXR in episode two

☐ No change ☐ Incresed lung markings ☐ Inflammatory shadowings

☐ Effusion ☐ Other ☐ Consolidation

Side.....
Lobe .....
Segment.....

CXR in episode three

☐ No change ☐ Incresed lung markings ☐ Inflammatory shadowings

☐ Effusion ☐ Other ☐ Consolidation

Side .....
Lobe.....
Segment .....

Outcome

	Date
☐ NG removed as swallowing improved	
☐ Referred for PEG	
☐ RIP	
No of episode of pneumonia (any)	
No of episode of aspiration	
No of antibiotic days	
No of different antibiotics	
Highest WCC/ CRP at any time	
Lowest oxygen saturation at any time	%
Change in body weight from baseline to Week 3	Kg

Appendix 13: SPSS calculations of predictability of CRP and WBC

C-Reactive Protein as a Predictor

Variables in the Equation

	B	S.E.	Wald	df	p-value	Odds ratio	95% C.I. for odds ratio	
							Lower	Upper
CRP	.045	.013	11.659	1	.001	1.046	1.019	1.073
Constant	-1.717	.562	9.316	1	.002	.180		

Nagelkerke pseudo-R^2 = .506, CRP-C-Reactive Protein

White Blood Cells as a Predictor

Variables in the Equation

	B	S.E.	Wald	df	p-value	Odds ratio	95% C.I. for odds ratio	
							Lower	Upper
WBC	.221	.083	7.061	1	.008	1.247	1.060	1.468
Constant	-2.267	.953	5.656	1	.017	.104		

Nagelkerke pseudo-R^2 = .232, C.I -Confidence Interval, WBC- White Cell Count

Predictability of the Combination

Variables in the Equation

	B	S.E.	Wald	df	p-value	Odds ratio	95% C.I. for odds ratio	
							Lower	Upper
WBC	.178	.114	2.439	1	.118	1.194	.956	1.493
CRP	.037	.013	8.327	1	.004	1.038	1.012	1.065
Constant	-3.401	1.278	7.077	1	.008	.033		

Nagelkerke pseudo-R^2 = .546, C.I Confidence Interval CRP- C-Reactive Protein, WBC- White Cell Count

CRP Cut-off Values

CRP cut-off value	Youden Index	Sensitivity	Specificity
25.6	0.568	0.85	0.72
36.5	0.567	0.73	0.84
64.7	0.566	0.61	0.96

Appendix 14: Standard Operating policy on nasogastric feeding of the Stroke Unit

The policy on the stroke unit was to perform a swallowing assessment in all stroke patients within the first 24 hours of admission. Patients are kept nil by mouth until a safe swallow is established. Assessment of swallowing was done by a nurse trained in the level 2 swallowing assessment as a part of routine patient care within 24 hours of admission. If swallowing problems were identified patients were reviewed by a speech and language therapist within the next 24 to 48 hours. If swallowing problems persisted and an adequate oral nutritional intake was not achievable, a nasogastric tube was considered within 24 to 48 hours of admission. When the need for a nasogastric tube was agreed by clinicians, patients or their next of kin were informed about the need of a nasogastric tube.

The swallowing assessment can only be performed in patients who are alert and cooperative, able to sit up for feeding and who maintain awareness during the time period of assessment, which is about twenty minutes. The test consists of administration of 5 ml of water on a spoon and observation of the patient's ability to clear this from the mouth and pharynx promptly. This can be done by watching the patient's swallow and feeling for laryngeal elevation during swallowing with fingers placed over the patient's larynx. The patients are observed for delayed or impaired swallowing and are watched for further 2 minutes for choking, respiratory distress, cough or change of voice. This procedure is repeated twice. If 5 ml of water is swallowed without difficulty, 50 ml of water in a beaker is given with the same observations before proceeding to a soft diet.

A level two swallowing assessment can only be done by a nurse who is trained to do such assessment or by a qualified speech and language therapist. In a patient who is unable to swallow water safely, fluid and foods of varying consistencies were tried to see what form of modified diet and thickened fluid can be given safely and in what quantities. During the testing oral transition, oral retention, initiation of swallow, possible delays, laryngeal excursion, voice change after the bolus and cough were assessed. Depending on the severity of the dysphagia and the risk of aspiration patients were placed on modified fluids ranging from syrup to custard thickness and modified diet ranging from pureed to fork mashed consistency. Also the quantities provided varied from a few teaspoons at a time with supervision and progress to normal portions. Various feeding strategies such as reducing the bolus size, keeping the chin tilted and the head turned while eating and the practice of double swallowing were carried out in addition.

Patients who are comatose or too drowsy to be assessed for the safety of their swallow and patients who are identified as being at high risk of aspiration by bedside swallowing tests or who continued to show signs of aspiration with pureed food and custard thick fluids were kept nil by mouth until it is considered safe to be commenced oral feeds. This was determined by swallowing assessments which were done at regular intervals depending on the clinical state of the patient. A nasogastric tube was inserted in all patients who were kept nil by mouth. Similarly, patients who were only on oral trials with limited oral input also had a nasogastric tube placed to supplement their oral intake (top up feeds). A flexible polyurethane nasogastric tube, with an inner diameter of 10 mm unless otherwise indicated (Medicina NG tubes, Medicina, Bolton, United Kingdom) was inserted by a doctor or a senior staff nurse. The same type of nasogastric tube was used in all patients. After initial placement correct position of the

tube was confirmed by a chest X-ray or by pH testing (pH testing strips, Medicina, Bolton, United Kingdom) as per the nasogastric feeding protocol. All patients were positioned in semi-reclined position throughout the nasogastric feeds and three hours after the feed. Being on nasogastric feeds did not preclude patients from being sat out or receiving therapy input. Nasogastric feeds were not interrupted during therapy sessions. Nasogastric feeds were commenced in the morning after the patients were washed to reduce the effect of changes of body posture on aspiration and as general patient's care is easier in this position. Feeding overnight was not routinely carried out as patients cannot be observed for feed-related complications.

Feeding regimes and the type of the feed was determined by the dietician based on the calorie and other nutritional requirements of the patient. The nasogastric feeds were started at a lower rate of 25 ml/hour, which was gradually increased daily by 25 ml/hour and kept to a maximum of 125 ml/hour. Before each feed the position of the tube was confirmed by assessing the pH of the nasogastric aspirate using the pH testing strips (Medicina, Bolton, United Kingdom). An acidic pH confirms that distal end of the tube is within the stomach. If the nasogastric tube was accidentally displaced or pulled out by the patient, a new tube was reinserted as soon as possible. If there was a problem confirming the accurate position of the nasogastric tube by pH assessment, the position was confirmed by a chest radiograph. Feeds were given by continuous flow over ten to twelve hours, rather than bolus feeds. Patients who were fed via nasogastric tubes were managed closer to the nurses' station so that they could be observed for complications such as vomiting and displacement of the nasogastric tube. When necessary, soft mittens were applied after consent from the next of kin to restless patients to prevent patients pulling at their nasogastric tubes. Reinsertion of a nasogastric tube when displaced,

confirmation of the position before each feed and application of mittens to prevent a restless patient pulling out the tube were part of routine patient care on the ward. Patients' other medications were continued as routine care.

Patients fed via nasogastric tubes were assessed regularly by the SALT team attached to the unit and oral feeds were commenced as soon as swallowing had recovered. The nasogastric tube was only removed once the team was confident that the patient was able to take adequate amounts of oral feeds. This was done by nutritional assessment of the oral intake balancing with their caloric needs. If the patient's swallowing had not recovered by the second week, insertion of a percutaneous endoscopic gastrostomy (PEG) tube was considered and appropriate referrals were done to the gastroenterological and nutritional teams.