Dysphagia and Respiratory Infections in Acute Ischemic Stroke

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1. Introduction
Eating and swallowing are activities that are normally performed without conscious thought. This complex behaviour – involving 5 pairs of cranial nerves and 26 pairs of muscles – can be interrupted by a stroke, leading to dysphagia. Dysphagia is associated with aspiration (where material passes into the respiratory tract) and aspiration carries a risk of pneumonia seven times greater than that of the normal population. Around 15% - 20% of all stroke patients will develop respiratory tract infections during the acute phase of their stroke. Pneumonia is one of the leading causes of mortality in the acute stroke patient. Respiratory infections add to hospital length of stay and are associated with significant increases in the cost of patient care, as well as being associated with poorer outcomes for the patient. This chapter will outline the association of dysphagia and other risk factors in the development of respiratory infections in acute ischemic stroke patients.

2. High early incidence of dysphagia, its causes, presentation and implications
Swallowing is a vital motor activity that serves alimentary purposes and protects the upper airway (Jean, 2001). Dysphagia (difficulty eating and swallowing) is very common after an ischemic stroke, affecting between 13% and 94% of all ischemic stroke patients, with the incidence depending on the size and location of the lesion (Barer, 1989; DePippo, Holas, Reding, Mandel & Lesser, 1994; Daniels, 2000; Ding & Logemann, 2000; Aydogdu, Ertekin, Tarlaci, Turman & Klyliogly, 2001; Marik, 2001). Dysphagia can lead to malnutrition, dehydration, aspiration pneumonia and increased length of hospital stay.
In a recent review of the costs to the US health system, dysphagia was found to be associated with significantly increased costs due to increased length of stay and infections. The median hospitalization days for patients with dysphagia was 4.04 compared with 2.40 days for those patients without dysphagia. Mortality was substantially increased in patients with dysphagia associated with rehabilitation, intervertebral disk disorders, and heart diseases (Altmann, Yu & Schaefer, 2010). A cohort study of 330 stroke survivors found that those who developed infections during their hospital admission had a median length of stay of 26 days, significantly longer than the median length of stay of 11 days of those who did not require antibiotic treatment (Langdon, Lee and Binns, 2010).
Best practice management of dysphagia in acute stroke encompasses the need to consider the patient holistically. The impact of various eating difficulties on nutritional status has not
received great attention in research (Westergren, 2006). Impaired arm movement, lip closure and swallowing have all been found to be significant predictors of decreased energy intake over 24-hours in patients with stroke (McLaren & Dickerson 2000).

Dysphagia that occurs due to a stroke is associated with an increased risk of material being aspirated during swallowing. This is due to the disruption to motor and sensory input and to protective reflexes (Holas, DePippo & Reding, 1994; Aviv, Martin, Sacco, Zager, Diamond, Keen & Blitzer, 1996; Daniels, Brailey, Priestly, Herrington, Weisberg & Foundas, 1998; Addington, Stephens, Gilliland, Rodriguez, 1999; Nakajoh, Nakagawa, Sekizawa, Matsui, Arai & Sasaki, 2000). ‘Aspiration’ occurs when matter (food, fluid, saliva or secretions), enters the airway and passes below the level of the true vocal folds. Pneumonia is up to seven times more likely to occur in patients who are known to aspirate (DePippo, Holas & Redding, 1994; Kidd, Lawson, Nesbitt & MacMahon, 1995; Smithard, O’Neill, England, Park, Wyatt, Martin & Morris, 1997). Dysphagia has been found to be associated with an increased risk of chest infections, dehydration and death (Gordon, Hewer & Wade, 1987). In stroke patients, pneumonia has been associated with an increased cost to the health system of US$14,836 per patient (Katzan, Dawson, Thomas, Votrubka & Cebul, 2007) and is strongly associated with poorer outcomes (Smithard, O’Neill, Park, Morris, 1996; Wang, Lim, Levi, Heller & Fischer, 2001; Wang, Lim, Heller, Fisher & Levi, 2003).

2.1 Infection in acute stroke
Infection in acute stroke has been, and remains, a significant problem, with pneumonia and urinary tract infections occurring the most frequently. In the GAIN study, a multicentre, multinational study of 1455 patients with strokes, 142 died during the first week following hospital admission. Thirty four (23.9%) of these died from pneumonia (Aslanyan, Weir, Diener, Kaste & Lees, 2004).

A study of 124 stroke patients who were admitted to Neurological Intensive Care Units in Cologne reported an incidence of pneumonia of 21%, occurring an average 1.8 days (±1.9 days), post stroke, although these figures did not distinguish between patients who required ventilator support for respiration and those who did not (Hilker, Poetter, Findeisen, Sobesky, Jacobs, Neveling & Heiss, 2003). Ventilator-associated pneumonia is common in patients who require mechanical respiratory support and is discussed in greater detail later in the chapter.

A Scandinavian study of 1,156 patients reported 19.4% developed infections within 3 days of hospital admission, with 49% of the infections diagnosed males and 27% of infections in females being respiratory tract infections. Early infection added 9.3 days on average to the patient’s hospital admission (Kammersgaard, Jorgensen, Reith, Nakayama, Houth, Weber, Pederse, & Olsen, 2001).

Using videofluoroscopy to examine swallowing, Kidd et. al., (1995) found 25 (42%) of a cohort of 60 stroke patients were aspirating at 72 hours post stroke. In the first 14 days after their stroke, 19 patients developed lower respiratory tract infections. Of these 19 patients, 17 (89%) were known to be aspirating. Of the 25 aspirators, 22 had returned to normal swallowing function when followed up at 3 months post stroke (Kidd, Lawson, Nesbitt & MacMahon, 1995).

Mann, Hankey and Cameron followed 128 acute stroke patients for six months and reported an incidence of dysphagia in 82 patients (64%) when examined using videofluoroscopy. In the six months of follow up, 26 patients (20%) experienced a chest infection (Mann, Hankey & Cameron, 1999). A limitation of this study was the exclusion of stroke patients who were
unable to tolerate the videofluoroscopy procedure, which excludes those patients with impaired conscious state. Often these patients with poor conscious level are the ones who are at greatest risk of aspiration due to impairment in their ability to protect their airway.

A study of 88 patients admitted to hospital with ischemic strokes found infection occurred in 25 of 80 survivors during the first month post-stroke. Respiratory infection was significantly more likely to occur in patients with dysphagia (Langdon, Lee & Binns, 2007). In a cohort of 330 acute ischemic stroke patients followed up for the first month after their stroke, there were 51 respiratory infections, with dysphagia again a significant predictor of patients who developed infections (Langdon, Lee & Binns, 2009).

2.2 Normal swallowing

Swallowing is something that is often taken for granted, yet it is a complex and tightly controlled event that coordinates breathing and deglutition, with an average of 2,400 swallows occurring daily. The frequency of swallowing changes depending on the activity. It occurs on the average at 6 swallows an hour during sleep to 10 per hour during normal activity to around 300 per hour while eating (Miller, 1982). The body produces 1500ml - 2000ml saliva daily (Witt, 2005), which is swallowed without conscious thought.

Successful swallowing is an extremely complex and dynamic process, involving 5 pairs of cranial nerves and coordination of some 26 pairs of striated muscles (Dodds, Stewart & Logemann, 1990; Bass & Morrell, 1992; Matsuo & Palmer, 2008) involved in the act of moving food or fluid from the oral cavity to the stomach. There is an extremely elaborate reflex mechanism that provides a close functional relationship between the pharynx (throat), larynx and oesophagus during swallowing, belching and reflux to help prevent aspiration or food/fluids going ‘the wrong way’ (Shaker, 2006). Studies have provided evidence that the process of swallowing is governed by specialised neural networks in a finely-tuned partnership with respiration and speech (Zald & Pardoe, 1999). Neural control of swallowing is multidimensional. The brainstem contains the swallowing central pattern generator – the first level of control. The second level of control incorporates the sub cortical structures; basal ganglia, hypothalamus, amygdala and midbrain. The third level of control is represented by suprabulbar cortical swallowing centres (Mistry & Hamdy, 2008).

Normal swallowing is generally arbitrarily divided into four stages for convenience of description, however, the normal swallow is a complex, fast, continuous sequence of coordinated muscle movements and there is some overlap between the phases. An efficient swallow involves an anticipatory phase, an oral phase, a pharyngeal phase and an oesophageal phase. These are illustrated in Figure 1 and described in greater detail below. The oral phase of swallowing is initiated voluntarily while the pharyngeal and oesophageal phases occur via intraphase reflexes (Lang, 2009). Control of the phases represent a coordination among the brain stem and central cortical pathways (Miller, 2008).

2.2.1 Oral preparatory phase (voluntary control)

The oral preparatory stage of swallow incorporates prior knowledge of feeding and swallowing, environmental, visual and olfactory cues. Once food enters the oral cavity, the lips seal, the tongue accepts and cradles the food and it is tasted. Information about the food is transmitted from the taste buds to the cortex and brainstem. The preparatory stage allows
prior knowledge to impact on eating and swallowing: for example, if a stroke patient has had recent choking events due to dysphagia, they may be reluctant to accept a particular texture or type of food.

2.2.2 Oral phase (voluntary and reflexive control)
Food is chewed and mixed with saliva using movement of the jaw, tightly coordinated with movements of the tongue, cheeks, soft palate, and hyoid bone (Matsuo & Palmer, 2008). When the prepared food has been formed into a ‘bolus’ suitable for swallowing, it is centred on the tongue and propelled backwards by the tongue to the pharynx. Difficulties with the oral stage of the swallow may occur because of muscle weakness or nerve dysfunction. These will often lead to an extension in the time taken for oral transit and/or retention of material in the oral cavity as residue, or may cause premature spillage of the bolus into the pharynx (Dodds, Stewart & Logemann, 1990; Matsuo & Palmer, 2008) which can impact on airway protection.

Disruption to the oral phase can occur due to poor dentition or poorly fitting dentures. Absent molar teeth can significantly impair bolus preparation, as these teeth grind food into smaller, more digestible particles. Gum disease and teeth in poor condition may cause pain when eating, which is associated with decreased intake of food. A weak tongue or jaw will also contribute to impairment of the oral phase of the swallow.

2.2.3 Pharyngeal phase (reflexive control)
The pharynx consists of the nasopharynx (superior and anterior to the soft palate) and oropharynx (from the nasopharynx to the larynx). It serves two purposes, acting as a conduit for air to and from the lungs and also moving food and liquids from the mouth to the esophagus (Miller, 2002). The pharyngeal stage of the swallow is an important and complex activity that coordinates: (1) food or liquids passing through the pharynx and upper esophageal sphincter (UES) to the esophagus and (2) airway protection – isolating the larynx and trachea from the pharynx during swallowing to prevent the bolus from entering the airway (Matsuo & Palmer, 2008). The pharynx is made up of the pharyngeal constrictor muscles (superior, middle and inferior) that overlap to form a sheath that extends from the base of skull to the esophagus. The pharyngeal swallow also involves muscles of the soft palate, the tongue, pharynx, larynx and hyoid bone. The pharyngeal swallowing muscles are innervated by the trigeminal (V), facial (VII) glossopharyngeal (IX), vagal (X), spinal accessory (XI) and hypoglossal (XII) nerves (Miller, 2002).

Breathing and swallowing are tightly coordinated by the brainstem. During swallowing, there is a brief cessation of breathing known as ‘deglutition apnea’. Studies of normal subjects have found that there is a small exhalation prior to the swallow being initiated, followed by the swallow, and finally a larger exhalation once the bolus has entered the esophagus (Martin, Logemann, Shaker & Dodds, 1994). Swallowing normally finishes with an exhalation of air. This serves to assist clearance of any material that may have entered the laryngeal vestibule during the swallow. This normal breathing/swallowing rhythm has been shown to break down in stroke patients (Leslie, Drinnan, Ford & Wilson, 2002), while the apnea associated with swallowing increases with age (Leslie, Drinnan, Ford & Wilson, 2005).

Stroke can impact on the timing of the pharyngeal swallow, or weaken the muscles of one side of the pharynx, resulting in a weak or incoordinated swallow, often associated with material being aspirated before, during or after the swallow is initiated.
Fig. 1. Stages of Normal Swallowing:
1. Food is chewed and mixed with saliva. This is shaped into a bolus by the tongue, and centred on the tongue prior to initiation of the swallow. The soft palate elevates to form a seal with the nasopharynx.
2. The tongue tip is pressed against the alveolar ridge, then the tongue base drops and the bolus is pushed into the pharynx. The vocal folds adduct and breathing is ceased momentarily.
3. The epiglottis deflects downward and the bolus enters the esophagus due to (a) tonic relaxation of the upper esophageal sphincter (b) hyolaryngeal traction opening the sphincter (c) pharyngeal squeeze.
4. The bolus is cleared into the esophagus by pharyngeal muscles exerting a stripping action.

2.2.4 Oesophageal phase (reflexive control)
After the bolus enters the oesophagus through the UES, peristalsis moves it down to the stomach and through the lower esophageal sphincter to the stomach. The peristaltic wave consists of an initial wave of relaxation to accommodate the bolus followed by a wave of contraction that propels it onward (Matsuo & Palmer, 2008). This phase of the swallow is considered the least complex, although it can still be subject to impairment leading to decreased safety and poor oral intake.
2.3 Causes of dysphagia in ischemic stroke

Stroke is a brain injury, and may impact on swallowing, either by damage to cranial nerves or nuclei, or by interrupting the interconnecting neural networks that regulate normal deglutition. A stroke patient may be drowsy in the acute phase, which impacts on their ability to remain conscious long enough to eat or drink sufficient amounts to ensure that their nutrition and hydration needs are being met. Poor conscious level may mean that the stroke patient’s ability to protect his or her airway is compromised. Difficulty in maintaining sitting balance and hemiparesis affecting the dominant hand may contribute to the person’s difficulties in self-feeding. Loss of facial tone may cause dentures to become ill-fitting, making chewing difficult for the patient. Loss of facial tone may also mean that the patient has difficulty containing the bolus in the oral cavity, forming a seal with the lips to drink easily, or prevent saliva spilling from the mouth (drooling). Loss of sensation from damage to the trigeminal nerve may mean that the patient is unaware that they are drooling, or that food may be pocketed in a flaccid cheek following mealtimes. The impact of different types of stroke on feeding and swallowing is more fully discussed below.

2.3.1 Cortical lesions

Swallowing has been shown using fMRI studies to involve the precentral and postcentral gyri, the anterior cingulated gyrus and the insula (Miller, 2008). By using Transcranial Magnetic Stimulation, Hamdy and his colleagues showed that swallowing is bilaterally but asymmetrically represented in the cortical hemispheres, and that this representation is unrelated to handedness. If a stroke involves the dominant swallowing centre, dysphagia is highly likely, though this has been seen to resolve if the non-affected side subsumes the functions of the dominant centre (Hamdy, Aziz, Rothwell, Singh, Barlow, Hughes, Tallis & Thompson, 1996).

A cortical stroke may interfere with motor planning of the swallow. Large lesions may involve association or projection tracts of the brain, penetrating into the internal capsule. Significant dysphagia is commonly associated with a TACI stroke (Langdon, 2007; Sundar, Pahuja, Dwivedi, Yeolekar, 2008; Langdon, 2010). Stroke that occurs in the right hemisphere has been shown to impact on the pharyngeal phase of the swallow, with impairment to initiation and duration and increased frequency of penetration and aspiration seen (Robbins, Levine, Maser, Rosenbek & Kampster, 1993), while strokes affecting the left hemisphere result in impairment in pharyngeal transit and longer oral transit (Miller, 2008).

For many patients with unilateral cortical strokes that affect the dominant swallowing centre, dysphagia is transient, with a large percentage recovering their ability to eat and swallow very quickly. Around 50% of patients admitted with strokes demonstrate dysphagia (Gordon, Hewer & Wade, 1987; Smithard, O’Neill, England, Park, Wyatt, Martin & Morris, 1997; Broadley, Croser, Cottrell, Creevy, Teo, Yiu, Pathi, Taylor & Thompson, 2003). This incidence tends to resolve by the end of the 5-7 days post stroke once acute edema and ‘cerebral shock’ start to resolve (Broadley et. al., 2003). Patients who have bilateral cortical strokes tend to have more severe and prolonged dysphagia; possibly due to the impairment affecting both hemispheres and precluding the subsumption of swallowing function by an unimpaired swallowing representation.

A cortical stroke patient who presents with dysphagia may demonstrate some or all of the following:
Dysphagia and Respiratory Infections in Acute Ischemic Stroke

- Facial droop
- Difficulty controlling saliva/secretions
- Slurred speech (dysarthria)
- Dysphasia/aphasia
- Weak or impaired cough
- Dysphonia
- Impaired conscious level

Any of these, or a combination of these, can impact adversely on the voluntary and reflexive aspects of the normal swallow and should be investigated and treated. This assessment is usually performed by a Speech and Language Pathologist. Formal dysphagia screening programmes for acute stroke patients are associated with a significant decrease in the risk of pneumonia and should be offered to all stroke patients (Hinchey, Shepherd, Furey, Smith, Wang & Tonn, 2005). There has been consideration in the past that patients who present with an impaired gag reflex are at high risk of swallowing problems or aspiration. The gag reflex should not be considered to be predictive of dysphagia: published evidence clearly shows that there is little or no relationship between the gag reflex and the ability to swallow safely (Smithard & Spriggs, 2003).

2.3.2 Brainstem lesions

In the brainstem, there are motor nuclei that are responsible for acting as swallowing Central Pattern Generators (CPG). The main motor nuclei involved in swallowing are the hypoglossal motor nucleus and the nucleus ambiguus. These contain motoneurons, which innervate the intrinsic and extrinsic muscles of the tongue, such as the genioglossus, geniohyoid, styloglossus and hyoglossus, and the pharynx, larynx, and esophagus (Jean, 2001). Swallowing neurons are located in two main brain stem areas:

1. In the dorsal medulla (within the nucleus tractus solitarius) (NTS) and the adjacent reticular formation, where they form the dorsal swallowing group (DSG)
2. In the ventrolateral medulla, just superior to the nucleus ambiguus, where they form the ventral swallowing group (VSG)

Anatomically, swallowing neurons are located in the same sites as neurons that belong to CPGs involved in respiration and cardiovascular regulation (Jean, 2001). Both breathing and swallowing share some interneurons. This may help to explain the close relationship between breathing and swallowing. This close relationship may be affected by an ischemic stroke in the brainstem, predisposing the person to aspiration and dysphagia.

Brainstem strokes may account for up to 15% of all strokes (Kruger, Teasell, Salter & Hellings 2007). They have been associated with severe and persisting dysphagia, although this is by no means seen in every patient who has a stroke involving the brainstem. A patient who has experienced a brainstem stroke usually presents quite differently to one who has had a cortical stroke. Commonly seen dysfunction includes hemi- or quadriplegia, ataxia, dysphagia, dysarthria, gaze abnormalities and visual disturbances. In contrast to hemispheric lesions, new onset of cortical deficits, such as aphasia and cognitive impairments, are absent. Brainstem stroke patients may demonstrate some other characteristic clinical features, including

- Dysarthria
- Vertigo, nystagmus, nausea and vomiting, due to involvement of the vestibular system
- Visual field loss or visuospatial deficits if there is occipital lobe involvement

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Common findings observed in patients with vertebrobasilar stroke include an abnormal level of consciousness, as well as hemiparesis or quadriplegia. Pupillary abnormalities and oculomotor signs are common, and bulbar manifestations, such as facial weakness, dysphonia, dysarthria, and dysphagia, occur in more than 40% of patients (Kaye & Brandstarter, 2009).

 Patients with brainstem lesions tend to demonstrate the most prolonged course of recovery or poorest outcomes. In an early study of dysphagia which reported on four patients with strokes involving the brainstem, two patients subsequently died, while the other two had resolution of their swallowing impairment by 25 days post onset and were discharged home (Gordon, Hewer & Wade, 1987). In a case series over a six year period, Chua & Kong (1996) reported 21 of 53 patients (40%) demonstrated dysphagia on admission, but did make some progress during their stay at a rehabilitation facility.

3. The time course of dysphagia

While dysphagia incidence is very high in stroke patients who are admitted to hospital, there tends to be a sharp decrease in prevalence over a short period, usually in the first few days to a week.

3.1 Studies of dysphagia in acute stroke patients

In an early study of dysphagia in stroke, (Gordon, Hewer & Wade, 1987) reported on a cohort of 91 stroke patients. Forty one patients in their study (45%) had swallowing problems on admission to hospital. This study used a water swallow test; bedside swallowing examinations have been found to be less sensitive than instrumental evaluation in determining the true incidence of dysphagia and aspiration, although instrumental evaluation tends to select only those patients with conscious level good enough to tolerate testing. The reported duration of dysphagia in survivors was

<table>
<thead>
<tr>
<th>Duration</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>8 days or less</td>
<td>15</td>
</tr>
<tr>
<td>9 - 14 days</td>
<td>3</td>
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<tr>
<td>14 – 40 days</td>
<td>3</td>
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</table>

Kidd examined a cohort of 60 acute stroke patients using videofluoroscopy and found 25 (42%) were aspirating at 72 hours post stroke, with resolution of aspiration in 22 of 25 patients by 3 months post stroke (Kidd, Lawson, Nesbitt & McMahon, 1995). Another study which followed 121 acute stroke patients found 61 (51%) had dysphagia on admission to hospital. When reviewed at 7 days post stroke, dysphagia had resolved in a significant number of patients, with only 28 still demonstrating swallowing impairment. By six-months post stroke, this had decreased further and dysphagia persisted in only 6 of the original 61 patients with swallowing impairment on admission (Smithard, O’Neill, England, Park, Wyatt, Martin & Morris, 1997).

Table 1 below clearly shows the decreasing prevalence of dysphagia during the first week post stroke, with a reduction from 51% to 27%, although it should be noted that this reported prevalence included cases of dysphagia that began during the first week post stroke, presumably from an extension of the original stroke, or a new event.
Table 1. Number of dysphagic patients at different time points in the study by Smithard et al., (1997).

<table>
<thead>
<tr>
<th>Day</th>
<th>N</th>
<th>Dysphagic (%)</th>
<th>New</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>121</td>
<td>61 (51)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>113</td>
<td>33 (39)</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>111</td>
<td>35 (32)</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>105</td>
<td>43 (39)</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>110</td>
<td>28 (27)</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>28</td>
<td>105</td>
<td>18 (17)</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>180</td>
<td>73</td>
<td>8 (11)</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Using a combination of videofluoroscopy and bedside swallowing examination, Mann, Hankey & Cameron (2000) reported that aspiration was present in 49% of a cohort of 128 acute stroke patients. By six months post stroke, 97 of 112 survivors had returned to their pre-stroke diet (Mann, Hankey & Cameron, 1999).

Daniels, Ballo, Mahoney and Foundas (2000) reported on a cohort of 56 ischemic stroke survivors and noted that, although initially 38 (68%) presented with moderate to severe dysphagia, at the time of their discharge from hospital 52 of 54 survivors consumed a regular diet, one required food to be diced and one remained on enteral feeding.

Steinhagen, Grossman, Benecke and Walter (2008) reported on a cohort of 60 patients with ischemic strokes. This cohort demonstrated an incidence of pneumonia of 39 patients: median time to infection was 3 days (1-16 days).

In a large cohort study of 369 stroke patients, 125 of 330 survivors (38%) demonstrated some degree of dysphagia on bedside examination at 7 days post stroke. Between 48 hours post stroke and seven days post stroke, dysphagia prevalence in acute ischemic stroke patients decreased from 153 (46.4%) to 125 (37.9%). Even among the patients with the most seriously impaired swallowing function, those who were ‘Nil by Mouth’, there was a significant amount of swallow improvement, with the initial 63 patients who were ‘Nil by Mouth’ decreasing to 41 by 7 days post stroke (Langdon, Lee & Binns, 2010).

As the studies above show, dysphagia is extremely common following a stroke, but tends to resolve quite quickly in the majority of patients. It has been recommended that percutaneous endoscopic gastrostomy (PEG) tubes be considered for those patients with severe dysphagia that persists beyond 7 to 10 days post stroke if the treating medical team feels the patient is likely to survive (Broadley et. al., 2003). Previous studies have demonstrated a relatively consistent mortality rate of around 15% of all acute stroke patients (Gordon, Hewer & Wade, 1987; Aslanyan et. al., 2004; Mann, Hankey & Cameron, 1999; Langdon, Lee & Binns, 2010).

4. How good management of dysphagia prevents respiratory infections

In the early acute phase of a stroke, quality management of dysphagia is focused upon ensuring that patients’ nutrition and hydration requirements are appropriately met, and that they receive medications. This needs to be done in such a way that aspiration is prevented or minimised. Stroke unit care using a multidisciplinary team with expertise in management of this population has been shown to be responsible for improved outcomes for patients.

There have been few randomized control trials of dysphagia management: this is because having a control group where treatment or management of dysphagia is withheld is
unethical. In a review of the literature, Doggett, Tappe, Mitchell, Chapell, Coates and Turkelson (2001) reported an estimated incidence of 43% - 54% of stroke patients with dysphagia leading to aspiration, with approximately 37% of these patients going on to develop pneumonia. Acute-care stroke patients with dysphagia were estimated to experience malnutrition at a rate of 48%. The authors also reported that introduction of a dysphagia management program dramatically reduces pneumonia rates: one study reported frequency decreased from 6.7% (95% confidence interval 3.1% - 14%) to 4.1% (95%CI 1.8% - 9.3%) in the first year, and reduced to zero (95%CI 0% - 3%) in the second year.

4.1 Assessment of dysphagia
Optimal stroke care involves early dysphagia assessment: this often takes the form of an initial screening by medical or nursing personnel, with patients who fail the screen undergoing more thorough clinical assessment from a Speech-Language Pathologist, with the option of patients undergoing instrumental assessment. It has been argued that a reliable bedside assessment is useful in identifying patients at risk of nutritional compromise, aspiration and poorer outcomes (Smithard, et. al., 1996). The current gold standard of dysphagia assessment is the videofluoroscopic swallow study (also known as the Modified Barium Swallow Study), where patients are assessed using a moving x-ray, which is recorded to allow detailed analysis. Another alternative is a fibreoptic endoscopic evaluation of swallowing (FEES). Both assessments have been shown to have excellent reliability in detecting and assessing dysphagia.

The choice of instrumental examination should be made based upon the information that the clinician seeks to obtain from the test. Videofluoroscopy is the superior study for obtaining information about the oral phase of the swallow, and to quantify aspiration. It also provides clear visualisation of the opening of the upper oesophageal sphincter, and is very useful if a cricopharyngeal dysfunction or Zenker’s pharyngooesophageal diverticulum is suspected. Negative aspects of videofluoroscopy include

- the need for patients to sit upright during the examination, which makes it a difficult procedure for patients with impaired conscious level or poor sitting balance
- the exposure to radiation, albeit a small amount of less than 0.2 mSv per procedure
- the taste and density of barium that is added to the materials to be swallowed changes the properties of the food or liquid
- the captured image is a two-dimensional representation of a three-dimensional act

The FEES examination allows excellent visualisation of the structures of the pharynx and of the larynx. It can be carried out in patients with poorer conscious state, and is comparatively portable compared to the videofluoroscopy equipment, allowing a clinician to conduct the examination in the ICU or at bedside. FEES allows the clinician to determine whether there are pooled secretions in the pharynx, and whether these are being aspirated. Due to the nature of the equipment, during the actual moment of swallowing, the view is obscured due to the action of pharyngeal squeeze against the fibreoptic camera. This phenomenon is called ‘whiteout’. Judgements regarding the oral phase of the swallow are not possible, and it is not possible to quantify the amount of material that is aspirated. FEES does allow for a much longer examination, as there is no radiation exposure associated with the procedure, so it is a much better instrument to identify the effects of fatigue over the course of a meal.

Once a diagnosis of dysphagia has been made, there is liaison between members of the multidisciplinary team in how best to manage the patient’s swallowing impairment. This involves communication between
4.1.1 Nursing
Nursing are responsible for the minute-to-minute management of the acute stroke patient. They are the eyes and ears of the ward. Nurses will be able to assist the patient with feeding and with drinking, if assistance is required. This is a skill, as careful assistance helps in preventing aspiration. Langmore et al., (1998) showed that being dependent for feeding was associated with an increased risk of developing aspiration pneumonia of nearly 20 times greater than those subjects who were able to feed themselves. Other important tasks that are the responsibility of the stroke patient’s nurse are monitoring the performance during the meal. In acute stroke, fatigue is often a problem for the patient, and their ability to protect their airway may decline as they get increasingly tired. The patient may have demonstrated excellent control and airway protection during their swallowing assessment with the Speech Language Pathologist: this may change rapidly. A proactive nurse who is aware of the variability of the patient’s swallow may decide that a reassessment is needed and act to ensure that an aspiration event is avoided. The nurse may assist the patient with finishing a meal if they are becoming too fatigued to feed themselves, or she may monitor the patient’s ability to maintain sitting balance throughout the duration of the meal, and re-position them into optimal sitting position if this is required. Nurses are responsible for one of the most important factors that contribute to the stroke patient’s wellbeing – oral hygiene and care. A patient’s nutritional status and immune function are closely linked. Poor oral health is associated with poor nutrition in the elderly (Mojon, Budtz-Jorgensen & Rapin, 1999). The association between poor oral hygiene and development of pneumonia is discussed in greater detail later in this chapter.

4.1.2 Speech language pathologist
The Speech Language Pathologist is well placed to assess, manage and treat the stroke patient’s dysphagia. They may also determine the presence of communication difficulties and assess and treat these. Communication impairment is common in acute stroke. This may be as a result of the stroke affecting the language areas of the brain, with the person presenting with aphasia. The person may demonstrate impairment to the motor planning of speech, with verbal dyspraxia resulting. Cranial nerve lesions may cause dysarthria, with the patient presenting with difficulty with execution of the smooth, controlled muscular movements required for precise articulation. These communication difficulties may further impact on an acute stroke patient’s eating and drinking: for example, an aphasic patient who is unable to read the hospital menu may require special assistance in completing their meal requests.
It is a recommendation that stroke patients be screened for dysphagia upon admission to hospital, due to the very high initial incidence of dysphagia. If dysphagia is suspected, a more comprehensive examination by the Speech Language Pathologist should be requested. As well as assessing the patient’s swallowing impairment, the Speech Language Pathologist may begin to treat the dysphagia. For some acute stroke patients, a fairly normal diet can be followed utilising strategies that overcome the impairments caused by the stroke. For example, for some patients a postural modification of tucking the chin slightly when swallowing helps to compensate for a slight delay in the triggering of the swallow.

Studies have shown that early intervention for dysphagia in acute stroke is efficacious. In a randomized control trial of 306 acute stroke patients assigned to ‘usual care’, ‘low level intervention’ or ‘high level intervention’, Carnaby, Hankey and Pizzi (2006) showed a significantly greater proportion of dysphagic patients who received the high level intervention had returned to their pre-morbid level of swallowing function by six months post stroke.

4.1.3 Pharmacist
A thoughtful review of a stroke patient’s medications by a Clinical Pharmacist will be of benefit, particularly for the dysphagic patient. If the Speech Language Pathologist has determined that the patient has difficulty swallowing medications, the Pharmacist may be able to suggest alternative methods of delivering pharmacology. This may include transdermal, liquid form, intravenous or intra muscular or medications may be administered via suppository.

Another reason that the Pharmacist is an important member of the multidisciplinary team is to review medications to determine which may be ceased, or if a medication interaction is likely. Potential for an adverse drug reaction occurring has been estimated at 6% if two medications are taken, rising to 50% for five different medications and 100% if eight or more different medications are taken (Larsen & Martin, 1999). Polypharmacy is a problem in elderly patients. Langmore, et.al. (1998) studied a cohort of 189 elderly male subjects and demonstrated that those who were taking 6 or more different medications per day were more likely to develop aspiration pneumonia. One study in 1998 found that a typical 65-year old patient will be taking two to three medications daily, while those that are in high-level residential care take an average of eight medications each day (Barczi, Sullivan & Robbins, 2000).

In a cohort study of 330 acute stroke survivors, 109 patients were found to be taking 8 or more different medications per day, with the majority of these 109 patients aged between 65 and 84 years (n=75). Langdon, (2007) noted that of the patients taking 6 or more different medications daily, 30 (27.5%) were later diagnosed with a respiratory infection. Chi-square test indicated a significant association between taking 6 or more medications daily and developing respiratory infections, $\chi^2(1)=18.143$, p<.0001, with an associated Odds Ratio of 2.08 (95% CI 1.54, 2.79).

<table>
<thead>
<tr>
<th>Number of Medications per Day</th>
<th>Pneumonia?</th>
<th>0-2</th>
<th>3-5</th>
<th>6-8</th>
<th>9 or more</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>13</td>
<td>8</td>
<td>16</td>
<td>14</td>
<td>51</td>
<td></td>
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<td>No</td>
<td>96</td>
<td>104</td>
<td>58</td>
<td>21</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>112</td>
<td>74</td>
<td>35</td>
<td>330</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Association between multiple medications and subsequent development of respiratory infections in acute stroke patients.
4.1.4 Dietitian
Dehydration and malnutrition are common in stroke patients, due to dysphagia, immobility and communication difficulties. These are worst in the first week after a stroke and are associated with poorer outcomes (NSF Clinical Guidelines, 2010). The dietitian’s role in managing the acute stroke patient is to ensure that their nutrition and hydration are being optimally maintained. This may take the form of an enteral feeding regime, an oral feeding regime that takes into account special dietary needs (diabetic, renal, low sodium etc.) or a transitional feeding regime, where the patient is moving from enteral to full oral feeding. Speech Language Pathologists and Dietitians work closely to achieve optimal outcomes for the acute stroke patient. Patients who are re-commencing oral nutrition will require a transitional feeding regime to ensure that they continue to receive adequate hydration and calories: this may mean partial oral diet; with the Dietitian re-adjusting enteral feeding regimes based on how much is consumed orally.

4.1.5 Medical
The medical team’s role includes liaising with the patient’s GP or the rehabilitation facility to ensure seamless transition of care. In an acute stroke unit, the medical team is led by a Consultant Neurologist, who supervises the management of patients with support from more junior medical colleagues.

The medical team is responsible for the overall coordination of the acute stroke patient’s care. They will monitor the person’s recovery, and ensure that they lead and coordinate the multidisciplinary team (SIGN, 2002). Their day to day responsibilities include ordering tests and medications and reviewing these to ensure that the patient’s physiological homeostasis is maintained.

4.1.6 Occupational therapist
The role of the Occupational Therapist in managing dysphagia in acute stroke patients is to assist with the promotion of self-feeding. Adaptive equipment may be needed to maximise functional independence. This includes angled cutlery, built up plates and equipment that will assist the patient overcome hemiplegia in preparing meals. Occupational Therapists will also work to provide equipment that optimises the patient’s positioning, such as customising wheelchairs to compensate for poor trunk control.

4.1.7 Physiotherapist
The Physiotherapist will work towards the patient regaining movement on the hemiplegic side, and will also contribute to respiratory health. If a patient has a weak cough or has developed a chest infection, the Physiotherapist will assist with clearance of purulent secretions.

Improving movement and control allows stroke patients to sit upright and eat or drink independently and also to perform their own oral care. Being dependent for feeding and/or oral care are factors that have been shown to contribute to patients developing aspiration pneumonias (Langmore, et. al., 1998).

Physiotherapists will assist the patient to regain mobility; early mobilisation is a feature of stroke unit care which is associated with benefits to the patient (SIGN, 2002). In a cohort of 330 stroke survivors, severely impaired mobility on admission to hospital was strongly associated with subsequent development of infections, with an Odds Ratio of 2.56 (95% CI 2.01, 3.34) (Langdon, Lee and Binns, 2010).
4.1.8 Family members
In an acute ischemic stroke, stress and anxiety are frequently experienced by family members. Stroke patients and their families and carers should be offered information about stroke, its treatment and rehabilitation (SIGN, 2002). Good quality information provided to stroke survivors and family members on an ongoing basis has been shown to be beneficial in minimising stress and depression caused by the complex adjustments that need to be made by the patient and their family (NSF Clinical Guidelines, 2010).

4.1.9 Social worker
Stroke may cause additional anxiety and depression among patients and their families and carers as it may mean unexpected absence from work, with the financial implications associated with this. There may be a complicated array of government departments to negotiate. In addition, the stroke patient may require high-level care due to ongoing disability. Social workers will bring their expertise to assist patients and their families in accessing benefits and services. They also bring expertise in counselling, and may be able to assist with families and patients’ adjustment to the changes that a stroke has necessitated.

5. Additional risk factors for respiratory infections in acute ischemic stroke patients
There may be other factors that the multidisciplinary team need to consider in order to provide the acute stroke patient with optimal care. These are factors other than dysphagia that may contribute to patients’ developing respiratory infections during the acute stroke period. They include
- Ventilators
- Tracheostomy
- Oral Hygiene
- Nasogastric tubes
- Gastroesophageal Reflux
These risk factors are briefly discussed below.

5.1 Ventilators
Patients who require mechanical assistance to breathe are at an increased risk of respiratory complications. Ventilator-assisted pneumonia (VAP) is a common occurrence in Intensive Care Units (ICU), with specific organisms (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*) associated with the highest incidence. VAP is associated with the duration of mechanical ventilation. Other factors associated with an increased risk of VAP developing include reintubation, tracheostomy, nasogastric tube, enteral feeding, supine positioning and use of gastric pH-altering agents (Cook & Kollef, 1998).

5.2 Tracheostomy
A tracheostomy tube may be needed for patients who are slow to wean from ventilators. Generally, a cuffed tube is inserted, as this helps prevent aspiration of saliva and secretions. However, it has been demonstrated that an inflated tracheostomy cuff is more likely to lead to patients aspirating (Davis, Bears, Barone, Corvo & Tucker, 2002). Tracheostomy is
associated with a high incidence of silent aspiration (aspiration without clinical signs), and it has been argued that all patients with tracheostomy should undergo instrumental examination of their swallowing function (Matthews & Coyle, 2010).

5.3 Oral hygiene
The mouth is colonised by over 400 different species of bacteria (Brook, 2003). Normal saliva has a concentration of $10^8$ organisms per millilitre, which can increase to $10^{11}$ per millilitre in a person with gingivitis (Mojon, 2002). Langmore et al., (1998) demonstrated that poor oral hygiene and being dependent for oral care are both associated with a significantly increased risk of patients developing aspiration pneumonia. One small study looked at residents of chronic care and compared them with community-dwellers. Respiratory pathogens were present in dental plaque for 25% of the care facility residents, with 4 of these 7 residents classified as ‘positively colonised’, compared to none of the people living independently (Russell, Boylan, Kaslick, Scannapieco, Katz, 1999).

Elderly patients and hemiplegic patients may require assistance for oral care, which may mean that this is sub-optimal. Dentures of 50 elderly patients who received help from carers to maintain their dentures were analyzed. Aerobic bacteria were isolated from all 50 patients, with 23 of 50 demonstrating dental plaque that was colonised by potential respiratory pathogens (Sumi, Sunakawa, Michiwaki, Sakagami, 2002).

Acute stroke patients with dysphagia are at risk of aspirating their saliva. If this saliva is colonised by bacteria, these bacteria will be aspirated into the lungs, where they may overwhelm respiratory defences. The patient may then proceed to develop a respiratory infection. A study of 95 patients with severe aspiration pneumonia took bronchial secretion samples and compared this to the pathogens found in dental plaque. They found that the bacteria in the respiratory samples and those found in plaque were the same (El-Solh, Pietrantoni, Okada, Bhat, Zambon, Aquilina, and Berbery, 2004).

Stringent oral care and strategies to minimize reflux in the acute stroke population has the potential to reduce respiratory infections (Langdon, Lee & Binns, 2009).

5.4 Nasogastric tubes
Colonisation by bacteria has been reported to have a high incidence in patients fed by nasogastric tubes. In one study of 103 elderly patients living in residential care facilities, those patients being fed using nasogastric tubes had a much greater incidence of colonisation with gram-negative bacteria, with 34 (64%) of tube-fed patients compared to 4 (8%) of orally fed patients showing colonisation. The pathogen most frequently recovered from the nasogastric tubes was *Pseudomonas aeruginosa* (Leibovitz, Dan, Zinger, Carmeli, Habot & Segal, 2003).

One prospective cohort study investigated 100 acute stroke patients tube fed due to dysphagia: 44% were diagnosed with pneumonia in the 2nd or 3rd day after onset. The authors concluded nasogastric tubes offered limited protection against aspiration pneumonia in dysphagic stroke patients (Dziewas, Ritter, Schilling, Konrad, Oelenberg, et. al., 2004).

Langdon, Lee and Binns (2009) studied acute ischemic stroke patients and found the incidence of overall infections (respiratory, urinary tract and other infections) in stroke patients who were tube fed was 69%, with 51 infections occurring in 74 patients. Thirty of these infections were respiratory. They reported a significant effect of time-to-event, with the majority of respiratory infections diagnosed on days 3 and 4 after stroke, and 39/51
(76%) of all infections diagnosed in tube-fed survivors occurring by day 7 after stroke. The relationship between tube feeding and subsequent development of respiratory infections is shown in Figure 2.

**Fig. 2. Relationship Between Tube Feeding and Respiratory Infections in the First Month Following Stroke.**

It has been hypothesized that nasogastric feeding tubes actually predispose patients to aspiration by:

1. Loss of anatomical integrity of the upper and lower oesophageal sphincters
2. Increase in frequency of transient lower oesophageal sphincter relaxations
3. Desensitization of the pharyngoglottal adduction reflex (Gomes, Pisani, Macedo & Campos, 2003).
In addition, presence of a feeding tube may lead to formation of biofilms which become colonized by bacteria, found to have an incidence of 60% of day one and 100% on subsequent days (Leibovitz, Baumoehl, Steinberg & Segal, 2005).

Data from the FOOD trial was inconclusive on efficacy of nasogastric feeding in early stroke, however it has been suggested that enteral feeding need not begin in the first few days after a stroke (Donnan & Dewey, 2005). Langdon, Lee and Binns suggested that it may be appropriate to hold off from instituting enteral feeding in the first 3-4 days post stroke, as this appears to be a period when patients are especially susceptible to developing respiratory infections.

5.5 Gastroesophageal reflux

Patients who have gastroesophageal reflux (GOR) and also a poor conscious state are considered at very high risk of aspiration, particularly if they have a large volume of gastric content (DeLegge, 2002). Langdon, Lee and Binns (2010) found that subjects with a prior history of GOR had a significantly increased risk of developing respiratory infections in acute stroke, with 19 of 55 patients with pre-existing GOR developing respiratory infections OR 1.89 (95% CI 1.23, 2.9), p=.01.

It may be that acute stroke affects gastric motility due to the neurological insult, predisposing patients to an increased risk of reflux. Oesophageal manometry studies performed in five patients with dysphagic stroke and PEG tubes found lower oesophageal sphincter dysfunction occurred in 80% with significant gastroesophageal reflux seen in two patients. One of these two patients recovered swallow function and resumed oral feeding, while the other developed three bouts of aspiration pneumonia and died four months after PEG insertion (Elphick, Elphic, Smith, DaCosta & Riley 2006). An earlier study examined 35 acute stroke patients with severe impairment requiring tube feeding and found lower oesophageal sphincter dysfunction in 24 patients; upper oesophageal sphincter function was lower than normal in 30 patients (Lucas, Yu, Vlahos & Ledgerwood (1999).

Positioning in stroke patients can be an important prophylactic measure for GOR events. Elphick et. al., (2006) found reflux events occurred significantly more frequently when patients were in either right lateral or supine position. Supine positioning is considered a risk factor for development of reflux-related and ventilator-assisted pneumonia (Cook & Kollef, 1998; Metheny, Chang, Ye, Edwards, Defer et. al., 2002).

6. A critical period of susceptibility to infection in acute ischemic stroke

Previous studies have shown that infection commonly occurs in the acute period immediately following a stroke. Gordon, Hewer & Wade (1987) reported that all eleven chest infections developed during the first seven days post stroke in their cohort of 91 dysphagic stroke patients. Mann, Hankey and Cameron (1999) reported 26/112 patients developed chest infections during the six-month post stroke period, with 10/26 diagnosed during the first week post-onset.

In the Copenhagen study, 24.5% of female subjects and 13.6% of males developed early infections (Kammersgaard, Jorgensen, Reith, Nakayama, Houth, Weber, Pedersoe & Olsen, 2001). The GAIN trial noted that the majority of infections occurred in the first week of the acute stroke period (Aslanyan, 2004). In an Australian cohort of 330 ischemic stroke survivors, 115 infections were treated in the first month post stroke. Sixty (52%) of these infections were diagnosed by the third day post admission. During the first seven days post stroke, 51 infections in females, and 45 infections in males were diagnosed (Langdon, Lee &
Binns, 2010). These represent 83% of all the infections treated in the first month, and demonstrate a strong argument that the first week post stroke is associated with a greater period of susceptibility to infections.

Recent studies in animal models have suggested that stroke induces a severe depression of immune function, and predisposes patients to infections. This phenomenon, stroke induced immunodepression (SIDS) leads to lymphocytopenia and functional deactivation of monocytes and T-helper cells (Dirnagl, Klehmet, Braun, Harms, Neisel, et al., 2007). This has been shown to be strongly related to the infarct volume and stroke severity (Hug, Dalpke, Wieczorek, Giese, Lorenz et al., 2009).

In animal studies, stroke increases susceptibility to aspiration-induced pneumonia. In a murine model, control animals required at least a 3 order of magnitude increase in the numbers of bacteria required to induce pneumonia compared to mice with induced MCA stroke (Prass, Meisel, Hoflich, Braun, Halle, et al., 2003).

There is evidence that overactivation of the sympathetic nervous system occurs in the first two days post stroke in humans. Within 3 days of the initial insult, up to 61% of patients will become febrile, with the most common cause being infection. Of these infections, pneumonia is most commonly reported (Mergenthaler, Dirnagl & Meiser, 2004).

In a cohort of 330 stroke survivors, 81 cases of nosocomial infection were diagnosed in the first month post stroke. Of these 81 infections, 56 (69%) were diagnosed in the first week post stroke; 28 infections in males and 28 in female subjects. Female subjects demonstrated a definite peak of infections occurring on Day 3 post stroke, while males were diagnosed on Day 3 and Day 4. Once the first 7 days post stroke were past, infection rates declined significantly for both genders (Langdon, Lee & Binns, 2010). Prass and colleagues (2006) have suggested that a stroke causes a shift from harmless aspiration to severe potentially life threatening infection.

7. Conclusions

Respiratory infections and urinary tract infections are the most common infections in acute stroke patients. Studies indicate that patients are particularly vulnerable to infection in the very acute period of their stroke: the first few days following an infarct. During this period it may be appropriate for patients to be ‘Nil by Mouth’ if they are at high risk of aspiration. Hydration can be maintained using either intravenous hydration or hypodermoclysis (subcutaneous fluids), while medications can be administered transdermally, intravenously or by suppository.

Multidisciplinary care that concentrates on minimizing risk factors for infection is essential. These include minimising aspiration risk with good dysphagia management, positioning and chest care, early mobilisation, stringent oral hygiene and encouragement of self-feeding.

While dysphagia is very common in the acute stroke period, for the majority of patients it is a transitory phenomenon and they can look forward to resuming normal eating and drinking within a short period of time. For those patients with more severe and persistent dysphagia, good management will help prevent respiratory complications. Early referral to a Speech Language Pathologist with expertise in dysphagia assessment and rehabilitation will ensure that patients have their best possible chance of return to eating and drinking normally - one of life’s great pleasures as well as an act essential to maintaining life.
8. References


Acute Ischemic Stroke


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Despite significant technological advances in recent years, their impact on our overall health and social, well-being is not always clear to see. Perhaps, one of the best examples of this can be highlighted by the fact that mortality rates as a result of cerebrovascular diseases have hardly changed, if at all. This places cerebrovascular diseases as one of the most prominent causes of both disability and death. In Cuba, for instance, a total of 22,000 cases of cerebrovascular diseases are reported each year in a country where life expectancy should increase to 80 years in the near future. In such a situation, to have a book that includes in a clear and summarized way, a group of topics directly related to the preclinical investigations advances and the therapeutic procedures for the cerebrovascular disease in its acute phase constitutes a useful tool for the wide range of the contributors to this affection's problems solution. In this group is included students, professors, researchers, and health policy makers whose work represents one of the greatest social and human impact challenges of the XXI century basic and clinical neurosciences.

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