6. Medical Complications Post Stroke

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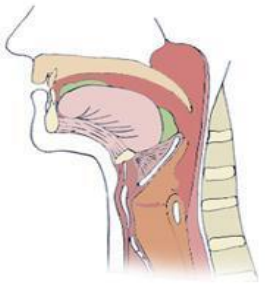
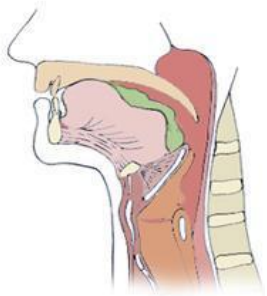
6.1.1 Normal Swallowing



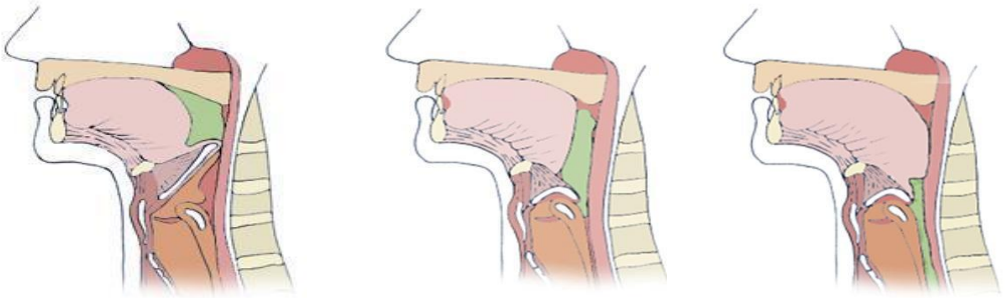
Consists of 4 Phases:

Oral Preparatory Phase
Food in the oral cavity is manipulated and masticated in preparation for swallowing. The back of the tongue controls the position of food, preventing it from falling into pharynx.

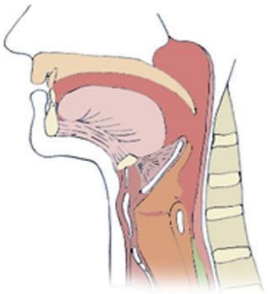
Oral Propulsive Phase
The tongue elevates and occludes the anterior oral cavity. The tongue then compresses the bolus toward the oropharynx. This triggers the pharyngeal swallow. Problems at this stage lead to drooling and pocketing.



Pharyngeal Phase
This phase involves complex and coordinated movements of the tongue and pharyngeal structures to propel the food bolus into the esophagus while protecting the airway. This is largely a reflex action. Aspiration is most likely to occur during this phase. This phase requires soft palate elevation and velopharyngeal port closure to prevent regurgitation into the oropharynx. Laryngeal elevation with folding of the epiglottis and vocal cord adduction serves to prevent aspiration along with coordinated pharyngeal constriction and cricopharyngeal relaxation. Difficulties at this stage are characterized by choking, coughing and aspiration.



Esophageal Phase
This is the final phase and involves coordinated contractions of the esophagus muscle move the bolus through the esophagus toward the stomach.



Definitions of Abnormal Swallowing Post-Stroke

- Dysphagia = difficulty with swallowing.
- Penetration = entry of material into the larynx but not below the true vocal cords.
- Aspiration = entry of material into airway below level of true vocal cords.

6.1.2 Dysphagia Post-Stroke

Dysphagia post stroke is very common with estimates varying widely from 19%-65% in the acute stage of stroke (Hebert et al. 2016). Finestone et al. (1995) found 47% of rehab admissions had dysphagia, and 49% were clinically malnourished. Dysphagia can lead to malnutrition and dehydration. Malnutrition is associated with worse functional outcomes. Dysphagia is associated with aspiration.

Signs and Symptoms of Dysphagia

- Choking on food.
- Coughing during meals.
- Drooling or loss of food from mouth.
- Pocketing of food in cheeks.
- Slow, effortful eating.
- Difficulty swallowing pills.
- Avoiding foods or fluids.

Think dysphagia when a patient is complaining of:

1. Food sticking in throat.
2. Difficulty controlling liquids and saliva.
3. Problems swallowing.
4. Reflux or heartburn.

Conclusions

Dysphagia is characterized by reduced coordination of oropharyngeal muscles potentially due to a reduction of cortical connectivity which may have a negative impact on factors of pulmonary function. Furthermore, oral weakness of the facial, palatal and pharyngeal muscles can contribute to dysphagic symptomology.

6.1.3 Aspiration Post-Stroke

Prospective studies of acute strokes (< 5 days) show 21%-42% aspirate early on. Aspiration rate improves to 8%-15% at 3 months post stroke

Risk Factors Associated with Aspiration Difficulties Post-Stroke

- Brainstem stroke.
- Difficulty swallowing oral secretions.
- Coughing/throat clearing, choking or wet gurgly voice quality after swallowing water.
- Weak voice and cough.
- Recurrent lower respiratory infections.
- Aspiration or pharyngeal delay on VMBS.
- Immunologically compromised or chronic lung disease.
- Poor oral hygiene.

Conclusions

The incidence of aspiration in the acute phase of stroke varies from 16% to 52%. Silent aspiration occurs in 8% to 27% of acute stroke patients. Of identified aspirators, 20% to 67% developed silent aspiration.

Factors indicative of the development of aspiration include: a delayed swallow reflex, reduced peristalsis, respiratory tract infection, abnormal volitional coughing and cough with swallow, dysphonia, soft palate dysfunction, and facial hypesthesia.
Tested factors that may not be predictive of aspiration include: poor oral motility and bedside evaluations (which were associated with the identification of non-aspirators).
While silent aspiration shows a lower incidence among acute stroke patients than aspiration, both are prevalent and reliably identified.

6.1.4 Pneumonia Post-Stroke

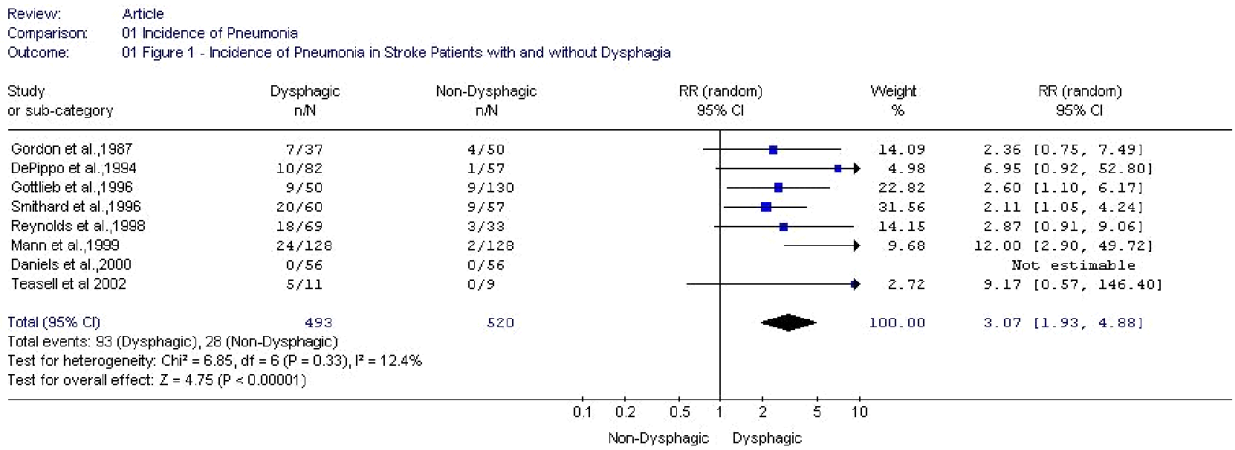
The diagnosis of pneumonia varies with the criteria used and population group studied. This accounts for the wide reported variance in older studies with 7% - 32% incidence reported in the acute stage. Early and aggressive management of dysphagia has made pneumonia much less common in stroke patients. Previously up to 20% of individuals with stroke-related dysphagia died during the first year post-stroke of aspiration pneumonia but this has dramatically improved with aggressive management of dysphagia.

Association of Dysphagia or Aspiration and Pneumonia Post-Stroke
Aspiration alone does not lead to pneumonia. Aspiration of small amounts of saliva during sleep occurs in ½ of elderly. Pneumonia is likely to occur when the lung's natural defenses are overwhelmed by excessive or toxic aspirate.

Table 1. Relationship between Dysphagia and Pneumonia

Study	Incidence of Pneumonia Among Patients with and without Dysphagia	OR (95% CI, fixed effects model)
Gordon et al. (1987)	7/37 vs. 4/50	2.63 (0.72 to 9.96)
De Pippo et al. (1994)	10/82 vs. 1/57	7.78 (0.97 to 62.6)
Gottlieb et al. (1996)	9/50 vs. 9/130	2.95 (1.10 to 7.94)
Smithard et al. (1996)	20/60 vs. 9/57	2.67 (1.09 to 6.50)
Reynolds et al. (1998)	18/69 vs. 3/33	3.53 (0.96 to 12.99)
Teasell et al. (2002)	5/11 vs. 0/9	-
Falsetti et al. (2009)	1/89 vs. 8/62	13.04 (1.44 to 286)
Combined estimate	70/398 vs. 34/398	2.28 (1.44 to 3.61)

Comparison of Pneumonia Frequency in Stroke Patients between Dysphagia and Non-Dysphagia



Conclusions

Stroke severity, level of consciousness, age, oral hygiene and other factors contributing to the aspiration of bacterial laden secretions and refluxed material are major indicators for increased risk of pneumonia.

6.1.5 Dysphagia and Nutritional Outcome Measures

There is a wide range of dysphagia and nutritional rehabilitation outcomes measures which have been utilized. They can be categorized into broad categories listed below:

Table 2. Lower Extremity Assessment and Outcome Measures

Category	Rationale	Individual Assessment Tools
Pharyngeal Phase	Assessed aspects of the pharyngeal phase of swallowing.	• Aspiration-Penetration Scale (aka the 8-point aspiration-penetration) • Duration of Stage Transition • Episodes of Aspiration • Higher Incidence of Aspiration • Hyoid Elevation • Incidence of Aspiration • Inter Swallow Interval • Laryngeal Elevation • Latency of Swallow • Normalized Residue Rating Scale • Pharyngeal Response • Pharyngeal Transit Time (PTT) • Swallow Response Time (aka Swallow Speed)
Esophageal Phase	Assessed aspects of the esophageal phase of swallowing.	• Cricopharyngeal Opening Duration • Esophageal Sphincter Function
Oral Phase	Assessed aspects of the oral phase of swallowing.	• Oral Transit Time (OTT) • Tongue Strength (Overall)
Dysphagia Evaluation	Assessed global tests of swallowing function, oral hygiene and eating behaviours in dysphagic individuals.	• Dysphagia Outcome Severity Scale (DOSS) • Dysphagia Severity Rating Scale (DSRS) • Functional Dysphagia Scale • North-western Dysphagia Patients Checklist • Repetitive Saliva Swallow Test

		• Repetitive Saliva Swallow Test • Mann Assessment of Swallowing Ability • Dysphagia limit test • Australian therapy outcome measures – Swallowing Scale • Functional Oral Intake Scale (FOIS) • Degree of Dysphagia • Proportion of Patients Returned to a Normal Diet in 6mos • Proportion of Patients with Oral Feeding Tolerability • Standardized Swallowing Assessment (SSA) • Swallow Function Scoring System (SFSS) • Swallowing Function • Total Oral Transit Time • Videofluroscopic Swallowing Study (VFSS) • Kubota Water Swallow Test • Volume Viscosity Swallow Test • Actual Nutrition Status • Actual Nutrition Status • Neurological examination of dysphagia
Respiratory Infections	Assessed respiratory sequelae of dysphagia including aspiration and pneumonia.	• Incidence of Chest Infection • Pneumonia Frequency • Reduction in Ventilator Associated Pneumonia • Higher Incidence of Aspiration Pneumonia
Lipid Consumption	Related to triglyceride body composition.	• Triglyceride levels • Cholesterol and Total Cholesterol levels • High Density Lipoprotein (HDL) • Daily Lipid Intake • Lipid Hydroperoxides • Low Density Lipoprotein (LDL)
Calorie Consumption	Assessed caloric intake and fluid intake.	• Proportion of Prescribed Feed Delivered • Total Fluid Intake • Caloric Intake
Protein and Carbohydrate Consumption	Amount of protein and carbohydrates consumed, usually daily.	• Protein Intake • Carbohydrate Intake • Carbohydrate-Protein Ratio
Vitamin and Mineral Consumption	Assessed the consumption of vitamin or minerals.	• Calorie-Nitrogen Deficit • 25-Hydroxyvitamin D Levels • Iron Intake
Body Composition	Different anthropometric measurements.	• Biceps Skinfold Thickness • Body Mass Index (BMI) • Mid-Arm Muscle Circumference (MUAC) • Triceps Skinfold Thickness • Waist Circumference • Weight Gain

Blood Glucose Management		• Fasting Glucose Level • Glucose Tolerance Test
Plasma Proteins	Deal with circulating protein levels in a participant's blood.	• Albumin Levels • Pre-Albumin • Transferrin • Hemoglobin
Blood Pressure	Measures of blood pressure.	• Systolic Blood Pressure • Diastolic Blood Pressure
Lymphocyte Count	Measure of neutrophil to lymphocyte concentrations	• Neutrophil-Lymphocyte Ratio
Activities of Daily Living	Assessed performance and level of independence in various everyday tasks.	• Barthel Index (BI) • Functional Independence Measure (FIM)
Stroke Severity	Assessed the severity of one's stroke through a global assessment of a multitude of deficits a stroke survivor may experience.	• Canadian Neurological Scale (CNS) • Modified Rankin Scale (mRS) • National Institutes of Health Stroke Scale (NIHSS) • European Stroke Scale (ESS)

Pharyngeal Phase

Duration of Stage Transition: Is also known as the initiation of the pharyngeal phase and is the time when the hyoid begins its anterior excursion. More precisely put, it is the time from which the bulls first passes the ramus of the mandible all the way until the beginning of maximum anterior hyoid excursion (Kim & McCullough 2007).

Episodes of Aspiration: Is a measure of how frequently a patient may aspirate within a given time period. Aspiration occurs when a patient ends up with food and/or fluid below the true vocal cords. It typically occurs when a patient has dysphagia leading to food/liquid going down the trachea (Matsuse et al. 1996).

Latency of Swallow: Is the amount of time that it takes for a patient to complete a swallowing action. Patients with dysphagia usually take a longer period of time to swallow compared to patients without dysphagia (Kobayashi et al. 1994).

Normalized Residue Rating Scale: is a measure designed to quantify the amount of residue present in the valleculae and the pyriform sinuses. It examines the amount of residue relative to the size of the valleculae of the participant. This method can more accurately determine the risk of residue overflow for a particular individual because it is relative to the available pharyngeal space and the size of the individual (Pearson et al. 2013).

Pharyngeal Transit Time (PTT): Is the amount of time it takes for the bolus to pass from the faucial arches, over the tongue and through the pyriform sinus into the esophagus. If PTT is increased (compared to a patient's age group), further testing is usually necessary (Nikhil et al. 2014).

Dysphagia Evaluation

Mann Assessment of Swallowing Ability: consists of 24 items, with each score being converted into a weighted 5- or 10-point score, which are then summed for maximum of 200 points. Based on the score, an individual can be categorized into no abnormality (170-200), mild (149-169), moderate (141-148) or severe (≤ 140) (Chojin et al. 2017).

Functional Oral Intake Scale (FOIS): Is a 7-point scale that evaluates how well a patient with dysphagia can consume liquids (1=no oral intake, 2=tube dependent with minimal/inconsistent oral intake, 3=tube supplements with consistent oral intake, 4=total oral intake of a single consistency, 5=total oral intake of multiple consistencies requiring special preparation, 6=total oral intake with no special preparation, but must avoid specific foods or liquid items, 7=total oral intake with no restrictions). It is typically evaluated by having patients consume liquids under the supervision of trained clinician (Crary et al. 2005).

Fiberoptic Endoscopic Evaluation of swallowing (FEES). This technique allows a trained clinician to insert a nasopharyngoscope into the patient and measure multiple swallows via a video monitor.

Videofluroscopic Swallowing Study (VFSS): Is a technique that is used to identify a patient's swallowing deficits in detail. A trained clinician uses radiography to view a patient's swallowing process in real time. This footage can then be played back to ensure a proper and adequate diagnosis. The videofluroscopic dysphagia scale (VDS) uses this study to grade various aspects of the swallow (Boesch & Deboer 2019).

Kubota Water Swallow Test: also referred simply as the water swallow test, has been modified several times since its inception. All procedures require an individual to take consecutive sips of water that (sometimes) increases in volume. Often, 3ml and/or 30ml are used as the volumetric amount. A score is given from 1-6 that grades the difficulty of swallow and any indication of airway obstruction (Horiguchi & Suzuki 2011).

6.1.6 Management of Dysphagia and Aspiration Post-Stroke

Goals of Dysphagia Management

- Meet the nutritional and hydration needs of the stroke survivor.
- Prevent aspiration-related complications.
- Maintain and promote swallowing function as much as possible.

Initial Management

Acute stroke survivors should be maintained NPO until their swallowing ability is determined. Clinical bedside screening should be conducted by a trained team member, preferably an SLP, using a valid screening tool. Need to carefully monitor hydration and nutritional status.

Initial Bedside Assessment

- Risk factors (see above) should alert the clinician to carefully assess for dysphagia.
- Oral motor assessment usually by speech language pathologist.
- Trial of 1-2 teaspoons of water.
- Followed by small cup of water.
- Choking, coughing or wet gurgly voice are all suggestive of aspiration.

Bedside Clinical Examinations

Several forms of clinical or bedside swallowing evaluations have been described for the purposes of screening and/or assessment. Some of these methods use clinical markers or indicators, such as irregularities of speech or voice (e.g., dysarthria, dysphonia, vocal change), sensitivity of gag reflex or volitional cough strength, while others evaluate swallowing ability using a combined approach. These methods may or may not include a water-swallowing test to evaluate voice change after swallow or cough after swallow (Daniels 2000, Daniels et al. 1998). While bedside clinical examinations are associated with reduced clinical validity when compared to instrumental methods, they are frequently used due to their relative ease of administration and acceptable level of usefulness (Warnecke et al. 2008). As mentioned before, early detection of dysphagia may shorten recovery periods and improve patient health outcomes. Bedside clinical examinations are relatively inexpensive and reduce the amount of radiation exposure for patients who may need to have repeat evaluations under videofluoroscopy modified barium swallowing assessments, as well as from overusing antibiotics as part of their dysphagia management.

Efficacy for Clinical Screening of Dysphagia

Clinical screening tests have been compared to VMBS studies and health outcomes. Only two clinical screening tests found correlations with the findings of VMBS: 1) failure on 50 ml water test and 2) impaired pharyngeal sensation (Sørensen et al. 2013)(Miles et al. 2003). There is limited evidence that clinical screening of dysphagia reduces pneumonia or length of hospital stay although it is considered standard of care.

Water Swallowing Test (WST)

This subset of screening methods is used frequently in clinical practice to diagnose aspiration and prevent pneumonia (Osawa et al. 2013). There are many variations of the WST all comprised of swallowing a pre-set amount of water as usual or without interruption. During which, observations of swallowing function are made. Originally, 3oz (90mL) of liquid was used however, difficulty was observed in swallowing large amounts of water in post-stroke and elderly patients so the 3mL modified water swallowing test was developed (Osawa et al. 2013, Shoji et al. 2010). Currently in the western world, volumes from 10mL to 150mL are used (Osawa et al. 2013). Different volumes and outcomes are incorporated depending on the study population, researcher and to ensure the safety of all involved.

Among the screening tools evaluated, two studies assessed the reliability and validity of the Toronto Bedside Swallowing Screening Test (TOR-BSST) to identify dysphagia. This screening tool combines independent measures with high predictive values in an attempt to produce dysphagia screening results with high sensitivity and negative predictive value between the acute and rehabilitation stages post-stroke (Martino et al. 2009). This study found a sensitivity of 91.3% and negative predictive value of 93.3% in acute settings and 89.5% in rehabilitation settings for the TOR-BSST. Martino et al. (2014) investigated the importance of the specific tools included in the TOR-BSST. The authors found that the number of teaspoons administered in the water swallowing test (WST) portion of this evaluation was the primary contributor to its high validity. Specifically, 10 sequential 5mL teaspoons was the most accurate procedure for detecting dysphagia (specificity=96% versus 79% with five teaspoons or 92% with eight teaspoons). While the WST is the major component contributing to the high predictive value of the TOR-BSST, a lingual motor test is necessary to identify dysphagia in patients who would otherwise have been overlooked by the WST alone (Martino et al. 2014). These two studies provide good support for the TOR-BSST, including at least a water swallowing and lingual motor test, as being more accurate than other single-item screening tools.

Conclusions

There was a wide range of sensitivity (68-97%) and specificity (53-86%) values for the different bedside clinical examinations.
There is a wide range in the validity and clinical usefulness of bedside clinical examinations.
There was a wide range of sensitivity (first-step=71.4-100%; second-step=13-76.4%) and specificity (first-step=38-100%; second-step=70.3-100%) values for the swallowing provocation test.
Combination of the Water Swallowing Test and oxygen desaturation test may result in an improvement in the predictive accuracy of detecting aspiration and pneumonia over either of these screening tests conducted alone.
There is no ideal or defined volume of water that is used to assess dysphagia on the water swallowing test.
There are a variety of clinical screening tests for determining dysphagia following stroke.
There is a wide range in the validity and clinical usefulness of the water swallowing test and the swallowing provocation test.
There is level 2 evidence that the introduction of swallow screening may reduce the incidence of pneumonia among patients with dysphagia when compared to no screening protocol or usual care.
The use of the swallow screen in patients with dysphagia may reduce the incidence of pneumonia compared to when no screening protocols are assigned or compared to usual care.

Silent Aspiration Post-Stroke
Silent aspiration is defined as passage of food below the level of the true vocal cords without cough or outward sign of difficulty. 8%-26% of aspirators acutely are silent aspirators (within the first 5 days post stroke). Reliability of clinical assessment can be uncertain because of the risk of silent aspiration resulting in increasing reliance on VMBS studies to definitively rule out aspiration, particularly in higher risk patients.

Video-fluroscopic Modified Barium Swallow (VMBS)
VMBS is considered the "gold standard" for the diagnosis of aspiration. VMBS allows direct visualization of swallowing function in the oral and pharyngeal phases. It allows diagnosis of the degree of aspiration and whether it is silent or accompanied by a cough or throat clearing. For a VMBS, the patient must be able to perform the test. Thin and thick fluids; pudding, bread, and cookies laden with barium are routinely used. Various aspects of oral and pharyngeal movements and coordination of bolus are observed as is presence and degree of aspiration. Based on anecdotal experience and clinical associations, the greater the degree of aspiration, the greater the risk of pneumonia, which makes intuitive sense. Aspiration of >10% of bolus or severe pharyngeal motility problems on VMBS are regarded as high risk of developing pneumonia. VMBS does result in x-ray radiation exposure.

Benefit of VMBS Studies in Stroke
- Establishes the presence and extent of aspiration.
- Reveals abnormal mechanics: reduced laryngeal closure and/or pharyngeal paresis, etc.
- Demonstrates efficacy of compensatory techniques.
- Allows for tracking of the progression of aspiration risk.

Indication for VMBS Studies
- Brainstem stroke.
- Obvious signs of choking or wet, hoarse voice after drinking.
- Problems maintaining adequate nutrition and hydration.
- Recurrent respiratory infections.

- Follow-up of previous positive VMBS study.

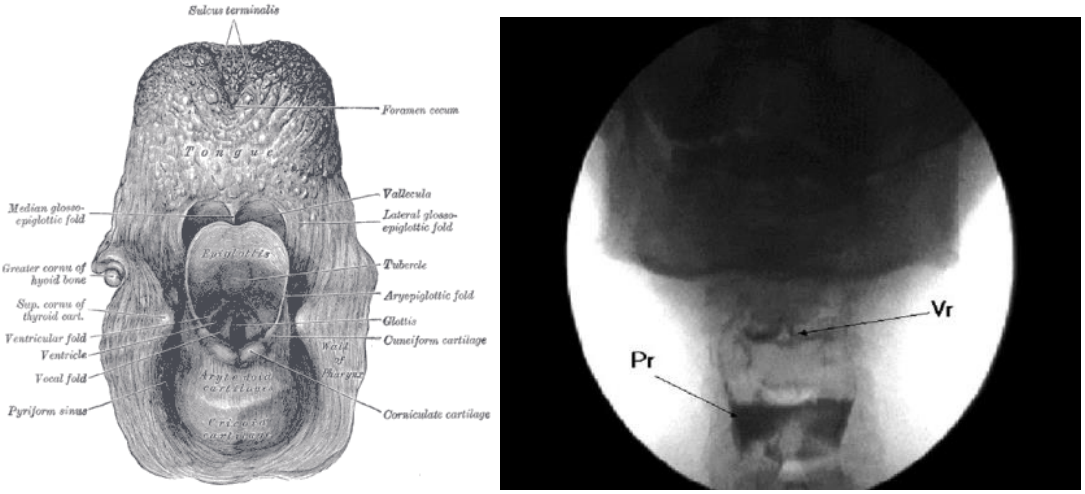


Figure. Anatomy of the Pharynx showing the Valleculae and Piriformis Sinuses where barium can pool in patients with dysphagia and at risk of aspiration

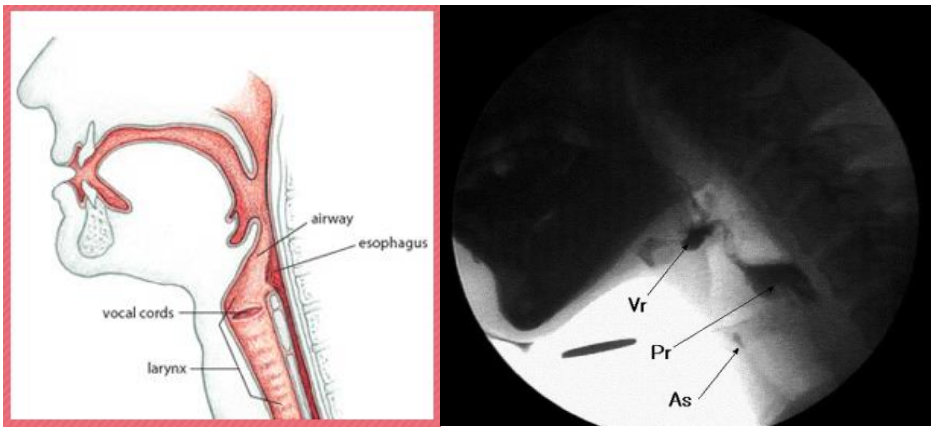


Figure. Anatomy of the Pharynx and Trachea and evidence of pooling in the Valleculae and Piriformis Sinuses as well as Aspiration of Barium (below the level of the true vocal cords)

<u>Conclusions</u>

Videofluoroscopic Modified Barium Swallow (VMBS) studies are considered the gold standard for dysphagia/aspiration diagnosis. Further research is required to determine conclusively when a VMBS study should be administered or re-adminstered.

There is level 3 evidence that scintigraphic and videofluoroscopic (VFS) results may be associated with swallowing function. Furthermore, scintigraphy provided good predictive values for VFS results (70-95%).

Sensitivity and specificity values for scintigraphy in predicting laryngeal penetration and/or aspiration were between 17-77% and 69-92%, respectively.

Scintigraphy may be a valid tool for the detection of aspiration and penetration in dysphagia. Further research is required.

Fiberoptic Endoscopic Evaluation of Swallowing (FEES)

Although VMBS studies are considered the gold standard for detection of aspiration, other clinical assessment techniques, designed to be less invasive, cheaper and easier to administer are in current use. Flexible endoscopic examination of swallowing (FEES), also referred to as fibertopic endoscopic evaluation of swallowing, is also recognized as an objective tool for the assessment of swallowing function and aspiration. The method has been demonstrated to be safe and well-tolerated (Warnecke et al. 2009). FEES is a procedure that allows for the direct visualization of the pharynx before and often the swallow. The procedure involves passing a very thin flexible fiberoptic tube through the nose to obtain a view directly into the pharynx during swallowing. As a result of the multiple benefits of flexible endoscopic evaluation of swallowing (FEES) (reliability, safety, ease of administration, low cost and lack of exposure to radiation), this tool has gained much support for the detection of dysphagia, particularly in acute stroke (Bax et al. 2014). One study suggested that a SLP-led FEES service significantly decreased the risk of pneumonia and improved discharge diet versus no FEES however, these benefits came at the cost of increased length of stay in hospital and additional time on non-oral feeding.

Canadian Best Practice Guidelines

Canadian Best Practice Guidelines; Update 2019 have noted that, "Videofluoroscopic swallow study or fiberoptic endoscopic examination of swallowing should be performed on all patients considered at risk for pharyngeal dysphagia or poor airway protection, based on results from the bedside swallowing assessment".

Conclusions

There is conflicting level 1b and level 2 evidence regarding the reported incidence of pneumonia after flexible endoscopic evaluation of swallowing (FEES) is used versus facial oral tract therapy or videofluoroscopy.

There is level 4 evidence from a large case series study indicating that the incidence of pneumonia may be reduced when dysphagic patients are assessed with FEES versus no assessment. Additionally, FEES may be responsible for a higher proportion of patients treated with instrumental assessment and on standard diet at discharge which may be related to longer periods of non-oral feeding.

Flexible endoscopic evaluation of swallowing may reduce the incidence of pneumonia and improve other important factors associated with dysphagia recovery; however, the evidence is limited and further research is required.

6.2 Management of Dysphagia

6.2.1 Swallow Treatment Programs

Dysphagia therapy usually involves a combination of approaches, including exercises aimed at strengthening muscles, and improving movement and coordination. Possible modified swallowing strategies may include the Mendelsohn maneuver (the patient holds the larynx up, either using the muscles of the neck or with the hand, during swallow for an extended period of time), the Masako

maneuver (patient protrudes tongue and then swallows), shaker exercise and gargling, among others. Other strategies include postural changes (head turn and chin tuck postures) and multiple swallows. These strategies are usually provided in addition to dietary modifications.

Highlighted Study

Carnaby et al. (2006)		
High intensity swallowing therapy vs low intensity swallowing therapy		
RCT (8) N_{start}=306 N_{end}=280 TPS=Acute	E1: Standard swallowing therapy (low-intensity intervention) E2: Standard swallowing therapy (high-intensity intervention and dietary prescription) C: Usual care Duration: 30min/d, 5d/wk for 4wk	E2 vs E1/C • Proportion of individuals returning to normal diet (+exp2) • Time until return to normal diet (+con) • Swallow recovery (+exp2) • Occurrence of chest infection (+exp2) • Modified Rankin scale (-)

Conclusions

Expiratory muscle training may be beneficial for improving the pharyngeal phase, but there is conflicting evidence for its ability to improve a dysphagia evaluation

6.2.2 Dietary Modifications

The evidence that dietary modifications affects the risk of aspiration pneumonia is not well established in stroke but is well accepted. Generally, foods with a variety of consistencies are tried: Solids: puree, minced, chopped, soft and regular, Liquids: pudding, honey, nectar and thin. The proper consistency of food or diet is dictated by VMBS studies and clinical assessment. Thin liquids are typically harder to manage than pudding thick, regular solids are harder to manage than puree diet. Thick fluids or even jelled water are used to eliminate thin liquids when this consistency proves hard to manage. Dysphagia soft diet eliminates all hard, small, and stringy food particles. Sequential VMBS in complicated cases allows for progression of diet with swallowing recovery.

Table 3. A Description of Four Levels of Diets

Level 1	Soft textured foods – may be pureed or mashed foods. Pudding may also be given.
Level 2	Minced and Moist – foods are soft, minced. This may include cooked cereals, yogurts, curds.
Level 3	Smooth pureed – foods may include soft bananas, ground meats and fish, cream soups, ice-cream etc.
Level 4	Foods are finely chopped.

Table 4. Diet Levels as Defined by a Canadian Hospital (Parkwood Institute-SJHC)

Dysphagia Diet Fluids	
Thin Fluids	All fluids that are thin at room temperature: water/ice chips/juices/ tea/liquid nutritional supplements/ regular or strained soups/ice cream/jello.
Nectar Thick Fluids	Thin fluids that are thickened to the consistency of nectar and are sipped from a cup: nectar thick juices, milk, water, soup.

Honey Thick Fluids	Thin fluids that are thickened to the consistency of liquid honey but can be sipped from a cup: honey thick juices, milk, water, soup.
Honey Thick/Thin Fluids	Honey thickened fluids with the addition of thin fluids as determined in consultation with the patients/ resident/SDM and the SLP/RD.
Honey Thick Clear Fluids	Only honey thickened CLEAR fluids are allowed (no textures): honey thick apple/orange/cranberry juice and honey thick water.
Honey Thick Full Fluids	Only honey thickened FULL fluids are allowed (no textures): honey thick juices/water/mild/soup/hot cereals/custard/pudding/smooth yogurt.
Pudding Thick Fluids	Thin Fluids that are thickened to the consistency of pudding and are eaten with a spoon: pudding thick juices/mild/water/soup/custards, high energy puddings/smooth yogurt.
Pudding Thick/Thin Fluids	Pudding thickened fluids with the addition of thin fluids as determined in consultation with the patient/resident/SDM/and the SLP/RD.
Pudding Thick Clear Fluids	Only pudding thickened CLEAR fluids are allowed (no textures): pudding thick/apple/cranberry juices and pudding thick water.
Pudding Thick Full Fluids	Only pudding thickened FULL fluids are allowed (no textures): pudding thick juices/water/mild/soups: hot cereals, custard, pudding, smooth yogurt.
Dysphagia Diet Textures	
Regular	All items are served unmodified.
Ready	Same as regular but roast meats are diced.
Diced Meat/Modified Vegetable	Most meats are diced/soft proteins are allowed whole (meatloaf); also allowed: bananas, watermelon, strawberries etc); not allowed: raw vegetables, brussel sprouts, large pieces of cauliflower, whole corn.
Minced meat/Modified Vegetable	Most meats are minced, soft protein items are allowed, nothing on a bun, no brussel sprouts, florets of cauliflower or broccoli, no stir fry (mince before serving); allowed: mashed potatoes, macaroni salads, bananas, sliced strawberries and seedless watermelon.
Minced	Minced meats, vegetables, mashed potatoes, potato puffs, scalloped potatoes, cheese, peanut butter sandwiches, fresh bananas, minced strawberries, seedless watermelon.
Minced/Pureed	Minced mead and vegetables, mashed potatoes (not rice), soft casseroles, scrambled eggs, pureed fruits, strained soups, oatmeal or cream of wheat.
Pureed Entrée/Modified Bread	Same as above; can add crustless bread toast, moist cakes.
Pureed with oatmeal	Oatmeal, foods with a pudding type consistency, all entree must be pureed.
Pureed	All foods with a pudding type consistency, all entrees to be pureed, bread with diet syrup. No bananas, cottage cheese, oatmeal, old cereal, peanut butter.

Dysphagia Diet Guidelines, Parkwood Institute, St. Joseph's Health Care London, London, Ontario

Highlighted Study

Thin/liquid fluid diet vs Thick fluid diet		
Diniz et al. (2009)		
Cross-over RCT (6) N_{start}=61 N_{end}=61 TPS=Subacute	E1: Liquid samples E2: Spoon-thick liquid samples Duration: 2 trial meals	• Incidence of Aspiration (+exp$_2$) • Incidence of Penetration (+exp$_2$)

Conclusions

- ***There is conflicting evidence on the efficacy of dietary modifications to improve the pharyngeal phase, or respiratory infections.***

6.2.3 Low-Risk Feeding Strategies

It is important to encourage stroke survivors to feed themselves as the risk of aspiration pneumonia increases 20-fold when they are fed by someone else, generally because they are encuraged to eat at a fasert rate. Feed with hand-over-hand support at eye level if necessary. Postural feeding strategies include chin tuck, head tilt, etc. Guidelines for low risk feeding strategies are listed below.

GUIDELINES: Heart and Stroke Foundation of Ontario Guidelines for Low-Risk Feeding Practices (2002)

- Check the food tray to ensure the correct diet type has been provided.
- Ensure the environment is calm during meals and minimize distractions.
- Position the stroke survivor with the torso at a 90° angle to the seating plane, aligned in mid-position with the neck slightly flexed.
- Support the stroke survivors with pillows if necessary.
- Perform mouth care before each meal to remove bacteria that have accumulated on the oral mucosa.
- Feed from a seated position, so that you are at eye level with the stroke survivor.
- Do not use tablespoons. Use metal teaspoons, never plastic for feeding individuals with bite reflexes.
- Use a slow rate of feeding and offer a level teaspoon each time.
- Encourage safe swallowing of liquids by providing them with wide-mouth cup or glass or in a cut-down nosey cup, which helps prevent the head from flexing backward and reduces the risk of aspiration.
- Ensure that swallowing has taken place before offering any additional food or liquid.
- Observe the stroke survivor for any signs or symptoms of swallowing problems during and for 30 minutes after the meal.
- Perform mouth care after each meal to ensure that all food debris is cleared from the mouth.
- Position the patient comfortably upright for at least 30 minutes after each meal to promote esophageal clearance and gastric emptying and to reduce reflux.
- Monitor the oral intake of the stroke survivor with dysphagia: note any food items that are not consumed and ensure that intake is adequate, especially important in individuals receiving a thickened-liquid diet.
- Document the patient's intake, any changes in swallowing status and any self-feeding problems.

6.2.4 Compensatory Strategies

There are a number of compensatory strategies for the stroke patient with dysphagia which are thought to reduce the risk of aspiration. Patients should be fed in the upright posture. Chin tuck facilitates forward motion of the larynx, thereby preventing food material from entering into the larynx and reducing the space between the base of the tongue and the posterior pharyngeal wall increasing pharyngeal pressure on the bolus moving through the pharynx. Head rotation to the paretic side closes the ipsilateral pharynx, forces the bolus into the contralateral, less affected side of the pharynx and decreases cricopharyngeal pressures. Head tilt uses gravity to guide the bolus into the ipsilateral pharynx. Supraglottic swallow involves concomitant breath holding and swallowing which closes the tracheal vocal cords to protect the trachea. Supersupraglottic swallow adds the Valsalva maneuver to maximize vocal fold closing. Double swallowing and coughing after swallowing helps to protect the airway. Close supervision with cueing may be required to slow down impulsive fast eaters, especially right hemispheric stroke patients.

Table 5. Five Postures to Improve Swallowing Function (Logemann 2008)

Chin Down Posture	Helpful for those who have tongue base retraction issues; Mechanism of change widens the valleculae, allowing the valleculae to contain the bolus in event of pharyngeal delay.
Chin Up Posture	Helpful for those who have oral tongue propulsion problems; Aids in gaining adequate lingual pressure to drive the food or liquid out of the mouth and into the pharynx.
Head Turn (left or right)	Involves rotating the head to the side that is injured; Bolus is then directed through the "normal" safe side.
Head Tilt (left or right)	Head is tilted toward the stronger side, to promote the flow of food and liquid through that side using gravity.

6.2.5 Thermal Stimulation

Thermal stimulation is a different, less invasive form of external stimulation designed to improve swallowing. For thermal stimulation, a cold stimulus is generally applied the anterior faucial pillar prior to the individual swallowing. This is believed that both the tactile and thermal stimuli will increase oral awareness and can improve the transition from the initiated oral phase to the involuntary pharyngeal phase (Malik et al. 2017).

Highlighted Study

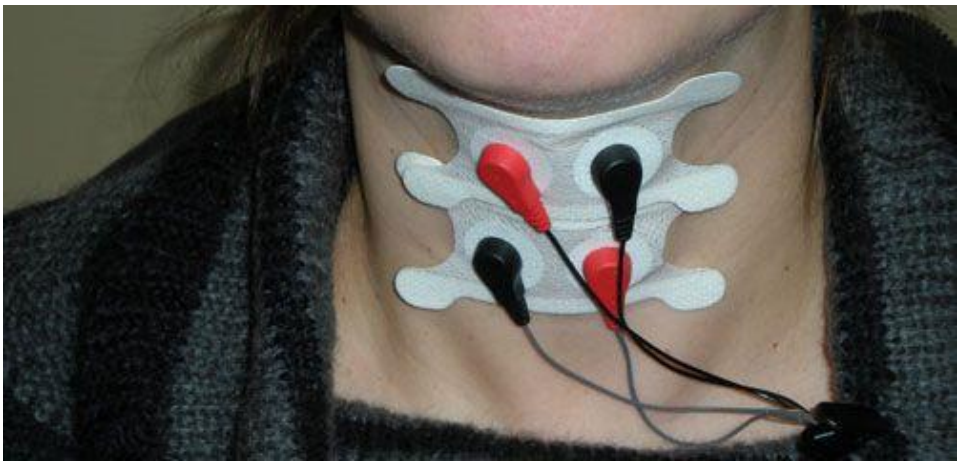
Li et al. (2017)		
RCT (4) N_{Start}=40 N_{End}=40 TPS=Not Reported (Acute)	E: Ice-swab swallowing training C: Conventional swallowing therapy Duration: 20min per session, 3x/d	• Kubota Water Test (-)

Conclusions

Thermal stimulation with NMES may be more beneficial than thermal stimulation alone for improving the pharyngeal phase, and dysphagia evaluations.

6.2.6 Transcutaneous Electrical Stimulation

Transcutaneous electrical stimulation or neuromuscular electrical stimulation (NMES) focuses on peripheral stimulation of the oropharyngeal muscles to enhance neuroplasticity and recovery of swallowing function (Jayasekeran et al. 2010). NMES results in greater muscular recovery than voluntary contraction due to recruiting a larger proportion of motor units (Sun et al. 2013).



Highlighted Study

Suprahyoid NMES vs Conventional Care/Sham		
Konecny et al. (2018)		
RCT (4) N_{Start}=108 N_{End}=108 TPS=Not Reported	E: NMES (60Hz, 300ms pulse length) to the suprahyoid muscle C: Conventional swallowing therapy Duration: 20min/d, 5d/wk for 4wk	• Oral transit time (+exp) • Pharyngeal transit time (+exp)

Highlighted Study

Zhang et al. (2016)		
RCT (5) N_{Start}=82 N_{End}=82 TPS=Acute	E1: Sensory NMES + Swallowing training E2: Motor NMES (Suprahyoid) + Swallowing training C: Swallowing training Duration: 20min/d (2x/d), 5d/wk for 4wk Statistical Analysis: ANOVA	<u>E1 vs C</u> • Standardized Swallowing Assessment: (+exp$_1$) • Functional Oral Intake Scale: (+exp$_1$) • Water swallow test (exp1) <u>E2 vs C</u> • Standardized Swallowing Assessment: (+exp$_2$) • Functional Oral Intake Scale: (+exp$_2$) • Water swallow test (+exp$_2$) <u>E1 vs E2</u> • Standardized Swallowing Assessment: (+exp$_1$) • Functional Oral Intake Scale: (+exp$_1$) • Water swallow test (exp1)

Highlighted Study

Suprahyoid and infrahyoid NMES vs conventional care
Xia et al. (2011)

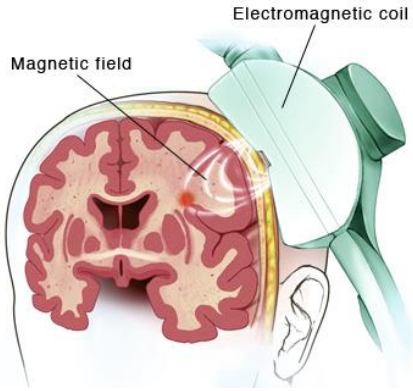
RCT (4) N_{start}=120 N_{end}=107 TPS=Chronic	E1: NMES (VitalStim) (Hyoid Bone Muscles) E2: NMES with conventional swallowing therapy C: Conventional swallowing therapy Duration: 30min/d, 5d/wk for 4wk Statistical Analysis: ANOVA	E1 vs E2 • Standardized swallowing assessment: (+exp$_2$) • EMG of swallowing muscles (+exp2) • Videofluoroscopic Swallowing Study (+exp$_2$) E2 vs C • Standardized swallowing assessment: (+exp$_2$) • EMG of swallowing muscles (+exp2) • Videofluoroscopic Swallowing Study (+exp$_2$)

Conclusions

Suprahyoid, or suprahyoid with infrahyoid NMES may be beneficial for improving the pharyngeal phase, oral phase and dysphagia evaluations.

Infrahyoid NMES alone may not be beneficial for improving dysphagia related outcomes.

6.2.7 Repetitive Transcranial Magnetic Stimulation



Repetitive transcranial magnetic stimulation (rTMS) uses magnetic fields to evoke electrical/excitable changes in the area being stimulated. In stroke, rTMS has been evaluated in the field of motor function; however, few studies have looked at its usefulness at improving dysphagia outcomes (Liao et al. 2017).

Highlighted Study

High Frequency rTMS vs Low Frequency rTMS vs Sham		
Du et al. (2016)		
RCT (9) N_{Start}=40 N_{End}=38 TPS=Acute	E1: High Frequency (3Hz) rTMS (ipsilesional) E2: Low Frequency (1Hz) rTMS (contralesional) C: Sham Stimulation Duration: 30min/d, 5d/wk for 1wk Statistical Analysis: ANOVA	E1 vs C • Water Swallow Test (+exp1) • Degree of Dysphagia (+exp1) E2 vs C • Water Swallow Test (-) • Degree of Dysphagia (-) E1 vs E2 • Water Swallow Test (-) • Degree of Dysphagia (-)

Conclusions

The literature is mixed concerning the efficacy of high frequency rTMS for dysphagia and activities of daily living.

Bilateral rTMS may lead to greater improvements in dysphagia than unilateral rTMS.

6.2.8 Transcranial Direct Current Stimulation (tDCS)

Recently, the use of non-invasive brain stimulation has quickly gained popularity among clinicians with potential benefits for ameliorating dysphagia post stroke (Langdon & Blacker 2010). This method of neurostimulation uses a constant low current applied peripherally via electrodes to stimulate the affected brain area.

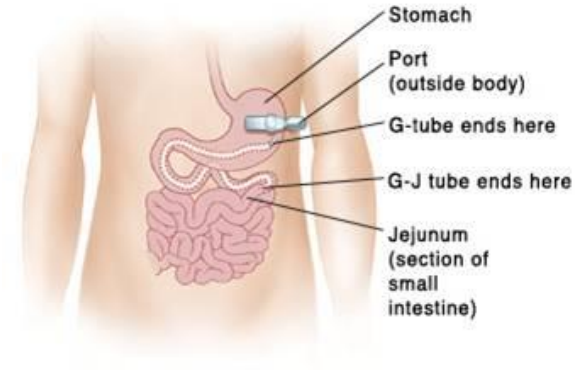
Highlighted Study

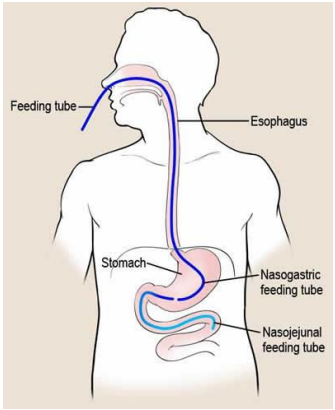
Contralesional Anodal tDCS vs Sham Stimulation		
Suntrup-Krueger et al. (2018)		
RCT (5) N_{Start}=60 N_{End}=59 TPS=Acute	E: Anodal tDCS (1mA contralesional) C: Sham tDCS Duration: 20min/d for 4d	• Fiberoptic Dysphagia Severity Scale (+exp) • Dysphagia Severity Rating Scale (+exp) • Functional Oral Intake Scale (+exp) • Dysphagia Limit Test (+exp) • Pneumonia incidence (-)

Conclusions

Contralesional anodal tDCS may be beneficial for improving dysphagia evaluations, but not respiratory infections.

6.2.9 Non-Oral Feedings





Non-oral feeding is a well-established practice for those patients who cannot handle oral feeds. Non-oral feedings can be implemented almost immediately following a stroke in high risk patients using a naso-gastric tube. If dysphagia is severe (i.e. patient is still aspirating in rehabilitation despite dietary modifications and compensatory strategies) and is expected to continue to do so for more than 6 weeks, a gastrostomy or jejunostomy tube is necessary. The FOOD study (Dennis et al. 2005) found that starting enteral feeds had a positive impact on post stroke recovery but that GI or jejunostomy tube placement should be postponed for 4 weeks due to morbidity associated with the procedure with no difference in complications when compared to NG tube. Nasogastric (NG) tubes, usually intended for short-term use, are positioned directly into the stomach (with extensions into the small bowel) or small intestine through the nose and throat. Alternatively, gastro-enteric tubes are used for long-term feeding and are placed into the stomach percutaneously or surgically. There are advantages and disadvantages to both tube types. Nasogastric tubes have been shown to be less effective with greater side effects compared to gastrostomy tubes for patients that require a longer duration of non-oral feeding (Hull et al. 1993, Park et al. 1992), although significant mortality and morbidity has been associated with more invasive enteric tubes, such as the percutaneous endoscopic gastrostomy (Anderson et al. 2004).

Highlighted Study

Early Nasogastric Tube Feeding vs No Tube		
Zheng et al. (2015)		
RCT (6) N_{Start}=146 N_{End}=146 TPS=Acute	E: Early Enteral Feeding (<72hr) C: Family-Managed Nutrition Duration: Both interventions started within 72hr and lasted 10d (consecutive)	• Infection rate (+exp) • Triceps skinfold (+exp) • Arm muscle circumference (+exp) • Hemoglobin (+exp) • Albumin (+exp) • Triglyceride (+exp)

Highlighted Study

Gastrotomy Tube vs Nasogastric Tube		
FOOD Trial (Dennis et al. 2005)		
RCT (7) N_{start}=321 N_{end}=321 TPS=Acute Note : Study 2 of 2 from publication	E1: Percutaneous endoscopic gastrostomy tube E2: Nasogastric tube Duration: 24hr/d, 7d/wk for 4wk	• Incidence of pneumonia: (-)

Highlighted Study

Early Tube Intervention vs Later Tube Intervention		
Dennis et al. (2005)		
RCT (7) N_{start}=859 N_{end}=858 TPS=Acute Note : Study 1 of 2 from publication	E1: early tube intervention (<7 days post- stroke) E2: late tube intervention (>7 days post-stroke Duration: 24hr/d, 7d/wk for 4wk	• Incidence of pneumonia: (-)

Conclusions

Gastrostomy tube feeding may be more beneficial than nasogastric tubes for improving body composition and calorie consumption but not respiratory infections

Figure. Assessment of Swallowing Post Stroke at Time of Admission

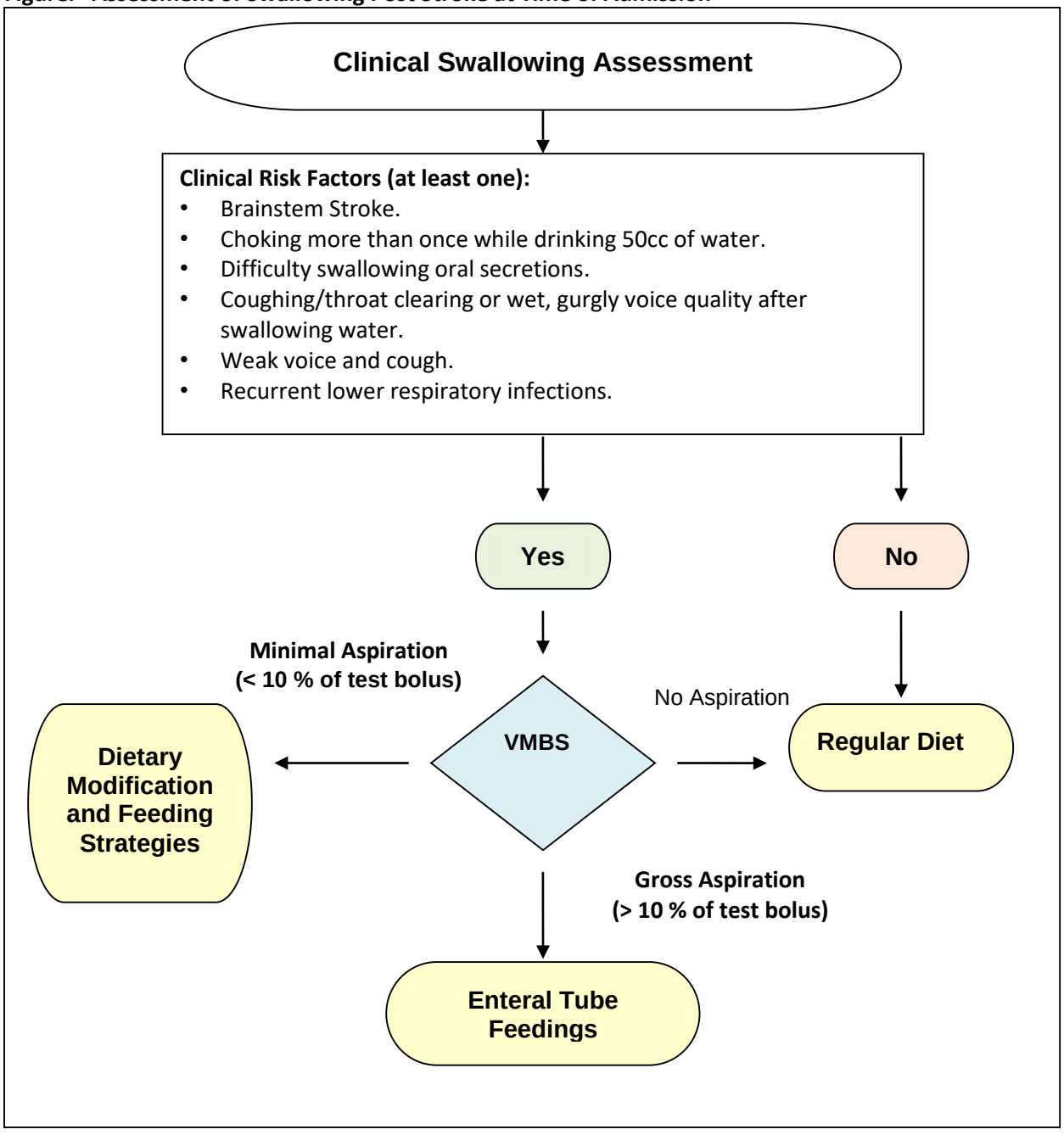


Figure. Continuing Management of Minimal Aspiration

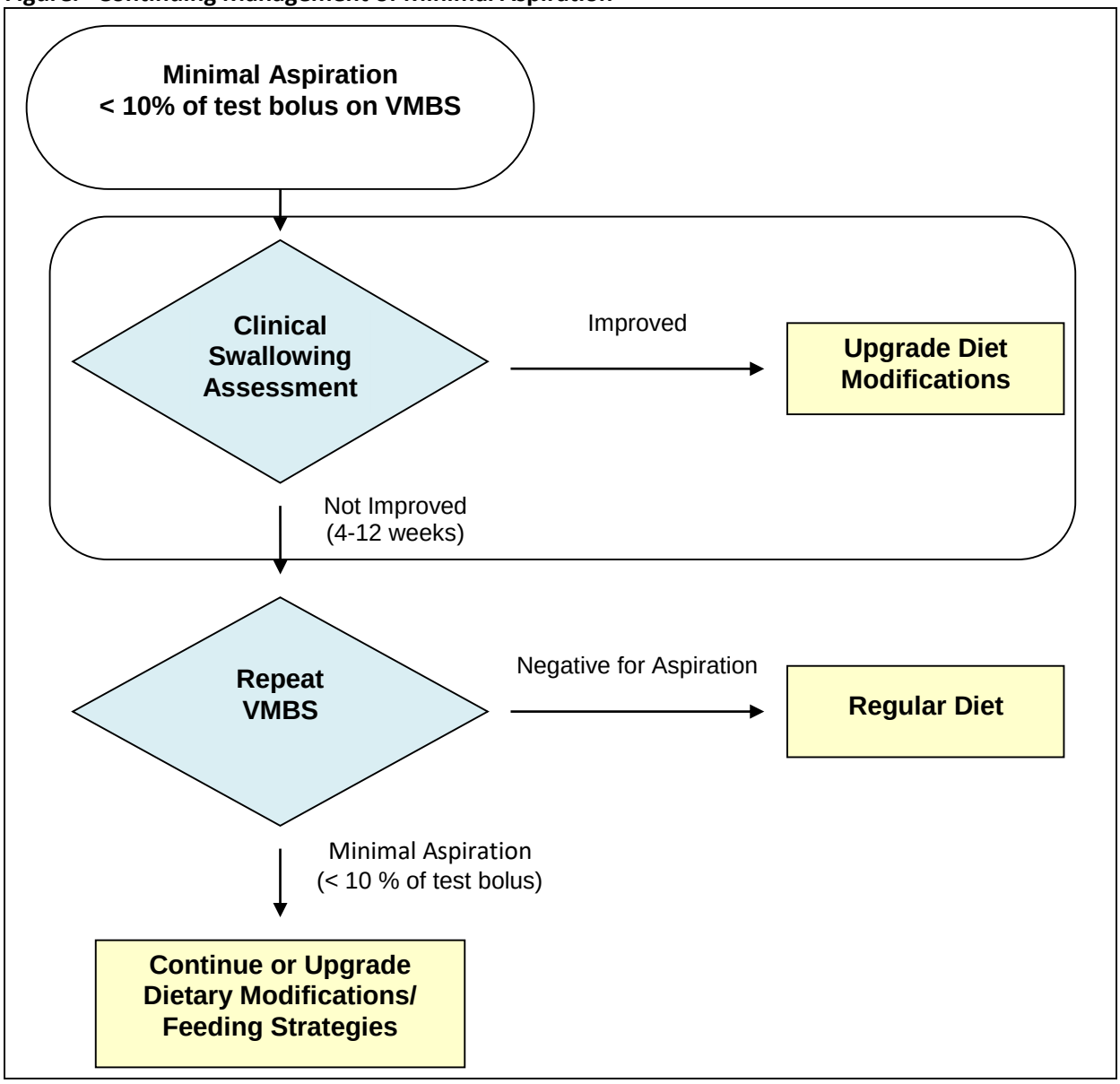
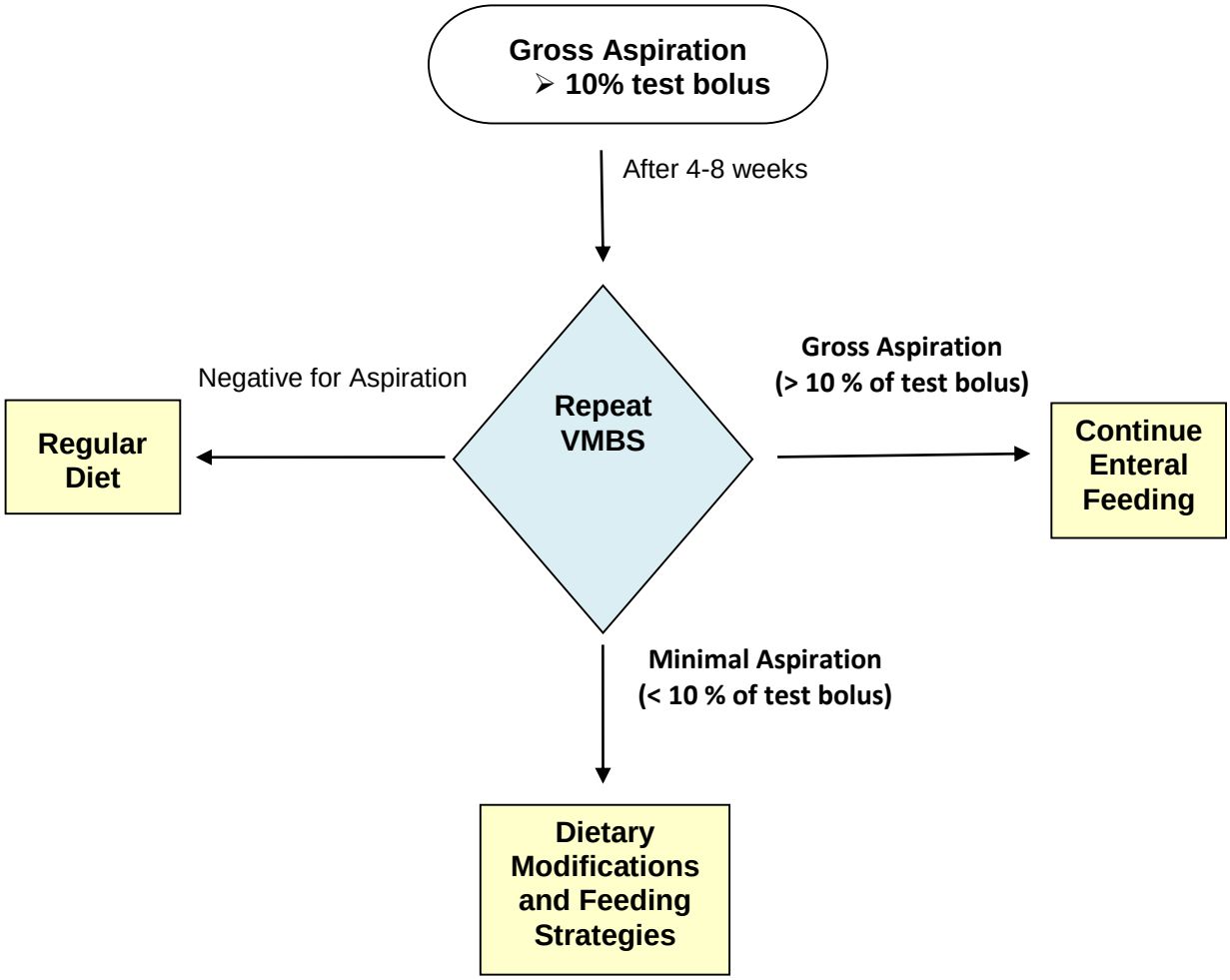


Figure. Management of Gross Aspiration



6.3 Nutrition Post-Stroke

6.3.1 Assessment of Nutritional Status Post Stroke

Decline in nutritional status following stroke is important given its potential negative impact on functional recovery and mortality in multiple medical and surgical populations. Preliminary results from the international FOOD Trial reported that poor nutritional status was associated with an increase in the odds of death and dependency at 6 months after adjusting for a number of confounders (OR 1.82, 95%CI 1.34-2.47) (FOOD Trial Collaboration 2003).

Poor nutrition has been found to predict lower functional status following stroke. In a study focusing on the functional consequences of malnutrition in stroke rehabilitation, patients' serum albumin used as an marker of nutritional status was associated with poorer functional mobility, increased complications, and lower self-care scores (Aptaker et al. 1994). Gariballa et al. (1998a) investigated the associations between a variety of anthropometric and biochemical parameters assessed on admission to hospital and outcome following stroke among 201 patients. After adjusting for age, sex, medications, stroke severity, and comorbid conditions, serum albumin was related to an increase in death at 3 months. Each decline of 1 g/L in serum albumin was associated with a 1.13-fold increase in death at follow-up.

Currently, there is no universally accepted gold standard for the assessment of nutritional status. The identification of malnutrition is typically based on the evaluation of a combination of biochemical and anthropometric markers and is inferred from single or multiple values falling outside of specific population reference ranges or below a certain percentile within these ranges. Since the combination of markers used and the cut-off values are chosen arbitrarily, reports of malnutrition are widely varied. As a result, the true incidence of malnutrition following stroke is likely unknown. Table 6 presents some the more commonly used biochemical indicators used as well as their limitations.

Table 6. Biochemical Markers of Nutritional Status (American Dietetic Association 2000)

Measure	Limitations
Serum Albumin	Large body pool Poor specificity to nutritional changes Not specific to nutritional status ↓ with acute illness
Serum Transferrin	Not specific to nutritional status ↓ with acute illness
Thyroxin Binding Prealbumin	Not specific to nutritional status ↓ with acute illness
Retinol Binding Protein	Not specific to nutritional status
Total Lymphocyte Count	Poor sensitivity and specificity

6.3.2 Malnutrition in Stroke

The prevalence of malnutrition following stroke has been reported to be between 6% and 62%. If widened to include secondary criteria from two studies, the range of estimates broadened to 1.3% and 73%. Some

of this variability can be attributed to differences in patient characteristics and the timing of assessments among studies. However, a substantial proportion of the variation in estimates may also be explained by the heterogeneity of nutritional assessment. Malnutrition increases while the stroke patient is in hospital. 50% of individuals with severe stroke have been reported to be malnourished at 3 weeks post-stroke onset and this improves to 20% among rehabilitation patients at 2-4 months.

Conclusions

The prevalence of malnutrition varies from 6 - 62% post stroke, depending on timing of assessment and criteria used to define malnutrition.

There is currently no "gold standard" for the assessment of nutritional status

6.3.3 Complications of Malnutrition Post-Stroke

Malnutrition is associated with:

1. Lower Barthel Index scores at 1-4 months.
2. Increased length of stay.
3. Greater risk of bedsores and UTIs.
4. Decreased response to physiotherapy.

6.3. Body Mass Index (BMI)

Body Mass Index (BMI) is often used to estimate whether a person is underweight, normal weight or overweight. While there are limitations associated with the use of BMI to detect overweight or obese individuals, it is useful to help quickly identify those who are underweight and may be malnourished.

BMI = **Weight** [in kilograms] / (**Height** [in meters])^2

$BMI=47/1.60^2$

BMI= 18.4

There are many interpretations of BMI although values between 18.5 and 24.9 are considered optimum by most professionals. A BMI of 25 to 29.9 is considered overweight and one 30 or above is considered obese. A value less than 18.5 is considered to be underweight.

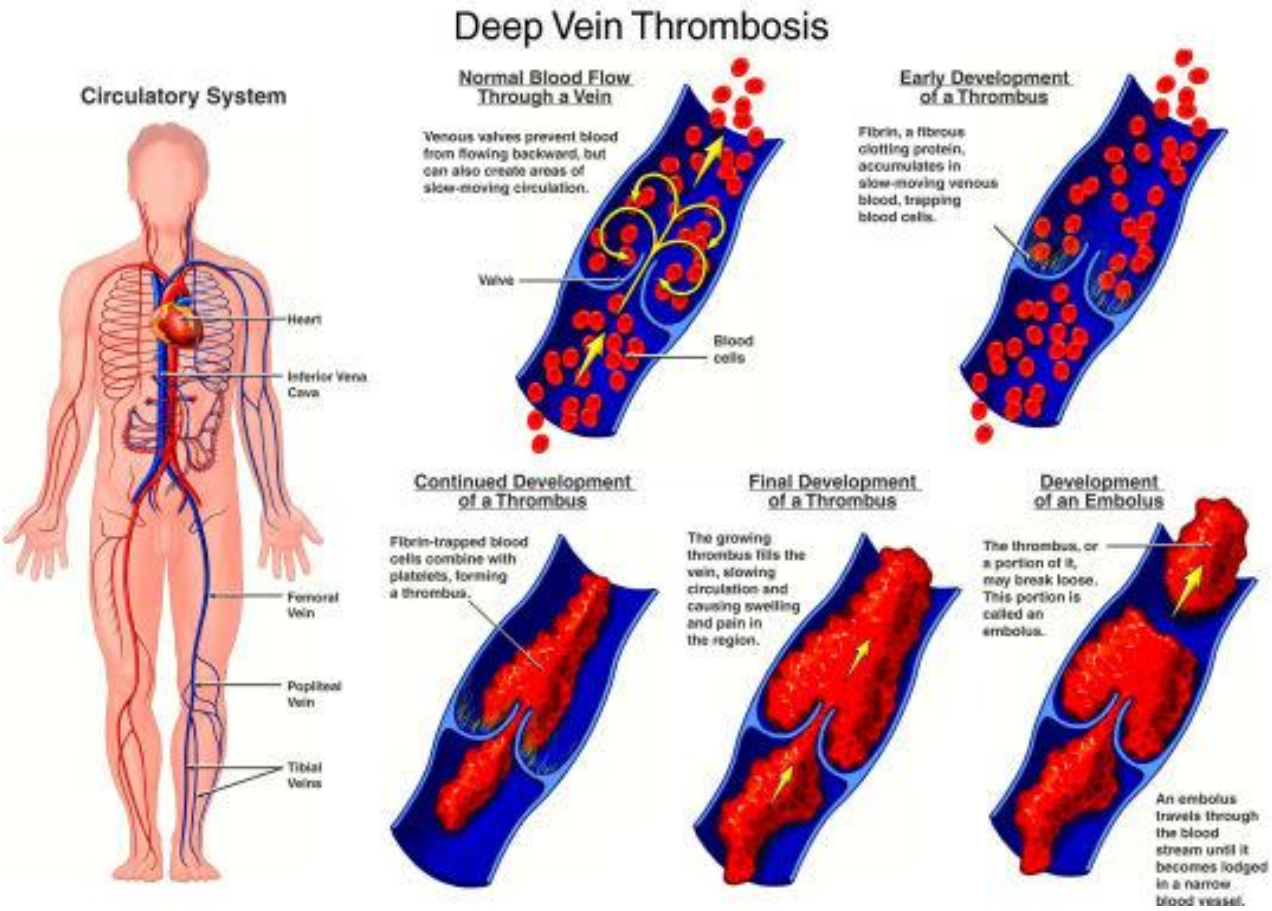
6.4 Venous Thromboembolism Post Stroke

6.4.1 Pathophysiology of Deep Venous Thromboembolism Post Stroke

Virchow's Triad describes the three major risk factors for thrombosis that contribute to venous thromboembolism. These are:

1. Hypercoagulability
2. Hemodynamic changes (stasis/turbulence)
3. Endothelial injury

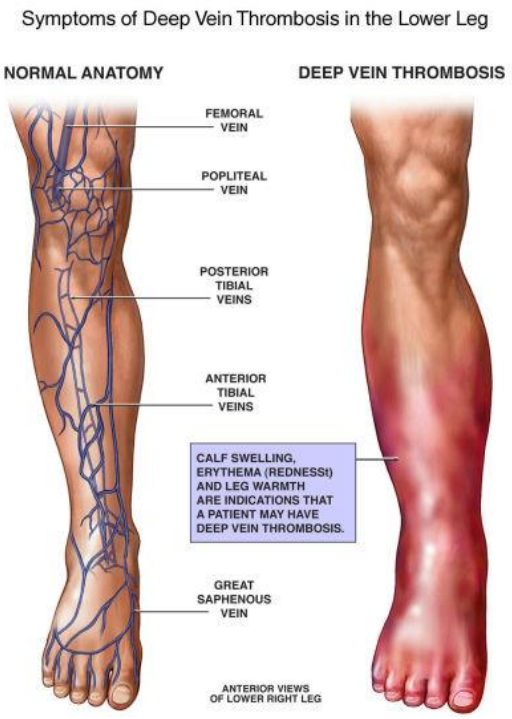
Following stroke the main risk factor is immobilization resulting in stasis of venous blood. Hypercoagulability may also contribute in certain subsets of stroke patients.



6.4.2 Clinical Picture of Deep Venous Thromboembolism

In the absence of prophylactic treatment, 50 – 75% of dense hemiplegics develop a DVT while 9 – 15% will have a pulmonary emboli and 1 – 2% will be fatal. The incidence of DVTs may be as high as 45% (many

are asymptomatic) in acute phase but falls to < 10% of subacute rehabilitation. The peak onset is 2-7 days post stroke. Venous thromboembolism usually begins with calf DVT. Most of these are asymptomatic but 5 – 10% are symptomatic. Untreated, 20% of distal calf DVTs will extend into the proximal veins. When DVT causes symptoms, over 80% involve the popliteal or more proximal veins; symptomatic DVTs are rarely isolated distal calf DVTs. Non-extending distal (calf) DVT rarely causes PE; proximal (knee or above) DVT often causes PE. Isolated distal calf DVTs extend proximally over one week. Clinically symptomatic DVTs are less common in subacute (rehab) phase. The odds of DVT are 17.6X greater if the patient is bedridden or wheelchair bound.



Pulmonary Emboli Post-Stroke

Pulmonary emboli are quite common post-stroke. Most are asymptomatic or unrecognized. Symptomatic PEs are large.

6.4.3 Diagnosis of Deep Venous Thromboembolism

Clinical Model of DVT

If any of the following are present score one point:

1. Active cancer
2. Paralysis, paresis or recent plaster immobilization of L/E
3. Recently bedridden > 3 days or major surgery within 4 weeks
4. Localized tenderness along the distribution of the deep venous system
5. Entire leg swollen
6. Calf swelling 3 cm > asymptomatic side
7. Pitting edema confined to the symptomatic leg
8. Dilated superficial veins (non-varicose)

Subtract 2 points if there is an alternative diagnosis as or more likely than DVT.

Table 7. The Likelihood of having a DVT

Probability	Total Points	Prevalence of DVT
High	≥ 3	85%
Moderate	1 or 2	33%
Low	0	5%

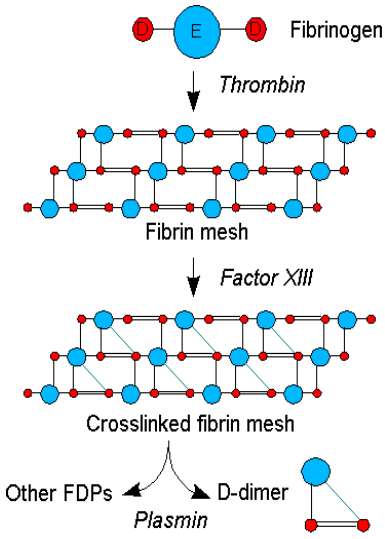
Venous Ultrasound

Venous ultrasound have a sensitivity of 95% and is diagnostic in almost all patients with symptomatic proximal DVT. Specificity of venous ultrasound is 96% which means it is normal in almost all patients with leg symptoms but no DVT. Sensitivity is 73% for distal calf DVTs. The majority of symptomatic distal DVTs that extend do so within a week. Serial testing may be used if the test is negative but the patient is symptomatic; it will become positive if it extends proximally.

D-dimer Assays

D-dimer assays are a rapid, non-invasive and inexpensive test. Fibrin is the main component of thrombus formation; fibrin degradation products include d-dimers. D-dimers are frequently found in the blood when venous thromboembolism is present. The positive d-dimer test is very sensitive but lacks specificity since d-dimers are also found in other disease states including cancer, congestive heart failure, and inflammatory conditions. D-dimers assays have a high negative predictive value, i.e. when it is negative you can relax (sensitive). D-dimers assays have a poor positive predictive value, i.e. when it is positive it could be something else and you don't know if it is VTE (not specific).

Figure. Degradation of Fibrinogen



Positive Diagnosis for DVT

A positive venous ultrasound at two or more sites proximal veins is needed for a positive diagnosis of a DVT.

Negative Diagnosis for DVT

A negative diagnosis for DVT include:

- Negative D-dimer test
- Normal venous ultrasound and
  - low clinical suspicion for DVT, or
  - normal D-dimer test, or
  - normal serial testing (repeat testing one week later)

6.4.4 Diagnosis of Pulmonary Emboli

The clinical diagnosis of a pulmonary embolus is unreliable being both insensitive and non-specific. Many cases of pulmonary emboli are clinically silent with only 30% having clinical features of a DVT and 70% DVT on venography.

Massive Pulmonary Embolus
Patients with massive embolus with 60% or more of the pulmonary circulation compromised are critically ill. Right heart failure may progress to cardiovascular collapse with hypotension, coma, and death.

Sub-massive Pulmonary Embolus
A symptomatic pulmonary embolus presents with tachycardia and tachypnea. There are signs of a pulmonary infarction with consolidation, rales, hemoptysis, pleuritic chest pain, pleural friction rub, pleural effusion, and fever. It is unusual to find all of the findings in a single patient and findings may be non-specific, such as malaise and fever.

Ventilation-Perfusion Scan
A normal perfusion scan exclude PE but is found in a minority. Perfusion defects are non-specific; about 1/3 of those with defects actually have a PE. The probability of a perfusion defect in a PE increases with the size, shape, and number of defects as well as the presence of normal ventilation scan. Mismatched perfusion defects (normal ventilation scan) which are segmental in size or larger are "high probability" defects; these are associated with a prevalence of PE ~ 80%. Three or more mismatched defects is associated with prevalence of ~ 90%. If there is a positive VQ scan and high clinical suspicion then the patient should be treated.

Spiral CT
This is a quick CT scan where the entire thorax is scanned in one breath-hold. Sensitivity is 64-93%; Specificity is 89-100% - best when embolism is large and poor when clots are smaller. Actually visualizes the clot and can diagnose other conditions. Cheaper than other tests.

6.5 Treatment of Venous Thromboembolism

Once diagnosis is established and particularly if symptomatic, patient should receive anticoagulation for 3 – 6 months.

Prophylaxis Post-Stroke

- Age – over the age of 40 moderate risk.
- Over the age of 60 even with minor surgery at high risk.
- Highest risk:
  - major surgery
  - hip and knee fractures
  - major trauma
  - SCI
  - hemiplegic stroke

A Cochrane review of 24 trials with 23,748 patients compared the effectiveness of various pharmacologic agents for of VTE prophylaxis post stroke (Sandercock et al. 2015), which was an update to a series of

previous reviews (Gubitz et al. 2000, Gubitz et al. 2004, Sandercock et al. 2008). Based on 11 trials with 22,776 patients, there was no evidence that initiating VTE prophylaxis within 14 days of stroke reduced all-cause mortality. Earlier initiation of therapy was associated with fewer ischemic strokes, but this finding was tempered by the concurrent increase in intracranial hemorrhages. Early therapy was also associated with a reduction in the frequency of symptomatic PE, but this finding was offset by increased risk of extracranial bleeding. The use of anticoagulation for VTE prophylaxis was associated with lower rates of VTE, including ischemic stroke, PE, and DVT, but was also associated with increased intracranial and extracranial hemorrhages. The authors concluded that the data does not support routine, widespread use of anticoagulation for VTE prophylaxis post stroke.

6.5.1 Heparin Therapy

Heparin has been shown to reduce the risk of DVT and PE in acute stroke survivors. Anticoagulation strategies include unfractionated heparin (UFH), low molecular weight heparin (LMW), and heparin analogues.

Table 8. Advantages and Disadvantages of Heparin Use

Advantages	Disadvantages
Acts immediately	Poor subcutaneous bioavailability when given in low doses
Proven Efficacy in high risk patients	Short half-life Repeated injections
Can be neutralized	Risk of thrombocytopenia (minimal with prophylaxis)
Reference drug	Risk of bleeding (minimal)
	Not sufficiently effective in very high risk groups

a) Unfractionated Heparin

Heparin acts as an anticoagulant by forming a complex with antithrombin, catalysing the inhibition of several activated blood coagulation factors: XIIa, XIa, IXa, Xa, and thrombin. UFH has an immediate onset of action and is most often used in acute conditions. It must be given parenterally, and it is typically given in intravenous or subcutaneous form. Although LMWH has become more popular in the treatment of DVT, the effects of intravenous heparin can be reversed rapidly. Bleeding is the most common adverse effect of heparin, while thrombocytopenia is an uncommon but serious side effect of the treatment (Pineo 2004).

Unfractionated Heparin in Acute Stroke Patients

In 2 RCTs of acute stroke patients, low-dose unfractionated heparin (5000 units s/c q8h) reduced the rate of DVT from 73-75% in the placebo group to 13-22% in the treatment group.

Unfractionated Heparin in SubAcute Stroke Patients

There are no studies of prophylaxis in rehab stroke patients. Accepted use is to maintain while at high risk (i.e., bedridden, in a wheelchair, paralysis). There is no accepted stop date with a trend to longer and more frequent use.

b) Low Molecular Weight (LMW) Heparin

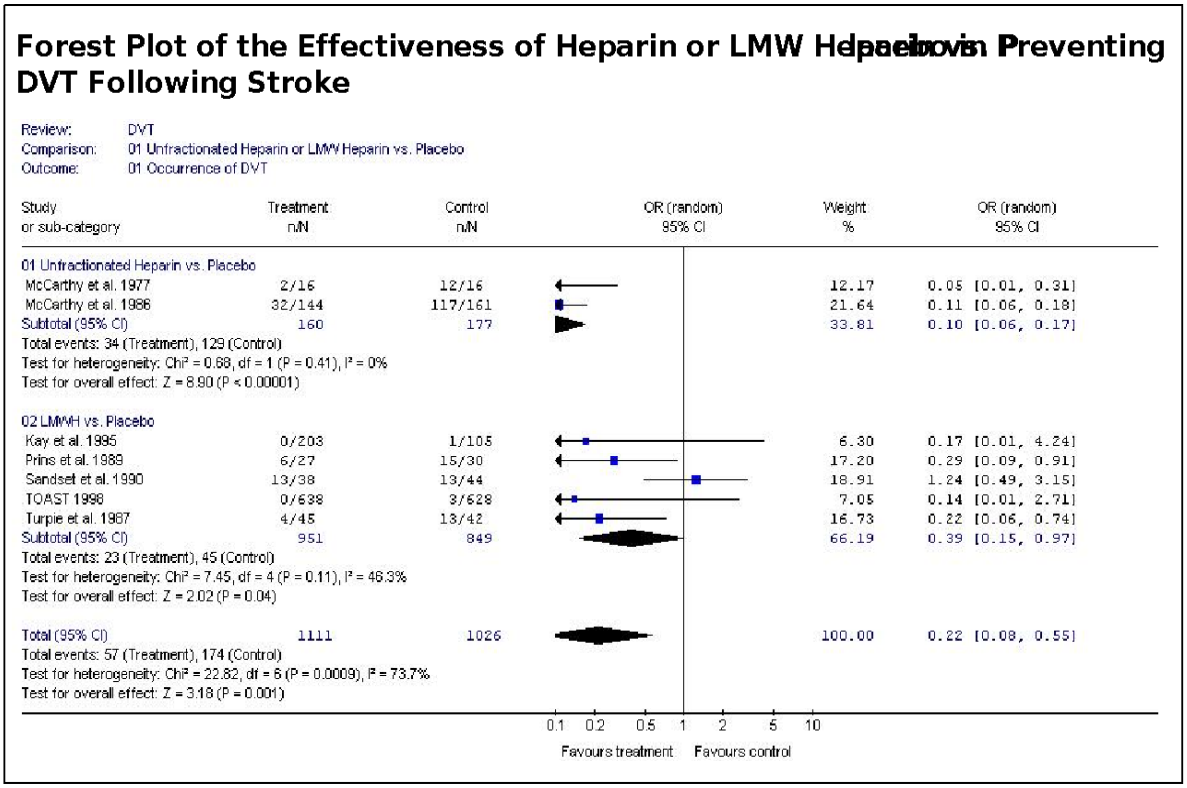
LMWH is derived from standard heparin through chemical or enzymatic depolymerization. Whereas UFH has a molecular weight of 5,000 to 30,000 Daltons, LMWH has a lower molecular weight, ranging from 1,000 to 10,000 Daltons. LMWH has the same mechanism of action as UFH, but binds less strongly to protein, has enhanced bioavailability, interacts less with platelets, and yields a predictable dose response (Rydberg et al. 1999). The clinical advantages of LMWH include predictability, dose-dependent plasma levels, a long half-life, and less bleeding for a given antithrombotic effect (Rydberg et al. 1999). Thrombocytopenia is not associated with short-term use of LMWH, unlike UFH (Pineo 2004). LMWH is administered once or twice daily, both during the high-risk period when prophylaxis for DVT is recommended and also while waiting for oral anticoagulation to take effect in the treatment of DVT. The activated partial thromboplastin time does not need to be monitored, and the dosage does not need to be adjusted (Rydberg et al. 1999).

LMW heparin has a quantifiable and predictable anticoagulant effect. It doesn't inactivate thrombin but does inactivate anti-thrombin. Drugs include:

- Daltaperin (Fragmin) 5000 units OD.
- Tinzaparain (Innohep) weight adjusted or 4500 units OD.
- Enoxaprin (Lovenox) 30 mg BID or 40 mg OD.

LMW heparin is easy to administer. There is no need to monitor. Patients appear to prefer it when monitoring is required. LMW heparin is standard treatment in high-risk patients:

- orthopedic surgery
- high risk medical patient
- DVT or pulmonary embolus



Highlighted Study

LMWH vs Placebo		
TOAST investigators (1998)		
RCT (9) N_{start}=1281 N_{end}=NR TPS=Acute	E: LMWH (danaparoid) C: Placebo Duration: 0.8 U/mL anti-factor Xa (LMWH) for 7d (consecutive) OR 0.8 U/mL placebo for 7d (consecutive)	• Incidence of DVT: 7d (-), 3mo (+exp) • Favourable outcome: 7d (+exp), 3mo (-) • Bleeding complications (+exp) • Incidence of PE (-)

LMW Heparin in Acute Stroke Patients

LMW vs UF Heparin in Acute Stroke Patients

There are 5 RCTs (Diener et al. 2006, Dumas et al. 1994, Hillbom et al. 2002, Sherman et al. 2007, Turpie 1992) comparing LMW to UF Heparin in acute stroke patients. 3 of the RCTs were positive (Hillbom et al. 2002, Sherman et al. 2007, Turpie 1992) and 2 RCTs showed no significant difference (Diener et al. 2006, Dumas et al. 1994). Meta-analysis of 1900 acute stroke patients found significant difference (23 DVT in treatment group and 45 in placebo group, p=0.04) (Sandercock et al. 2008). There is an associated dose-dependent risk of intra- and extra-cranial hemorrhage with UFH. There is strong evidence that low molecular weight heparin is more effective with less risk of hemorrhagic complications than unfractionated heparin. Warfarin is an effective anticoagulant but is less reliable, more cumbersome to use and has more bleeding complications than LMW heparin when it comes to prophylaxis.

Table 9. LMW vs UFH Heparin

Authors	Details
Turpie et al. (1992) PEDro=7	87 stroke patients randomized within 7 days to Orgaran or UFH s/c bid x max 14 days. DVT incidence 9% in LMWH and 31% in UFH.
Dumas et al. (1994) PEDro=8	179 stroke patients randomized within 3 days to Orgaran OD or UFH BID for minimum of 9 days. No significant difference in DVT incidence.
Hillbom et al. (2002) PEDro=8	212 stroke patients randomized within 2 days to either enoxaparin or UFH for 10 days. Over 3 months incidence of DVT or PE was 19.7% in LMWH and 34.7% in UFH (p=0.044).
Diener et al. (2006) PEDro=9	545 acute stroke patients received 3000 units certoparin OD or 5000 UFH TID x 12-16 days. During Rx period 17 LMWH and 24 UFH patients developed DVT (p=0.29).
Sherman et al. (2007) PEDro=7	1,762 acute stroke patients non-ambulatory randomized 40 mg enoxaparin OD or 5,000 units UFH BID x 10 days. Symptomatic DVT 1 in LMWH vs 4 in UFH (p=0.18). Asymptomatic DVTs 66 vs 114 (p<0.0001).

Highlighted Study

LMWH vs UFH		
Sherman et al. (2007) PREVAIL		
RCT (7) N_{start}=1762 N_{end}=NR TPS=Acute	E: LMWH (enoxaparin) C: UFH Duration: 40mg of LMWH (subcutaneously; 1x/d) for 10d (consecutively) OR 5000U of UFH (subcutaneously; 1x every 12hr) for 10d (consecutively)	• Incidence of DVT (+exp) • Favourable outcome (+exp) • Bleeding complications (+exp) • Incidence of PE (-) • Reduction of Mortality (-)

Highlighted Review

Sandercock P, Counsell C, Tseng MC. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischemic stroke. Cochrane Database Syst Rev. 2008 Jul 16; (3): CD000119.

Methods
5 RCTs of LMW Heparin vs. UF Heparin (n=705).
Results
DVT in 13% of LMWH and 22% of UFH. Odds ratio 0.52 (CI 0.56-0.79). More important outcomes of death and intracranial hemorrhage were small and no significant differences.

Dabigatran
Dabigatran, an oral direct thrombin inhibitor, was studied in a non-inferiority trial compared to warfarin for the treatment of acute VTE (Schulman et al. 2009). In the RECOVER trial, patients in both groups were initially treated with parenteral anticoagulation for an average of 10 days, followed by either dabigatran (150mg twice daily) or warfarin (dosed to the International Normalized Ratio between 2-3). There was no significant difference between groups with respect to recurrent DVT, and both had similar safety profile

with respect to episodes of any bleeding. As a result, the study concluded that fixed dose dabigatran is as effective as warfarin for the treatment of acute VTE (Schulman et al. 2009).

Highlighted Study

Schulman S et al. for the RE-COVER study group. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. New England Journal of Medicine. 2009 Dec 361; 2342-2352. NEJMoa0906598.

Methods

In the RE-COVER study, a double-blind, double-dummy, randomized trial, six months of treatment with dabigatran, at a fixed dose of 150 mg twice daily, was compared to dose-adjusted warfarin therapy, after initial parenteral anticoagulation.

Results

It was shown that dabigatran is noninferior to warfarin (when warfarin is dose-adjusted to achieve and maintain an INR in the range of 2.0 to 3.0) in the prevention of recurrent events. Venous thromboembolism or related deaths occurred in 30 patients in the dabigatran group as compared with 27 patients in the warfarin group. The rates of bleeding with dabigatran were similar to or lower than those with warfarin. There were 20 major bleeding events in the dabigatran group as compared with 24 in the warfarin group, and there were fewer episodes of nonmajor bleeding with dabigatran than with warfarin.

Rivaroxaban

Rivaroxaban, an oral factor Xa inhibitor, has also been studied for the treatment of DVT and PE in the EINSTEIN trials. These open-label, non-inferiority trials compared rivaroxaban (15mg twice daily for 3 weeks, then 20mg once daily for a total of 6 months) to a standard therapy of subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for the same time frame. There was no difference in rate of recurrent DVT and risk of major bleeding between the groups (EINSTEIN Investigators 2010). As well, the two groups had similar rates of recurrent PE, although the rivaroxaban group had fewer episodes of major bleeding than the standard therapy (EINSTEIN Investigators 2010, EINSTEIN Investigators 2013).

Highlighted Study

Bauersachs et al. (2010)

Methods

The Acute DVT Study was a randomized, open-label study that compared the efficacy and safety of rivaroxaban with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients with acute, symptomatic DVT. The Continued Treatment Study (EINSTEIN–Extension) was a double-blind study in which patients with confirmed symptomatic DVT or pulmonary embolism who had been treated for 6 or 12 months with a vitamin K antagonist or rivaroxaban were randomly assigned to receive continued treatment with rivaroxaban or placebo. For both studies, the primary efficacy outcome was symptomatic, recurrent venous thromboembolism.

Results

The principal safety outcome — first major or clinically relevant nonmajor bleeding — occurred in 139 patients (8.1%) given rivaroxaban and in 138 patients (8.1%) given standard therapy (hazard ratio with rivaroxaban, 0.97; 95% CI, 0.76 to 1.22; P=0.77). Rivaroxaban alone is as effective as standard therapy, with similar safety, for the treatment of acute DVT and that when treatment is continued, rivaroxaban is

very effective in preventing recurrences, as compared with placebo, and has an acceptable risk of bleeding.

Highlighted Study

The EINSTEIN-PE Investigators (2012)

Methods

The EINSTEIN–PE study was a randomized, open-label trial of the efficacy and safety of rivaroxaban as compared with standard therapy consisting of enoxaparin and a vitamin K antagonist in patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was clinically relevant bleeding, which was defined as a composite of major or clinically relevant nonmajor bleeding.

Results

Recurrent nonfatal venous thromboembolism was suspected in 491 patients in the rivaroxaban group and in 453 patients in the standard-therapy group. The primary efficacy outcome occurred in 50 patients (2.1%) in the rivaroxaban group as compared with 44 patients (1.8%) in the standard-therapy group, for a hazard ratio of 1.12 (95% confidence interval [CI], 0.75 to 1.68; P=0.003 for a one-sided noninferiority margin of 2.0 and P=0.57 for superiority). By day 21, at the end of twice-daily rivaroxaban administration, the primary efficacy outcome had occurred in 18 patients (0.7%) in the rivaroxaban group and in 21 patients (0.9%) in the standard-therapy group.

Oral rivaroxaban alone provided protection from recurrent venous thromboembolism that was similar to the protection provided by standard therapy, with similar bleeding rates. During a mean study duration of approximately 9 months, there was a recurrence in 2.1% of patients in the rivaroxaban group and 1.8% of those in the standard-therapy group. The primary safety outcome of major or clinically relevant nonmajor bleeding was observed in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group, and major bleeding was observed in 1.1% and 2.2% of patients, respectively.

Conclusions

It is unclear whether low molecular weight heparin and unfractionated heparin are effective in preventing venous thromboembolism post stroke, without an increased risk of bleeding complications. However, the efficacy of these medications has been demonstrated in non-stroke populations.
LMW Heparin agents would offer patients a safe and simple treatment alternative to vitamin K antagonist like warfarin, with no need for regular laboratory monitoring and a similar risk of bleeding.

6.5.2 Warfarin

Warfarin is a vitamin K antagonist that inhibits the synthesis of clotting factors II, VII, IX, and X, as well as anticoagulation proteins C and S. Therapeutic doses of warfarin reduce the production of vitamin K-dependent clotting factors by approximately 30 to 50 percent (Horton & Bushwick 1999). The dose of warfarin is titrated to clinical effect by monitoring the International Normalized Ratio (INR), a measure of anticoagulation effect. An INR of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism while minimizing the risk of haemorrhage associated with higher INRs. Anti-coagulation effect of warfarin is accomplished by inhibiting vitamin K epoxide reductase. Initially there is

a greater decrease in levels of protein C and protein S than the vitamin K dependent factors II, VII, IX, X. This disproportionate decrease in coagulation factors increases the risk of developing a clot in the first 5 days after warfarin initiation. Concomitant use of heparin is usually required during the transition in therapy.

Table 10. Advantages and Disadvantages of Warfarin Use

Advantages	Disadvantages
Oral administration	Risk of bleeding
Proven Efficacy	Delayed onset of action
	Delayed neutralizing
	Frequent monitoring necessary
	Many drug interactions

6.5.3 Mechanical Treatments for Deep Venous Thrombosis

Compression stockings have not been shown to reduce the incidence of DVTs post stroke.

Highlighted Study

Muir et al. (2000)

Methods
98 acute stroke patients Rx with standard treatment (control) or standard treatment and compression stockings.
Results
There were no significant difference between the groups.

Highlighted Study

Graded compression stockings (GCS)		
CLOTS (Clots in Legs Or sTockings after Stroke 1) (Dennis et al. 2009)		
RCT (8) N_{start}=2518 N_{end}=NR TPS=Acute	E: Thigh-length GCS C: Standard care Duration: 24hr/d, 7d/wk for 4wk	Incidence of DVT (-) Skin issues (+exp)
2,518 patients admitted to hospital (64 sites) within 1 week of stroke and immobile randomized to routine care +/- graduated compression stockings. There was no significant difference between the groups.		

Highlighted Study

Graded compression stockings (GCS)		
CLOTS (Clots in Legs Or sTockings after Stroke 2) (Dennis et al. 2010)		
RCT (6)	E: Thigh-length GCS	• Incidence of DVT (+exp)

N_{start}=3114 N_{end}=NR TPS=Acute	C: Below-knee GCS Duration: 24hr/d, 7d/wk for 4wk	• Skin Issues (+con)
3,114 acute immobile stroke patients from 112 centres randomized to wear thigh-length or below-knee stockings. Incidence of proximal DVT within 30 days was significantly higher in below-knee stocking group compared with above-knee group (8.8% vs. 6.3%, p=0.008).		

Highlighted Study

Intermittent pneumatic compression (IPC)		
CLOTS (Clots in Legs Or sTockings after Stroke 3) (Dennis et al. 2013)		
RCT (6) N_{start}=2876 N_{end}=1880 TPS=Acute	E: IPC C: Standard care Duration: 24hr/d, 7d/wk for 4wk	• Incidence of DVT (+exp) • Skin issues (+exp)
2876 acute immobile stroke patients from 94 centres randomized to receive intermittent pneumatic compression (IPC) or not within 3 days of stroke; IPC was worn at all times for a minimum of 30 days or until second screening. Compression Doppler ultrasound (CDU) of both legs performed at 7-10 days, 25-30 days or when symptomatic of DVT. 3,114 acute immobile stroke patients from 112 centres randomized to wear thigh-length or below-knee stockings. Incidence of proximal DVT within 30 days was significantly higher in non-IPC group compared with IPC group (12.1% vs. 8.5%, p=0.001); adjusted OR was 0.65 (95% CI 0.51-0.84). There were significantly more skin breaks in the IPC group.		

The CLOTS trials were large, high-quality, multicentre RCTs that examined various interventions for the prevention of DVT post stroke. In the first trial, thigh-length GCS demonstrated similar rates of incident DVT to standard care, and were associated with notable skin issues (e.g. breaks, blisters, blisters, necrosis) (Dennis et al. 2009); these findings supported the results of a previous trial comparing GCS to standard care (Muir et al. 2000). In the second trial, thigh-length GCS demonstrated superiority to below-knee GCS in reducing the rate of DVT (Dennis et al. 2010). In the third trial, IPC devices were found to be superior to standard care in reducing the incidence of DVT, although they were associated with similar skin issues to GCS (Dennis et al. 2013). Similarly, the VICTORIAH trial found that a combination of IPC and GCS was more effective in reducing incident DVT than GCS alone (Lacut et al. 2005). While an older trial reported no significant difference between IPC and standard care in reducing DVT incidence (Prasad et al. 1982), it should be noted that it had a considerably smaller sample and poorer methodological quality than CLOTS3 and VICTORIAH.

Conclusions

The literature is mixed regarding the efficacy of intermittent pneumatic compression and graded compression stockings as an effective prophylactic intervention for deep vein thrombosis.

There is <u>strong</u> evidence that graduated compression stockings do not reduce the risk of DVT.

There is <u>strong</u> evidence that thigh length compression stockings reduce the risk of DVT when compared to below knee stockings.

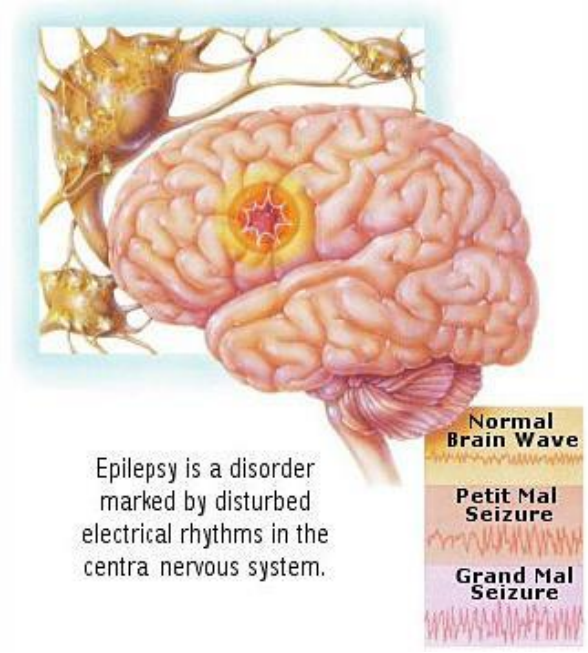
There is <u>strong</u> evidence that intermittent pneumatic compression (IPC) reduces the risk of DVT when compared to no treatment with IPC.

There is <u>moderate</u> evidence heparin equivalent to both pneumatic compression and electrical stimulation in reducing risk of DVTs.

6.6 Post-Stroke Seizures

6.6.1 Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires more than one seizure. One seizure in association with an enduring disturbance of the brain is capable of giving rise to other seizures has been defined as epilepsy (Fisher et al. 2005). ***Post stroke seizures may occur soon after stroke or be delayed***; each appears to be associated with differing pathogeneses. Most seizures are single, either partial or generalized (Ferro & Pinto 2004). Wiebe and Butler (1998) noted that***, "Seizures are the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex."*** Younger patients and men are at increased risk for seizure activity post stroke (Arboix et al. 1997, Giroud et al. 1994). A lesion involving the cerebral cortex is a prerequisite for the development of epilepsy (Olsen et al. 1987).



6.6.2 Incidence of Post Stroke Seizures

Wiebe and Butler (1998) observed that the incidence of seizures following ischemic or hemorrhagic stroke in earlier series is noted to be highly variable ranging from a low of 7.7% to a high of 42.8%. In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). ***The average risk of seizures is 10% within 9-10 years after stroke*** and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burn et al. 1997). At least two studies suggest a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo 1992, Paolucci et al. 1997). ***Seizures usually occur during the first 1 to 2 weeks following stroke.***

Hemorrhagic stroke patients have been found to have an almost 2-fold risk of developing a seizure following stroke compared to patients with an ischemic lesion (Bladin et al. 2000).

Highlighted Study

Post-stroke seizures (Black et al.). Stroke 1983; 14:134.

Methods
Clinical data prospectively collected on 827 patients with completed stroke.
Results
10% of patients had seizures during their first admission during 2 to 5 years follow-up. Seizures occurred only in those patients with hemispheric lesions. 39% of seizures occurred by the first day, 57% occurred by the first week and 88% occurred by the first year.

6.6.3 Types and Timing of Post-Stroke Seizures

Black et al. (1983) reported that 39% of seizures occurred within the first 24 hours, 57% within the first week and 88% within the first year. The overall percentage after stroke of focal seizures was 50%, generalized seizures 32%, focal seizures with secondary generalization 15%, and complex partial seizures 2.5% (Wiebe-Velazquez, Blume 1993). Camilo and Goldstein (2004) reported on Timing of Seizures Post Stroke and found some variation: < 24 hours (2% Sol et al. 1996 to 6.3% Beghi et al. 2011; mean 4.1%); < 1 week (1.2% Alvarex et al. 2013 to 11% Haapaniemi et al. 2014; mean of 9 studies mean 4.6%); < 2 weeks (2.5% Kotila and Waltimo 1992 to 33% Gupta et al. 1998; mean 8.3%); at one year 3% Vitanen et al. 1988 to 15% Paolucci et al. 1997; mean 7.2%).

6.6.4 Risk Factors for Seizures Post Stroke

Despite considerable variability in the definitions and methodology between studies, common risk factors have emerged from the literature: cortical strokes, severe strokes, greater disability, and younger age. Stroke type may also predict seizure development, with hemorrhagic strokes being more likely than ischemic strokes (Alvarez et al. 2013). Lamy et al. (2003) identified cortical strokes, large strokes, and early-onset seizures as independent risk factors for later seizures, with a 4.5- to 10-fold increase in risk (Lamy et al. 2003).

The Copenhagen Stroke Study, a community-based, prospective study of 1197 patients with acute stroke, identified stroke severity as the single largest risk factor for early PSS (Reith et al. 1997). In two large population-based studies, younger age and stroke severity were found to be predictors of seizures post stroke occurring within 24 hours (Krakow et al. 2010, Szaflarski et al. 2008). One of these studies also found acute, non-neurologic infection and history of previous TIA to be predictive of developing PSS in both hemorrhagic and ischemic stroke (Krakow et al. 2010). In a cohort of patients from the Registry of the Canadian Stroke Network (Burneo et al. 2010), stroke severity, hemorrhagic stroke, and neglect were found to be independent predictors of PSS during the initial period of hospitalization post stroke.

Conclusions
Post-stroke seizures not a common complication post stroke, although the rates vary widely across studies and stroke onset.

Common risk factors for post-stoke seizures include cortical strokes, severe strokes, greater disability, and younger age.
The majority of seizures post stroke are simple partial seizures.
Post-stroke seizures appear to be more common in hemorrhagic and cortical strokes, although this may be more directly related to stroke severity rather than etiology or location.

6.6.5 Impact of Seizures on Outcomes

Whether seizures worsen outcomes remains unclear. Vernino et al. (2003) reported new-onset seizure among patients with ischemic stroke to be an independent risk factor for mortality on multivariate analysis (Relative risk 1.81; 95%CI 1.16-2.83). Bladin et al. (2000) also reported higher mortality among patients with seizures at 30 days and 1 year, compared to patients who were seizure free (25% vs. 7% and 38% vs. 16%). However, the authors did not control for the confounding effects of stroke severity or comorbidity. The results of other studies have not supported an increased risk of mortality (Labovitz et al. 2001, Reith et al. 1997).

6.7 Treatment of Post-Stroke Seizures

6.7.1 Prevention of Post-Stroke Seizures

In a Cochrane review, Sykes et al. (2014) sought to examine the efficacy of antiepileptic drugs for prevention or treatment of PSS. Only one study was found to be suitable for review: a prospective, randomized, double-blind, placebo-controlled trial for primary prevention of seizures post stroke; the study compared valproic acid to placebo in 72 patients with intracerebral hemorrhage (Gilad et al. 2011). The authors concluded that there is insufficient evidence to support the routine use of antiepileptic therapy for primary or secondary prevention in patients with PSS. The evidence was also insufficient to aid in the selection of antiepileptic drugs for the management of PSS.

Highlighted Study

Primary Prevention of Seizures		
Gilad et al. (2011)		
RCT (6) N=84	E: Valproic acid C: Placebo	• NIH Stroke Scale (+exp) • Seizures (-)

<u>Conclusions</u>
There is no evidence that prophylactic anticonvulsive treatment is beneficial post stroke.
Treating all stroke patients with anticonvulsants as primary seizure prophylaxis is not recommended.

6.7.2 Treatment of Post-Stroke Seizures

Standard first-line therapy usually includes carbamazepine, valproic acid and phenytoin. Phenytoin is known to interact with warfarin. Newer anti-epileptic drugs such as lamotrigine may be better tolerated

and have a better side-effect profile than some of the older drugs. There is some concern that anti-epileptic drugs may impair recovery post stroke. Benzodiazepines as an ongoing treatment should be avoided due to its sedating effects unless seizure activity is uncontrolled.

Highlighted Study

Gilad et al. (2007)		
RCT (3) N_{start}=64 N_{end}=64 TPS=Chronic	E1: Lamotrigine E2: Carbamazepine Duration: 100mg/d of Lamotrigine, 7d/wk for 12wk OR 300mg/d of Carbamazepine for 12wk	• Reduction of Adverse Events: (+exp_1) • Seizure-free patients (-)

Highlighted Study

Rowan et al. (2005)		
RCT (9) N_{start}=593 N_{end}=NR TPS=Chronic	E1: Lamotrigine E2: Gabapentin E3: Carbamazepine Duration: 150mg/d (Lamotrigine), 7d/wk for 52wk OR 1500mg/d (Gabapentin), 7d/wk for 52wk OR 600mg/d (Carbamazepine), 7d/wk for 52wk	• Reduction of Adverse Events: (+exp_1, +exp_2) • Seizures (-)

Conclusions
Insufficient evidence exists to guide selection of monotherapy for antiepileptic medications in patients with post-stroke seizures.
There is Level 1b and Level 2 evidence that lamotrigine, gabapentin, and carbamazepine are similar in reducing the rate of recurrent post-stroke seizures, but carbamazepine is more poorly tolerated.
Decisions to initiate antiepileptic therapy should be tailored to patients' individual needs.

Treatment of Status Epilepticus Post Stroke
Benzodiazepines are considered the best first-line drugs for managing status acutely with a seizure control rate of approximately 79%. Both Lorazepam and Diazepan given intravenously are acute treatment strategies, although Lorazepam may be more effective in terminating status epilepticus (59-89% vs. 43-76%) and has longer lasting anticonvulsant properties (12 hours vs. 20 Minutes for Diazepam). Midazolam 10 mg given by the buccal and intranasal route is an alternative where intravenous medications are difficult to give.

6.7.3 Driving and Post-Stroke Seizures

The patient should be assessed by a neurologist and an EEG performed. The patient will need to be seizure-free for at least 6 months, on stable treatment and assessed by a neurologist conducting the EEG before they can drive again. Individual circumstances may warrant prolonging or reducing the time period suggested. Regulations regarding driving post stroke and Post seizure can vary between regions so contact your local ministry of transportation for specific requirements.

6.8 Thalamic/Central Pain States Post Stroke (CPSP)

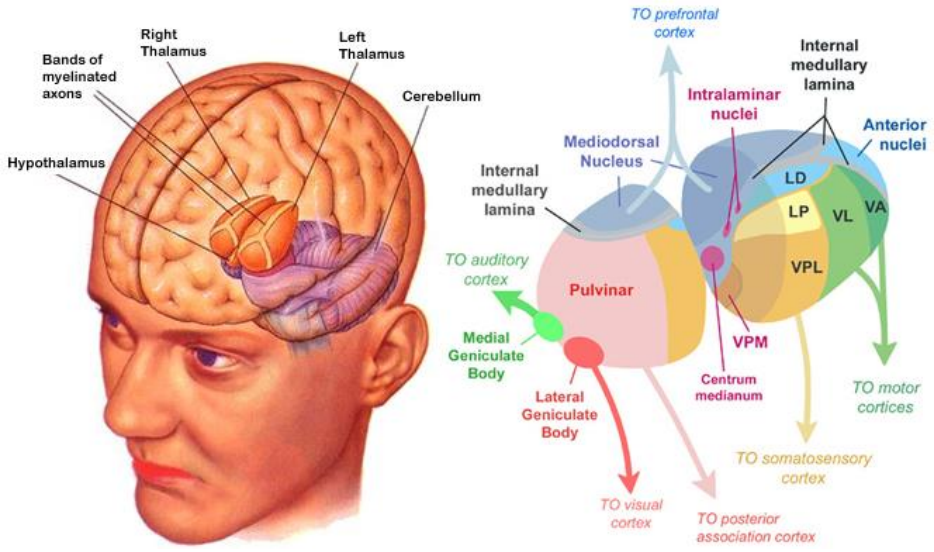
CPSP is a syndrome characterized by sensory disturbances and neuropathic pain. In 40-60% of CPSP patients, the onset of central pain occurs more than one month following the stroke. The incidence of CPSP has been reported as high as 8% but is generally felt to be much lower. According to the best studies, central post-stroke pain occurs in less than 2% of stroke patients.

The largest prospective cohort study of chronic pain syndromes to date, the Prevention Regiment for Effectively avoiding Second Stroke (PRoFESS) trial, reported that the incidence of new chronic post-stroke pain from total of 15,754 participants was 10.6% (O'Donnell et al. 2013). The authors further identified the incidence of post-stroke pain subtypes: 2.7% for CPSP; 1.5% for peripheral neuropathic pain; 1.3% for spasticity-related pain; 0.9% for shoulder subluxation pain; and 4.7% for all other pain syndromes combined. Risk factors associated with any post-stroke pain condition included increased stroke severity, female sex, alcohol intake, previous depression, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and prescription of aspirin/dipyridamole.

6.8.1 Pathophysiology of CPSP

CPSP is often referred to as “thalamic pain”. CPSP can occur post lower brainstem, thalamic and even suprathalamic strokes. CPSP is associated with lesions involving the spino-thalamic pathway (STP) with disturbance in temperature and pain sensation. The pathophysiology of CPSP remains unknown. Although it requires damage to spino-thalamic pathway; however, not all damage to the STP leads to CPSP. All patients with CPSP have impaired sensation to temperature (hot, cold) and pain (pinprick) which is indicative of damage to the spinothalamic tract. Touch, 2-point discrimination and vibration sense remain intact; CPSP is therefore not mediated by the lemniscal pathway.

CPSP is a specific type of neuropathic pain that is thought to be due to stroke-related injury to pathways or brain centres involved in pain processing (de Oliveira et al. 2012, Henry et al. 2008). In this condition, pain and sensory abnormalities occur in the parts of the body that correspond to the stroke lesion (Klit et al. 2009). In 40-60% of patients, the onset of pain occurs more than one month after the stroke (Hansson 2004). Delayed onset combined with language or cognitive impairments, prioritization of other medical complications, and depression have been postulated to contribute to underdiagnosis and undertreatment of this debilitating pain (Hansson 2004, Henry et al. 2008, Jensen & Lenz 1995, Segatore 1996).



Post-stroke, most cases develop at 1-2 months although some develop it at 1-6 years. Often there is a delay in the onset of symptoms after the onset of stroke. One potential mechanism is the subthreshold activation of nociceptive neurons in which nociceptive neurons discharge in response to a normally non painful stimulus. Most commonly CPSP involves lesions within the ventrocaudal nuclei of the thalamus, particularly within ventroposterior inferior nucleus. Cutaneous nociceptive input is encoded and conducted via specific neurons in ventromedial thalamus. Release of inhibition may produce the CPSP. Most cases of CPSP are associated with hyperalgesia +/or allodynia. Paradoxical sensory deficit and hyperalgesia suggests central sensitization of 3rd and 4th order CNS neurons as a result of loss of spino-thalamic or thalamo-cortical input.

Conclusions Regarding the Pathophysiology of Central Post-Stroke Pain

The precise pathophysiology of central post-stroke pain is unknown, but it appears to be associated with a lesion involving the spino-thalamo-cortical pathway.

6.8.2 Clinical Symptoms of CPSP

CPSP is described as a "burning" sensation in association with parasthesiae (tingling, pins & needles, numbness). It is often described as ripping, tearing, pressing, twisting, aching, pricking and lacerating pain. Leijon and Boivie (1989) in their study of 23 CPSP patients noted little difference in pain character in relation to the stroke site. "Burning" pain was more commonly described with brainstem lesions while lacerating pain was seen more often with suprathalamic strokes. Pain normally occurs within an area smaller than the area of sensory impairment. Generally it is described as constant pain and often associated with spontaneous paroxysms of pain; can be exacerbated by physical movement, emotional stress, loud noises or voices, changes in weather, cold and light touch. Virtually all cases of CPSD report spontaneous or evoked parasthesias +/or dysaesthesia.

Dysesthesia: Unpleasant sensations, either spontaneous or evoked (Andersen et al. 1995).

Allodynia: Abnormally unpleasant somatosensory experience, often poorly localized, elucidated by normally non-nociceptive stimuli (Andersen et al. 1995).

Hyperalgesia: Increased pain response to a normally painful stimulus (Andersen et al. 1995).

Conclusions Regarding Clinical Features of Central Post-Stroke Pain
Central-post stroke pain generally involves some form of spontaneous and evoked sensory abnormality on the affected side including dysesthesia, allodynia, and hyperalgesia. Development of central post-stroke pain is most often within the first month of stroke onset.

6.9 Treatment of Central Pain Post Stroke

CPSP has been generally regarded as intractable to treatment. It is typically treated with pharmacological interventions – tricyclic antidepressants and anticonvulsants combined with opioid analgesics has been usual management. Treatment has been generally unsatisfactory.

6.9.1 Amitriptyline

Highlighted Study

Leijon & Boivie (1989)		
RCT Crossover (6) Nstart=15 Nend=15 TPS=Chronic	E1: Amitriptyline (75mg/d) E2: Carbamazepine (800mg/d) C: Placebo Duration: 75mg/d (maximum dose) of Amitriptyline, 7d/wk for 4wk OR 800mg/d (maximum dose) of Carbamazepine, 7d/wk for 4wk OR placebo (dosage not specified), 7d/wk for 4wk	E1 vs E2/C Verbal Rating Scale (+exp1) Comprehensive Psychopathological Rating Scale (-)
Double-blind, 3 phase cross-over placebo controlled trial of 15 patients. Treatment given in randomized order, for 4 weeks, separated by 1 week washout periods where patients administered amitriptyline, carbamazepine and placebo. Amitriptyline produced significantly greater reduction of pain when compared to placebo at week 4.		

Highlighted Study

Lampl et al. (2002)		
RCT (7) Nstart=39 Nend=37 TPS=Chronic	E: Amitriptyline (75mg) C: Placebo (75mg) Duration: 75mg/d (1x/d) of amitriptyline 7d/wk for 52wk OR 75mg/d (1x/d) of placebo 7d/wk for 52wk	• Visual Analog Scale (-) • Average Time to Pain (-) • Hypoesthesia/Allodynia (-)
39 CPSP patients randomly receive amitriptyline (n=20) or placebo (n=19) over 1 year. No differences in occurrence, intensity, type, site or distribution of pain between 2 groups.		

Conclusions
There is conflicting evidence (based on 2 RCTs) amitriptyline reduces pain post-stroke (Leijon and Boivie 1989; Lampl et al. 2002).

6.9.2 Naloxone

Highlighted Study

Bainton et al. (1992)		
RCT (5) N_{start}=20 N_{end}=20 TPS=Chronic	E: Naloxone (8mg) C: Saline (20mg) Duration: 8mg (injection) of naloxone 1x/wk for 3wk OR 20mg (injection) of saline 1x/wk for 3wk	• Verbal Rating Scale (-) • Visual Analog Scale (-)
20 CPSP patients received naloxone (up to 8 mg) vs. normal saline in randomized cross-over trial. VAS and verbal pain scores obtained before and after injection with 2-3 week washout period. No immediate or long-term differences in pain relief between 2 groups.		

6.9.3 I.V. Lidocaine

Highlighted Study

Attal et al. (2000)

Methods
16 patients (6 with stroke) received both lidocaine vs. saline intravenous injections 3 weeks apart in a randomized cross-over trial. Patients recorded pain using VAS.
Results
Lidocaine significantly better than saline in reducing intensity of spontaneous ongoing pain for up to 45 minutes post injection; no difference at 6 hours post injection.

Conclusion
There is moderate evidence (1 RCT) lidocaine results in short-term (45 min) pain relief only (Attal et al. 2000).

6.9.4 Anticonvulsants

Highlighted Study

Kim et al. (2011)		
RCT (9) N_{start}=220 N_{end}=NR TPS=Chronic	E: Pregabalin C: Placebo Duration: 150mg/d to 600mg/d pregabalin, 7d/wk for 13wk OR 150mg/d to 600mg/d placebo, 7d/wk for 13wk	• Daily Pain Rating Scale (-) • Clinician Global Impression of Change (CGIC) (+exp) • Medical Outcome Study-Sleep (MOS-Sleep) (+exp) • Hospital Anxiety and Depression Scale-Anxiety (HADS-A) (+exp)

Highlighted Study

Serpell et al. (2002)		
RCT (8) N_{start}=307 N_{end}=234 TPS=Chronic	E: Gabapentin C: Placebo	• Clinician and Patient Global Impression of Change (+exp)

	Duration: Start at 900mg/d of Gabapentin (1x/d) for 3d, then 1800mg/d of Gabapentin (1x/d) for 2wk, then 2400mg/d of Gabapentin (1x/d) for 6wk for a total of 7d/wk for 8wk OR Start at 900mg/d of placebo (1x/d) for 3d, then 1800mg/d of placebo (1x/d) for 2wk, then 2400mg/d of placebo (1x/d) for 6wk for a total of 7d/wk for 8wk.	• Visual Analog Scale (+exp) • Short-Form McGill Pain Questionnaire (+exp) • SF-36 (+exp)

Highlighted Study

Jungehulsing et al. (2013)		
RCT (8) N_{start}=42 N_{end}=33 TPS=Subacute	E: Levetiracetam (3000mg) C: Placebo (3000mg) Duration: Start at 500mg (2x/d) and then increase to 3000mg/d (Levetiracetam; during week 2), 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern) OR Start at 500mg (2x/d) and then increase to 3000mg/d (placebo) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern).	• Likert Scale (-) • McGill Pain Questionnaire (-) • Beck Depression Index (-) • Short Form-12 Health Survey (-)

Highlighted Study

Vestergaard et al. (2001)		
RCT (8) N_{start}=31 N_{end}=26 TPS=Chronic	E: Lamotrigine (25mg, 50mg, 100mg, 200mg) C: Placebo (25mg, 50mg, 100mg, 200mg) Duration: 25mg/d of Lamotrigine (for 2wk), then 50mg/d of Lamotrigine (for 2wk), then 100mg/d of Lamotrigine (for 2wk), then a maximum of 200mg/d of Lamotrigine (for 2wk) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern) OR 25mg/d of placebo (for 2wk), then 50mg/d of placebo (for 2wk), then 100mg/d of placebo (for 2wk), then a maximum of 200mg/d of placebo (for 2wk) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern)	
30 CPSP patients in double-blind, placebo-controlled cross-over study of lamotrigine – two 8-week Rx periods separated by 2 weeks of washout. Lamotrigine 200mg/day reduced median pain score to 5, vs. 7 for placebo (p=0.01); no effect for lower doses. 44% of CPSP patients responded to treatment.		

Conclusions

Lamotrigine and Gabapentin have been shown in 1 RCT each to reduce pain; Pregabalin have been shown to improve other important mood and quality of life issues but not pain per se; Levetiracetam has not been shown to alter pain when compared to placebo.

6.9.5 Narcotics

Highlighted Study

Attal et al. (2002)
Methods

Morphine infusion (9-30mg) assessed in double-blind, placebo-controlled crossover study of 15 patients (6 CPSP + 9 SCI pain).
Results
Morphine significantly reduced intensity of brush-induced allodynia only; no change in VAS overall. However, 7 (46%) responded to morphine. All were put on oral morphine after study; only 3 (20%) were taking morphine at one year.

Conclusions
There is moderate evidence (1 RCT) high strength u-opioid agonist levorphanol reduces CPSP.
There is moderate evidence (1 RCT) I.V. morphine results in analgesia; only a minority may benefit from long-term treatment (Attal et al. 2002).

6.9.6 Mexilitine

Highlighted Study

Awerbuch & Sandyk (1990)

Methods
9 patients (8 with stroke) given 150mg mexiletine x 3 days followed by 300mg/day for 3 days and then 10mg/kg/day x 1 month.
Results
Significant improvement in pain in 8 of 9 patients.

Conclusions
There is limited evidence Mexilitine reduces CPSP.

6.9.7 Motor Cortex Stimulation

Highlighted Study

Katayama Y et al. (1998)

Methods
31 CPSP patients treated with motor cortex stimulation through surgically implanted devices delivering a pulse of 0.2 msec duration, frequency of 25-50 Hz and intensity of 2-8V; Stimulation applied 10-20 min for each time.
Results
Satisfactory pain control was achieved in 74% (23) during first one-week period.

Highlighted Study

Katayama et al. (2017)

Methods
45 patients with CPSP received spinal cord stimulation (SCS) and if that failed were considered for deep brain stimulation (DBS) +/or motor cortex stimulation (MCS). VAS used to evaluate.
Results

Stimulation at higher levels produced more frequent satisfactory pain control (7% SCS, 25% DBS, 48% MCS).

Highlighted Study

Lefaucheur et al. (2004)		
RCT (4) N_{start}=60 N_{end}=52 TPS=Chronic	E: 10Hz rTMS C: Sham rTMS Duration: 20min/d, 1x/wk for 2wk + 1wk of observation	• Visual Analog Scale: % Pain Reduction (+exp)
rTMS and sham stimulation were compared in patients with pain after stroke, spinal cord injury, brachial plexus injury, or trigeminal neuralgia resulting in a reduction of pain.		

Conclusion

There is limited evidence that brain stimulation reduces CPSP (motor cortical stimulation> deep brain stimulation > spinal cord stimulation).

rTMS may provide benefit for post-stroke pain when compared to sham stimulation.

6.9.8 Fluvoxamine

Highlighted Study

Shimodozono et al. (2002)

Methods

28 patients with CPSP received SSRI fluvoxamine 50 mg/day. Doses increased or maintained (max 125 mg/day) depending on symptoms for 2-4 weeks.

Results

Patients mean VAS and Zung's Self-rating Depression Scale decreased ($p<0.01$). Subset analysis showed in stroke < 1 year, VAS decreased ($p<0.001$); > 1 year no change in VAS.

Conclusion

There is limited evidence SSRI fluxoxamine is useful in CPSP relatively early after stroke onset.

6.9.9 Algorithmic Treatment Approach to Central Post Stroke Pain

The majority of patients suffering from CPSP are intractable to therapeutic interventions.

First line treatments include tricyclic antidepressants and antiepileptics, in particular Gapapentin and Lamotrigine.

Second-line treatment would include stronger narcotic analgesics such as Oxycodone (short-acting or long-acting) or Morphine (long-acting).

Alternative anti-epileptics such as Dilantin, Carbamazepine and Pregablin.

Conclusions

A wide range of pharmacological interventions are available for the treatment of central pain post stroke, including anticonvulsants, antidepressants, anesthetics, and narcotics.

The majority of these require further research to determine their effectiveness in pain reduction with Gabapentin, Lamotrigine and perhaps Amitriptyline showing the most promise; narcotics are a treatment of last resort.
Repetitive transcranial magnetic stimulation may be effective in reducing central pain post stroke when delivered at higher frequencies, although further research is required.

6.10 Fatigue

6.10.1 Introduction

Fatigue is a subjective term and there is no universally accepted definition (Choi-Kwon & Kim 2011, Van Eijsden et al. 2012). Abnormal or pathological fatigue has been characterized as a state of general tiredness or weariness unrelated to exertion levels that is usually not ameliorated by rest (De Groot et al. 2003). A review by Choi-Kwon & Kim (2011) proposed that the predisposing factors to post-stroke fatigue (PSF) be classified into 3 main categories: (1) physiological, including pre-stroke fatigue, functional disability, medical comorbidities, sleep disturbances, nutritional problems, and medication; (2) psycho-cognitive, including depression and cognitive dysfunction; and (3) organic, including damage to particular brain areas with consequent neurochemical alterations due to perfusion deficit in stroke.

Prevalence, Risk, and Consequences of Post-Stroke Fatigue
Estimates of the prevalence of PSF vary widely, from 30-74%, depending on the measure used to assess it and the timing of assessment. Many studies demonstrated that the patients continue to experience PSF without much fluctuation over time. There is also evidence that fatigue both increases and decreases in frequency over time post stroke (Duncan et al. 2012).

The most common type of PSF experienced was reported to be physical fatigue (69.6%), followed by activity-related fatigue (67.9%) and mental fatigue (62.5%) (Muina-Lopez & Guidon 2013). The presence of PSF was found to restrict participation in various activities including those involving self-care (Miller et al. 2013, Young et al. 2013), which can negatively affect functional recovery especially when comorbid depression exists (Badaru et al. 2013).

Conclusions Regarding Prevalence of Post-Stroke Fatigue
Fatigue is a common condition post stroke, although there is variation in reported rates.
Risk factors for post-stroke fatigue include depression, chronic pain, and sleep disorders; it may be associated with poor recovery.

6.10.2 Treatment of Post-Stroke Fatigue

Treatment of PSF is an often varied or even unmet despite its high prevalence and negative impact on patient outcomes. This situation may be due to variation in its clinical definition and assessment, limited understanding of its pathophysiology, as well as a paucity of effective treatment options. An updated Cochrane review of various interventions for PSF included 12 trials with 708 participants (Wu et al. 2015a). The authors found no evidence to support any of the studied interventions and noted major methodological limitations including small sample sizes, high risk of bias, and PSF as a secondary outcome (Wu et al. 2015b).

Modafinil

Highlighted Study

Poulsen et al. (2015)		
RCT (6) N_{start}=41 N_{end}=36 TPS=Chronic	E: Modafinil C: Placebo Duration: 400mg modafinil, 7d/wk for 12wk OR 400mg placebo, 7d/wk for 12wk	• Multidimensional Fatigue Inventory (-) • Fatigue Severity Scale (+exp) • Stroke Specific Quality of Life Questionnaire (+exp)

Highlighted Study

Bivard et al. (2017)		
RCT (6) N_{start}=36 N_{end}=36 TPS=Chronic	E: Modafinil C: Placebo Duration: 200mg modafinil, 7d/wk for 6wk	• Multidimensional Fatigue Inventory (+exp) • Stroke-Specific Quality of Life scale (+exp)

Highlighted Study

Lillicrap et al. (2018)		
RCT (6) N_{start}=36 N_{end}=36 TPS=Chronic *12 month follow-up to Bivard et al. (2017)	E: Modafinil C: Placebo Duration: 200mg modafinil, 7d/wk for 6wks	• No between group comparisons for follow-up

Cognitive Therapy/Graded Activity Training

Highlighted Study

Zedlitz et al. (2012)		
RCT (8) N_{start}=73 N_{end}=68 TPS=Subacute	E: Cognitive therapy + Graded activity training C: Cognitive therapy Duration: 2hr/d, 1d/wk for 12wk (cognitive therapy) + 2hr/d, 2d/wk for 12wk (graded activity training) Statistical Analysis: ANCOVA	• Checklist Individual Strength – Fatigue (+exp) • Self-Observation List – Fatigue (+exp) • Hospital Anxiety and Depression Scale (-) • Stroke Adapted Sickness Impact Profile (-) • 6-Minute Walk Test (-) • Visual Analog Scale (-)

Conclusions

Limited evidence shows that and cognitive behavioural therapy with graded activity training may be effective treatments for post-stroke fatigue.
Antidepressants may not be effective treatments.
The literature is mixed on the use of Modafinil for treating post-stroke fatigue.

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