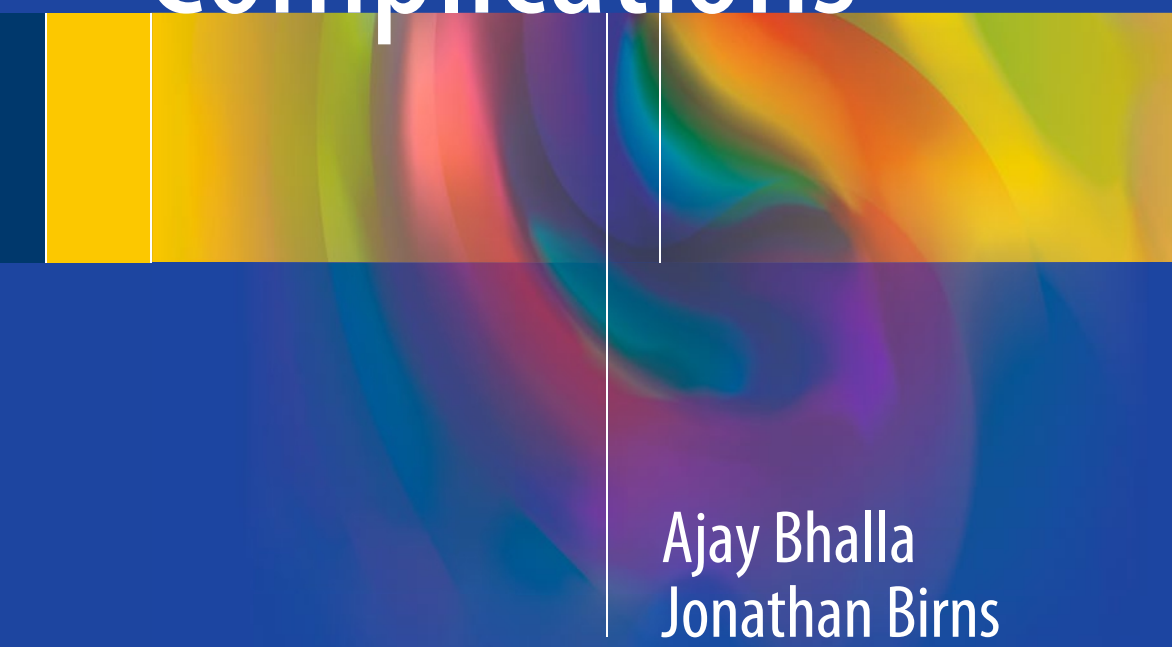
Management of Post-Stroke Complications



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Foreword

Post-stroke complications occur with distressing frequency, while our understanding and management remain limited. Many books deal with stroke and often include chapters on complications, but to my knowledge, this is the first book entirely devoted to the subject.

The approach is comprehensive while mindful of practical applications, aided by diagrams and key statements. The contributors have been carefully selected, and the chapters are arranged for easy reference. We are very aware of timing of treatment in the hyperacute phase of stroke. Only now are we beginning to learn about the timing and the nature of interventions required thereafter, not only to avoid complications, but to assure maximal recovery. This volume goes a long way in systematising what we know and setting the stage for further progress.

May this book prove a landmark in improving our ability to understand, treat, and prevent post-stroke complications.

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Chapter 1
Introduction

Ajay Bhalla and Jonathan Birns

Abstract Prevention and specialist management of complications that arise following stroke may improve both short-term and long-term outcome. Anticipating potential post-stroke complications may also expedite initiation of preventative and therapeutic measures in high-risk patients. Complications related to stroke are both dynamic and transitional in their onset and are heterogeneous in nature. Neurological issues as a direct influence of the stroke on the brain include cerebral oedema, haemorrhagic transformation of infarction, and seizure activity, as well as death subsequent to brain herniation. Neuropsychiatric complications include cognitive impairment, delirium, depression, and anxiety. Complications resulting from impairments after stroke include venous thromboembolism, urinary tract infections, aspiration pneumonia, pressure sores, falls, malnutrition, and complications arising from the cardiac systems. Patients with stroke should therefore be closely monitored for the early detection of these complications. Multidisciplinary stroke unit care provides the best environment to prevent and manage these complications effectively.

Keywords Complications • Stroke • Post-stroke • Medical • Neurological

Key Messages
- Post-stroke complications are common, with a frequency reported between 30 and 95 %.
- Post-stroke complications are heterogeneous in nature and include both medical and neurological complications.
- Post-stroke complications are associated with poor outcome, including death and disability.
- Many post-stroke complications are potentially preventable and treatable.
- Stroke unit care offers the most effective strategy in identifying high risk individuals.

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Complications Post-stroke

Complications post-stroke have traditionally been neglected, but there is increasing evidence that medical complications are common sequelae after stroke, and rates have been reported between 30 and 96 % in a variety of studies [1–9]. The variation of frequency observed in these studies has been considered to be driven by the heterogeneity of study design. Studies varied in their diagnostic and patient selection criteria; in being single-centre or multicentre, population or hospital-based, prospective or retrospective; or including patients with differing stroke subtypes at different phases of their stroke recovery and pathway, or concentrating on a specific complication such as venous thromboembolism [10]. In the Randomised trial of Tirilizad Mesylate in Acute Stroke (RANTTAS), of 279 patients enrolled, 95 % had at least one complication [1]. The most common complication was pneumonia, occurring in 5 % of patients, and the most common serious neurological complication was new cerebral infarction or extension of infarction, occurring in 5 % of patients. This trial employment of rigorous identification and assessment of safety data collection and acute prospective methodology has been considered to be the reasoning for the very high percentage of complications seen. Complications that tend to occur in the subacute phase of stroke during the rehabilitation phase have tended to be under-reported in studies purely focusing on the hyper-acute phase [4, 5, 8, 9]. Complications such as falls, pain, venous thromboembolism, and depression have tended not to be explored in acute studies that focus on management during the first week only. Conversely, studies focusing on the medical complications occurring solely in rehabilitation units [1–3, 6, 7] tend to under-report neurological complications that occur as a direct result of the initial cerebral insult such as haemorrhagic transformation of infarction, cerebral oedema, brain herniation, and death. Knowledge of the frequency of complications post-stroke will help to benchmark the quality of stroke services provided.

Complications post-stroke can be defined in a number of ways (see "Box 1.1" below) and often relate to whether the complications are directly neurological or non-neurological in nature [6]. The way complications have been recorded in studies varies considerably due to different methods of diagnostic criteria and inter-observer reliability [11–13]. For example, deep-vein thrombosis rates vary between 11 and 75 % in different studies owing to different imaging modalities used (Doppler versus iodine radiolabelling) [14–16]. Other complications such as depression may go undetected clinically if nonsensitive assessments are carried out and the study design is retrospective in nature [17].

Box 1.1 Post-stroke Complications

- *Neurological*: recurrent stroke, haemorrhagic transformation of infarction, epileptic seizures
- *Cardiac*: myocardial infarction, cardiac failure, cardiac arrhythmias

- *Infection*: urinary tract infection, chest infection
- *Thromboembolism*: deep vein thrombosis, pulmonary embolism
- *Gastrointestinal*: dysphagia and nutrition
- *Genitourinary*: urinary and faecal incontinence
- *Complications of immobility*: falls and fractures, pressure sores, spasticity, contractures
- *Cognitive*: dementia and delirium
- *Pain*: shoulder pain, central post-stroke pain
- *Psychological*: depression, anxiety, emotionalism, fatigue

The timing of post-stroke complications is important in relation to the onset of stroke, as this will have an impact on prognosis and recovery. Langhorne et al. demonstrated that the majority of complications develop within the first 6 weeks of stroke [3] (Fig. 1.1). Langhorne et al. identified complications such as pain, infections, and pressure sores as early onset with an overall complication rate of 34 %, 24 %, and 21 %, respectively. During follow up at 6, 18, and 30 months, other complications such as falls (25 %) and depression (16 %) appeared to develop gradually [3]. With regard to depression, this may reflect that this symptom may have been under-recognised in the acute phase or there was a reluctance to assess this. Other

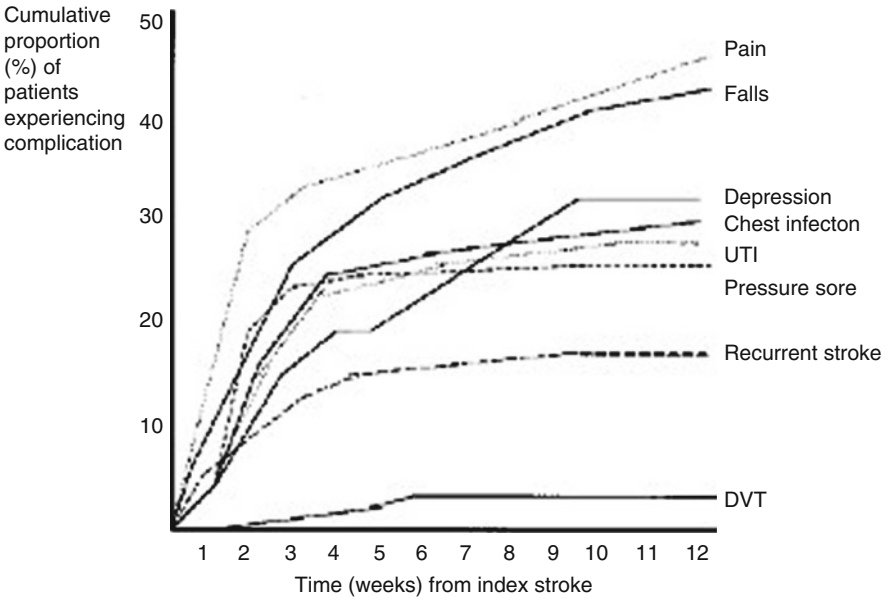

Fig. 1.1 Timing of symptomatic complications after stroke. Results are expressed as the cumulative proportion (%) of patients who were noted to have a symptomatic complication in hospital during the first 12 weeks after stroke. *UTI* indicates urinary tract infection, *DVT* deep-vein thrombosis (From Langhorne et al. [3]. Reprinted with permission from Wolters Kluwer Health)

studies have shown that neurological complications peak during the first week after stroke (43 %) and that between week 2 and 22 after stroke, 22 % of complications are related to immobility [1, 3, 8].

Prevention

In order to prevent complications after stroke, it is important to identify which patients are at particularly high risk of complications. Davenport et al. identified a number of important factors that included older patients, pre-existing disability and handicap, diabetes mellitus, total anterior circulatory stroke, presence of urinary incontinence, and length of hospital stay beyond 30 days [6]. Other factors such as stroke severity measured by the functional independence measure (FIM) have been associated with higher risk of infections, pressure sores, anxiety, and depression [3]. Identification of these factors is crucial in order to implement preventative strategies and continue monitoring for further recognition and treatment early in the course of stroke.

The impact of post-stroke complications is considerable. It is associated with high mortality rates, increased disability, long lengths of stay, institutionalisation, and rising costs of stroke care [1, 5]. In-hospital mortality rates from medical complications vary between 29 and 40 % [6, 18]. Early deaths during the first week were associated with the direct insult of the stroke itself leading to cerebral oedema, but deaths in the following weeks were due to potentially preventable medical complications such as infections, venous thromboembolism, and cardiac complications [19, 20]. Over half the patients who died (14 %) at 3 months following recruitment into the RANTTAS study did so relating to their medical complications [1]. Population-based registers have also demonstrated that incurring at least one medical complication in hospital leads to increased length of stay and increased 30-day (12 %) and 1-year (35 %) mortality [21]. Medical complications may also impair recovery independently from age and stroke severity and can lead to worsening disability rates through a number of mechanisms including impeding restorative rehabilitation and precipitating depression, and thus lowering motivation [1, 10]. Physiological parameters such as hypoxia, pyrexia, dehydration, and low blood pressure can also affect neuronal cell function in the ischaemic penumbra and thus impair cerebral function, leading to stroke progression [22, 23].

What is evident is that many post-stroke complications are preventable through multidisciplinary assessment and close attention to detail through structured protocols [24]. Ingeman et al. demonstrated that high-quality processes of care tailored around stroke unit admission, early mobilisation, initiation of anti-platelet treatment, and early therapy assessments were associated with lower risks of medical complications [24]. The hallmark of organised stroke care in specialist stroke units lends support to this model whereby one of the main mechanisms of survival benefit is through the prevention of and early interventions for medical and physiological

complications [25, 26]. In a systematic review, interventions to prevent aspiration, treat pyrexia, and improve oxygenation were shown to be used more frequently in stroke units compared to conventional settings. In addition to this, stroke unit care reduced complications associated with immobility, such as infections and thromboembolism [25]. We are now just beginning to understand and appreciate the effects of adverse medical and neurological complications after stroke. Improving the awareness of stroke clinicians and multidisciplinary professionals involved in stroke care of post-stroke complications is crucial, and ongoing education and training is paramount. Stroke specialists need to be aware of the significance of observations for post-stroke complications and be alert for atypical presentations of these complications. Staff also need to be committed to the use of protocols for the prevention and early detection of post-stroke complications. More research, through well-designed randomised controlled trials, is required to understand the best policies for preventing complications after stroke and for delivering interventions that may lessen the adverse effects on individuals.

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Chapter 2
Early Neurological Deterioration

Ajay Bhalla

Abstract Early neurological deterioration is common after acute stroke and is associated with increased disability and mortality. There are a number of mechanisms involved with neurological deterioration which can be divided into firstly, neurological causes as a result of the direct consequence of the neurological insult to the brain, and secondly, non-neurological causes such as abnormal physiological parameters. Both of these mechanisms can lead to secondary neuronal damage within the ischaemic penumbra. Many of these factors are potentially reversible, and therefore it is crucial that appropriate monitoring is undertaken to identify high risk patients.

Keywords Neurological deterioration • Haemorrhagic transformation • Cerebral oedema • Physiological homeostasis

Key Messages

- Early neurological deterioration is a frequent occurrence and is associated with increased morbidity and mortality.
- Neurological factors such as haemorrhagic transformation, cerebral oedema, haematoma expansion, poor collateral blood supply, clot progression, re-occlusion, and post-stroke seizure are important mechanisms of early neurological deterioration.
- Non-neurological factors leading to abnormal physiological homeostasis such as changes in blood pressure, glycaemic, oxygen, temperature, and hydration status can lead to early neurological deterioration.
- Regular physiological monitoring is important to identify high-risk patients for early neurological deterioration as well as delivery of appropriate interventions to maintain physiological homeostasis.

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Introduction

Early neurological deterioration (within 48–72 h of onset) after acute stroke is a common sequela and occurs in between 25 and 45 % of patients [1]. The variation observed in clinical practice reflects differing diagnostic criteria, selection bias, case mix (stroke subtype), interventions offered (such as thrombolysis), and time frame [2, 3]. For example, early neurological deterioration may be defined as a change in the National Institute of Health Stroke Scale Score (NIHSS) by 2 or more points from admission to day 5, or a change in at least 2 points in the Scandinavian Stroke Scale (SSS) from admission to 24 h [3, 4]. Early neurological deterioration is associated with both short and long term morbidity and mortality [4, 5]. A study by Kwan et al. demonstrated that patients with early neurological deterioration were more likely to have worse functional outcome, longer lengths of stay in hospital, higher fatality rates in hospital, and higher rates of institutionalisation than those patients without early neurological deterioration [4]. The main underlying causes of early neurological deterioration include direct neurological complications (haemorrhagic transformation, raised intracranial pressure (ICP), recurrent stroke, clot progression, and seizures) and non-neurological factors (abnormal physiological disturbances such as hyperglycaemia, dehydration, hypoxia, pyrexia, and changes in blood pressure (BP), as well as infections and other metabolic disturbances) [1, 6]. These factors are of importance as they are crucial in maintaining the viability of the ischaemic penumbra and are potentially reversible if managed correctly in a timely fashion in the context of organised stroke unit care [7] (Table 2.1).

Table 2.1 Factors associated with early neurological deterioration

Neurological causes	Non-neurological causes
Haemorrhagic transformation of cerebral infarct	Sepsis
Cerebral oedema (leading to raised intracranial pressure)	Metabolic disturbance such as hyponatraemia and hypercapnia
Clot progression and re-occlusion (following thrombolysis)	Drugs leading to toxic encephalopathy
Recurrent stroke	Hyperglycaemia
Poor collateral circulation	Hypoxia
Large vessel occlusion (leading to hypodensity >33 % in the middle cerebral artery territory, hyperdense middle cerebral artery sign on CT imaging)	Blood pressure (high and low)
Post-stroke seizure	Dehydration
	Pyrexia
	Atrial fibrillation

Neurological Causes of Early Deterioration Post-stroke

Neurological causes account for around 50 % of deaths during the first week of stroke [8] with the majority of deaths being attributed to cerebral oedema (44 %) and parenchymal haemorrhage (25 %) [2]. There are a number of clinical and radiological factors that predict early neurological deterioration [3, 9, 10]. Patients with large vessel occlusion associated with total anterior circulatory stroke tend to undergo early neurological deterioration, as do patients with primary intracerebral haemorrhage (ICH) (30 % will deteriorate in the first 6 h post onset due to haematoma expansion) [11] (Fig. 2.1a, b). Initial stroke severity is also another important factor for early deterioration with one study suggesting that 66 % of patients with ischaemic stroke will deteriorate neurologically if their initial NIHSS was greater than seven [12]. Other clinical factors such as initial reduced consciousness, older age, admission delay, history of diabetes, coronary artery disease, and the presence of atrial fibrillation also tend to favour increased risk of early neurological deterioration [2]. The main neurological causes explaining early neurological deterioration include haemorrhagic transformation of infarcted brain, cerebral oedema, reocclusion and clot progression, recurrent stroke, failure of collaterals, and post-stroke seizure activity.

Haemorrhagic Transformation

Haemorrhagic transformation after ischaemic stroke is not uncommon with rates of up to 50 % being reported at variable stages post infarction [13]. It is responsible for approximately 10 % of cases which present with early neurological deterioration [14]. The majority of haemorrhagic transformation occurs within the first 72 h of ischaemic

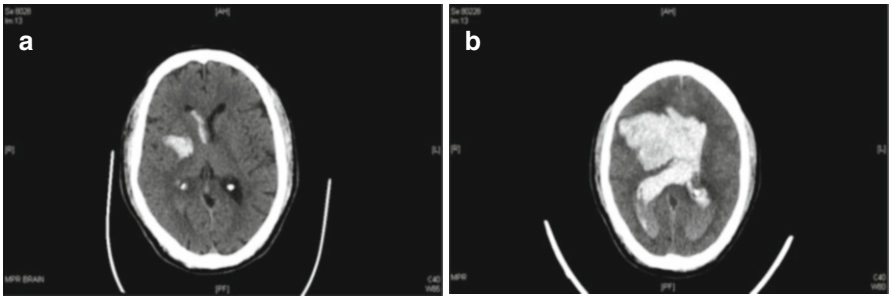

Fig. 2.1 (**a**) Right basal ganglia haemorrhage with extension into right lateral ventricle. (**b**) Follow-up scan 3 h later after deterioration, revealing the extension of haemorrhage into right parietal and frontal lobes, occupying lateral and third ventricles and associated midline

stroke and usually within 24 h of those patients receiving intravenous thrombolytic therapy [15]. Fortunately, symptomatic transformation occurs only in a small number of patients, not receiving thrombolytic agents ranging from 0.6 to 6.5 % [15], whereas the incidence of symptomatic transformation occurs between 6.4 and 19.8 % in patients receiving intravenous thrombolytic therapy [15]. Haemorrhagic transformation is classified into four main types: haemorrhagic infarction type 1 (small petechiae) and 2 (confluent petechiae) and parenchyma haematoma type 1 (<33 % of the infarcted area with some mild space occupying effect) and type 2 (>33 % of the infarcted area with significant space occupying effect) [16]. The majority of haemorrhagic transformation appears to be petechial haemorrhage rather than parenchymal hematoma. Although most haemorrhagic transformation is spontaneous, there are number of factors that predict haemorrhagic transformation including the use of intravenous thrombolysis, anticoagulant agents, delayed arterial recanalisation, proximal large artery occlusion, absence of collateral blood supply, increasing age, hypertension, large cortical infarction, and cardio-embolic stroke [17]. The mechanisms for haemorrhagic transformation are twofold, including preserved collateral perfusion in the presence of vascular occlusion and infarction of the vessel wall, resulting in diapedesis of red blood cells from subsequent reperfusion at high pressures [1]. Patients often present with signs of early neurological deterioration with evidence of increasing focal neurological deficits and should be managed with immediate imaging, withholding antithrombotic therapy, and consideration of neurosurgical intervention where necessary.

Cerebral Oedema

A rise in ICP (defined as >20 mm/Hg for 5 min or longer) is frequently seen in patients after ICH and is thought to account for approximately 20 % of cases of early deterioration [18, 19]. This is thought to be secondary to a reduction in cerebral perfusion pressure and thus cerebral blood flow (CBF), leading to further neuronal ischaemia and/or cell necrosis. The risk of raised ICP in patients with anterior circulatory ischaemic stroke is approximately 10–20 %, and the timing of such an occurrence starts after 48 h has evolved, but may occur earlier in posterior circulatory stroke leading to obstructive hydrocephalus [20]. In the European Co-operative Acute Stroke Study (ECASS) 1, early hypodensity greater than one-third of the middle cerebral artery territory (OR: 2.5: 95 % CI: 1.6–4.9) and brain swelling (OR: 1.8; 95 % CI: 1.1–3.2) have also been associated with an increased risk of early neurological deterioration [2]. As a result of raised ICP, cytotoxic and vasogenic oedema are usually maximal at 72 h. Malignant middle cerebral artery territory infarction, which tends to occur in 3 % of all strokes, resulting from proximal occlusions of the middle cerebral artery, is characterised by severe neurological deficits and decreases in consciousness levels which progress relentlessly to death. Cerebral oedema tends to occur in these patients with 24 h of onset, and hemicraniectomy is the only proven evidence-based intervention for malignant stroke syndrome [21]. General strategies to reduce ICP include osmotic diuretics, head elevation, hyperventilation, sedation, and decompressive craniectomy. Steroids tend not be effective, owing to the cytotoxic nature of cerebral oedema post stroke.

Re-occlusion and Clot Progression

Re-occlusion after treatment with intravenous thrombolysis can occur in up to one-third of cases. There are a number of factors that predict re-occlusion including stroke severity, partial recanalisation, ipsilateral carotid stenosis, and poor collateral circulation [22]. The term "clot progression" has been used previously to explain the mechanism for early neurological deterioration, but this has not been demonstrated with serial MR imaging [23]. It has been purported that vessel occlusion with impaired collateral blood supply in association with impaired clear out of distal emboli may be responsible for early neurological deterioration [23]. Recurrent stroke is another important factor in early neurological deterioration, with the risk being reported at 1 % at 6 h, 2 % at 12 h, 3 % at 2 days, and 5 % at 7 days [24].

Impairment of Collateral Supply

The development of collateral circulation plays a pivotal role in protecting the brain from vascular occlusion and subsequent ischaemic damage. A reduction in cerebral blood flow and fall in cerebral perfusion pressure can be tolerated in the presence of an adequate collateral circulation such as that in the setting of large vessel occlusion; this event may be either asymptomatic or potentially devastating, resulting in a massive hemisphere stroke if collateral circulation is inadequate [25]. Studies suggest that the presence of large vessel occlusion is a major independent risk for early neurological deterioration and, in 20 % of cases, has been responsible for deterioration in patients who present with minor stroke who have not undergone reperfusion therapy [20]. In patients with diabetes and chronic hypertension, failure of collateral formation may occur due to the impairment of microvascular function. Once microvascular occlusion occurs, there is a series of complex cellular and metabolic consequences that occur, leading to focal ischaemic damage. These include glutamate release with subsequent intracellular calcium influx, resulting in free radical formation and, ultimately, cellular death [26]. The key factors in determining whether ischaemia will lead to infarction will be determined by the presence and extent of collateral circulation and timing at which recanalisation takes place within the ischaemic penumbra. Imaging techniques such as positron emission tomography (PET), MR and CT, and transcranial Doppler ultrasound remain important diagnostic tools in measuring CBF and haemodynamics [27].

Non-neurological Causes of Early Deterioration

Randomised controlled trials comparing stroke units treating patients in the acute and rehabilitation phase versus conventional care found considerable reductions in early death in patients managed in stroke units [28]. The reduction in early death was believed to be due to monitoring and control of abnormal physiological parameters in the acute phase, which may have aggravated cerebral damage. Significant

differences in the management of acute physiology during the first 2 weeks of admission included the use of intravenous saline in the first 24 h, antipyretic, antibiotic and oxygen therapy, and insulin infusions [29]. Monitoring of acute physiological parameters with treatments aimed at maintaining physiological homeostasis also reduced early neurological progression [30]. There is now experimental evidence suggesting that the control of these abnormal physiological parameters acts as a form of neuroprotection, which may potentially improve the viability of ischaemic neuronal tissue [31]. Interventions aimed at maintaining physiological homeostasis are now recommended by a European review of management of acute stroke care [32]. The main non-neurological causes explaining early neurological deterioration include hypoxia, dehydration, hyperglycaemia, BP, and temperature control. Infections after stroke have already been covered in the previous chapter.

Hypoxia

More than 60 % of stroke patients have been shown to have at least one episode of hypoxia (defined as oxygen saturations <96 %) for more than 5 min [33]. There is also evidence that hypoxia may be particularly more prevalent nocturnally [33]. Stroke patients are at the risk of hypoxia due to abnormalities in respiratory function such as hypoventilation, aspiration pneumonia, atelectasis, sleep apnoea, left ventricular failure, Cheyne-Stroke respiration, and pulmonary embolism. Improving oxygen content may therefore prevent neurological deterioration in stroke. Evidence shows that stroke patients have lower oxygen saturations compared to matched controls, and that positioning patients upright improves oxygen saturations as well as reducing ICP [34, 35]. It has been suggested that supplemental oxygen should be administered if oxygen saturations are below 95 %. The use of supplemental oxygen for non-hypoxic patients is, however, more controversial. In animal models, highly enriched oxygen atmospheres increase mortality [36]. A quasi-randomised controlled study by Ronning and colleagues showed that routine 100 % oxygen supplementation for 24 h after stroke onset had no benefit in survival [37]. However, in a subgroup of minor to moderate stroke patients, this intervention worsened survival at 7 months, possibly as a result of free radical formation during reperfusion. Following these findings, it is not advisable for oxygen therapy to be given routinely to non-hypoxic patients after stroke. This has been confirmed by the recent Stroke Oxygen Study (SOS), which demonstrated that routine oxygen given continuously or specifically nocturnally (2 l/min if baseline saturation >93 % and 3 l/min if ≤93 %) for 72 h compared with control in unselected patients did not improve outcome [38].

Hydration

Initial dehydration is frequently hyperosmolar caused by an inadequate intake of water due to drowsiness or dysphagia, a reduction in thirst, or the presence of infection. Dehydration, leading to a rise in haematocrit and a reduction in BP, can worsen

the ischaemic process during stroke [39]. Stroke patients with high plasma osmolality levels on admission have worse survival at 3 months [40]. Previously, it was recommended that stroke patients should be "under-filled" in order to prevent cerebral oedema, but studies have shown that early intervention with intravenous saline may contribute to improving functional ability in stroke patients managed in a multidisciplinary environment [41]. It was hypothesised that routine use of saline infusions in the first 24 h may have improved cerebral blood flow by limiting dips in systemic BP and preventing dehydration. Trials of haemodilution have not shown any clear benefits as yet and require further investigation [41].

Glucose Control

Some 20–50 % of acute stroke patients are hyperglycaemic (blood glucose >8 mmol/l) on presentation and, in the Copenhagen Stroke Study, 20 % of patients presenting with stroke were diabetic [42, 43]. Various mechanisms have been suggested to explain the worse prognosis in diabetic and hyperglycaemic patients. These patients have impairment of CBF and cerebral autoregulation, reduced leukocyte and erythrocyte deformability, increased thrombotic states, and endothelial cell activation [44]. Hyperglycaemia increases lactic acid production by increasing the available glucose for anaerobic glucose metabolism and also by inhibiting mitochondrial respiration. Most studies agree that high glucose levels after stroke are associated with early neurological deterioration in non-diabetic patients, and this generally holds true with diabetic patients, too [45, 46]. Studies have suggested that hyperglycaemia influences stroke outcome independently of stroke severity and diabetic status [47, 48].

The Glucose Insulin in Stroke Trial-UK (GIST-UK) aimed to address the effects of normalising glucose levels (4–7 mmol/l) using glucose/potassium/insulin infusions within 24 h of stroke in patients with initial glucose levels between 6 and 17 mmol/l [49]. There were no significant differences in mortality or functional disability at 3 months, although the trial was stopped due to low recruitment (933 patients). Blood glucose levels were only reduced by 0.6 mmol/l in the insulin-treated group. Of interest, however, the authors stated that there were significantly lower BP recordings (9 mm/Hg) in the insulin treatment arm compared with the control arm. Whether the vasodepressor response of insulin acutely masked the potential benefit of glycaemic control in this trial was unclear. A randomised controlled pilot trial addressing the effects of aggressive glycaemic control with insulin in patients with glucose levels >8.3 mmol/l post-stroke (Treatment of Hyperglycaemia in Ischaemic Stroke [THIS] study) demonstrated significantly lower glucose levels and non-significant better outcomes in the active treatment arm compared with controls [50]. Further trials are now required to investigate the best regimen of delivering insulin therapy practically, what level of glucose should be treated, and how aggressive glycaemic control should be with monitoring of hypoglycaemic episodes. European guidelines advocate insulin therapy if glucose levels are >10 mmol/l, whilst American guidelines advocate treatment if glucose levels are >7.7 mmol/l [51]. The avoidance of glucose-containing solutions in the first 24 h post-stroke has also been advocated [32, 51].

Blood Pressure

Approximately 30 % of patients have a history of hypertension prior to ischaemic stroke and 80 % have high BP on presentation [52]. Due to spontaneous falls in BP over 4–10 days, approximately 60 % are left normotensive [53]. Hypertension may promote early brain oedema and increase in haemorrhagic transformation [1]. Robinson and colleagues demonstrated that an increase in systolic BP by 10 mmHg after stroke was significantly associated with poor outcome [54]. However, the International Stroke Trial suggested a U-shaped relationship between BP and mortality, with evidence that systolic blood pressures <100 mmHg are associated with early rates of neurological deterioration [55]. The mechanism may be that BP lowering may result in the reduction of CBF because of the impairment of cerebral auto-regulation after ischaemic stroke, which leads to further ischaemia in the penumbra. In view of the potential dangers of acute BP reduction, American Heart Association (AHA) guidelines suggest that BP post-ischaemic stroke should be lowered if systolic BP is >220 mmHg and diastolic BP is >120 mmHg, with a goal of reducing BP by 15 % during the first 24 h. The presence of acute heart failure, aortic dissection, and hypertensive encephalopathy are other indications for acute BP reduction [51]. There have, however, been a number of studies that have attempted to address the dilemma of acute management of high BP after stroke. The China Antihypertensive Trial in Acute Ischaemic Stroke (CATIS) demonstrated that early reduction of BP within the first 24 h to a target BP of 140/90 mmHg in patients with ischaemic stroke failed to translate into significant differences in death and disability at 14 days or at 3 months [56]. The Acute Candesartan Ciliexitil Evaluation in Stroke Survivors (ACCESS) trial demonstrated that Candesartan given for 7 days after acute ischaemic stroke, compared with placebo, improved outcome but with no significant difference in BP between both groups [57]. The CHHIPS study (Controlling Hypertension and Hypotension Immediately Post Stroke) demonstrated that active BP reduction using lisinopril and labetalol in patients with ischaemic stroke with systolic BP levels >160 mmHg not only significantly lowered BP acutely but also reduced mortality at 3 months compared with placebo [58]. The COSSACS (Continue or Stop post Stroke Antihypertensive Collaborative Study) demonstrated that the continuation of antihypertensive therapy post-stroke did not alter outcome defined as death or dependency at 2 weeks, but suggested that this practice was not associated with early neurological deterioration [59]. The SCAST (the angiotensin receptor blocker candesartan for treatment of acute stroke study) demonstrated that early BP reduction was associated with worse function at 7 days and 6 months [60]. The majority of studies have very much focused on ischaemic stroke, but a study evaluating rapid blood pressure lowering in patients with ICH suggested, although there was no difference in primary outcome of death and dependency, there was a significant improvement in functional outcome at 6 months in the active BP-lowering arm [61]. Low BP is uncommon after stroke and may be related to volume loss. Limiting excessive drops in BP by routinely giving patient intravenous saline on admission may be an important element in acute stroke care [28]. Vasopressor drugs such as phenylephrine may be used in treating hypotension; however, randomised controlled trial evidence investigating the use of inotropes is lacking [62].

Temperature Control

Pyrexia following ischaemic stroke may be caused by an acute phase response, disturbance of cerebral mechanisms of temperature control, or the presence of infection. Evidence suggests that temperatures up to 38 C post-acute stroke are associated with increased mortality and morbidity [63]. Fever is common after ICH and correlates with ICH volume and third ventricular shift, suggesting a role of hypothalamic compression in "central fever" [64]. A fever >38.5 C at 72 h is an independent risk factor for mortality and disability post-ICH [65]. Although there are no clinical data to guide clinicians as to the appropriateness of routine use of antipyretics, recommendations have been made to maintain normothermia (36–37 °C) either using paracetamol when required or treating underlying infection [32]. Induced hypothermia (32–33 °C) has been shown to reduce mortality in patients with severe middle cerebral artery stroke, but large trials are required to confirm the use of this intervention given the risk of raised ICP on rewarming [66].

Conclusion

Early neurological deterioration is an important complication after stroke and is associated with poor outcome including in-hospital death and longer-term survival. There are a number of important predictors, including radiological and clinical factors, which may identify patients at high risk of early neurological deterioration. Direct neurological factors as a result of either cerebral infarction or haemorrhage play an important role in understanding the mechanism of neurologic worsening. Systemic processes such as abnormal physiological factors are also crucial in aggravating secondary neuronal damage and, therefore, identification of these factors through monitoring should aid correction through acute stroke unit care. These interventions may reduce the frequency of such neurological complications and facilitate early recovery and improved functional outcome, but this need to be tested and confirmed in randomised controlled trials.

Patient Questions

Q. What are the main causes of early deterioration after stroke?

A. Early neurological deterioration occurs in 25–45 % of all stroke patients and can be associated with a worse prognosis than in those patients without such deterioration. The main causes of deterioration result from the direct consequence to the injured brain. Bleeding into the injured brain (haemorrhagic transformation), expansion of bleeding after cerebral haemorrhage, raised cerebral intracranial pressure (cerebral oedema), seizures, and recurrent stroke are the main

mechanisms responsible. Other important factors include changes in blood pressure, oxygen, temperature, and glucose levels, which may be responsible for aggravating further brain injury.

Q. What treatments can be offered to reduce the impact of early neurological deterioration?

A. Many of the factors involved with early neurological deterioration are potentially reversible, and therefore it is important that regular monitoring of physiological variables (vital signs such as blood pressure, temperature, glucose, oxygen levels, and signs of infection) as well as regular neurological assessments occur regularly. This should be carried out in an acute stroke unit. There are many interventions that are used in the early phase of stroke to correct physiological variables, but how aggressively to manage them is still unclear and requires further research.

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Chapter 3
Post-stroke Cardiac Complications

Laura C.S. Izzard and Ajay Bhalla

Abstract Cardiac complications such as myocardial infarction, heart failure, cardiomyopathy, and arrhythmias are common after acute stroke and are associated with increased morbidity and mortality. Cardiac disease shares a similar burden of risk factors with stroke. Patients with pre-existing cardiac disease have both larger and more severe strokes. Notably, cardiovascular disease is the most common cause of death in 1-year stroke survivors. Hence, timely recognition and prompt treatment of cardiac complications early on in their course is needed, particularly in high-risk patients with comorbidities (such as diabetes, chronic heart failure, and renal insufficiency), in order to improve overall prognosis and prevent cardiac related mortality post-acute stroke.

Keywords Stroke • Cardiac • Complications • Myocardial infarction • Chronic heart failure • Cardiomyopathy • Arrhythmias

Key Messages

- Cardiac complications following acute stroke are common and associated with increased mortality rates.
- Both stroke and cardiac disease share similar burden of risk factors.
- Patients with congestive cardiac failure, diabetes, renal insufficiency, prolonged QTc on ECG, and severe strokes have the poorest prognosis and greatest risk of serious cardiac complications (e.g. cardiac failure, arrhythmias, cardiac arrest).
- How best to investigate patients with cardiac complications post-stroke, appropriate risk stratification, the timing of the necessary intervention(s), the type of monitoring needed, and the duration of such monitoring requires clarification.

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Introduction

Central nervous system disorders are known to cause a wide array of cardiovascular system dysfunction, ranging from electrocardiogram (ECG) changes and transient myocardial dysfunction to sudden cardiac death [1]. Cardiac mortality is the second commonest cause of death behind direct neurological causes (see Fig. 3.1) Therefore, cardiac abnormalities and complications are common post-stroke and are often apparent early after stroke onset [2]. Timely recognition and prompt treatment may serve to ameliorate cardiac complications, such as cardiac dysrhythmias, early on in their course, thus improving outcomes. Moreover, as in the case of post-stroke myocardial infarction, there may be a need to withhold or delay conventional treatment, such as revascularisation and thrombolytic therapy, with both treatment modalities posing a potential bleed risk and thus further injury to the stroke-afflicted brain. However, little data exists to guide the management of such complications. Consequently, the need to study the effects of medical complications on stroke recovery, and to improve the interventions intended to prevent and treat such complications, is deservedly acknowledged in the literature [3].

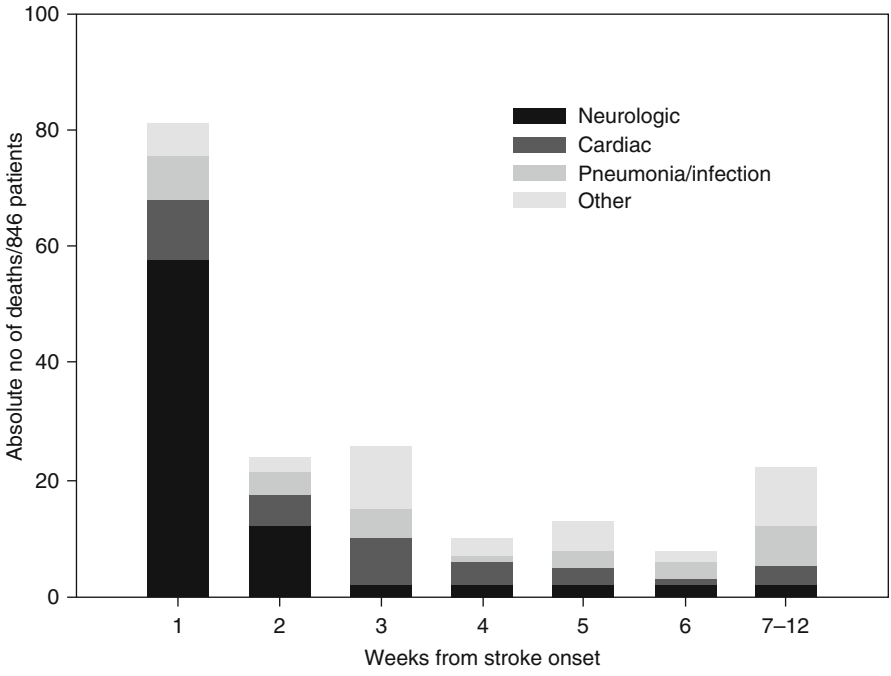

Fig. 3.1 Frequency distribution of numbers of deaths and cause of death per week from stroke onset; weeks 7–12 have been compressed because of low absolute numbers (From Prosser et al. [2]. Reprinted with permission from Wolters Kluwer Health)

Cardiac Complications

The annual risk of serious coronary artery events including myocardial infarction after stroke equates to 2 %, with the highest risk being in the first 3 months with a reported cardiac mortality rate between 2 and 6 % [2]. Cardiac death rate is higher in the first 4 weeks after stroke and then gradually declines [3]. However, the vast majority of deaths after ischaemic stroke can be directly attributed to the initial neurologic injury. At least one of several serious cardiac events such as acute coronary syndromes, symptomatic heart failure, ventricular tachycardia, ventricular fibrillation, and cardiac arrest have been reported to occur in up to 19 % of stroke patients within the first 3 months of stroke, with a peak occurrence in the first 3 days of stroke [2]. This highlights the importance of cardiac monitoring in the acute phase of stroke [4, 5].

Serious cardiac events are deemed as poor prognostic factors, with higher case fatality rates being described in patients (46 % vs 21.3 %) with such events compared with those without at 3 months after onset [3]. Data from the Virtual International Stroke Trials Archive (VISTA) has demonstrated patients with congestive heart failure, diabetes, severe strokes, renal insufficiency, and prolonged QTc on ECG to be at particularly high risk [2]. There is therefore a need to identify these high-risk patients and employ pre-emptive strategies which would encompass the monitoring, investigation, and subsequent treatment of this high-risk cohort of patients post-stroke.

The serious nature of cardiac complication after stroke is not surprising, given that cardiac disease shares a very similar burden of risk factors with stroke. Patients with pre-existing heart disease (atrial fibrillation in particular) have been shown to have both larger and more severe strokes [6]. Furthermore, such severe strokes are typically associated with a more pronounced inflammatory and metabolic stress response, which potentially leads to more severe cardiac and autonomic derangement [7]. It is therefore important to consider whether cardiac abnormalities caused the stroke, arose as a consequence of the stroke, or are unrelated to the stroke, when considering the appropriate management of cardiac complications. The main post-stroke cardiac complications that will be described include myocardial infarction, cardiac failure (including cardiomyopathy), and cardiac dysrhythmias.

Myocardial Infarction

Stroke patients have an increased risk of death resulting from myocardial infarction when compared to the general population [8], with cardiovascular disease being the most common cause of death in 1-year stroke survivors [9]. A substantial amount of stroke patients have asymptomatic coronary stenosis, thus indicating coronary artery disease [10]. Despite this known increased risk and, indeed, the presence of asymptomatic coronary artery disease, systematic evaluation of asymptomatic

patients with coronary artery disease in the form of coronary angiography is not currently recommended following a recent ischaemic stroke. This, in part, may have resulted from safety concerns regarding coronary angiography in stroke patients and relates to the increased risk of brain haemorrhagic transformation and parenchymal haemorrhage secondary to anticoagulation therapy during the procedure. In a study published in 2010 in which coronary angiography was conducted to show previously unknown coronary artery disease in a large cohort of patients with ischaemic stroke, coronary angiography proved to be safe even 6–11 days post-stroke (acute phase), with only 1 adverse procedural event (groin haematoma), in the 315 patients who underwent coronary angiography [10]. Nonetheless, whether stroke patients with asymptomatic coronary artery disease should be investigated with coronary angiography as a matter of routine continues to be debated. A meta-analysis of 39 studies which included 65,996 patients with a mean follow-up of 3.5 years post-acute stroke or transient ischaemic attack, revealed the annual risk of both myocardial infarction and non-stroke vascular death to be approximately 2 %. The accumulation of risk was linear, with the risk of myocardial infarction 10 years after acute stroke being approximately 20 % [11]. Additionally, stroke of carotid origin is viewed as a coronary heart disease risk equivalent implying that this should hold true to stroke patients without carotid artery disease or without coronary artery disease [12].

There are a number of mechanisms through which acute stroke may induce myocardial injury. These include catecholamine-induced cardiac dysfunction, whereby neurohumoral changes post-stroke can contribute to cell death, coronary artery vasospasm, and cardiac arrhythmias [1, 13, 14]. Indeed, stroke affecting the insular cortical area, which is involved in normal cardiac autonomic regulation, has been associated with adverse cardiac events including myocardial infarction [14]. This implies neurogenic cardiac damage due to autonomic activation after acute ischaemic stroke as a potential mechanism. Interestingly, there is now greater focus on the association between specific markers of myocardial injury and acute stroke and whether examining the levels of cardiac muscle regulatory protein troponin T (cTnT) can lend support to the different pathophysiological mechanisms of myocardial injury and subsequent diagnostic cardiac work up [10]. Increased levels of troponin are seen in between 5 and 34 % of patients with acute ischaemic stroke, and there is an association between elevated levels and stroke severity, cardiovascular abnormalities (including left ventricular dysfunction, hypotension, and pulmonary oedema), right insular cortical involvement, and unfavourable short- and long-term outcomes [15]. The main causes of elevated troponin levels in the absence of renal dysfunction are twofold. Acute coronary syndrome in association with acute stroke caused by coronary vascular occlusion leading to myocardial necrosis is one mechanism, but the prevalence of this event using coronary angiography is limited [10]. Secondly, cerebral autonomic dysregulation with subsequent catecholamine surge leading to myocardial injury and ventricular dysfunction is an increasingly recognised phenomenon [14]. Whether coronary angiography should be implemented in patients with elevated Troponin levels is unclear, and such intervention needs to be carefully balanced with the risks of the procedure and subsequent therapeutic

intervention such as dual antiplatelet and anticoagulation therapy. Clearly, careful risk stratification is important in identifying patients who are at high risk of cardiac events, and these may include patients with previous cardiac events, diabetes, peripheral vascular disease, atrial fibrillation, and large-vessel strokes. How best to investigate these patients however, and the timing of such intervention, requires clarification [16].

Cardiac Failure

The prevalence of chronic heart failure increases with age, with 1–2 % of adults in developed countries living with a chronic heart failure diagnosis. In those over 80 years old, one in ten adults have chronic heart failure, and those aged over 40 have a lifetime prevalence of one in five [17, 18]. Studies have indicated that the risk of ischaemic stroke is two to three times higher for patients with chronic heart failure than it is for patients without chronic heart failure [19, 20]. In fact, epidemiological data suggest that between 10 and 24 % of patients with stroke have evidence of congestive heart failure, and that the stroke risk is highest within the first month after diagnosis of heart failure but normalises within 6 months [21–24]. It is therefore unsurprising that prospective studies have demonstrated that the annual stroke rate is increased in patients with congestive cardiac failure and concomitant atrial fibrillation, with annual stroke rates described between 10 and 16 % [25]. Moreover, there is reportedly a 9–10 % risk of recurrent stroke per year in stroke patients with chronic heart failure [26].

There are a number of mechanisms that contribute to stroke in patients with chronic heart failure. These include thrombus formation secondary to left ventricular hypokinesia, reduced ejection fraction and atrial fibrillation, increased coagulation (D Dimer and thrombin concentration), increased endothelial cell activation and damage, in addition to both large- and small-vessel cerebrovascular disease with their association with both hypertension and diabetes [27].

Patients with congestive heart failure have higher mortality associated with stroke, with one study depicting a doubling risk of death (OR: 2.3; 95 % CI, 1.8–2.9) [20]. In addition, patients with congestive heart failure have more severe neurological deficits and longer hospital stays than those without heart failure [24]. Of note, acute coronary syndrome, arrhythmia, excessive fluid hydration, and poor or non-compliance with medication can precipitate a worsening of heart failure in high-risk patients. There is also increasing evidence of an association between the severity of cardiac dysfunction and cerebral ischaemic lesions described on MR findings giving rise to “silent strokes” [28]. These features may be exhibited by alterations in neuropsychological function including decreased attention, memory loss, and concentration deficits [29], occurring as a consequence of impaired cerebrovascular reactivity. The Rotterdam Scan Study demonstrated that these “silent strokes” on MR imaging occurred in approximately 20 % of patients aged between 60 and 90 years with congestive heart failure [30].

Echocardiographic wall motion abnormalities have also been described in patients with both ischaemic and haemorrhagic stroke as a result of disturbance in autonomic central control, resulting in excessive catecholamine release. Left apical ballooning and subsequent left ventricular dysfunction, leading to a unique kind of cardiomyopathy termed Takotsubo syndrome, has been described [31]. This syndrome is associated with impaired apical ventricular contraction, resulting in an increased risk of sudden death, congestive heart failure, and arterial thrombus formation. This syndrome is seen in patients with elevated troponin levels in the absence of obstructive coronary artery disease and is associated with temporary ST elevation followed by significant T wave inversion in the anteroseptal leads on a 12-lead ECG. Incidence of this syndrome in a Japanese hospital-based study has been described in 1–2 % of patients with ischaemic stroke acutely [32]. A similar incidence has been reported in patients with subarachnoid haemorrhage [33]. Tokotsubu syndrome has a predisposition to females, with stroke affecting the insular cortex and brain stem involvement [34].

Both chronic heart failure and ischaemic stroke represent manifestations of similar underlying risk factors, such as diabetes and hypertension [35]. However, present studies regarding additional risk factors for stroke in patients with heart failure are inconsistent. For example, whilst retrospective analysis of the prospective Survival and Ventricular Enlargement (SAVE) study reported no significant impact of hypertension (and diabetes) in 2,231 chronic heart failure patients [36], the prospective Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study did [35]. The latter study revealed a hazard ratio of 1.9 (95 % CI, 1.1–3.1) for stroke when hypertension was present at randomization of 2,144 heart failure patients without concomitant atrial fibrillation. A history of hypertension has also been reported to be associated with an increased risk of hospitalisation for stroke (hazard ratio = 1.4; 95 % CI, 1.01–1.8) [37]. Hypotension and its association with increased stroke risk has been described in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study [38]. The validity of the results have been questioned, however, in view of the fact that patients self-reported heart failure, stroke, and transient ischaemic attack diagnoses.

A review published in 2011 summarised the emerging data regarding chronic heart failure as a risk factor for ischemic stroke. In summarising the available literature, it notes that prior stroke, arterial hypertension, and diabetes are additional risk factors in male chronic heart failure patients. However, in women, stroke risk is reported to increase with concomitant atrial fibrillation, diabetes, and the degree of left ventricular (LV) dysfunction. Moreover, it comments that advancing age does not appear to be an additional stroke risk factor in chronic heart failure patients, despite the known rise in the prevalence of heart failure with advancing age [27].

There is currently no evidence base for antithrombotic therapy in stroke prevention for chronic heart failure patients in sinus rhythm; however anticoagulation is clearly indicated in chronic heart failure patients with concomitant atrial fibrillation [17, 39, 40]. Evident within the literature is the fact that chronic heart failure with or without atrial fibrillation is a common cause of ischaemic stroke. Close attention needs to be paid not only to modifying the vascular risk factors common to both stroke and chronic heart failure, such as diabetes and hypertension, but also to

ensure optimal management of heart failure per se, when its diagnosis is first made. This may serve to be advantageous not only in reducing the mortality associated with a heart failure diagnosis in itself, but also (knowing its association with increased stroke risk) give rise to an advantageous side effect of potentially reducing the burden of stroke-associated neurological and neuropsychological sequelae that a patient with heart failure is predisposed to, in light of the aforementioned increased stroke risk a heart failure diagnosis brings.

Cardiac Arrhythmias

Cardiac dysfunction after a stroke is manifested by a wide variety of arrhythmias, ECG changes, elevated cardiac markers, and haemodynamic instability, which can lead to cardiogenic shock and subsequent death, as we have already alluded to earlier in the chapter [1]. Arrhythmias post-stroke are reported in up to 51 % of patients after ischaemic stroke and 78 % of patients after haemorrhagic stroke and are thus a common occurrence [41].

There are a wide variety of arrhythmias that can occur after stroke, including sinus bradycardia, supraventricular tachycardias, atrial flutter, atrial fibrillation, multifocal ventricular tachycardia, torsades de pointes, and ventricular fibrillation [1, 41]. However, no accurate data is available from population studies measuring their exact frequency. Atrial fibrillation is the most common arrhythmia, accounting for approximately 10–20 % of ischaemic strokes, and is associated with worse outcomes and subsequent risk of future cerebral and systemic thromboembolism. Atrial fibrillation independently increases the risk of stroke fivefold [42] and doubles the risk of recurrent stroke [43]. Recurrent stroke risk is reportedly similar for both sustained and paroxysmal atrial fibrillation [44], both of which are optimally treated with anticoagulation. Timely detection of paroxysmal atrial fibrillation after ischaemic stroke is crucial when aiming to optimise the uptake of treatment with anticoagulants [45].

The Virtual International Stroke Trials Archive (VISTA) register is an international collaborative repository for stroke clinical trial data which has been collated and anonymised for use in exploratory analyses [46, 47]. Data from the VISTA register including 2,865 patients with ischaemic stroke suggested that serious cardiac events (including sudden death, symptomatic heart failure, coronary artery disease, ventricular tachycardia, and fibrillation) occurred more frequently in patients with atrial fibrillation than without atrial fibrillation (14.2 % vs 6 %, OR: 2.58, 95 % CI: 1.97–3.37) [48]. It was hypothesised in this study that increased early cardiac complications contributed to the adverse effects of atrial fibrillation on early mortality within 3 months (OR: 1.44, 95 % CI: 1.14–1.81) after adjusting for baseline characteristics [48]. Of importance from another analysis from the same registry, the rate of first serious cardiac events peaked between day 2 and day 3, and a number of predictive variables were associated with the occurrence of serious cardiac adverse events [2]. These included a past history of heart failure, diabetes mellitus, elevated creatinine, increasing stroke severity, and prolonged QTc interval or ventricular extrasys-

toles on ECG [2]. Prolonged QTc interval changes on ECGs have been related to insular cortex involvement with subsequent alteration in autonomic tone, leading to increased sympathetic tone [49]. In fact, it has been shown that in patients with right insular involvement, increased QTc interval and left bundle branch block on ECG independently predict vascular mortality [50]. Moreover, right insular involvement may lead to increased risk of tachyarrhythmias and cardiac death post-stroke [51].

Despite the high frequency of cardiac complications post-stroke, it is unclear from both American and European stroke guidelines for how long physiological monitoring is required, in which particular patients this should be used, and what measures need to take place to address cardiac arrythmias, some of which may be asymptomatic [4, 5]. Identification of early cardiac arrythmias post-stroke may have the potential to lessen the frequency of serious cardiac events. Non-invasive cardiac event monitoring for 7 days post-stroke has increased the detection of atrial fibrillation and subsequent anticoagulation within 14 days, compared with standard practice in a study of 100 patients [52]. Future trials are required to address the optimal duration and benefits of continuous cardiac monitoring in high-risk patients.

Conclusion

Cardiac complications during the stroke recovery period are, unfortunately, a common occurrence (often apparent early after stroke onset, with a peak occurrence in the first 3 days) and are associated with increased mortality rates, and both poor short-term and long-term outcomes. The highest risk of cardiac-associated mortality occurs within the first 3 months, declining thereafter. Thus the need for early detection and treatment is obvious, particularly in those with the greatest risk of serious cardiac events, and therefore a poorer prognosis, namely patients with congestive heart failure, diabetes, severe strokes, renal insufficiency, and prolonged QTc on ECG. It is these patients who are most likely to experience at least one of the serious cardiac events such as acute coronary syndrome, symptomatic heart failure, ventricular tachycardia, ventricular fibrillation, and cardiac arrest within 90 days of their acute stroke. Currently, a little data exists to guide pre-emptive strategies to tackle such complications, however early monitoring, risk stratification, and an understanding of the pathophysiological mechanisms involved in post-stroke cardiac complications (with cardiac disease sharing a similar risk factor burden with stroke), has been proposed.

Patient Questions

Q. How common are cardiac arrhythmias (abnormal heart rhythm) after a stroke?

A. Arrhythmias post-stroke are common and are reported in up to 50 % of patients after ischaemic stroke and 80 % of patients after haemorrhagic stroke. Atrial

fibrillation is by far the most common arrhythmia, accounting for approximately 10–20 % of ischaemic strokes. The presence of atrial fibrillation independently increases the risk of stroke fivefold and doubles the risk of recurrent stroke. Stroke caused by atrial fibrillation tends to be associated with a high burden of brain damage and poor outcome. Detection of this type of arrhythmia is therefore important in stroke prevention with appropriate medical therapy (anticoagulation).

Q. How common is a heart attack after a stroke?

A. Heart attacks after stroke are a common occurrence and are associated with an increased risk of death in stroke patients. The risk of having a heart attack after a stroke increases by approximately 2 % each year. Therefore, a person who had a stroke 10 years ago would have a 20 % risk of having a heart attack today. People with known heart disease, diabetes, peripheral vascular disease, and atrial fibrillation, or who have suffered a large stroke, are most at risk of having a heart attack after a stroke. How best to investigate patients most at risk of a heart attack after stroke is still unclear and requires more research.

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Chapter 4
Post-stroke Seizures

Neil S.N. Graham, Paul A. Holmes, and Anthony G. Rudd

Abstract Seizures affect between 4 and 6 % of patients within a week of stroke, and between 2.5 and 6.5 % of patients will develop epilepsy post-stroke. Incidence estimates are particularly variable due to differing definitions, study methodologies, populations, and follow-up durations. Stroke types such as subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH), and large-volume cortical infarct are likely risk factors.

Investigations should be undertaken to rule out alternative diagnoses such as cardiac disease causing syncope and non-stroke causes of seizures including electrolyte and metabolic abnormalities, malignancy, and drug or alcohol withdrawal. Due to the large number of possible explanations for seizure-like activity, MR imaging is recommended and EEG may be considered to support a probable diagnosis of post-stroke epilepsy. Where the diagnosis remains uncertain, ambulatory monitoring and video telemetry may be helpful.

With the exception of status epilepticus, which requires urgent intervention, antiepileptic drugs should be initiated in a specialist setting after formal diagnosis of epilepsy, taking into account the patient's age, gender, childbearing potential, comorbidity, and medication history.

A diagnosis of epilepsy has significant psychosocial effects, particularly related to restrictions on driving, which must be addressed appropriately. The DVLA (Driver and Vehicle Licensing Agency) has specific rules where provoked seizures are concerned. Although most patients achieve long-term seizure remission with therapy, epilepsy has been independently associated with greater mortality post-stroke.

Keywords Seizures • Stroke • Status • Epilepsy • Cerebrovascular • Treatment

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Key Messages

- Epilepsy is known to impair quality of life, and mortality is likely to be greater in those with post-stroke epilepsy than matched individuals.
- Haemorrhagic type and large-volume cortical infarct are well-recognised predictors of post-stroke epilepsy.
- An epilepsy diagnosis should be made by a specialist with access to appropriate investigations such as MRI and EEG, as it has significant medical and psychosocial implications for patients.
- Primary seizure prophylaxis with antiepileptic drugs is not recommended. Other than for urgent treatment of status epilepticus, treatment should be initiated only after a formal diagnosis of epilepsy.
- Antiepileptic drugs should be carefully selected in older patients who have higher rates of comorbidity and polypharmacy. Prescribers should consider concordance issues and be aware of adverse effects including bone density changes and psychiatric problems.

"It is not very uncommon to find when a patient has recovered or is recovering from hemiplegia, the result of embolism of the middle cerebral artery, or of some branch of this vessel, that he is attacked by convulsion beginning in some part of the paralyzed region," Hughlings Jackson stated in 1864 [1], with William Gowers describing similar cases as "posthemiplegic epilepsy" [2].

Seizures have been associated with stroke since the nineteenth century, yet uncertainty remains about their epidemiology, identification, ideal management, and prognosis. Clearly defining "seizures" and "epilepsy" is essential at the outset.

Seizure Classification

A seizure is a transient occurrence of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures have traditionally been classified into "generalised" and "focal" following a widely employed International League Against Epilepsy (ILAE) 1981 document, updated recently incorporating advances in neuroscience, imaging, and molecular genetics (Table 4.1) [3, 4].

Focal seizures are considered to originate within networks confined to a single hemisphere, whereas generalised seizures originate at some point within one hemisphere and rapidly engage bilateral neural networks. Consciousness is always impaired in generalised seizures, as a result of the involvement of both hemispheres and may place the patient at greater risk of harm through accident, respiratory arrest, and convulsive status epilepticus.

Focal seizures may be subdivided by maintenance or impairment of awareness, previously termed "simple" or "complex" and anatomical location of onset. If

Table 4.1 Classification of seizures

Generalised seizures
1. Tonic-clonic (in any combination)
2. Absence
Typical
Atypical
Absence with special features
Myoclonic absence
Eyelid myoclonia
3. Myoclonic
Myoclonic
Myoclonic atonic
Myoclonic tonic
Focal seizures[a]
Unknown
1. Epileptic spasms

Adapted from ILAE Proposed Classification of Seizures 2010 [4]
[a]May evolve to generalised seizure

convulsions occur in this context, the seizure may be described as tonic-clonic or "grand mal" and is said to be secondarily generalised.

The proximity of a seizure to an acute cerebral insult further aids classification. Events soon after an insult such as hypoglycaemia, drug withdrawal, or stroke, are termed "early," "acute symptomatic," or "provoked," with those outside this period described as "late" or "remote symptomatic" and "unprovoked." An arbitrary division at 1 week is commonly used post-stroke, but investigators have used a range of periods [3]. The distinction, of uncertain prognostic significance post-stroke, is thought to reflect a difference in pathophysiology. Early events have been attributed to glutamate-mediated excitotoxicity and late seizures to gliosis, cortical hyperexcitability, and the formation of meningocerebral cicatrices [5].

Epilepsy

Epilepsy may be understood as a diverse collection of disorders characterised by a chronic predisposition to recurrent seizures, requiring at least one seizure to have taken place. It has been proposed that a single seizure in the presence of an enduring structural brain abnormality be sufficient to diagnose epilepsy [6], but many patients meeting these criteria have, in fact, been found to have low risk of seizure recurrence (see section "Epidemiology" below).

The ILAE's practical definition of epilepsy advocates diagnosis when two unprovoked seizures have taken place more than 24 h apart, or after one unprovoked

seizure occurs with a recurrence risk greater than approximately 75 %, a risk equivalent to that typically observed after two unprovoked seizures. At least two seizures are required in the case of reflex (e.g. photosensitive) epilepsy [7].

Within this framework, patients may be considered free of epilepsy after at least 10 years without seizures, in the absence of antiepileptic drugs (AEDs), or in the case an age-dependent epilepsy syndrome which, due to advancing age, is no longer applicable [7].

Epidemiology

Epilepsy has a prevalence in the developed world of around 7/1,000 and shows a bimodal distribution. Incidence peaks in early life and again over 75 years of age [8]. Stroke is the most commonly identified cause of late-onset disease, though tumours and neurodegenerative disease further contribute to this second peak in incidence [9].

New-onset epilepsy in older patients is a recognised predictor of subsequent stroke [10]. It has been suggested that a significant proportion of late-onset epilepsy may result from occult cerebrovascular disease, underlying the recommendation that such patients undergo a detailed assessment and optimisation of vascular-risk factors.

Differing study populations, definitions of seizures and epilepsy, and follow-up durations make confident assertions of incidence post-stroke challenging.

Early and Late Seizures

Incidence for early seizures of 4.1–6.3 % is observed in well-designed studies defining early as within 7 days of stroke [11–13], though there is evidence that this may be an underestimate in non-Western populations [14]. Many seizures occur within 24 h of stroke, a time period referred to in the literature as "stroke presentation," with incidence ranging between 1.5 and 4.5 % [13, 15, 16].

A cumulative probability for a single late post-stroke seizure in the region of 3–6 % at 1 year, 5–8 % at 2 years, and 7–12 % at 5 years has been described [13, 16]. Some studies have categorised early seizures as less than 2 weeks and late-onset seizure beyond 2 weeks, making comparisons between studies difficult.

Development of Epilepsy

Defining epilepsy as two or more seizures post-stroke, an incidence of 2.5–6.5 % for a range of durations from 2 to 7 years has been found in a number of well-designed studies [13, 16–19].

Estimates of seizure risk after a single post-stroke seizure are highly variable. An accurate risk assessment is, however, critical in establishing whether a diagnosis of epilepsy is appropriate, and thus whether treatment is indicated: the ILAE's diagnostic threshold is a recurrence likelihood of around 75 % or greater.

The Oxford Community Stroke Project (OCSP) investigators found early seizures to be less epileptogenic than late, with approximately one-third progressing to epilepsy [16]. After a first late post-stroke seizure, the risk of developing epilepsy was two-thirds in the large prospective Rochester Study [13], compared with 90 % in a large Turkish cohort including ischaemic and haemorrhagic strokes [20]. This compares with an epilepsy risk of 50 % for patients who had a single seizure at least 1 day after stroke in the OCSP study of ischaemic and haemorrhagic strokes [16]. Another large multicentre study found the risk of epilepsy to be 55 % after first late seizure following ischaemic stroke, and 100 % after first late seizure post-haemorrhage [19]. Following any seizure, early or late, a recurrence risk ranging from around 25 % to 55 % has been observed [18, 19, 21].

Though estimates vary, early seizures appear to be equally or less likely to produce epilepsy compared with late seizures, which may be due to the presence of transient concurrent abnormalities at presentation with stroke not affecting long-term recurrence risk.

For a single seizure after ischaemic stroke, it is probable that the recurrence risk is less than 75 %, while for haemorrhagic stroke the data remain highly variable, limiting inference. Patients should in any case be individually risk-assessed in an appropriate setting when considering a diagnosis of epilepsy.

Predictors of Post-stroke Epilepsy

Certain characteristics are consistently associated with seizure recurrence in observational studies. Type of stroke is important: subarachnoid haemorrhage, intracerebral haemorrhage, and infarcts with haemorrhagic transformation appear to be higher risk for seizures and epilepsy than infarcts [12, 16, 22]. Venous sinus thrombosis has been associated with early seizures and epilepsy, though the strength of the association is unclear due to the rarity of the syndrome [23–25].

Cortical location independently predicts post-stroke seizures and epilepsy, a finding that is corroborated in detailed neuroimaging research [12, 16, 17, 26]. Size (volume) of lesion is predictive, with total anterior circulation infarcts greater risk than partial anterior circulation infarcts, lacunar infarcts, and posterior circulation infarcts, respectively [16, 17].

Young age has been increasingly identified as a risk factor for seizure recurrence, predicting seizures within 24 h of stroke, 14 days of stroke, and post-stroke epilepsy [17, 20, 27, 28], though not all investigators have shared these findings [13, 16].

Stroke severity, assessed using various clinical indicators, has not been consistently associated with the development of post-stroke epilepsy: it remains a challenge to identify those at high risk. Variables including stroke type, location, neurological deficit, vascular encephalopathy, and early and late seizures have been

used to form a post-stroke epilepsy risk scale ('PoSERS') [29]. Prospective evaluation suggested moderate sensitivity and good specificity, but adoption has been poor, presumably due to the risks associated with antiepileptic drug therapy and paucity of trial data to support prophylaxis.

Clinical Manifestations and Relevance in Stroke

Post-stroke seizures are typically focal or secondarily generalised. Seizures may be preceded by a sense that an event is likely to occur, the "prodrome." Patients with partial seizures may experience an "aura," essentially a non-motor manifestation of the seizure, which may propagate to a secondarily generalised seizure.

Following the event, a post-ictal state of confusion or drowsiness is a common finding, which may feature focal neurological abnormalities, described as "Todd's paresis." This is a heterogeneous entity usually lasting fewer than 36 h, which may classically feature weakness, but has also been recognised to produce aphasia, gaze palsy, and sensory changes [30]. Such a focal deficit may be difficult to differentiate from a stroke-related deficit, if the two are concurrent. Due to the possibility of focal neurology secondary to disease other than stroke, such as tumour or indeed Todd's paresis, the UK licence for alteplase (recombinant tissue plasminogen activator, rtPA) lists seizure at presentation of stroke as a contraindication to thrombolysis [31].

The American Stroke Association guidelines suggest that this need not be absolute. "Intravenous rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon," a recommendation based on case series using further neuroimaging (such as CT angiography, perfusion, or MRI) to aid diagnosis in the acute setting [32–34]. Clinically differentiating the Todd's paresis and stroke remains very challenging and there are no validated tools to assist.

Seizures during thrombolysis have been observed and attributed to reperfusion of ischaemic tissue, associated in a case series with improved outcome [35]. Such findings clearly require further investigation and do not reflect the general finding that post-stroke seizures tend to have deleterious effects on morbidity and, it is suspected, mortality (see section "Prognosis" below).

Focal Seizures

Clinical manifestations of focal seizures are largely dependent on the site of origin and propagation path. Transient loss of consciousness is a common presentation particularly in older patients, with a broad differential diagnosis including cardiac and psychogenic causes (Table 4.2) [36].

Table 4.2 Transient loss of consciousness: differential diagnosis

Aetiology	Diagnoses
Neurogenic	Seizure, vasovagal syncope
Psychogenic	Psychogenic nonepileptic seizures, panic attack, hyperventilation
Sleep disorder	Parasomnia, narcolepsy with cataplexy
Cardiac	Bradyarrythmia, carotid sinus hypersensitivity

Adapted from Shorvon et al. [36]

Table 4.3 Localising and lateralising signs and symptoms in seizures

Clinical characteristics	Likely cerebral territory
Dystonic posturing	Contralateral
Unilateral clonic movements	Contralateral
Forced head version (sustained extreme rotation of head)	Contralateral (relative to side towards which head rotates)
Todd's paralysis	Contralateral
Rhythmic ictal non-clonic hand automatisms (e.g. finger rolling)	Contralateral temporal
Automatisms (unilateral)	Ipsilateral
Blinking	Occipital (ipsilateral cortex if unilateral only)
Speech during event	Non-dominant hemisphere
Retching	Insular cortex
Vomiting	Right temporal

Adapted from Alarcon et al. [37]

Specific clinical signs may help clinicians to identify the site of seizure onset, who should be aware, in particular, of auras which may not initially be volunteered by patients [37]. Temporal lobe seizures may present with visceral sensations such as rising epigastric sensation or affective symptoms including déjà-vu. Accompanying oro-alimentary automatisms (such as lip-smacking or swallowing) or gestural automatisms may be more easily identified (Table 4.3).

Generalised Tonic-Clonic Seizures and Status Epilepticus

Focal seizures may secondarily generalise to produce tonic seizures, with sudden loss of consciousness associated with a phase of whole body tonic contraction, followed by a clonic phase of bilateral jerks decreasing gradually in intensity and frequency [36].

Generalised tonic-clonic status epilepticus, defined typically as lasting greater than 30 min (but requiring treatment much sooner than this), is a medical emergency, associated with excess morbidity and mortality [38]. Entities such as subclinical status (non-convulsive status epilepticus) may present with reduced conscious level only, causing considerable diagnostic difficulties. Timely neurophysiological involvement in such circumstances is key.

Investigating Post-stroke Seizures

A detailed history and examination are necessary to exclude differential diagnoses and to help ascertain the underlying cause in a patient who presents with a suspected acute symptomatic seizure.

Differential Diagnosis of Seizures
- Trauma
- Malignancy
- Neurovascular (e.g. stroke)
- Intracranial infection
- Autoimmune disease
- Drug/alcohol use or withdrawal
- Congenital structural
- Metabolic and endocrine: hypoxia, hypomagnesaemia, hypo/hyperglyaemia, hypo/hypernatraemia, uraemia, hyperthyroidism, porphyria, congenital metabolic abnormalities
- Psychogenic nonepileptic seizures (PNES)
- Idiopathic

The post-stroke seizure history should be taken with particular reference to witness accounts to help ascertain events during, before, and following the possible seizure. In a focused clinical examination, possible cardiac causes should be investigated with postural blood pressure measurement and evidence of previous seizures sought: there may be evidence of a severe lateral tongue bite or skeletal injury following a tonic-clonic seizure. Resisted eye-opening, gaze avoidance, retained pupillary light, corneal reflexes, and downgoing plantar reflexes are features supporting a diagnosis of psychogenic nonepileptic seizure.

Bedside and Blood Investigations, Imaging and Neurophysiology

Where patients present with transient loss of consciousness post-stroke, investigations should aim to exclude common differential diagnoses. Coronary disease is a common finding in patients with cerebrovascular disease: electrocardiography (ECG) should be performed with consideration of echocardiogram and tilt table testing where cardiogenic syncope is suspected, for example where the clinical picture is not typical of a seizure disorder. Blood tests should include full blood count, urea and electrolytes, glucose and calcium [39].

Routine assessment of serum prolactin is not recommended, though assessment 10–20 min after an event may help to differentiate nonepileptic attacks from

generalised tonic-clonic seizures or complex partial seizures. Prolactin measurement is not of value in differentiating seizure from syncope [40].

Neuroimaging is urgently indicated following seizure post-stroke. Computed tomography (CT) may be employed to exclude gross abnormalities, if magnetic resonance imaging (MRI) is unavailable or contraindicated: MRI is of greater sensitivity for epileptogenic abnormalities such as cortical and hippocampal disease and vascular malformations. Electroencephalography (EEG) with photic stimulation and hyperventilation is not a diagnostic test and should only be performed to support a diagnosis of epilepsy where the clinical history is suggestive: due to the risk of false positives, it is not recommended as a "rule-out" test in cases of probable syncope. Where the standard EEG is unclear, sleep or sleep-deprived EEGs should be considered. Video telemetry or ambulatory EEG may be of use where diagnostic difficulties are encountered [39]. There is limited data around the EEG in post-stroke seizures specifically. A group in Italy performed EEG within 1 day of stroke and observed patients prospectively for 1 week, finding focal or diffuse slowing of background activity in over 80 % of patients, epileptiform focal abnormalities in 10 %, and periodic lateral epileptiform discharges (PLEDs) in around 5 %. The only abnormalities predictive of early seizures were PLEDs [41].

Treatment, Adverse Effects, and Monitoring

Prophylaxis of Seizures

There is no robust evidence to support primary prophylaxis with AEDs in infarcts and it is therefore not advised [42]. The value of prophylaxis in spontaneous intracerebral haemorrhage was assessed in a Cochrane review based on a single qualifying study of valproate versus placebo, which found no significant difference in early seizures, late seizures, or mortality. It found no evidence to justify the practice in general, although the American Stroke Association suggests consideration in selected high-risk patients with lobar haemorrhage [43–45]. This recommendation is based on a single non-randomised observational study with no specific protocol for AED choice or regimen [46].

Status Epilepticus

Generalised tonic-clonic status epilepticus is a medical emergency that should be managed according to local policy. A consensus treatment algorithm for AED use in this setting has been proposed: benzodiazepenes such as intravenous lorazepam, buccal midazolam, or rectal diazepam are suggested for the treatment of early status (0–10 to 30 min), infusions of AEDs such as phenytoin or valproate for established status (10–30 to 60–90 min) and anaesthetic agents such as propofol and thiopental for refractory status (refractory status) [38, 47].

Approach to Epilepsy Therapy

Patients should have contact with specialist epilepsy services and a comprehensive care plan delivered by a multidisciplinary team. Healthcare professionals should offer education to patients, carers, and family members. It is strongly recommended that AEDs be given to prevent recurrent seizures, though risks of AED treatment which should be considered include idiosyncratic reactions, toxic effects, interactions with other medications, and teratogenicity [42]. Medications should be appropriate to seizure type, age, sex, childbearing potential, comorbidity, and drug history.

There are no large double-blinded randomised controlled trials of AEDs in post-stroke epilepsy; hence studies of epilepsy treatment in older people, a large proportion of whom will have underlying cerebrovascular disease, are pragmatically used to inform treatment.

In older patients, particular consideration needs to be given to altered absorption, protein binding, and hepatic and renal clearance [48]. The newer agents gabapentin and lamotrigine appear to have similar efficacy to carbamazepine in older patients, but with a reduced withdrawal rate, implying better tolerability [49]. Other comparisons of lamotrigine with sustained-release carbamazepine in elderly patients and those with first post-stroke seizure suggest better tolerability of lamotrigine, though not all investigators have demonstrated this [50–52].

First-Line Treatment Options

Seizures related to stroke are of the focal onset type and the medication choice should reflect this. In focal onset seizures, there are many AED choices with monotherapy indications including carbamazepine, levetiracetam, lamotrigine, oxcarbazepine, and topiramate. Sodium valproate may also be used first line for focal onset seizures, and loading with phenytoin should be considered in status epilepticus after lorazepam.

Due to its efficacy, tolerability, and lack of drug-drug interaction, levetiracetam has fast become the first-line drug choice, followed by carbamazepine and lamotrigine. It is important to warn patients about a rash in the latter two. In older patients, non-enzyme inducing agents such as lamotrigine or gabapentin followed by low-dose topiramate are reasonable first-line options.

Second-line “refractory” or adjunctive therapy with levetiracetam, pregabalin, lacosamide, or gabapentin may be considered if the first or second monotherapy trial with first-line treatments fails (Table 4.4) [48].

Table 4.4 Drug treatment of post-stroke seizures (partial seizures with or without generalisation)

	Suggested dose titration	Target daily dose range (mg/day; frequency)	Target plasma concentration (mg/L)	Serious/frequently occurring adverse effects
New onset disease				
Levetiracetam	500 mg every 3 days	1,000–3,000 (divided BD)	N/A	[a]TEN/SJS, weight changes, gastrointestinal (GI) upset, movement disorders, drowsiness, behavioural change with aggression
Carbamazepine	200–400 mg every 3–7 days	600–1,200 (divided BD or TDS)	3–12	Atrioventricular conduction block, TEN/SJS, GI upset, liver dysfunction, drowsiness, movement disorders
Lamotrigine	25 mg for 2 weeks, 50 mg next 2 weeks (as monotherapy, adjust if on enzyme inducers)	100–400 (divided OD or BD)	2–15	Hypersenitivity syndrome (fever, rash including SJS/TEN, bone marrow-failure), GI upset, movement disorders, drowsiness
Topiramate	25 mg for first 1–2 weeks; beyond 100 mg, 25–50 mg/week	100–400 (divided BD or TDS)	N/A	GI upset, cognitive impairment, movement disorders, metabolic acidosis, nephrolithiasis, SJS
Gabapentin	300 mg every 1–3 days	900–3,600 (divided BD or TDS)	N/A	SJS, GI upset, movement disorders, drowsiness
Oxcarbazepine	150 mg every 3–7 days	800–1,800 (divided BD or TDS)	N/A	(See carbamazepine)
Valproate	500 mg every 3–7 days	600–1,500 (divided BD slow release or TDS)	40–120	Liver, bone marrow and pancreatic toxicity, GI upset, hair loss, hyperammonaemia, movement disorders
Refractory disease				
Pregabalin	75–150 mg every 3–7 days	150–600 (divided BD or TDS)	N/A	(See gabapentin)
Lacosamide	100 mg every 7 days	200–400 (divided BD)	N/A	Atrioventricular conduction delay, GI upset, movement disorder, mood or cognitive disturbance
Zonisamide	100 mg every 7 days	200–500 (divided BD or TDS)	N/A	SJS/TEN, GI upset, peripheral oedema, mood, cognition or movement disorders, nephrolithiasis

(continued)

Table 4.4 (continued)

	Suggested dose titration	Target daily dose range (mg/day; frequency)	Target plasma concentration (mg/L)	Serious/frequently occurring adverse effects
Perampanel	2 mg every 7 days	8–12 (OD)	N/A	GI upset, mood, cognition and movement disturbance, liver dysfunction
Clobazam	10 mg daily	10–60 mg for target daily dose for clobazam (OD or divided BD)	N/A	Confusion, dependence, movement disorder, drowsiness, GI disturbance

Adapted from British National Formulary and Schmidt et al. [47, 48]

[a]*SJS/TEN* Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, *OD* once a day, *BD* twice a day, *TDS* three times a day

Adverse Effects

Prescribers should be vigilant for adverse effects of treatment. Particular care should be taken to negotiate risks of teratogenicity in women of child-bearing age. Many AEDs are associated with significant foetal abnormalities and the drug label and up-to-date regulatory advice should be consulted.

Although many adverse effects are dose-dependent, the main role of assessing plasma drug concentrations is in monitoring patients' clinical course and concordance, which may be of difficulty in those with cognitive decline. Monitoring of levels is not advised for optimising doses and administration schedules, other than for phenytoin whose plasma concentrations should be monitored due to non-linear pharmacokinetics [48].

Fracture risk in patients with epilepsy is increased approximately two to six-fold compared with the general population, an association attributed to the effects of epilepsy, AEDs and enzyme-inducing AEDs, such as phenobarbital, phenytoin, and carbamazepine [53]. It is advised that all postmenopausal women using AEDs be considered for falls prevention interventions and that patients receive sufficient calcium and vitamin D [54]. Assessment of bone mineral density should be considered in all long-term AED users with additional risk factors for bone disease.

There is limited evidence that AEDs such as phenytoin, benzodiazepines, and phenobarbital may impair motor function post-stroke, in addition to concerns that topiramate may exacerbate word-finding difficulties or motor deficit [55–57]. An analysis by the US Food and Drug Administration associated all AEDs with an increased risk of suicidal ideation, attempt, and completion: as the association remains controversial with questions around causality, a cautious approach is advised in those with psychiatric comorbidity [58].

Duration of Treatment

Epilepsy therapy is typically long term and decisions to withdraw AEDs are usually addressed in a specialist setting with respect to the timing of the last seizure, an individual assessment of recurrence risk, and patient preferences.

In the specific case of spontaneous intracerebral haemorrhage, based on a 1994 study of 55 cases finding a lower recurrence risk for seizures 2 weeks after stroke, it has previously been suggested that if AEDs are initiated for seizures within 2 weeks of stroke, with no further seizures, medication may be stopped after 30 days [59, 60]. No robust consensus has since developed around this practice, probably due to the large variation between observational studies. Seizure risk assessment and plans with respect to treatment withdrawal must be patient-specific, in the absence of any clear evidence or guideline to assist clinicians.

Prognosis

Large population-based studies have found that around two-thirds of patients with epilepsy will enter long-term remission with treatment [61, 62]. Studies in populations with poor access to drug treatment have highlighted a significant treatment gap to be addressed, affording an insight into the natural history of untreated epilepsy. Indeed, it has been found in some cases that approximately 45 % of patients enter remission off-treatment: The relevance of these findings to other populations is not clear [63, 64].

Epilepsy is known to impair self-reported vitality, physical function, and quality of life [65]. Effects of post-stroke seizures on mortality have historically been difficult to characterise due to the effects of confounders, such as stroke severity, producing inconsistent findings in the literature. Most recently, a study of 10,000 patients with ischaemic stroke identified seizure during hospital admission as an independent risk factor for mortality at 30 days and within 1 year [15].

Patient Questions

Q. **I have been told that I had a fit after my stroke. Does this mean that I have epilepsy**?

A. The diagnosis of epilepsy should not usually be made after a single seizure unless a particularly high-recurrence risk is suspected. Patients should be referred to an epilepsy specialist for further investigation.

Q. Should I start taking medicines to stop my fits?

A. Treatment with medications is advised after a formal diagnosis of epilepsy has been made. Drug choice should be made with reference to an individual's particular requirements, with appropriate counselling and monitoring for adverse events.

Q: **Does this mean that I may not drive**?

A. The DVLA has responsibility for assessing fitness to drive and imposing appropriate restrictions in the UK, providing specific guidance where medical conditions may impair this [66]. After a stroke or seizure, patients are required to abstain from driving and contact the DVLA for formal advice.

In the absence of seizures post-stroke, Group 1 (comprising cars and motorcycles) licence holders must refrain from driving for 1 month and will need to inform the DVLA if there is any residual neurological deficit at this point. Group 2 (comprising large lorries and buses) licence holders may not drive for 1 year post-stroke or TIA and will need to contact the DVLA for further assessment after the year elapses.

Seizures occurring at stroke onset or within 24 h are treated by the DVLA as "provoked" and are dealt with on an individual basis. The DVLA considers a single seizure

>24 h post-stroke to be "unprovoked," and drivers may be permitted to drive if free of seizures for 6 months (Group 1) or 5 years (Group 2), depending on the DVLA assessment of recurrence risk (if the DVLA feels the seizure was "isolated" with low-risk neuroimaging and EEG). The regulations in respect of epilepsy are more complex, with some important exceptions based on seizure type and timing. In general, Group 1 licence holders with epilepsy are usually required to be seizure-free for 1 year or seizure-free without AEDs for 10 years in the case of Group 2 licence holders.

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Chapter 5
Infections After Stroke

Mehool Patel and Angela Kulendran

Abstract Infections are the most common medical complications after stroke, occurring in up to 65 % of stroke patients, and are associated with significant morbidity and mortality. Severe neurological impairment resulting from stroke, advancing age, and co-morbidities all increase the risk of infection after stroke. Stroke-induced immunodepression is also thought to play a role. Prevention as well as prompt recognition and treatment of infections are essential for reducing morbidity and mortality from stroke and may improve functional outcomes. There are recently completed and ongoing clinical trials to evaluate strategies for prevention and management of post-stroke infections.

Keywords Stroke • Post-stroke • Infection • Complications • Neurological deterioration

Key Messages

- Infections are the most common medical complications that occur during the acute phase of a stroke and are associated with poor short-term and long-term outcomes.
- There are several risk factors associated with the development of infection following stroke, including stroke severity, decreased conscious level, dysphagia, advancing age, medical co-morbidities, and stroke-induced immunodepression.
- Comprehensive structured assessment of all stroke patients should occur to identify post-stroke infection as a potential cause for early neurological deterioration.
- There are various clinical trials that are recently completed or currently recruiting subjects to examine the merits of prophylactic antibiotics for post-stroke infections.

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Introduction

Stroke is associated with a wide range of medical complications. Infections are the most common complications during the acute phase of stroke. Infections are the leading cause of death after the first day of stroke onset. Early neurological deterioration after stroke may be a sign of infection. Pneumonia and urinary tract infections are the most frequently observed infections. These are associated with poor outcomes that include neurological deterioration and disability, increased length of hospital stay, and death. This chapter focuses on the prevalence of post-stroke infections, risk factors, and measures for prevention and treatment of infections after stroke.

Prevalence of Post-stroke Infection

The rates of infection after stroke range between 5 and 65 % [1]. This wide variation is due to the varying population groups in the studies, definition of infection, and study design. Westendorp et al. conducted a systematic review of post-stroke infection and reported the pooled infection rate following stroke to be about 30 % (95 % confidence interval: 24–36 %); of the 30 %, pneumonia and urinary tract infection accounted for 10 % each [1]. That review pooled 87 studies, including cohort studies, stroke registries, and randomised control trials, involving 137,817 patients in total.

Urinary tract infection (UTI) is a common complication after stroke. The rates vary between 3 and 44 % [2]. One prospective cohort study of 412 stroke patients showed that 65 patients (15.8 %) had a UTI at a median of 14 days post-stroke [2]. Another study of 1,455 acute stroke patients recruited to a randomized controlled trial found an incidence of 17.2 % of UTI [3]. A third study of 489 unselected acute stroke admissions showed a UTI incidence of 16 % in the first week and 27.9 % at 3 months [4]. Davenport's study found an in-hospital UTI incidence of 16 % in 613 stroke patients [5]. Another multicentre study of 311 acute stroke patients reported the incidence of UTI to be 24 % [6].

Pneumonia is the most common infection after stroke. The incidence rates vary according to the cohort of stroke patients examined in various studies [7]. For example, the incidence in neurological intensive care units varies between 9.5 and 56.6 %; in medical intensive care units it ranges between 17 and 50 %, whereas in studies on patients in standard stroke units, the incidence was between 3.9 and 12 % [7]. The heterogeneous nature of the patients examined in these studies makes it difficult to make any meaningful comparisons between them [7].

Factors Associated with Post-stroke Infection

There are several risk factors associated with the development of infection following stroke. These include characteristics of study population (for example, patients

in intensive care units), stroke severity, decreased conscious level, presence of dysphagia, advancing age, female gender, and diabetes mellitus. The list below outlines the factors associated with the development of chest infections (pneumonia) after stroke.

Risk Factors Associated with Pneumonia After Stroke

- Aspiration—failure to clear secretions
- Dysphagia
- Nasogastric feeding
- Poor nutrition
- Immobility
- Reduced conscious level
- Cognitive impairment
- Reduced chest movement on affected side
- Reduced/dependence for oral care
- Current smoking
- Underlying conditions, e.g. diabetes, COPD, atrial fibrillation

There are various broad categories of pneumonia that occur following stroke: community acquired pneumonia, aspiration pneumonia, or health-care associated pneumonia [7]. Data suggests post-stroke pneumonia is often due to aspiration [7]. Unwell hospitalized patients routinely aspirate and patients with an impaired swallowing mechanism due to neurological injury are at especially high risk [8]. Pneumonia after stroke is associated with higher stroke severity (National Institute of Health Stroke Scale [NIHSS]) and depressed consciousness [7]. Consequently, infection rates were higher in intensive care unit (ICU) studies and in studies with a longer period of observation [7]. A review article by Hannawi et al. [7] identified various risk factors leading to pneumonia after stroke, including stroke severity measured by the NIHSS or the modified Rankin Scale [9–11], dysphagia [9, 12, 13], old age [4, 14], mechanical ventilation [10, 12, 13], APACHE II score/organ failure status [9], male sex [12], brain stem infarction [13], multihemispheric infarction [13], nonlacunar basal ganglia infarct [10], atrial fibrillation [11], admission from a nursing home [15], dysarthria [12, 16], altered level of consciousness, coma, or abnormal papillary exam [10], diabetes, congestive heart failure, chronic obstructive pulmonary disease or smoking, history of pneumonia, and low serum albumin level [9].

Recently, Hoffmann et al. developed a clinical A2DS2 score to predict pneumonia in acute ischaemic stroke and validated using data of two independent stroke registers [17]. This 10-point risk score (points) includes age ≥75 years (1), atrial fibrillation (1), dysphagia (2), male sex (1), stroke severity according to the National Institute of Health Stroke Scale 0–4 (0), 5–15 (3), and ≥16 (5) [17]. The proportion of pneumonia varied between 0.3 % in patients with a score of 0 points and 39.4 % in patients with a score of 10 points.

Risk Factors Associated with Urinary Tract Infection

Urinary tract infections (UTI) after stroke are associated with urethral catheterization, stroke severity ($p = 0.01$), decreased conscious level, greater post-stroke disability (higher modified Rankin score), advancing age, acute urinary retention, and increased post-void residual urine volume (PVR) [1, 2, 18]. A study reported that UTI is more common if PVR is over 100 ml irrespective of gender and age. Close monitoring of PVR and appropriate intervention is therefore needed to reduce the occurrence of UTI in stroke patients [18]. The common risk factors, such as female sex, diabetes mellitus, obstructive uropathy (enlarged prostate, renal stones), and oestrogen deficiency, can also predispose to UTI in stroke patients.

Immunosuppression After Stroke

Another emerging concept of increased susceptibility to infections following stroke is one of post-stroke immunodepression [19]. Counter-regulatory responses, triggered by the pro-inflammatory response to stroke, appear to effect systemic immunodepression via suppression of both innate and adaptive immune responses. A range of anti-inflammatory and immunosuppressive changes have been identified in experimental and clinical studies, including reduced mononuclear phagocyte and natural killer cell function, induction of anti-inflammatory cytokines, apoptotic lymphocyte loss, and altered T lymphocyte activity. Stroke-induced immunosuppression mainly results from the activation of sympathetic mediated pro-inflammatory cytokine production. In contrast, the vagus nerve releases acetylcholine which inhibits the production of pro-inflammatory cytokines, but maintains the production of anti-inflammatory cytokines [8, 20–22]. Those mechanisms are part of the "central nervous system injury-induced immune deficiency syndrome" mediated by the sympathetic nervous system, the N. vagus (parasympathetic nervous system), and the hypothalamo–pituitary–adrenal (HPA) axis [23]. The identification of markers of immunodepression in the early post-stroke phase may prove useful for identifying patients who may have increased susceptibility to infection. It also seems likely that post-stroke immunodepression will need to be taken into account where stroke treatments impact upon inflammatory and immune pathways [19].

Organisms Causing Infection After Stroke

In clinical practice, it is fairly common for no causative organism to be detected in post-stroke pneumonia. This is due to difficulty in collecting sputum or aspirate for culture due to neurologic deficit or lowered level of consciousness, some cases of suspected pneumonia actually being non-infectious aspiration pneumonitis, or infection could be caused by anaerobic bacteria that require special culturing

techniques [1]. A systematic review that examined the data of patients with post-stroke pneumonia to identify microorganisms reported that the organisms were mainly those associated with early onset nosocomial pneumonia, or a community acquired aspiration syndrome [1]. These included Streptococcus species, Staphylococcus aureus and gram-negative bacteria such as Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli or Enterobacter species. Gram-negative bacteria and Staphylococcus aureus are known to cause pneumonia by aspiration of endogenous material from the colonized oropharynx and are often seen in nosocomial infections [24]. Streptococcus species is still the most detected pathogen in community acquired pneumonia [25]. In stroke patients, it could be a cause of 'community acquired aspiration pneumonia', with aspiration occurring at the time of stroke [26].

Stroke Outcome and Post-stroke Infection

Infections following stroke are associated with worse short-term and long-term outcomes. In pooled analyses by Westendorp et al., the mortality rate in patients with infection was 48 % versus 18 % in patients without infection [1]. Kwan et al. conducted a study of 439 patients (398 with stroke and 41 with transient ischaemic attack) exploring the clinical consequences of post-stroke infections [27]. They found that patients with post-stroke infections were more likely to develop other complications such as pressure sores and seizures. Furthermore, post-stroke infections were significantly associated with in-hospital mortality and institutionalization on discharge [27]. In a consecutive cohort study that looked at 521 acute stroke patients, stroke-associated infection was independently associated with poor functional outcome at discharge and at 1 year [28]. Pneumonia is the most common post-stroke infection and has been associated with a relative risk of 3.0 for mortality in a study of 14,293 patients with stroke [15]. In pooled analyses of effects of infection on outcome after stroke, pneumonia was significantly associated with in-hospital mortality [1]. Mortality rates were also higher in patients with pneumonia (26 % vs. 5 %) than those without pneumonia [1]. Post-stroke pneumonia also increases the financial burden on the medical system, with the annual cost of this complication reported to be about $459 million US [14].

Stott et al. found that in a study of 412 stroke patients, UTI was associated on univariate analysis with an increased risk of death and/or post-stroke disability at 3 months after stroke [2]. They postulated biologically plausible reasons for UTI causing a worse outcome after stroke: (1) During the acute phase of a UTI, UTI-induced systemic inflammation and raised temperature may cause further damage to vulnerable brain tissue in the ischaemic penumbra [29–31]. (2) Infections are associated with a catabolic response, with loss of skeletal muscle; this is likely to be due to multiple complex factors, including inflammation and cytokine release, increased glucocorticoids and activation of the sympatho-adrenal axis [32]. The associated loss of skeletal muscle is likely to adversely affect physical rehabilitation.

Clinical Assessment and Investigations

Infections are a recognised cause of morbidity and mortality following stroke. Neurological deterioration and changes in physiological parameters associated with stroke can make it more difficult to diagnose infections. It is quite common for fever and inflammation to develop after stroke as a result of disturbance of the thermoregulatory centre and an acute phase response, respectively [33, 34]. Since infections are common after stroke, a search for infection should still be undertaken and antibiotics given when appropriate [34]. Non-specific clinical indicators of infection also include delirium, neurological deterioration, and dehydration. Furthermore, infection can impede rehabilitation. Since pneumonia and UTI are the most common infections, initial investigations should include a chest radiograph, urinalysis with a mid-stream urine sample sent for culture, and blood cultures if pyrexial. However, raised inflammatory markers could also be associated with other complications, such as deep-vein thrombosis, pressure sores, and seizures, or may be indicative of the cause of stroke, such as vasculitis or infection (infective endocarditis). If any of these are suspected, clinical correlation is necessary followed by the appropriate investigations.

Potential Strategies to Minimise Post-stroke Infection

Urinary Tract Infection

There are various recommendations that can reduce the prevalence of urinary tract infection (UTI) following stroke. Usual methods for preventing UTI are adequate hydration, use of cranberry juice, and oestrogen supplementation (topical) [35]. In hospitalized patients, other strategies include improving mobility with physiotherapy, preventing constipation, and avoiding or minimising the use of urinary catheters [35]. Minimising and avoiding unnecessary catheterization is probably the single most effective strategy in preventing UTI [36]. In certain circumstances it is necessary to use a urinary catheter, such as in acute urinary retention due to urethral obstruction (enlarged prostate, stone) or neurogenic bladder (stroke, multiple sclerosis, spinal injury), urological surgery, to allow healing of sacral pressure sores, and accurate measurement of urine output in critically ill patients [37]. It may be possible to reduce the risk of associated infection by early removal, vigilance in catheter-care, or by use of modified catheters coated with antimicrobials. A structured reminder to nurses by physicians to remove unnecessary catheters in ICU has been shown to reduce duration of catheterization and associated infections [38]. High aseptic standards of catheter care, correct positioning of the drainage tubing and collection bag, and maintaining a closed system may all help to reduce the risks of clinically significant infection [39]. Using modified catheters such as nitrofurazone-coated silicone or silver-coated latex may reduce the risk of infection with short-term catheterization [39, 40].

Chest Infection (Pneumonia)

Bearing in mind that aspiration is an important risk factor for chest infection after stroke, appropriate management of dysphagia following stroke is vital in reducing chest infections. A strict vigilant swallowing assessment after stroke is important. The most widely accepted measure is to keep a stroke patient nil by mouth until the swallow has been formally assessed [41]. Formal swallow assessment including a water swallow assessment also significantly reduces the risk of pneumonia [42, 43]. It has been shown that patients having intensive (daily) standard swallow therapy developed fewer chest infections secondary to aspiration compared to those receiving usual care (26 % vs 47 %) [44]. Nasogastric feeding or percutaneous gastrostomy tube are common ways of providing nutrition to stroke patients who have an unsafe swallow. However, these methods do not eliminate the occurrence of pneumonia, since aspiration of oral contents may continue [45]. A recent Cochrane review of the clinical trials showed no difference between these two methods regarding the occurrence of pneumonia in patients with dysphagia; however, percutaneous gastrostomy tube was safer and more effective in terms of feeding [46]. Regular oral hygiene is also important in reducing the development of chest infections.

Early mobilisation and good pulmonary care have also been shown to reduce the risk of pneumonia [47–49]. Preventative measures include body positioning to maintain airway patency (usually in a semi-recumbent position), suctioning of accumulated secretions, and early mobilisation [47]. In a population-based Danish follow-up study, mobilization within the first day post-admission was associated with a substantially lower risk of pneumonia and UTI [49]. Cuesy et al. conducted a randomised controlled trial of 223 acute stroke patients that implemented a "turn-mob program": turning and passive mobilization carried out by a previously trained relative [50]. This is a mobilization programme in bed that involves changing a patient's position (e.g. from lateral recumbent to supine) and mobilising all four limbs for 10 s ten times. The trial showed that there was a relative risk reduction of 0.39 in the incidence of nosocomial pneumonia. The "turn-mob" program applied on patients during the acute phase of an ischaemic stroke decreases the incidence of pneumonia [50].

There are various clinical trials that have recently been completed or are currently recruiting stroke subjects to examine the management and prophylaxis of post-stroke infections [51–55]. The Early Systemic Prophylaxis of Infection After Stroke (ESPIAS) was a randomized, double-blind, placebo-controlled study of antibiotic prophylaxis in 136 acute stroke patients using intravenous levofloxacin or placebo in addition to optimal care [52]. That study showed that prophylactic levofloxacin was no better than optimal care for the prevention of infections in stroke patients [52].

The Mannheim Infection in Stroke Study (MISS) was another randomised, controlled study of antibiotic prophylaxis in 60 acute stroke patients using prophylactic mezlocillin plus sulbactam for 4 days versus conventional management [53]. That study showed that the intervention lowered the rate of all cause infection ($p<0.01$) and may be associated with a better clinical outcome ($p=0.01$), though it was not powered enough for clinical outcomes.

The Preventive ANtibacterial THERapy in acute Ischaemic Stroke (PANTHERIS) was a randomised, double-blind, placebo controlled trial in 80 acute stroke patients using intravenous moxifloxacin [54]. The study showed that at 11 days, on intention to treat analysis, the infection rate was non-significantly lower in the treated group compared to placebo (15.4 % vs 32.5 %). In this study, neurological outcome and survival were not significantly influenced by treatment with moxifloxacin [54].

The Stroke Infection study (STROKE INF) is a cluster randomised trial of different strategies of antibiotic use to reduce the incidence and consequences of chest infection in acute stroke patients with dysphagia [55]. The study aims to recruit 1,200 acute stroke patients and randomise them to receiving prophylactic amoxicillin (or equivalent co-amoxiclav) and clarithromycin for 7 days. Outcome measures include incidence of chest infection, functional outcomes, and mortality.

The treatment of stroke-associated pneumonia is prompt early use of antibiotics using the local hospital guidelines for aspiration and/or hospital acquired infections, as these are the most common chest infections after stroke. The decision of empirical antibiotic treatment depends on the individual's risk factors, disease severity, time of onset, and general microbiology of pneumonia [7, 56].

Infections Associated with Stroke

In this chapter, we have discussed infections after stroke. It is also important to note that various infections have also been associated as potential risk factors *for* stroke [57]. Acute systemic infections that cause vasculitis (inflammation of the blood vessels) or infective embolisation; examples include infective endocarditis, meningitis (bacterial, fungal, and tuberculous), human immunodeficiency virus (HIV), herpes zoster, neuro-syphilis, hepatitis B or C, Rickettsial diseases, Helminthic infections, and Chagas disease [57]. The association between these acute infections and stroke is due to the pro-coagulant state caused by the inflammatory response induced by these infections rather than the actual microbial agents. Chronic infections such as upper respiratory infections, urinary tract infections, Helicobacter pylori infections, and periodontal infections have also been associated with stroke, although their exact patho-physiological mechanisms or indeed their causal relationship is not yet fully established [57].

Conclusion

Although infections are the most common medical complications after stroke, the reported rates of infection vary considerably. Pneumonia is the most common type of post-stroke infection, probably followed by urinary tract infection. Stroke severity is an important determinant of susceptibility to infection. This can be due to the degree of neurological impairment directly caused by stroke or the consequences

of neurological impairment relating to feeding and nutrition, mobility, invasive medical devices, and suboptimal acute stroke care. Preventative measures revolve around the consequences of stroke, specifically early involvement of the stroke multi-disciplinary team for regular intensive therapy, use of stroke care pathways, and consideration of potential risk factors such as urinary catheters. Stroke patients are at high risk of developing infection, therefore careful clinical assessment is needed to make a diagnosis so that antibiotic therapy can be started promptly. There is ongoing research into methods of prevention and management of post-stroke infections.

Patient Questions

Q. What are common infections that occur following a stroke?

A. The two most common infections following stroke include chest infection and urinary tract infections.

Q. What are the reasons for these infections to occur following a stroke?

A. There are several risk factors that predispose stroke patients to develop infections. Risk factors for developing chest infections following a stroke include aspiration (failure to clear secretions), swallowing difficulties, artificial tube feeding, poor nutrition, prolonged immobility, reduced conscious level, cognitive impairment, reduced chest movement on affected side, reduced/dependence for oral care, and current smoking.

Risk factors for developing a urinary tract infection following a stroke include female sex, diabetes mellitus, obstructive lesions (enlarged prostate, renal stones), oestrogen deficiency (atrophic vaginitis), urethral catheterization, decreased conscious level, and advancing age.

Q. Can infections following stroke be prevented?

A. Simple measures to minimise urinary tract infections include adequate hydration, oestrogen supplementation, improving mobility, preventing constipation, and avoiding the use of urinary catheters. Simple measures to reduce the incidence of chest infections include regular swallowing assessment to minimise aspiration, regular oral hygiene, early mobilisation, and judicious use of artificial feeding methods.

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Chapter 6
Venous Thromboembolism

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Abstract Venous thromboembolism after acute stroke has long been a diagnostic and management problem. From the realisation in the 1970s that the incidence of deep-vein thrombosis could be as great as 75 % because of a high unrecognised subclinical element, and silent pulmonary embolism may be the cause of a high proportion of post-stroke deaths, the concern has been on how to prevent this potentially deadly complication. The use of subcutaneous low-dose anticoagulation successful in other groups of high-risk patients has been fraught with the fear of causing intracranial haemorrhage in ischaemic stroke and extending bleeding in intracranial haemorrhage. Some have felt that the benefits of anticoagulation outweigh the risk, especially when using low-molecular-weight heparin, others have opted for mechanical prophylaxis which until recently had scant evidence in acute stroke. Meanwhile, improvements in acute stroke care appears, in itself, to have led to a fall in the incidence of venous thromboembolism, making the case for benefit over risk of prophylactic anticoagulation less clear. Recent large trials have also both clarified and strengthened the case for mechanical thromboprophylaxis, showing clearly that graduated compression stockings were not beneficial, but intermittent pneumatic compression did prevent deep-vein thrombosis and reduce mortality. Venous thromboembolism when it occurs should be treated as a matter of urgency with anticoagulation or an inferior vena cava filter if the risk of bleeding is high.

Keywords Stroke • Venous thromboembolism • Deep-vein thrombosis • Pulmonary embolism • Subclinical • Prevention

Key Messages
- Occurs early after stroke and presents a diagnostic and management challenge.
- Risk factors include severity of the stroke, immobility, and dehydration.

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- Prevention measures include early mobilisation, hydration, intermittent pneumatic compression devices, and prophylactic anticoagulation.
- Prophylactic anticoagulation may carry the risk of intracranial and extracranial bleeding.
- Graduated compression stockings are no longer recommended
- Intermittent pneumatic compression devices should be considered first-line treatment if tolerated.
- Clinical venous thromboembolism should be treated as a matter of urgency by anticoagulation and/or inferior vena cava filter.

Introduction

Venous thromboembolism (VTE), which usually comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), remains one the challenging complications of the post-stroke period. Many aspects from incidence, prevention, and detection, to treatment, have been subject to uncertainty and controversy [1–4]. The majority of the studies in the area have been on DVT rather than PE, and on detection and prevention rather than treatment. Over the last few years, some large studies have brought some clarity to the area of DVT prevention and led to changes in management, and these will be discussed. This chapter will also cover some landmark studies from previous years to show the development of thinking behind VTE management over the last few decades, and why it remains an important part of post-stroke care.

It has been clear from at least the nineteenth century is that acute stroke provides a milieu which is conducive to the development of DVT. Ferriar in 1810 described clinical signs of a DVT, and Lobstein in 1833 the actual thrombus in the paralysed limb of a stroke patient [5]. Why VTE occurs after acute stroke is not fully explained [1], but Virchow's triad is probably fulfilled in the loss of muscle pump and blood stasis of the paralysed limb, repeated minor trauma contributing to endothelial damage [6], and the recognised state of heightened thrombosis after the stroke [1, 7]. Dehydration is also a contributory factor to a change in blood viscosity [8]. It is accepted that DVT can occur as early as the second day after a stroke, and most (80 %) occur in the first week to 10 days [6, 9, 10]; and it is the more severely impaired patients who are most likely to develop DVT [11], the older [6, 11] and those with greater co-morbidities such as atrial fibrillation [11, 12]. There is second, smaller, peak of incidence (20 %) between the first week and the first month [10].

DVT can occur in all types of strokes. It is felt to be more common in haemorrhagic than ischemic stroke [13]. The paralysed limb is most commonly involved, but DVT can be bilateral in 17–22 % or involve the stronger leg in 1–11 % [10, 11]. The incidence has been described as similar to that in the post-surgical orthopaedic patient and probably more common than in the acute medical and surgical patient [14–16], but the whole concept of incidence is open to interpretation [17], with only between 7 and 35 % of all DVT being symptomatic [10, 11].

Incidence of VTE

The clinical diagnosis of VTE in stroke can be straightforward if the classical symptoms and signs of DVT and PE are present. For instance patients with DVT presenting with lower limb pain, swelling, redness, and warmth, and those with PE with chest pain, shortness of breath, and haemoptysis. The earliest descriptions by Ferriar in 1810 were based on clinical signs in a leg previously affected by a paralytic stroke. However as seen in non stroke patients, the symptoms and signs of VTE can be non-specific, for instance, patients with DVT presenting with leg pain but not swelling or swelling without pain [10, 18]; and patients with PE can often also develop a temperature and raised inflammatory markers mimicking an infection [19, 20], sometimes in the absence of chest pains [21]. In stroke patients, there are additional confounding factors such as the common occurrence of oedema in an immobile limb [22] and the co-existence of pneumonia in patients with pulmonary embolism [23]. Pulmonary infection can follow infarction due to a PE. There is always a danger that once a different diagnosis is made, the possibility of a VTE is no longer considered. This is in a group of patients who are often unable to complain of symptoms because of dysphasia, cognitive impairment, confusion, drowsiness, or anaesthesia of the affected limb. The use of the D-dimer test to aid with diagnosis is also hampered by the fact that stroke itself causes a rise in D-dimer levels [24].

Although a lack of recognition of clinical features may be an issue, the greater problem with VTE in stroke patients is the complete absence of clinical symptoms. There is an absence of pain, swelling, or redness of the affected limb in DVT, and no evident shortness of breath and chest pain in PE. Which brings us to one of the pivotal issues in VTE management after stroke: that the incidence of asymptomatic or subclinical VTE is considerably higher than the symptomatic or clinical, and the question that arises—does this matter and require prevention?

If you look at the incidence of VTE in studies, you will find a wide variation, depending on the cohort of patients studied, the timing and method of investigation, and in which decade the studies took place (Table 6.1). The earliest studies in 1970s

Table 6.1 Variation in VTE incidence in absence of prophylaxis over time and with different modalities

	1970s fibrinogen I^{125} [5, 6, 25, 26]	1980s fibrinogen I^{125} [28, 29]	1990s Doppler USS, fibrinogen I^{125} venography [9, 30, 31]	Early 2000 MRI dti [11]	Late 2000 Doppler USS [32, 33]
Numbers	30–76	60–305	75–103	102	2,518–2,860
Any DVT (proximal)[a]	53–75 %	50–73 %	22–34 % (16)	40 % (18)	17–21 % (10–12)
Clinical DVT	32–36 %		7 %	3 %	4–6 %
Any PE[a]				11 %	
Clinical PE or autopsy	13–16 %	7–20 %	0–9 %	5 %	1–2 %

[a]Including subclinical

were performed on small numbers, possibly on more selected admissions to rehabilitation units, used radioiodine labelled fibrinogen uptake, impedance plethysmography or venography, and found the incidence of DVT to be as high as 75 %. The clinical incidence of DVT in this era was 32–36 %, with the clinical incidence of PE being 13–16 % [5, 6, 25, 26]. This is before the routine use of any VTE prophylaxis and of aspirin as prophylaxis against ischaemic stroke. There is evidence that aspirin has some effect on preventing VTE [27]. In the 1980s studies started testing prophylactic heparin, then low-molecular-weight heparins, as DVT prophylaxis in stroke, but the incidence of DVT in the control arms of these studies were not much different from the previous decade [28, 29]. In the 1990s, the incidence of VTE in the absence of prophylaxis did seem to fall, but the studies done specifically to look at post-stroke DVT remained quite small, and it was difficult to say with certainty a true reduction had occurred [30, 31].

From 2000 onward, studies have tended to be larger multicentre trials on a less selected group of patients, usually using compression ultrasound. In patients not on VTE prophylaxis in the control arm of these interventional trials, the incidence of detected DVT was now lower at around 10–20 % (proximal 10 %, all DVT including distal 20 %), with clinical incidence being 1–3 %. In these studies, subclinical PE were not looked for, and the clinical incidence of PE was around 1–3 % [32, 33].

It may well be that greater emphasis on acute care of stroke, which includes better hydration and early mobilisation, has reduced the incidence of VTE, but it could also be said that compression ultrasound may not pick up all the DVT using older methods like radioiodine-labelled fibrinogen or venography. A novel study using magnetic resonance direct thrombus imaging (MRDTI) in 102 patients from 1999 to 2000 found the incidence of subclinical proximal DVT to be 18 %, and all DVTs (proximal and distal) to be 40 %, with a clinical incidence of 3 %. The study had the advantage of also picking up subclinical PE, and this was found in 12 % of patients with a clinical incidence of 5 % [11]. It is interesting that the clinical incidence of PE was higher than that of DVT, which is often not the case. The pick-up rate with MRDTI for DVT would be almost as good as venography and closer to the true incidence, and the same may be said for PE.

Nevertheless, it still could be argued that improvements in acute management of stroke even since the turn of the century have brought the incidence of VTE down. Note the clinical incidence of PE from the MRI study at 5 % is higher than the 1 % found in the latest studies.

Intracerebral Haemorrhage

As mentioned in the Introduction, studies suggest that VTE may occur more frequently in intracerebral haemorrhage (ICH). This may be a result of more severe weakness, depressed level of consciousness, and the avoidance of routine

antiplatelets in the ICH. Retrospective studies comparing the clinical incidence of VTE in ischemic stroke (IS) and ICH have consistently found a higher rate of DVT and PE in ICH than in IS. In one cohort, the rate of DVT was 1.9 % of 1,126 patients with ICH vs. 0.5 % of 15,599 patients with IS, the rate of PE 0.4 % vs. 0.1 % [34]. In another, larger, cohort DVT occurred in 1.37 % of 1,606,000 ICH vs. 0.74 % of 14,109,000 IS, PE 0.68 % vs. 0.51 % [13]. In patients with hemorrhagic stroke initially included in the International Stroke Trial, it was found that patients with ICH had a higher rate of clinically diagnosed PE than patients with IS (1.3 % vs. 0.7 % $P = 0.06$) [35].

Below-Knee, Distal, or Calf DVT

The incidence of below-knee, distal, or calf DVT from control groups without any planned prophylaxis in recent trials has been between 7 and 9 % [32, 33]. And these constitute 40 % of all DVT, though it is likely that some are missed by compression ultrasound. In the MRDTI study, the incidence of below-knee DVT was 22 % and constituted 55 % of all DVT [11]. The figures above are the total incidence; the symptomatic or clinical incidence of below-knee DVT is around 1–3 %, and probably just slightly less than symptomatic proximal DVT. Without treatment, proximal extension into the popliteal vein occurs in 20 % of calf DVT after 2 weeks [11]. There is a risk of PE resulting from calf DVT either because of propagation or embolism from the calf itself. There are no studies of the risk of PE in stroke patients, but in other patients with calf DVT, the risk of symptomatic PE is up to 1 % and asymptomatic PE up to 6 % [36].

Pelvic and Inferior Vena Cava DVT

DVT in the pelvis and inferior vena cava (IVC) after stroke being less common than DVT in the legs have been less studied. Also, the usual imaging methods used to pick up DVT would not have easily detected pelvic and IVC DVT. The overall incidence of these DVT in the stroke population is probably low. In the study using MRDTI to detect VTE, isolated pelvic DVT was found in 2 % of patients and constituted 5 % of all VTE [11]. In selected groups of stroke patients, the incidence can be higher; for instance, in patients with cryptogenic stroke, the incidence of pelvic DVT can be as high as 20 % [37]. In another selected patient group, autopsy series from medical patients with pulmonary embolism, the source of emboli was identified as the pelvic veins in 11 % and the IVC in 5 % [38]. Whilst these DVT can be an extension of femoral DVT, they can often occur alone. In a study using MRDTI in 44 medical patients with PE, the source of emboli was found to be the pelvis, and IVC in 4 (9 %) of the patients, with the thrombus being an extension of a femoral DVT in only 1 case (2 %) [39].

Upper-Extremity DVT

There a no studies looking at the incidence of upper-extremity (axillary, subclavian, and internal jugular) DVT in stroke. From experience, it does occur in the paralysed upper limb, and there are a few case reports [40], but it less common. It is surprising that DVT in the equally paralysed arm does occur less frequently than in the leg, and there is no adequate explanation for this. Some have pointed to the difference in venous anatomy of the arm or greater fibrinolytic activity in the arm [1, 41]. In the literature from unselected patients, it could account for around 4 % of DVT [40]. Whilst there are no studies in stroke, upper-extremity DVT carry a risk of PE with figures of 9–36 % in other groups of patients [40, 42].

Impact of VTE in Stroke (Clinical and Subclinical)

There is a high morbidity and mortality in patients with clinical VTE after stroke. It is the third (or fourth) leading cause of post-stroke mortality after the stroke itself, and secondary infection (and possibly cardiac disease) [43, 44]. The consequences of PE are not just death but significant morbidity, with debilitating symptoms of pain and shortness of breath, and further complications including pulmonary infarction and infection, pleural effusion and empyema, and in the longer term, pulmonary hypertension [45]. There is association with greater disability and longer length of stay [46]. In terms of the impact of clinical DVT, there is, of course, the risk of PE and death, but furthermore, there is the morbidity around limb pain, immobility, and later, the post-thrombotic syndrome [45, 47]. The prevention of VTE may not only improve mortality and morbidity but also recovery and rehabilitation, as it has been shown that DVT prophylaxis is one of the processes of care associated with good outcome, including reduced rates on institutionalisation [48].

In the past when the incidence of DVT after acute stroke was high, between 50 and 75 %, and anticoagulants were felt to be unsafe, the impact of VTE was very clear. There was a high clinical incidence, around half DVT were clinical and 22–30 % of patients with clinical and subclinical DVT went on to suffer a PE—a mixture of half clinical and half unsuspected post mortem diagnosis (13–16 % of the study population) and 25–50 % of those patients with PE died (3–8 % of the population). Of the patients with clinical PE, up to 30 % of patients died, but the majority of the patients with PE who died were found in autopsy and were subclinical [5, 6, 25, 26]. Understanding whether subclinical PE was the primary cause of death in these cases can be sought through post-mortem evidence.

Examining studies with post-mortem evidence, one reported 50 % of PE after stroke presented as sudden death, with confirmatory findings of massive PE including saddle emboli, which were likely to be fatal in all the cases [49]. The peak incidence for mortality from PE is felt to be 2–4 weeks after stroke onset, but can occur as early as the first 3 days [49, 50]. Looking at post-mortem series from the 1970s to 1980s of patients who die after acute stroke, the PE were detected in up to 13 %, but

increased to 30 % for deaths in the second to fourth week, mostly undiagnosed before death [44, 51, 52], lending evidence that subclinical PE may be leading to death. The presence of PE could be underestimated even in such studies because autopsies are not carried out in all post-stroke deaths. In one heparin prophylaxis study from the 1980s on a selected group of older stroke patients, autopsies were carried out in over 80 % and the presence of PE was detected in 56 %. There was also a link with ante-mortem diagnosis of DVT, with PE being found in 76 % of deaths compared to 20 % of those without DVT. Most of the DVT were subclinical, and further evidence of relationship between subclinical DVT and PE-related deaths was that the group receiving prophylaxis had fewer DVT, 22.2 % vs. 72.7 %, fewer deaths, 22 % vs. 33 %, and in those who died fewer PE were found, 29 % vs. 70 % [28].

So in summary it does seem there is reasonable evidence that subclinical DVT was leading to subclinical PE, which in turn was contributing to post-stroke deaths. In other patient groups, it has been suggested that one-third to two-thirds of PE found at autopsy caused or contributed to the death [53, 54]. So at that time both clinical and subclinical VTE did seem to matter, and whilst subclinical PE may not have been the final cause of death in all cases, its presence may have been contributory, and in patients who do not die, the presence of PE may well be impeding recovery and rehabilitation [25, 48].

The incidence of VTE and death from that era was quite high, as prophylaxis was not a standard practice, and conventional treatment with anticoagulation—even for established VTE—was felt to be hazardous after acute stroke. There has been a fall in clinical DVT and PE after stroke in the last few decades, with greater use of antithrombotic medication and better acute stroke care [32, 33, 55, 56]. With clinical PE being about 1 %, the impact of VTE has been less evident, and whilst the significance of clinical PE is still high, with mortality rate of up to 40–50 % [57], the case for prevention is less overwhelming, especially if it involves some risk like prophylactic anticoagulation.

So prevention in this era is based around the benefits of prevention of subclinical VTE. Extrapolating from hospitalised medical patients, having subclinical events still matter, subclinical proximal DVT was associated with higher mortality than subclinical distal DVT, which again was higher than no DVT [58]. The MRDTI study mentioned previously gives a more recent perspective of subclinical post-stroke VTE, having the advantage of detecting not only subclinical DVT, but PE as well. In this unique study, DVT was found in 40 % of patients, proximal in 18 % of patients, and only 3 % of these DVT were clinical; PE was found in 12 %, 5 % clinical and 7 % subclinical, and attributed mortality from PE was 2 % [11]. The incidence and mortality from PE could have been higher, as patients with proximal DVT were anticoagulated when found, including those who were subclinical. Of the 5 % clinical PE, only 3 % had been recognised, and in the 3 % clinical DVT, only 1 % recognised.

It is felt that fatal PE usually arise from proximal DVT, and from studies in other groups of patients, especially postoperative patients, the mortality from PE in untreated clinical proximal DVT can be as high as 40 %. The mortality from PE in untreated subclinical proximal DVT is felt to be lower, at 5–15 % [47]. Using this

MRDTI study as a model, the mortality of 2 % out of a total PE incidence of 12 % approximates to 20 % of patients with PE. Also, 2 % mortality out of a total proximal DVT incidence of 18 % equates to a mortality rate of just over 10 % in patients with proximal DVT. To simplify, it could be suggested that in patients with proximal DVT after acute stroke (which is mainly subclinical), PE occurs in 50 % or more, and 10 % or more may die. Even if the mainly subclinical incidence of proximal DVT may have fallen to 10 % in this era of hyperacute stroke management [32, 33], this still equates to PE rate of 5 % (the majority may be subclinical as the rate of clinical PE in recent trials is 1–2 %) and mortality of 1 % (some of which may be unrecognised as deaths due to PE). It is figures such as these which justify the prevention of VTE, otherwise many remain undiagnosed and untreated, with significant consequences, hidden or otherwise.

Prevention of VTE

Once the incidence of VTE in stroke patients was investigated for in the early 1970s and found to be excessively in high in immobile patients with attendant mortality, various forms of prevention have been tried to reduce the incidence of VTE. In addition, 5 % of stroke patients will have a previous history of VTE, putting them at greater risk regardless of whether there is paralysis and immobility [33]. There has been a debate over the best form of prophylaxis, with a different stance being taken on either side of the Atlantic, especially on using anticoagulants as thromboprophylaxis. The components of current clinical guidelines are reviewed below (Table 6.2) [59–73].

Early Mobilisation

Early mobilisation is almost universally mentioned in clinical guidelines as one of the first measures for the prevention of DVT (as shown in Table 6.2). There is, however, no direct evidence so far that it prevents DVT and it was a component in the immobility related adverse events that was not lower in the very early mobilisation group in the latest results of the AVERT trial [74]. In the time before stroke units were commonplace, DVT rates were historically lower in stroke units where early mobilisation was one of the components of effective stroke care. Prior to the recent cautionary results on very early mobilisation from the AVERT trial, early mobilisation was linked with other beneficial outcomes like increased independence, fewer pressure sores, fewer cases of pneumonia, increased psychological well-being, and a reduced length of stay [75–77] There were some concerns in the past that early mobilisation should stop after the diagnosis of DVT because of the risk of PE [78], but that was in the era when intravenous heparin and warfarin were used. In a recent meta-analysis of trials using LMWH, this was found not to be the case, and recommended once treatment started, early mobilisation should positively be encouraged, as there was a trend toward lower mortality and less progression of DVT [79].

Table 6.2 Summary from the clinical guidelines of their guidance on prevention of VTE

UK			US		Europe	Australia	Japan
RCP 2012 [59]	SIGN 118, 122 [60, 61]	NICE 2009 [62]	AHA/ASA 2007.2010, 2013 [63–66]	ACCP 2008. 2012 [67, 68]	ESO 2008, 2014 [69, 70]	ANSF 2010 [71]	2009 [72, 73]
Ischaemic stroke	**Ischaemic stroke**	**Ischaemic stroke**	**Ischaemic stroke**	**Ischaemic stroke**	**Ischaemic stroke**	**Ischaemic stroke**	**Ischaemic stroke**
Early mobilisation and hydration mentioned (GCP)	Early mobilisationand no evidence to support or refute		Early mobilisation to prevent subacute complication (Class I, Level C)		Early mobilisation and hydration (Class IV GCP)	Early mobilisation and hydration (GPP)	
GCS should not be used as prophylaxis (Class 1, Level A)	IPC should be considered. (Grade A). Above knee GCS not recommended (Grade A)	Do not offer GCS	IPC for those who cannot receive anticoagulants (Class IIa, Level B then)	IPC first line or prophylactic UFH or LMWH (Grade 2B) GCS suggested against (Grade 2B)	GCS (Class IV GCP then)	Thigh-length GCS not recommended (Grade B)	Insufficient evidence for IPC and GCS at the time (Grade C1)
	Aspirin is recommended in the first 2 weeks (Grade A)		Aspirin reasonable in patients who cannot receive anticoagulants (Class IIa, Level A)			Antiplatelets should be used to prevent DVT/PE (Grade A)	Aspirin is not recommended for the prevention of PE in patients with ischaemic stroke

(continued)

Table 6.2 (continued)

UK			US		Europe	Australia	Japan
RCP 2012 [59]	SIGN 118, 122 [60, 61]	NICE 2009 [62]	AHA/ASA 2007.2010, 2013 [63–66]	ACCP 2008. 2012 [67, 68]	ESO 2008, 2014 [69, 70]	ANSF 2010 [71]	2009 [72, 73]
Prophylaxis with anticoagulants should not be used routinely after stroke. Where anticoagulation is needed for prevention LMWH is preferred to UFH	Anticoagulation in the first 2 weeks can cause haemorrhage and has no net benefit. Patient at particularly high risk can be given prophylactic heparin. LMWH recommended over UFH (in addition to IPC). After 2 weeks risk should be re-assessed	Prophylactic LMWH should be considered for those at high risk of VTE or UFH in patients with renal failure	Subcutaneous anticoagulants recommended in immobilised patients. Ideal timing of initiation not know (Class I, Level A)	Prophylactic UFH or LMWH but low dose LMWH suggested over UFH (Grade 2B)	Low dose UFH or LMWH should be considered for those at high risk of VTE (Class 1 Level A)	LMWH can be used with caution on selected patients at high risk or UFH if contraindicated (Grade B)	LMWH or UFH is recommended for patients with ischaemic stroke with paralysis of lower extremities but not routinely because of the risk of bleeding (Grade C1)

Intracerebral haemorrhage	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**	**Intracerebral haemorrhage**
No specific recommendations		No specific recommendations	Initial use of IPC (Class I, Level B) treat hypertension	Initial use of IPC (Grade 2C then) GCS suggested against (Grade 2B)	GCS not recommended Initial use of IPC as first line—moderate		IPC or GCS or combination of the 2 (Grade B)
		Bleeding risk mentioned as contraindication to LMWH or UFH in ischaemic stroke	Prophylactic dose LMWH or UFH may be considered after cessation of bleeding 1–4 days from onset (Class IIb, Level B)	Prophylactic dose LMWH or UFH started between 2 and 4 days (Grade 2C). LMWH suggested over UFH (Grade 2B)	Insufficient evidence to make recommendation about anticoagulants—Low	Antithrombotics not recommended (GPP)	Low dose heparin can be considered for ICH patients without rebleeding 3–4 days after onset

ACCP American College of Chest Physicians, *ANSF* Australian National Stroke Foundation, *ESO* European Stroke Organisation, *RCP* Royal College of Physicians, *GCS* graduated compression stockings, *GPP* good practice points, *ICH* intracerebral haemorrhage, *IPC* intermittent pneumatic compression stockings, *IST* International Stroke Trial, *LMWH* low-molecular-weight heparin, *NICE* National Institute of Care Excellence, *SIGN* Scottish Intercollegiate Guidelines Network, *UFH* unfractionated heparin

Hydration

Dehydration is linked with DVT after acute stroke. A urea level above 7.5 mmol/l, a urea/creatinine ratio over 80, and serum osmolality of greater than 297 mOsm/kg were associated with greater odds of developing a DVT [8]. Therefore, it has been surmised that better hydration will prevent DVT, but there has not been a trial to prove it. In a Cochrane review of heamodilution trials mostly using dextran to unselected patients, there was a tendency to fewer VTE [80]. Changing osmolality in patients can be difficult, even in patients on intravenous fluids [81], but perhaps with closer monitoring of hydration parameters than is done routinely, this can be achieved [82]. Some of the current National Guidelines do recommend hydration as a first-line measure in stroke prevention [59, 69, 71].

Heparin, Heparinoids, and Low-Molecular-Weight Heparin in Ischaemic Stroke

Studies looking at the use of chemical thromboprophylaxis with heparin in stroke started as early as 1977 [26] and was in routine use as recommended prophylaxis after ischaemic stroke in United States since the 1980s [83]. In the UK, heparin prophylaxis was used in trials and selected patients, but the concern about secondary cerebral haemorrhage limited its use. In a meta-analysis from 1993, heparin was seen to show a significant 81 % reduction of DVT after acute stroke; there was also 58 % reduction of PE and 18 % reduction in mortality, but these latter two results were not significant. There was also a non-significant 12 % increase in haemorrhagic transformation of infarct [84]. The reasons these results were far from conclusive, apart from inadequate numbers, were that not all these trials were designed primarily to look at VTE thromboprophylaxis; a mixture of high and low doses of heparin were used, and the effects of secondary haemorrhagic transformation not fully understood. The large International Stroke Trial [85] had the numbers, but again was designed to look at antithrombotics as treatment for ischaemic stroke rather than prophylaxis against VTE. It had a factorial design and compared aspirin, together and against two doses of heparin (high-dose 12,500 units bd and low-dose 5,000 units bd) and placebo, started within 48 h of stroke onset, but did not have DVT as an endpoint. Clinical PE was an endpoint, and with heparin (combined high and low dose), there was a significant reduction from 0.8 to 0.5 % ($p=0.02$) – 3 fewer PE/1,000 patients. There was, however, a significant increase in intracerebral haemorrhage (1.2 % vs. 0.4 % compared to not using heparin)—8 more cerebral bleeds per 1,000, which more than outweighed the benefit of reduction in PE. Aspirin did not show a significant increase in intracerebral haemorrhage (0.9 % vs. 0.8 %) and there was a slight trend to PE reduction 0.8–0.6 %, but this was not significant ($p=0.08$). There was also no long-term survival or functional outcome benefit with heparin. When the outcomes with the two doses were subdivided in subgroup analysis, the protection against PE was associated with higher dose 12,500 units bd

(0.5 % vs. 0.9 % control), but so was the haemorrhagic risk (1.8 % vs. 0.3 % control); the lower dose 5,000 units bd had the similar PE incidence as aspirin (0.8 % vs. 0.7 %) and intracranial haemorrhage (0.7 % vs. 0.5 %). Both doses demonstrated similar protection against ischaemic stroke as aspirin. The combination of lower dose of heparin 5,000 units bd and aspirin, which is sometimes used as VTE prophylaxis today, did seem to prevent early recurrent ischaemic stroke (2.1 % vs. 3.5 %) without a significant excess in intracerebral haemorrhage over aspirin alone (0.8 % vs. 0.5 %), but did not show a significant reduction in PE, 0.5 % vs. 0.7 %. Therefore, from these findings, the use of anticoagulation early after acute ischaemic stroke was discouraged in the UK guidelines.

In the US before and after IST, unfractionated heparin (UFH) and then low-molecular-weight heparin (LMWH) continued to be used immediately after acute ischemic stroke as thromboprophylaxis against VTE, and subsequent systematic reviews [86–88] continued to suggest that anticoagulants did prevent VTE, but with the risk of intracerebral haemorrhage. When the reviews were done combining high and low doses of UFH and LMWH, the conclusion was often that the benefits of VTE prevention were outweighed by the risk of symptomatic intracranial haemorrhage (sICH). In one systematic review, the low doses and high doses were separated, it was shown that a lot of the bleeding risk was associated with the high doses of heparin or LMWH, and that the lower doses had less of a bleeding risk but also less thromboprophylactic benefit, with low doses of UFH being shown to prevent DVT but possibly not PE. The best risk profile seemed to be with LMWH, with a significant reduction in DVT OR 0.34 (0.19–0.59) and PE OR 0.36 (0.15–0.87) and non-significant rise in sICH OR 1.39 (0.53–3.67) [88].

In the PREVAIL trial, LMWH was seen to be superior to UFH; Enoxaparin reduced the risk of venous thromboembolism by 43 % compared with UFH (10 % vs. 18 %; relative risk 0.57, 95 % CI 0.44–0.76, $p = 0.0001$), with no difference in symptomatic intracranial haemorrhage, 1 % vs. 1 % [89]. A criticism was that this trial was comparing two heparins, probably combined with aspirin which was in common use as stroke prophylaxis by then, and had no placebo arm. Since IST, a trial has not been done to look specifically at aspirin and low-dose anticoagulant versus aspirin and placebo, which is what is practised today as VTE prophylaxis in some parts of the world. In different countries, either it is taken as a given that anticoagulation is the standard prophylaxis, or that is generally discouraged unless under special circumstances and other methods are being looked at. Another point made about the PREVAIL trial was that there was no difference in survival, despite there being not only a difference in asymptomatic DVT, but there was also a difference in total numbers of symptomatic DVT and PE, 1 vs. 4 DVT and 1 vs. 6 PE, in favour of Enoxaparin (the numbers being small, the differences in symptomatic VTE did not reach significance). There are still concerns that only the symptomatic VTE events matter, and the symptomatic PEs prevented did not outweigh symptomatic extracranial haemorrhage in this trial and did not outweigh an increase in sICH when compared to placebo in other trials [90].

If prophylactic anticoagulation is used it should be continued for at least a month in patients with an immobile limb, for although the majority of DVT develop early, a significant proportion can occur up to a month (26–30 days) after the event, and extended prophylaxis beyond 10–14 days has been shown to reduce this [10, 91]. In stroke patients from the EXCLAIM Study, extended prophylaxis reduced VTE from 8 to 2.4 %, with one fatal PE in the placebo group, this albeit with an increase in major bleeding (1.5 % vs. 0 %), and one fatal intracranial bleed in the treatment group. Prophylactic anticoagulation may not need to be continued long term and it may not be practical to do so. There is evidence from chronic paraplegics that after some time has elapsed from the acute event, the risk of DVT is a lot less, possibly due changes in fibrinolytic activity in the limbs [41].

Heparin, Heparinoids, and Low-Molecular-Weight Heparin in Primary Intracerebral Haemorrhage

With the invention of the CT scan in 1972 and the first clinical head scans only being installed in the mid-1970s, the early heparin trials in the 1970s did not routinely use CT head scans, and thromboprophylaxis was given to strokes in general. With the more widespread use of CT in the 1980s, distinguishing between ischaemic stroke and intracerebral haemorrhage (ICH), anticoagulant prophylaxis was not used early in ICH, and in some countries not at any time, and most of the trials of anticoagulant prophylaxis in acute stroke have concentrated on ischaemic strokes. The US guidelines did allow its use after 48–96 h, based on evidence that it did prevent PE without increase in the number of patients with rebleeding [65, 68, 92], and there has been a recent study from a stroke registry showing that the use of prophylactic anticoagulation within 7 days did not seem to cause extension of the intracrebral haemorrhage in a majority of patients [93]. A meta-analysis from 2011 again showed a significant reduction in PE with anticoagulant prophylaxis, but not DVT, with a non-significant trend toward increased survival, but also a trend toward greater hematoma growth [94]. There have really not been any large well-designed controlled trials of anticoagulation prophylaxis in ICH. Other guidelines, including those of the UK, do not recommend its use at any time in intracerebral haemorrhage.

The Novel Oral Anticoagulation Agents as Prophylaxis in Acute Stroke

Over the last few years, several new oral anticoagulation agents have been introduced which have been in situations traditionally occupied by LMWH and warfarin, such as the prevention and treatment of VTE and the prevention of stroke in atrial fibrillation. The novel oral anticoagulants (NOACs) can be separated into direct thrombin inhibitors, such as Dabigatran, and direct Factor Xa inhibitors, such as Rivaroxaban and Apixaban. In the sphere of VTE thromboprophylaxis, these NOACs have been shown to be superior to LMWH at preventing VTE in post-operative orthopaedic patients without an increase risk of bleeding [95]. As yet, there are no trials of VTE prophylaxis using NOACs after acute stroke.

Graduated Compression Stockings

With the controversy over whether the benefits prophylactic anticoagulation outweighed the risk, graduated compression stockings (GCS) became the mainstay of prophylaxis in the UK [96]. GCS, used first in post-operative surgical patients from the 1970s, was adopted for use in stroke patients despite lack of evidence for benefit in stroke. Many physicians, however, felt it to be ineffective in stroke and there was a small trial which was inconclusive [9]. Then the publication of the large CLOTS Trial in 2009, with over 1,200 patients in each group including ICH, showed no significant difference in the incidence of proximal DVT when using thigh-length GCS compared to avoidance of GCS, 10 % vs. 10.5 % OR 0.97 (0.75–1.26). This was a combination of clinical and subclinical DVT diagnosed with compression ultrasound. The incidence of clinical DVT was 2.9 % vs. 3.4 % OR 0.84 (0.53–1.31). There was also no significant difference in the incidence any DVT (proximal and distal) 16.3 % vs. 17.7 % OR 0.9 (0.73–1.11), any clinical DVT 4.4 % vs. 4.8 % OR 0.9 (0.62–1.31), and any PE 1 % vs. 1.6 % OR 0.65 (0.32–1.11). In addition, GCS was associated with a higher incidence of skin breakdown, ulceration, and necrosis 5 % vs. 1 % OR 4.16 (2.40–7.27) [32]. This was a clear result that thigh-length stockings were of no benefit for DVT prophylaxis after stroke. There were few unanswered questions, however, when these results were taken in conjunction with the CLOTS 2 trial, as to why thigh-length stockings were of no benefit and yet better than below-knee stockings. Did below-knee stockings cause DVT or was there a small benefit which could not be shown [97]? Nevertheless, from these trials the recommendation is to avoid any form of compression stocking after stroke and subsequent guidance have reflected this [59, 62].

Intermittent Pneumatic Compression

Like the previous prophylactic measures against VTE, intermittent pneumatic compression (IPC) was first used in surgery and has been shown to prevent DVT (Fig. 6.1). It is thought to prevent DVT by reducing venous stasis, but there is also some

Fig. 6.1 Intermittent pneumatic compression (IPC) device with sleeves applied to the patient's legs

conflicting evidence that it may have an effect on fibrinolytic pathways [43]. Its efficacy in prevention of PE was not so clear, as its benefits in non-surgical patients. Guidelines have recommended it use especially in ICH for some time, but there were a few inconclusive trials in acute stroke until the CLOTS 3 Trial, a multicentre trial, published in 2013 [33]. The trial with over 1400 patients in each arm including 13% ICH showed that IPC did reduce the incidence of proximal DVT compared to control by 3.6 % (8.5 % vs. 12.1 %), with adjusted OR 0.65 (0.51–0.84 $p=0.01$). There was also a significant reduction in all DVT, clinical and subclinical, proximal and distal 16.2 % vs. 21.1 % OR 0.72 (0.6–0.87 $p=0.01$) and in all clinical DVT 4.6 v 6.3 % OR 0.72, (0.52–0.99, $p=0.045$). There was no significant difference in the incidence of PE but numbers were small 2.0 % vs. 2.4 %. The combined VTE incidence of any DVT and PE was significantly reduced 17.2 % vs. 22.6 % OR 0.72 (0.59–0.86, $p=0.00035$). At 30 days, there was a non-significant reduction in mortality 10.8 % vs. 13.1 % OR 0.8 (0.63–1.01, $p=0.057$), but the combined incidence of VTE and death was significantly reduced 27.2 % vs. 34.1 % OR 0.72 (0.61–0.84, $p<0.0001$). There was no excess of DVT and PE in the post-treatment period when sleeves were removed, to indicate that IPC simply deferred VTE to later. At 6 months there were a few more DVT and PE and many more deaths, but significant combined difference between the two groups still held 35.6 % vs. 42.3 % ($p=0.002$). Using the Cox model adjustments, there was also a significant reduction in the cumulative hazard of death during the 6 months after randomisation in the IPC group, with a hazard ratio of 0.86 (0.74–0.99) $p=0.042$. Although there was no difference in confirmed PE, the autopsy rate was low, and the authors suggest that the difference in mortality may be due to a reduction in undiagnosed PE that contributed to death.

The IPC has a few drawbacks in that the use is not advised with skin conditions like dermatitis and leg ulcers, congestive cardiac failure, and other conditions causing severe oedema and significant peripheral vascular disease, which were all exclusion criteria in the study. The incidence of skin breaks and ulceration with use was higher in the treatment group (3 % vs. 1 %, $p=0.02$), though the authors mention that local investigators did not attribute many of these to the IPC, occurring after the sleeves were removed, or on the heels, which are not covered by the sleeves. A more common drawback was the fact that IPC was not tolerated by all patients, and the mean time the devices were on for was 12.5 days, with a median of 9, significantly less than the 30 days envisaged. Perfect adherence was achieved in 31 % of patients, and mean adherence was 59.2 %. Also, from practical experience, the sleeves often had to be taken on and off for therapy, and there are sometimes concerns that if for any reason the sleeves are left off for a reasonable length of time, legs need to checked for DVT and scanning done. The other concern raised is the effect of IPC on other DVT, for instance more proximal DVT in the pelvis and IVC, and that it would clearly have no benefit in preventing upper-extremity DVT. Nevertheless, despite these concerns, this is one intervention that showed unequivocal benefit on reducing DVT and mortality without significant side effects and should be considered first-line for prevention. Some guidelines have it on equivalence with LMWH, but more recent guidelines published have started to make it first-line prevention [60, 61], especially in ICH [70]. On analysis, however, there were no significant cost- or quality-adjusted survival gains [98].

Diagnosis of VTE

Despite prevention measures, post-stroke VTE occur, and even if subclinical VTE are not sought by some form of screening it is known from recent trials that the incidence of symptomatic DVT in the modern era of stroke care will be between 1 and 5 %, and incidence of symptomatic PE will be in the order of 1–3 % [32, 33, 89]. Bearing in mind all the while, there is a much higher subclinical incidence in the order of 20 % for all types of DVT, 10 % for proximal DVT, and perhaps 2–5 % for PE. As mentioned at the start of this chapter, stroke patients may not be able to report limb discomfort, and factors like hemiplegic oedema and pneumonia can mask VTE. So the clinician's index of suspicion must be high and there should be awareness of subtle signs such as slight increases in calf diameter and tension, a raised respiratory rate and/or heart rate, and minor changes in oxygen saturation. It has to be said these clinical signs may only have moderate predictive value, for instance in the MRDTI study of severe ischemic stroke patients a calf diameter change of 1 cm had a sensitivity of 44 % and positive predictive value of 53 %, whilst using 2 cm change had a greater positive predictive value of 78 % but sensitivity fell to 28 % [99]. Nevertheless, under current processes of care, relying on clinical signs are the mainstay of diagnosis, and knowing the greater risks associated with clinical VTE, it is better to investigate any suspicion and not dismiss them or presume infection or oedema.

The alternative avenue for VTE diagnosis, which has been proposed because of the unreliability of clinical symptoms and signs, would be screening for high-risk patients using a combination of stroke-related features such as severity and immobility and the D-dimer test. As yet, there has not been any recommendation for such a course in clinical guidelines, so now outside of clinical trials, only those suspected of VTE will go on to further investigation.

D-dimer

D-dimer is a cross-linked fibrin degradation product that is generated during thrombus formation and has been used with clinical features to select patient presenting to the emergency departments with a swollen leg or chest pain for further imaging for VTE. In VTE in the general population the plasma level of D-dimer can be increased eight times more than controls and then levels fall with the duration of symptoms and introduction of anticoagulant therapy [100, 101].

The use of D-dimer testing as a screening tool to aid the diagnosis of VTE is less useful in stroke patients, as concentration of D-dimer is increased in conditions associated with enhanced fibrin formation and subsequent degradation by plasmin, such as age, cancer, surgery, infections, acute coronary syndromes, cardiac or renal failure, atrial fibrillation, and stroke [102–105], so standard D-dimer thresholds cannot be relied upon.

Nevertheless, the same D-dimer tests are used in stroke as in other groups of patients, enzyme-linked immunosorbent assays (ELISAs), which have very high sensitivity but low specificity and traditionally take longer to anlyse and quicker modern latex agglutination tests, which tend to be somewhat less sensitive but more specific. More recently, highly sensitive latex agglutination tests have been developed, so that their performance characteristics tend to approach those of the ELISAs [100, 101].

Many studies have shown that D-dimer levels are elevated after stroke and remain elevated for some weeks, but did not select out confounding variables. A paper from the MRDTI study mentioned earlier excluded patients with VTE and also those with other confounders like inter-current infection and found that the median level still remained elevated above standard thresholds. At 2 days post-stroke, the overall median value for the VIDAS ELISA assay was 652 ng/ml (433–1,097) higher than the standard diagnostic threshold of 500 ng/ml. This was even more pronounced in older patients (>70 year) and in patients with severe strokes, with 2-day median of 1,051 ng/ml (663–1,441 ng/ml) and 858 ng/ml (623–1,882 ng/ml). There was no group where standard thresholds would be useful. Median levels in total anterior circulation infarct levels were higher, but lacunar levels were still above the threshold (VIDAS 1,251 ng/ml vs. 721 ng/ml). In those aged <70 year and in non-severe strokes, the median levels of 515 ng/ml (343.5–717 ng/ml) and 612 ng/ml (430–858 ng/ml) were lower but still above the standard [24].

Studies have tried to find a higher D-dimer level which could give greater specificity whilst maintaining the safety of high sensitivity to use for DVT screening and exclusion. A study in the 1990s using an older ELISA assay showed that optimal cut point for predicting DVT with D-dimer was 1,591 ng/ml, resulting in 79 % sensitivity and 78 % specificity, however that would mean missing some DVT, so the group found that lowering the D-dimer cut point to 1,092 ng/ml improved the sensitivity to 100 %, albeit with a fall in specificity to 66 % [106]. Various things, including the older batch assay and the rehabilitation setting with recruitment 3 months after stroke, probably means this D-dimer level is not applicable for use for acute stroke today. The more recent MRDTI study found the VIDAS ELISA test of 2,096 ng/ml and the IL agglutination test of 1,174 ng/ml had a sensitivity of 78 % and 83 % for proximal DVT, but at the cost of imaging 30 % of the patients [99].

With the use of different D-dimer tests around the world and the loss of sensitivity of the test in the pursuit of greater specificity to make it a reasonable proposition, it does seem that using a D-dimer level for screening regime for VTE after stroke is currently not feasible, and that clinical suspicion remains the main method of diagnosis. Current standard thresholds for D-dimer tests with a likely sensitivity and negative testing predictive value of 100 % after acute stroke could at least be used to exclude patients highly unlikely to have VTE in acute stroke. In the MRDTI study, all 40 patients with DVT of the 102 studied had an elevated D-dimer level [99]. The clinical reality is that anyone with a suspicion of a VTE should go to further imaging.

Imaging Techniques for the Diagnosis of DVT

Ultrasound and contrast venography are the chief imaging modalities currently available to most clinicians when DVT is suspected, each of which have shortcomings if used as screening tools for asymptomatic DVT. These techniques together with others that are mainly of historical or research interest are discussed.

Contrast Venography

Contrast venography has been used since the 1940s to diagnose DVT [107]. It was the gold standard for the investigation of lower-limb DVT and is still considered as such [108]. Most of the current tests for DVT have been measured against it. The test, however, is invasive, reliant on locating a vein to inject into, difficult in very oedematous legs, and painful. It also involves the use of contrast, which apart from radiation exposure, is associated with allergic reactions, extravasations, local skin reaction, and the risk of nephrotoxicity. Some of these issues would be expected in patients with severe strokes, for instance oedema of the paralysed limb or renal impairment. Also, a high percentage of scans (5–15 %) could not be interpreted [109]. Therefore, although accurate, its use as a general diagnostic or screening test for DVT is not practical, and it is a test that is hardly used now. The last big stroke trial to use venography as a screening and diagnostic tool was the PREVAIL trial published in 2007, and 14 % of patients had to be assessed by compression ultrasound [89].

Fibrinogen Uptake Test

As the widespread use of contrast venography was not practical, other tests were developed to use for diagnosis and screening and to use in studies. The fibrinogen uptake was one test used from the 1970s and utilised the expected incorporation of injected radioiodine-labelled fibrinogen into the developing thrombus as a marker along the leg veins to pick up DVT. A scintillation counter is then used to measure radioactivity level at various marked points on the calf and thigh. Fibrinogen reuptake scanning possibly led to a higher rate of DVT diagnosis than venography, the accepted standard. These could be due to small thrombi that are non-occlusive and not detected by venography, or perhaps a spurious result for other reasons. Some of the highest incidence studies for post-stroke DVT were using radioiodine-labelled fibrinogen. Nevertheless, it was not very sensitive at picking up thrombi in the groin or pelvis. The test was mainly used as a study tool but went out of favour because of the infection risk associated with injecting blood products [110].

Plethysmography

Plethysmography is the term given to the recording of changes in the size of the limb due to tissue fluid or pooled blood in the veins. This measurement can be undertaken in various ways: photoplethysmography, strain gauge, and electrical

impedance. Some of these techniques have been used in a research setting in the past rather than in general clinical usage. Also some of these scans' standardised cut points may be affected by hemiplegic oedema.

Impedance Plethysmography

Impedance plethysmography was historically the one most commonly used and is based on the principle that the volume of blood in the leg affects the ability of blood to conduct an electrical current between two electrodes placed along the calf. A cuff is inflated around the thigh to obstruct venous outflow but not arterial inflow. As blood accumulates in the leg below the cuff, impedance between the calf electrodes falls. The sudden release of the cuff results in a fall in blood volume and a rapid increase in impedance. Obstruction to venous flow, such as with a deep-vein thrombosis, causes a reduction in the rate of venous emptying and slower increase in impedance. The technique is operator dependent, and the sensitivity in some studies has been low. At best it can have sensitivities of over 90 % for symptomatic proximal DVT, but it really is not that useful for calf vein DVT and asymptomatic DVT [111, 112].

There are newer automated plethymography techniques which may be more sensitive. Digital photoplethysmography depends on the absorption of light by haemoglobin in the red cells and by the characteristics of the reflected light the venous refilling time after repeated foot dorsiflexion is calculated [113]; automated strain plethysmography relies on the detection changes in calf size after the release of venous occlusion, with slowed emptying being seen in thrombosis as in the impedance technique [114]. Small studies in symptomatic patients have shown good sensitivity, especially in proximal DVT, and are simple screening tests to perform and could be useful for excluding DVT, but will require other imaging for diagnosis. It is unlikely they will be used now in diagnosis or screening studies of DVT in stroke.

Ultrasound

Ultrasound scanning (USS) is now the initial investigation of choice in clinically suspected DVT. There are different USS techniques in general use for the diagnosis of DVT; the most basic, B mode, looks for non-compressibility of the vein in the presence of a thrombus (Fig. 6.2). This can be combined with blood flow characteristics in the vein using a pulse Doppler signal. Blood flow is normally in phase with respiration and can be augmented by squeezing distally. The loss of the phasic pattern can suggest the presence of a proximal venous obstruction. This is called duplex USS. Colour flow Doppler, by assigning colour to the direction of the flow, can be used to distinguish veins from arteries to aid in diagnosis and for imaging flow around partial thrombus—this is called colour flow duplex USS. The most commonly used technique is B Mode and some have suggested that the other elements to USS do not add much to the sensitivity of the test [115], but maybe in selected circumstances as mentioned above they could be useful.

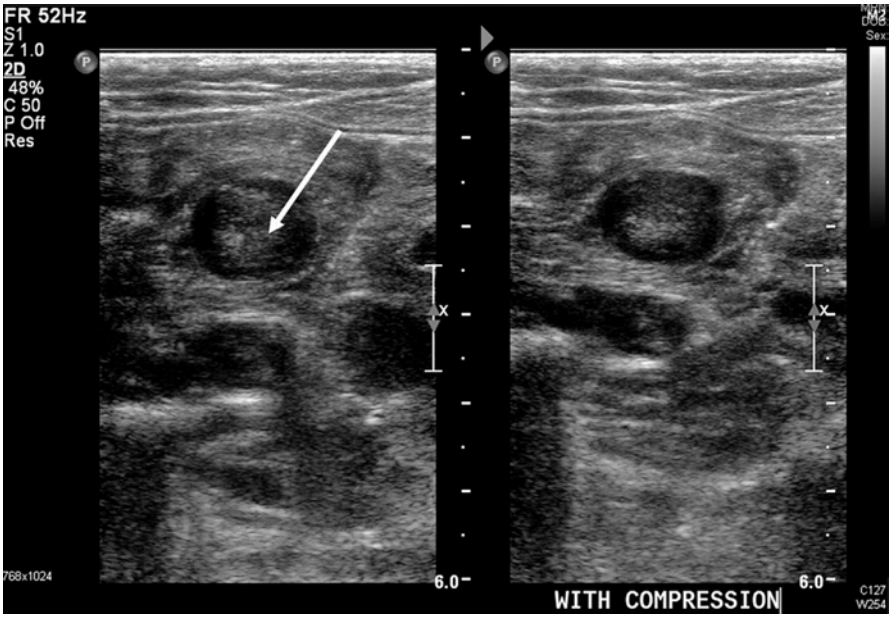

Fig. 6.2 Compression ultrasound demonstrating a gastrocnemius vein thrombus. The thrombus is *arrowed* in the *left image*. In the *right image*, the probe is used to compress the tissue. The thrombus prevents compression of the vein (Courtesy of the Vascular Laboratory, King's College Hospital London)

If used for the purpose of diagnosis in clinically suspected DVT, it compares favourably with venography. There are no specific studies looking at the sensitivity of USS in stroke patients, but in studies of unselected patients with symptomatic proximal DVT, duplex USS has been shown to have sensitivity of 92–95 % and a specificity of 96–100 % [109]. Reported causes of false-negative tests included missing small clots in the popliteal vein, mistaking a patent deep femoral vein as the superficial femoral vein when the latter was thrombosed, and failing to detect thrombosis in the adductor canal and in the iliac vein. It may be difficult to be confident that a segment of vein is truly non-compressible in an extremely obese or well-muscled individual [109].

The sensitivity of USS in below-knee DVT is much lower, with a mean around 73 % in one analysis and a range in the studies looked at from 0 to 100 %, but the problem with the comparison was the use of different USS techniques and different patient populations studied (inpatients, outpatients, medical patients, post-op surgical patient) [109]. It is also not very sensitive at detecting isolated pelvic DVT.

In asymptomatic patients, the accuracy of ultrasound, as with other techniques, is again lower [116]. The reduced sensitivity is attributable to the fact that asymptomatic thrombi are more likely to be fresh, smaller, and non-occlusive than their symptomatic counterparts, and are therefore less likely to generate abnormal venous dynamics [115, 116].

So in conclusion, with good sensitivity for proximal DVT, the current general use of USS for the purposes of diagnosis in stroke patients with clinical symptoms is appropriate, especially if repeated to look for any proximal propagation of a missed calf DVT to account for its lower sensitivity for below-knee thrombus.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been put forward as next non-invasive examination for patients in whom ultrasound has not been possible or helpful, and even as an alternative investigation of choice for the future. A meta-analysis of 14 studies in 2007 mostly comparing MRI with venography in patients with clinically suspected DVT showed a pooled sensitivity of 91.5 % and the pooled specificity was 94.8 %. Sensitivity for proximal DVT was higher than sensitivity for distal DVT (93.9 % versus 62.1 %). However, the pooled estimates should be interpreted with caution, as estimates of both sensitivity and specificity were subject to significant heterogeneity. MRI appears to have equivalent sensitivity and specificity to ultrasound, but has been evaluated in many fewer studies, using a variety of different MRI techniques [117].

MR Direct Thrombus Imaging (MRDTI) for DVT

MRDTI, a newer application of MR technology, is based on the transformation of haemoglobin into methaemoglobin when a thrombus is formed. Using a T1 sequence, methaemoglobin in the thrombus gives a strong signal that disappears after about 6 months, allowing direct visualisation of thrombus as a high signal against a background of suppressed blood and fat, instead of a filling defect, reproducing the pitfalls of other imaging modalities and giving little information about the thrombus (Fig. 6.3) [118]. MRDTI in a prospective study of 101 patients with suspected DVT was compared to contrast venography and had an overall sensitivity of 94–96 % and specificity of 90–92 %. The sensitivity for below-knee DVT was 83–92 %, proximal DVT 97 %, and pelvic DVT 100 % [119].

This non-invasive technique has many attractive attributes. Magnetic resonance (MR) technology has the advantage that it allows simultaneous imaging of both lower limbs, the pelvic veins, IVC, and if required, thoracic imaging, enabling detection of hidden DVT in the pelvis and IVC and allowing calculation of thrombus volume, which may be a more powerful predictor of PE-risk than its proximal extent (but this has not yet fully evaluated). The technique does not require intravenous contrast and is better than venography for the diagnosis of isolated pelvic vein thrombosis [15, 120]. MRDTI has been used in a study already much quoted in this chapter to detect subclinical DVT and PE incidence [11].

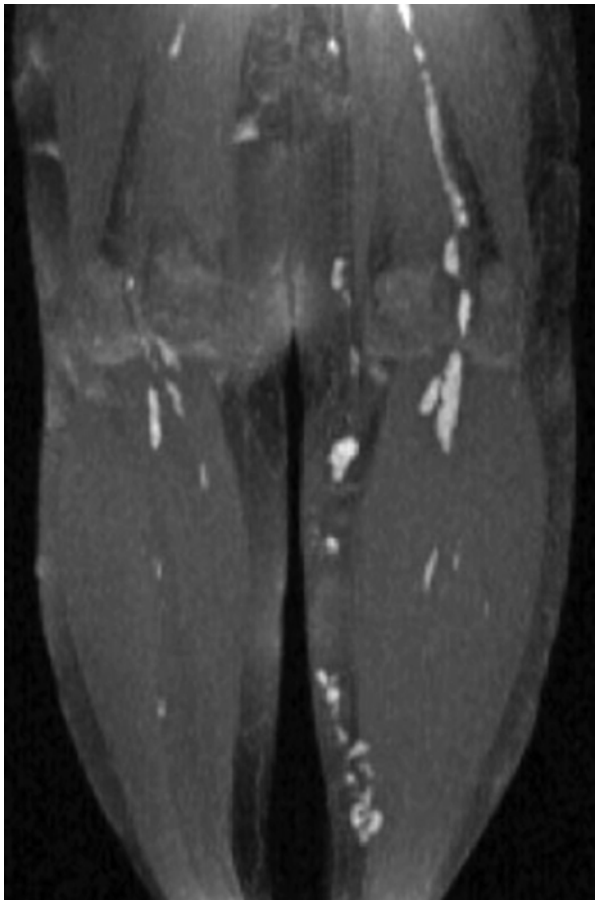

Fig. 6.3 Magnetic resonance direct thrombus imaging demonstrating acute proximal and distal thrombi in both lower limbs (From van Beek et al. [131]. Copyright © 2003 Wiley-Liss, Inc. Reprinted with permission from John Wiley and Sons)

Diagnosis of PE

Pulmonary Angiography

Pulmonary angiography has been standard practice from the late 1960s onward for the diagnosis of PE [121]. Digital subtraction angiography has improved image quality further. The criteria for the diagnosis of acute PE require direct evidence of a thrombus, either as a filling defect or amputation of a pulmonary arterial branch. Pulmonary angiography could visualise thrombi as small as 1 or 2 mm within the subsegmental arteries [122]. However, with the development and refinement of CT pulmonary angiography, direct pulmonary angiography with contrast injection into the pulmonary arteries is now rarely performed. Pulmonary angiography is invasive

and not devoid of hazards, with a mortality of 0.2 % [123]. However, the rare deaths attributable to pulmonary angiography have usually occurred in patients already unstable due to large PE with haemodynamic compromise or acute respiratory failure. Although pulmonary angiography has been the gold standard for the diagnosis or exclusion of PE against which other newer tests have been measured, the technique is now rarely employed because non-invasive CT pulmonary angiography (CTPA) offers as good information about PE and better information about the surrounding lung tissue, identifying associated pulmonary infarction and also diagnosing conditions that may mimic PE, for instance, pneumonia or aortic dissection. Most recent trials have not used pulmonary angiography for the diagnosis of PE after stroke, and in the past, before the advent of CTPA, most of the diagnoses were made clinically or on post mortem.

Ventilation/Perfusion Scan

A ventilation/perfusion lung scan, also called a V/Q lung scan, uses scintigraphy and radioactive isotopes to evaluate the circulation of air and blood in the lungs. The ventilation part of the test, which involves inhalation of radionuclide, looks at the ability of air to reach all parts of the lungs, while the perfusion part evaluates how well blood circulates within the lungs. A mismatch between the two demonstrating decreased perfusion in the presence of normal ventilation, especially in a wedge or pie-shaped configuration, can denote the presence of PE. However, in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study in 1990, it was shown that the accuracy of V/Q scanning was low, with the sensitivity of high-probability scans being only 41 % [124].

Since then, the value of V/Q scanning has been questioned with its low sensitivity and high number of nondiagnostic examinations. One of the key problems was the interpretation of a V/Q scan in the presence of abnormal chest X-rays. This significantly degrades V/Q interpretation, and a sizeable proportion of stroke patients will have abnormal chest X-ray. In the event of a suspected PE after stroke with the attendant dangers of anticoagulation, the diagnosis needs to be as certain as possible, and therefore V/Q scanning is probably not the investigation of choice, even if a high-probability result was obtained. The main use would be a normal scan in the presence of low clinical suspicion which could rule out a PE [125] or if CTPA could not be performed. Even with newer methods and adjuncts to VQ scanning, it probably is a less than optimal study for stroke patients. Some stroke patients may also not be able to complete the inhalation part the scan.

CT Pulmonary Angiography

CT pulmonary angiography (CTPA) is a test that employs computed tomography to obtain an image of the pulmonary arteries to diagnose PE. From its emergence in the early 1990s, it has become the preferred choice of imaging in the diagnosis of PE

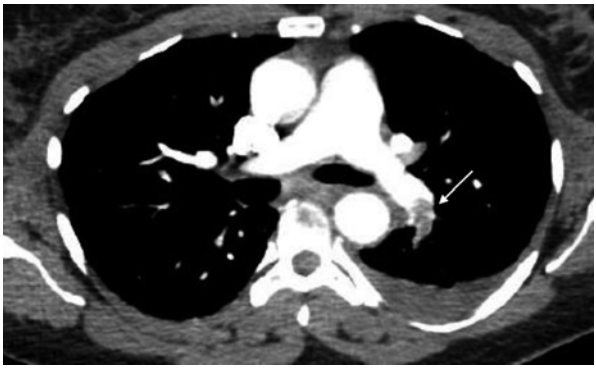

Fig. 6.4 Pulmonary embolus (*arrowed*) seen as a filling defect in left pulmonary artery with associated pleural effusion

due to its minimally invasive nature for the patient, whose only requirement for the scan is an intravenous line. Modern multi-detector CT (MDCT) scanners are able to deliver images of sufficient resolution within a short time period, that CTPA has now supplanted previous methods of testing, such as V/Q scanning or direct pulmonary angiography, as the routine test for the diagnosis of pulmonary embolism [122]. It also enables alternative diagnosis to be made [126].

The patient receives an intravenous injection of an iodine-containing contrast agent at a high rate using an injector pump. A normal CTPA scan will show the contrast filling the pulmonary vessels, appearing as bright white. Any mass filling defects, such as an embolus, will appear dark in place of the contrast, filling/blocking the space where blood should be flowing into the lungs (Fig. 6.4).

Two systematic reviews from 2000 comparing CTPA and pulmonary angiography have given the test sensitivity between 53 and 100 % and specificity between 81 and 100 % [127, 128]. CTPA will miss small pulmonary emboli, but there is evidence that withholding anticoagulation on negative CTPA is probably safe [129].

From the pathway suggested by PIOPED II, stroke would be a high-risk probability and should proceed direct to CTPA and perhaps even a repeat, if negative and the suspicion remains high. If there is a contraindication to CTPA for whatever reason in stroke patients, for instance allergy to iodine-based contrast radiation or renal toxicity from contrast, V/Q remains an alternative, bearing in mind previous reservations about certainty of diagnosis before treatment, combined with a search for a peripheral DVT with bilateral USS of the lower limbs or, if available, MRDTI could be asked for.

MRI for Diagnosis of PE

As in the case of DVT, MRI offers a new way of diagnosis which could rival the current tests. There are various MRI settings and techniques that could be used to detect PE. One advantage that MRI may offer over CTPA is that contrast does not have to be used avoiding radiation and nephrotoxity. The common MRI settings without contrast uses either gradient ECHO or time of flight, but in one study

when compared with CTPA only had 69 % sensitivity [130]; however, all the PE in the main pulmonary arteries were detected and it was segmental and subsegmental PE that were missed. The specificity was 100 %. MRA using gadolinium contrast shows a greater sensitivity that ranged from 70 to 95 % with a specificity that ranged from 96 to 100 %. The sensitivities again depended on the size of vessel and thrombus, with best results for central/lobar PE [131]. These results are comparable to the early (single-slice helical) CT, but not to the more modern mutidetector CTPA [131]. A major problem with MRA as seen in the PIOPED III study was the high number of un-interpretable scans, noted in up to 25 % of patients [132].

MR Direct Thrombus Imaging of PE

MRDTI shows possibly the greatest promise as a second-line test after CTPA. As mentioned above, based on a predictable change that occurs to blood when it clots, the intermediate product methaemaglobin demonstrates a high signal on a T1 weighted sequence allowing the detection of a subacute thrombus without the use of contrast (Fig. 6.5). By recognition of newly formed thrombus, this method can be used to distinguish between old and new clots. This, in addition to being able to detect hidden sources of PE, shows what advantages it can have as a specialist second-line investigation even if it is not going to be the standard test [15, 39, 118, 119].

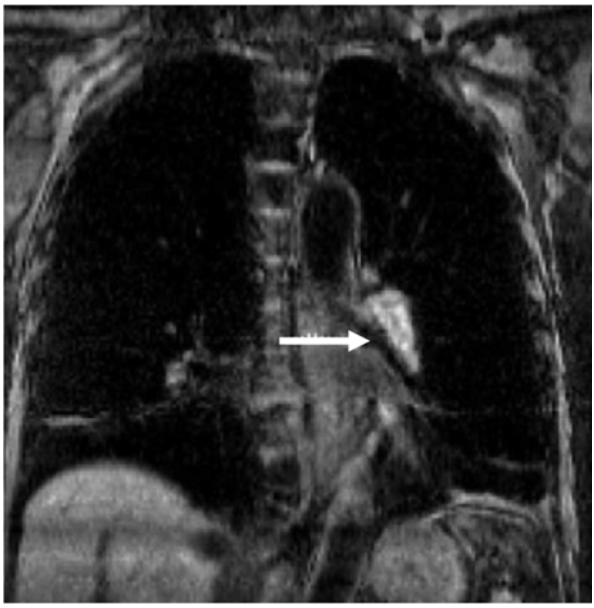

Fig. 6.5 Magnetic resonance direct thrombus imaging demonstrating pulmonary embolus (*arrowed*) in left main pulmonary artery (From van Beek et al. [131]. Copyright © 2003 Wiley-Liss, Inc. Reprinted with permission from John Wiley and Sons)

Treatment of VTE

Despite prevention measures, post-stroke VTE occur, and even if subclinical VTE are not sought, the incidence of clinical DVT in the modern era of stroke care will be between 1 and 5 %, and with 60–70 % of clinical DVT being due to proximal DVT, which carry a high risk of PE and mortality, these will require treatment. The incidence of clinical PE as seen in recent trials will be in the order of 1–3 %, and similarly these will require treatment [32, 33].

Untreated PE in the pre-anticoagulation era in the 1940s in unselected patients carried a mortality risk of anything between 18 and 87 %, with a pooled risk of 26.6 %; and in patients with untreated proximal DVT between 3 and 40 %, with a pooled risk of 16.2 % [53, 133]. In stroke patients, before the use of anticoagulation, the mortality in untreated clinical PE was around 14–25 %, with deaths from all PE resulting from untreated clinical and sucblinical DVT being higher, with autopsy findings of PE in 50–76 % of patients with DVT [6, 25, 28]. The standard treatment for VTE is anticoagulation and has been shown since the 1960s to reduce mortality in unselected patients by over 90 %, in PE from a pooled risk of 26.6 to 2.6 %, and in proximal DVT from 16.2 to 0.7 % [53]. Not having significant thrombolytic properties, these agents act by altering the balance between fibrinolysis and thrombogenesis, in most cases halting the propagation of thrombus and allowing the fibrinolytic processes of body to lyse the clot, thereby preventing PE in patients with DVT and recurrent PE in those who already have a PE.

Medication used in the 1960s included subcutaneous UFH and coumarins. Later intravenous (IV) heparin and warfarin became the standard, and then treatment doses of LMWH. This is being replaced by the novel oral anticoagulation agents, which have shown equivalent or greater efficacy treating VTE. Rivaroxaban and Apixaban have been shown to be non-inferior to warfarin in treating DVT and PE, and Apixaban had significantly fewer major bleeds [95, 134–136]. There are no randomised trials looking at the treatment of VTE in acute stroke. The guidelines for acute stroke management reflect this lack of evidence being quite general in their recommendations, with some guidelines not covering treatment.

Cerebral Infarcts

For cerebral infarct, guidance states that these should be treated with full anticoagulation [59]. The timing is not specified, but possibly this can be started very early after the infarct, especially in case of proximal DVT and PE where the risks of mortality are high. With distal DVT where the risk of embolism is lower, the decision on whether to treat depends on the risk of bleeding, whether secondary haemorrhagic transformation or bleeding elsewhere. If the risk of cerebral bleeding is felt to be relatively high with full anticoagulation, for instance early on in large cortical infarct, then sequential Doppler scanning looking for proximal extension of the thrombus may be justified [11, 47].

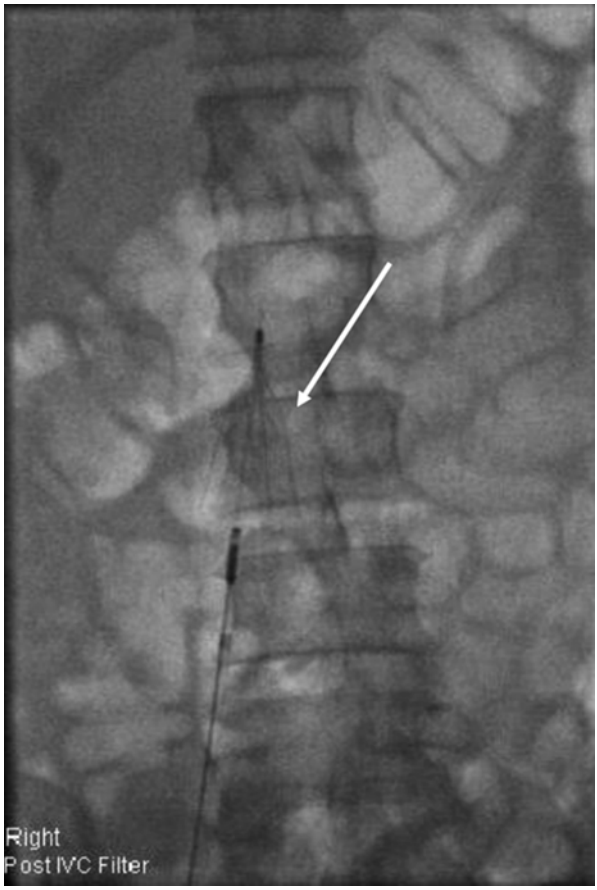

Fig. 6.6 Inferior vena cava filter (*arrowed*)

Cerebral Haemorrhage

For cerebral haemorrhage, the guidance suggests treatment with either anticoagulation or inferior vena cava (IVC) filter in cases of clinical DVT and PE (Fig. 6.6) [59, 65]. There are no randomised trials comparing the two in cerebral haemorrhage or cerebral infarcts. In deep primary ICH, starting anticoagulation after 1 week is reasonable if blood pressure is controlled [137]. Clinical DVT and PE are usually not discovered earlier. Starting with intravenous heparin and aiming for an APTT between 1.5 and 2 or LMWH may be an option and it may be safer to delay or not use warfarin, which seems to have a higher risk of bleeding [137, 138]. There should not be any bolus dosing, as there is evidence that heparin boluses may increase the risk of bleeding [137, 139, 140]. Intravenous heparin can take time to reach the required range and is notoriously difficult to hold in the range, so it may be overall safer to use LMWH or convert to it after a few days of intravenous heparin. The

novel oral anticoagulants shown to cause less cerebral bleeding than warfarin in atrial fibrillation could be of use in these situations but there is no evidence, no current reversal agents, and is contraindicated for use in ICH at the moment [95, 141].

In lobar bleeds where the risk of re-bleeding may be up to four times higher because of possible amyloid angiopathy an IVC filter may be justified [65, 141, 142]. MRI scanning for microbleeds should be considered to help guide the use of anticoagulation and/or IVC filter placement, in the case of lobar bleeds. One study found the risk of re-bleeding in patients with six or more microbleeds to be as high as 51 % [143]. IVC filters should also be considered in other high-risk patients, for instance those with suspected arterio-venous malformations, whilst investigations are carried out. If used, IVC filters do still need anticoagulation cover at some point to prevent DVT and IVC thrombosis, but perhaps a prophylactic dose rather than full anticoagulation, depending on circumstances [65]. Such measures can result in a low risk of re-bleeding [144]. They also should be removed at the earliest opportunity. Currently, there is no detailed guidance of the use of IVC filters in stroke patients [138, 141].

Patient Questions

Q. A stroke patient develops oedema of their hemiplegic lower limb without pain or redness. What would you do?

A. Arrange a compression ultrasound looking for a DVT, for although the oedema can be due to limb immobility, the clinical diagnosis of DVT can be difficult in acute stroke, as the usual clinical signs may be absent and patients may not be able to complain of pain, so DVT are missed. Also always bear in mind, there is a high subclinical incidence of VTE. Testing for D-dimer is unlikely to be helpful in stroke as levels are raised by the stroke itself.

Q. What prophylaxis would you use immediately after ICH?

A. Intermittent pneumatic compression (IPC) device. This is one of the few large-scale interventions to show benefit at reducing DVT and mortality without significant adverse events, and one of the few to include patients with ICH. IPC is also mentioned in many guidelines as first-line prevention in ICH.

Q. Patient with ICH is found to have a DVT—what do you do?

A. If it is a below-knee DVT, the safest option would be to not do anything but rescan with compression ultrasound in 5–7 days, looking for proximal progression into the popliteal vein, which occurs in 20 %. If it remains distal, rescan again up to 14 days.

If proximal extension has occurred, and it is more than 1 week after the event, there are several options depending on the bleed. If it deep bleeds due to hypertension, provided blood pressure control is good, the patient could be considered for anticoagulation with either IV heparin or LMWH. If it is within a week or it is a lobar bleed possibly due to amyloid angiopathy, then placement of an IVC

filter should be considered, especially for the initial management. As time passes, the options are then to progress to full anticoagulation in the case of a deep bleed, but with a lobar bleed, MRI scanning for cerebral microbleeds may be helpful to stratify risk, as to whether to consider full, modified dose, or no anticoagulation. Bear in mind there are risks of DVT and IVC thrombosis with the IVC filter itself.

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Chapter 7
Swallowing and Nutritional Complications

David Smithard and C. Elizabeth Weekes

Abstract Malnutrition and dysphagia are common after stroke and frequently occur together. Failure to recognise their presence and manage them effectively will result in increased morbidity and mortality. Infection risk may be raised, recovery and rehabilitation will be slowed, and people will be more likely to end up in long-term care. Treatment of malnutrition and swallowing difficulties requires early recognition, e.g. through routine screening procedures, and their management requires input from the multi-disciplinary team.

Monitoring of nutrition and swallowing status needs to be regular and consistent and may need to continue beyond hospital discharge into the care home environment and in those living at home. Consequently, issues around the detection and management of malnutrition and dysphagia need to be raised with all care staff and professionals.

Keywords Malnutrition • Dysphagia • Obesity • Aspiration • Prognosis • Stroke outcome

Key Messages
- Dysphagia and nutritional problems are common after stroke.
- Poor nutritional status may predate the stroke, as may dysphagia.
- People may not eat due to post-stroke co-morbidities, depression, infection, and psychological and social issues.
- Poor nutrition and dysphagia are markers of poor outcome and increased mortality.
- The management of both dysphagia and malnutrition requires multi-disciplinary input.
- Ongoing nutritional care needs (including swallowing problems) should be considered during discharge planning.
- Patients with long-term care needs should be reviewed regularly post-discharge.

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Introduction

Dysphagia after stroke is common as is under-nutrition. Both are indicators of a poorer prognosis and an increase in dependency. It is therefore essential that they are recognised and managed appropriately at the earliest opportunity.

Definitions

Malnutrition

No universally accepted definition of malnutrition exists; however, one that is commonly cited in the UK literature is as follows:

> A state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function, and clinical outcome. [1]

This definition encompasses both over- and under-nutrition and emphasises the impact of malnutrition on functional and clinical outcomes in individuals. Recently, an International Guideline Consensus Committee [2] categorised malnutrition, i.e. under-nutrition, in the following three ways:

1. *Starvation-related malnutrition* where chronic starvation occurs in the absence of inflammation such as might result from a range of social and/or psychological issues.
2. *Chronic disease-related malnutrition* where there is chronic, mild to moderate inflammation such as might be associated with chronic diseases such as COPD, cancer, or chronic renal failure.
3. *Acute disease or injury-related malnutrition* where there is acute, severe inflammation and the patient is usually hospitalised.

While this provides a useful aetiological classification of under-nutrition, and recognises the effects of illness and other factors on nutritional status, there remain no clear criteria for how each category might be identified in clinical practice. Taken together however, these two definitions [1, 2] encapsulate both the potential causes and adverse impacts of malnutrition.

Overweight and Obesity

Overweight and obesity are defined as “abnormal or excessive fat accumulation that may impair health” [3]. In this chapter, the term malnutrition will be taken to mean under-nutrition and the terms overweight and obesity will be used to describe over-nutrition.

Dysphagia

Dysphagia is defined in the *Oxford English Dictionary* as "A condition in which swallowing is either difficult or painful. It may be caused by diseases of the mouth, pharynx, or larynx, neuromuscular disturbances, or obstruction of the oesophagus". Aphagia is just an extreme form of dysphagia.

Other relevant definitions in this context are eating, i.e. "The transfer of food/drink to the mouth" and swallowing, i.e. "The transfer of food from the mouth to the stomach".

Malnutrition

Epidemiology

Malnutrition has widespread adverse effects on physical, social, and psychological function including decreased muscle strength, low mood, decreased ability to perform everyday tasks [4], and poorer quality of life [5]. In the presence of illness, malnutrition results in delayed recovery, increased complications, and increased mortality [6] and is associated therefore with increased hospitalisation and use of health and social care resources [7]. As a result, malnourished individuals cost twice as much to manage as the well-nourished [8], and in the UK the cost of managing malnourished individuals has been estimated to be up to £13 billion per year [9]. Furthermore, caring for nutritionally vulnerable family members or friends imposes a significant burden on carers, with around 60 % of carers worrying about the nutrition of the person they care for, and one-quarter looking after someone who is underweight [10]. In the UK, national surveys using a validated nutrition screening tool [11] suggest that, at any time, around three million individuals are at risk of malnutrition or are malnourished, i.e. nutritionally vulnerable, with more than one million being elderly [12]. Until recently the focus of detecting and managing malnutrition has been in hospitals [7]; however, it is evident that the vast majority of nutritionally vulnerable individuals (90 %) live in their own homes in the community with only 5 % being in sheltered housing, 3 % in care homes, and 2 % in hospital [13].

In stroke populations, reported prevalence rates of malnutrition vary widely from 6 % up to 62 % [14]. While this variation may in part depend on the care setting, type, and severity of stroke or time since initial insult [15–21], there is also considerable variability in the methods and thresholds used to define malnutrition [14]. For example, of the 18 studies included in the review by Foley et al., only three used structured nutritional assessment methods that had been validated previously [17, 19, 20], i.e. the Mini Nutritional Assessment [22] and the Subjective Global Assessment [23], and one large, multi-centre study [24] used a variety of methods in the different recruitment sites ($n = 25$ hospitals) including a previously validated

"informal assessment" [25]. In a recent study in two stroke units in south London, the use of a validated nutrition screening tool, i.e. the Malnutrition Universal Screening Tool (MUST), suggested around 30 % patients are at medium or high risk of malnutrition on admission to hospital following an acute stroke [26].

Similar to other malnourished populations, malnourished stroke patients are more likely to develop complications in hospital such as gastrointestinal bleeds, pneumonia, and other infections [20, 21, 24] and as a result they stay in hospital longer [16, 20, 27], suffer poorer functional outcomes [21], are less likely to be discharged home [28], and have higher hospitalisation costs [27]. They are also more likely to die in hospital or soon after discharge [16, 17, 21]. Indeed, being malnourished has been shown to be an independent predictor of poor outcome in patients who have had a stroke [18, 26].

Following a stroke, those patients who survive frequently develop swallowing and other feeding difficulties secondary to their stroke and often become more malnourished during their hospital stay [29]. Furthermore, in a significant proportion of patients, malnutrition continues beyond hospital discharge and can last for many months after the initial insult. For example, in a study of 206 stroke survivors more than 65 % reported some eating difficulties at 6 months post-stroke, with eating disabilities having a significant adverse effect on quality of life [30], and in a study of 305 stroke survivors weight loss persisted for up to 12 months post-stroke in one-quarter of patients [31]. Patients discharged to nursing homes appear to be at particular risk of eating difficulties, with one study reporting that more than 80 % of stroke patients in nursing homes were assessed as having some sort of dependence in eating [32]. These studies suggest that stroke patients who are malnourished at hospital discharge are likely to require longer term nutritional support and regular monitoring in care homes and/or the community to avoid the negative outcomes associated with malnutrition, e.g. hospital readmissions, decline in functional status, and poor quality of life.

Aetiology

Following a stroke, the most obvious cause of malnutrition is dysphagia. However, there are a whole host of other potential causes that could either exacerbate pre-existing malnutrition or precipitate it in the nutritionally vulnerable (Table 7.1). While in hospital, the reasons for poor dietary intake and subsequent weight loss are most likely to be illness related and may include disease- or drug-induced anorexia, periods of temporary starvation (nil by mouth) for dysphagia or medical procedures, feeding difficulties secondary to impaired mobility and/or perception issues, pain, anxiety, or depression [33]. In both hospitals and care homes however, organisational issues might further limit individuals' choice, availability, and access to food. Furthermore, a lack of attention to nutritional care might also have an adverse impact on an individual's intake. For example, provision of unfamiliar or inappropriate foods, inadequate supervision or support during mealtimes, patients

Table 7.1 Factors impacting on nutritional intake and/or nutritional status

Disease-related	Psychological	Social and environmental
Anorexia	Depression	Social instability
Dementia	Bereavement	Financial issues
Gastrointestinal symptoms	Mental illness	Social isolation
Pain	Psychosis	Access to shops
Co-morbidities, e.g. diabetes	Anxiety	Cooking and food storage facilities
Poor dentition	Apathy	Religion
Chewing difficulties	Poor motivation	Cultural meanings of illness and food
Swallowing problems	Loneliness	Support from family and informal carers
Altered taste and smell	Low self-esteem	Social networks
Medication	Dependence	Access to formal social care services
Impaired mobility	Substance abuse	Access to health services
Dyspraxia		Homelessness
Poor eyesight		
Fatigue		
Early satiety		

being in an uncomfortable position to eat, food placed out of reach, utensils or packaging presenting difficulties for eating, and environmental factors such as staff interrupting meal times or long gaps between evening meal and breakfast have all been shown to have a negative impact on dietary intake in hospitalised or institutionalised individuals [34–37]. Following hospital discharge, in addition to the continuing effects of the stroke and its management, sub-optimal nutritional status may be further compounded by previously existing, or a new range of, psychological and social issues (Table 7.1). While many individuals function alone very effectively when healthy, this often changes during and following illness. Even the most independent individual may require practical help after a stroke, and it is therefore important to identify patients with minimal social support, e.g. the recently bereaved, homeless, or recent immigrants, while they are in hospital in order to start addressing their likely nutritional, and other, care needs on discharge. The effort involved in shopping, preparing, or cooking a meal can seem insurmountable during or after illness, and many patients may need some assistance with this in the early stages of recovery. If these social and psychological issues are not recognised prior to, or soon after discharge, this can result in a vicious, self-perpetuating cycle of inadequate intake, associated complications, repeated hospital admissions, and poor outcomes [7].

Detection

Malnourished individuals, or those who have been identified as at medium or high risk of malnutrition, are more likely to benefit from nutritional intervention than those who are adequately nourished or at low risk of malnutrition [6]. On admission

to hospital following a stroke, the focus should be on identifying those who are nutritionally vulnerable, i.e. malnourished or at medium/high risk of malnutrition. In clinical practice this can be accomplished by the routine use of nutrition screening tools. Nutrition screening using a validated tool has been recommended by a number of professional organisations in the USA and Europe, among them the American Society for Parenteral and Enteral Nutrition [38], the British Dietetic Association [39], the European Society for Parenteral and Enteral Nutrition [40], the British Association for Parenteral and Enteral Nutrition (BAPEN) [11], and the National Institute for Health and Clinical Excellence [7].

The role of a nutrition screening tool (NST) is to aid the identification of patients who are nutritionally vulnerable, i.e. currently malnourished or at risk of becoming malnourished, in order that they might be referred for further assessment and nutritional intervention if required [1]. NSTs are not designed to assess the nutritional status of patients, establish the severity of malnutrition, or identify the reasons for poor status; they simply indicate that a patient has actual or potential nutritional problems and requires further investigation. While providing a useful, structured *aide memoire*, NSTs support, but do not replace, clinical judgement. NSTs are usually completed by nursing staff or health-care assistants who are not nutrition specialists, and thus people identified as at medium or high risk of malnutrition during a screening procedure should be referred for a full nutritional assessment by a nutrition specialist such as a dietician. Similar to all screening tools, NSTs should be valid and reliable, and since they should be completed on all patients in a particular setting, they should be quick to administer, easy to use and to interpret, and acceptable to both patients and health-care professionals [41]. Examples of validated nutrition screening tools used in the UK and Europe include the Malnutrition Universal Screening Tool (MUST) [11], the Nutrition Risk Score-2002 (NRS-2002) [42], the Short Nutritional Assessment Questionnaire (SNAQ) [43], and the short-form Mini Nutritional Assessment (Short-form MNA) [44]. The majority of these screening tools require the measurement of height and weight to determine body mass index (BMI) and also require a record of recent weight change and/or change in dietary intake. People who eat almost nothing for 5 days lose about 5 % of their body weight, even in the absence of disease. Furthermore, minimal dietary intake for a few days in the presence of disease results in poor muscle function, increased risk of infection, and delayed wound healing, even in the absence of recorded weight loss [6]. Therefore, patients who are nil by mouth (or have minimal intake) for more than 5 days, e.g. due to dysphagia following a stroke, should be considered to be at nutritional risk, even if their nutritional status was adequate when they were admitted to hospital.

Recently, it was shown that a validated NST is a good predictor of poor outcome in patients who have had a stroke. In a study of 537 patients screened using MUST within 72 h of hospital admission for acute stroke, there was a strong positive correlation between risk of malnutrition and mortality rate which remained significant after adjustment for possible confounders [26]. At 6 months those patients who were at high risk of malnutrition on admission to hospital were twice as likely to die than those at low risk. Furthermore, for patients who survived there was a strong positive correlation between the risk of malnutrition and both length of hospital stay

and hospitalisation costs, which again remained significant after adjustment for possible confounders [26]. Patients at high risk of malnutrition were likely to stay in hospital three times longer than those at low risk and cost nearly twice as much [26].

It is perhaps not surprising, therefore, that to aid the identification of at-risk and malnourished patients, the National Institute for Health and Clinical Excellence recommends that all patients should be screened routinely on admission to hospital and care homes, at regular intervals throughout their stay, during outpatient and GP visits, and on first contact with community care teams [7]. In England and in other countries, similar recommendations around the use of validated nutrition screening tools have been incorporated into recent guidelines for the management of acute stroke [45–47].

Assessment

Following nutrition screening, patients identified as malnourished or at medium/high risk of malnutrition should undergo a full nutritional assessment conducted by a health-care professional with specialist nutrition knowledge, usually a dietician [7]. Nutritional assessment establishes the nutritional status of an individual and explores the causes and duration of nutritional problems. The assessment forms the basis for determining treatment goals and the nature, mode, and duration of nutritional intervention.

A full nutritional assessment usually comprises five major components: anthropometry, i.e. measurements of weight, height, and body composition; a review of laboratory data; an assessment of clinical status; an assessment of dietary intake; and consideration of environmental factors. There are a number of validated nutrition assessment tools available, e.g. the Mini Nutritional Assessment (MNA) tool [22], Subjective Global Assessment (SGA) tool [23], and Patient-Generated SGA [48], all of which include at least some of the following components.

Anthropometry

Body weight is usually recorded routinely as part of the nutrition screening process and provides valuable information on both current and past nutritional status. While most clinicians will readily identify someone who is thin as either malnourished or at risk of malnutrition, individuals who are not thin may also be at risk of malnutrition, even if they look (or are) overweight or obese. Whereas low body mass index (BMI) reflects chronic malnutrition, recent weight loss reflects acute changes in nutritional status and suggests underlying physical or psychological illness or social issues. Regardless of BMI, unintentional weight loss greater than 10 % over 3–6 months, or more than 5 % in 1–3 months, is generally considered to be clinically significant because it is associated with loss of body function and poor clinical and functional outcomes [11].

In a recent study of 543 acute stroke patients, 109 (20 %) participants had unintentionally lost weight prior to hospital admission for a variety of reasons unrelated to their stroke, including gastrointestinal symptoms, excess alcohol intake, previous surgery, taste changes, loss of interest in food, and bereavement [49]. In this study those who had experienced pre-admission weight loss had a significantly higher risk of mortality and a significantly longer hospital stay at 6 months post-stroke, and cost significantly more (£8,416 versus £5,506 per patient) than those who had been weight stable prior to the stroke. Furthermore, those who had lost the most weight were at greatest risk of poor outcomes. A history of unintentional weight loss before admission should therefore send warning bells to any clinician who might be considering the nutritional needs of their patient, particularly if the patient has had a severe stroke and/or has dysphagia, and oral intake is likely to be compromised for more than a couple of days [7].

Since BMI provides useful information regarding nutritional status in both the malnourished and obese, the accurate measurement of height is an important component of a full nutritional assessment. Both in the outpatient and inpatient setting, health-care professionals have a role in ensuring that, wherever possible, all patients have their height measured and documented at least once in adulthood [7]. In those patients where height is not known, and where it cannot be measured safely due to mobility issues, surrogate measures for height such as ulna length [50], demi-span [51], or knee-height [52] can be used. All three of these techniques provide a reliable estimate of height, suitable for determining BMI, if undertaken by a trained practitioner.

During the first few days following a stroke, a small proportion of patients will be unsafe or unable to mobilise and it may not be possible to weigh them, either to obtain information for a weight history or to calculate BMI (although hoist scales should be available on most stroke units). In this case a measurement of mid-arm circumference (MAC) by a skilled practitioner may be used in the absence of weight to estimate BMI. Data collected from 1,561 hospitalised patients included in a nutrition intervention trial [53] suggest that those with a MAC less than 25.0 cm are likely to have a BMI less than 20 kg/m^2 and those with a MAC less than 23.5 cm are likely to have a BMI less than 18.5 kg/m^2 [53, 54].

Biochemistry

During a full nutritional assessment, laboratory data will be reviewed to help determine the patient's hydration status, clinical condition, e.g. raised CRP, and low serum albumin levels indicating metabolic stress, and nutritional markers such as vitamin and trace element status. Some patients could be at risk of re-feeding syndrome [55, 56] if dietary intake has been poor for a prolonged period prior to (or during) hospital admission and phosphate, potassium, calcium, and magnesium levels should be reviewed prior to implementation of nutritional support in all patients with known re-feeding risk factors [7]. There are several published regimens for managing patients at risk of re-feeding syndrome. The lack of randomised

controlled trials in this area, however, means that management is based on consensus and expert opinion rather than evidence [56]. Irrespective of which regimen is employed, the common principles are to prevent re-feeding syndrome by cautious re-introduction of energy and correction of biochemical abnormalities [7, 55]. It is likely that the problems associated with re-feeding are less likely to arise with oral nutritional support since illness is usually accompanied by a loss of appetite; however, care should be taken in the prescription of oral nutritional supplements in those at high risk of re-feeding syndrome [7].

Clinical

Quite apart from the direct impacts of a stroke, e.g. dysphagia, hemianopia, arm weakness, or neglect, patients who have had a stroke often present with a number of nutritionally relevant co-morbidities such as diabetes, hypertension, hyperlipidaemia, gastro-oesophageal reflux, or depression. All of these conditions will need to be taken into account when devising a nutrition action plan whether the patient is capable of consuming an oral diet or requires tube feeding.

Dietary

The onset of malnutrition is usually insidious, although in conditions of acute metabolic stress such as critical illness, nutritional depletion and weight loss can be very rapid and severe [6]. While there tends to be a focus on inadequate energy and protein intakes, it should be recognised that in people with a poor dietary intake, micronutrient intakes are also likely to be deficient [7]. It is also important to recognise that micronutrient intakes may be sub-optimal even in the presence of adequate macro-nutrient intakes, particularly if individuals follow a restricted diet or a diet of limited variety or poor quality [57].

Dietary assessment should take account not only current (i.e. inpatient) nutritional intake but also previous (prior to stroke) and likely future intakes (post-discharge). Dietary intake may be assessed in a number of different ways (and for varying lengths of time) depending on the nutrient or food of interest, the care setting, and the patient's ability to provide valid and accurate information [58]. In the acute setting, dietary intake is usually estimated from data recorded by nursing staff on food record charts. Since food record charts are rarely fully or accurately completed [59], a dietician may also ask the patient (and/or their carer or nurse) to describe everything they have eaten and drunk in the previous 24 h (24-h recall method) [58]. In order to obtain information on a patient's habitual intake, e.g. pre-admission, a diet history may be taken [58].

In patients who have had a stroke, dietary assessment aims to determine the patient's actual and potential ability to meet their nutritional needs by normal texture diet via the oral route. In a significant proportion of patients, this will be unlikely (or unsafe) and alternative routes and methods of feeding will need to be considered.

While it might be expected that patients who have had a stroke would have a poor dietary intake in hospital, very few studies exist that describe the nutritional intakes of hospitalised stroke patients. One study suggests that the energy intake of hospitalised stroke patients with adequate swallow is similar to that of other hospitalised patient groups, i.e. an average of 75 % of predicted energy requirements over 2 weeks [60]. One other study which examined energy and protein intakes following stroke reported that, on average, regardless of diet type (oral or non-oral) and texture (regular diet or texture modified because of swallowing impairment), hospitalised patients consumed an average of 85 % of their energy requirements, and 86 % of protein requirements, during the first 21 days following stroke [61]. While these deficits might appear relatively small, over time they are sufficient to result in weight loss and may have an adverse effect on outcome in malnourished or medium/high-risk patients. If not treated, this could have a profound impact on rehabilitation, functional recovery, and outcome, even in previously adequately nourished patients [6].

Environmental

This final part of the assessment aims to establish how well the patient functioned in their home environment with regard to food purchase, preparation, and cooking prior to admission. For example, was the patient coping alone, did they require practical help and support from family and friends, or were they in receipt of a package of care which included help with these activities? Since a stroke is likely to have an adverse impact on several aspects of a person's physical, social, or psychological function, the dietician will need to assess whether or not the patient is going to be capable of undertaking these activities on discharge (or soon afterwards) and start to make appropriate arrangements prior to discharge. Together with the multidisciplinary team, the dietician will assess the patient's need for post-discharge support including intermediate care, sheltered housing, care home admission, home meal delivery, shopping, or befriending services.

Management

Observational studies have shown an association of reduced mortality after stroke with nutritional assessment [62] and adequate nutrition and hydration (with antiplatelet therapy if required) [63]; however, a recent systematic review seeking to evaluate the impact of nutritional supplementation versus no supplementation in non-dysphagic stroke patients showed little benefit from supplementation [64]. This review should, however, be interpreted with caution since, although eight RCTs were included (4,391 participants), all included studies except the FOOD trial [24] were small and of relatively short duration. The inclusion criteria for the review failed to examine both nutritional risk status at baseline and compliance with

intervention, and included studies conducted in patients recruited at any time up to 6 months post-stroke. Furthermore, the included studies described a variety of different nutritional interventions (including one assessing antioxidant and ω-3 fatty acids and one that included some tube-fed patients) in a variety of stroke populations. It is impossible therefore to determine if the observed lack of effect was due to heterogeneity in the interventions and populations, the result of inadequate intake due to poor compliance, or to failure of the intervention per se.

The underlying causes of inadequate intake in patients who have had a stroke are multi-factorial and multi-disciplinary and may originate in any part of a health-care organisation from the strategic policy level down to the individual feeding of a patient. Therefore, in the management of malnutrition in the acute setting, it is necessary to take into account not only the patient-specific issues that might impact on nutritional status, e.g. nutrition risk status on admission, severity of stroke, or ability to swallow but also to consider the systems for food and drink provision as well as the ward environment and nutritional care procedures. As a result, some interventions may be targeted and tailored for individuals while others may be non-targeted and implemented at ward or unit level. The need for these latter interventions assumes that a significant proportion of the stroke unit population are nutritionally vulnerable, and prevention of nutritional deterioration is the key aim. Examples of such interventions include protected mealtimes, red trays, feeding assistance, food fortification, or altering the mealtime environment to encourage food and drink consumption [65].

Goals of Treatment

In patients who have had a stroke, the goals of nutritional treatment are likely to include one or more of the following:

- Meeting all nutritional requirements (macro- and micronutrients and fluid) in patients who are nil by mouth
- Meeting nutritional needs while minimising the risk of aspiration by provision of a texture-modified diet for patients with dysphagia
- Nutritional support (supplementation) for patients who are not meeting their full nutritional requirements (for whatever reason)

Nutritional Requirements

One of the aims of devising a nutritional prescription is to provide a patient with their complete requirements either via a single route or any combination of oral, enteral, or parenteral nutrition, while avoiding the known complications associated with both under- and over-feeding [7]. The nutritional requirements of an individual

following a stroke will depend on their nutritional status, clinical condition, physical activity level, nutritional goals, and likely duration of nutritional support [7]; however, the nutritional requirements of patients who have had a stroke have yet to be fully characterised. While evidence suggests there is a small, temporary increase (7–14 % above predicted resting energy expenditure) in metabolic rate post-ischaemic stroke [66, 67], there is conflicting evidence around the impact of haemorrhagic stroke on metabolic rate [68–70].

A recent review of the evidence around energy requirements in healthy and sick populations by the Scientific Advisory Committee in Nutrition [71] concluded that while acute illness may result in a temporary increase in basal metabolic rate, this is usually accompanied by a significant reduction in physical activity such that total energy expenditure is usually around the same, or a little less than, healthy populations of the same age and gender. In the absence of stroke-specific studies, an energy prescription of 20–30 kcal/kg body weight/day is likely to be adequate for the majority of patients, although those who are severely malnourished (at risk of refeeding syndrome), or are acutely unwell, might need to commence feeding at lower levels, and specialist advice should be sought [7].

Together with the assessment of dietary intake (see above), estimated nutritional requirements will indicate if there are any nutritional deficits, e.g. low energy intake, sub-optimal micronutrient intake, inadequate fluid intake, that need to be taken into account when devising the nutritional prescription.

Feeding Route

Wherever possible, nutritional and fluid requirements should be met via the oral route [72, 73]. In those who are unable to meet all their nutritional needs via the oral route, tube feeding should be considered [7]. Parenteral nutrition to meet all, or a proportion, of nutritional needs in those patients with a non-functioning gastrointestinal tract who are unable or unsafe to meet their needs by any other route is very rarely used in patients who have had a stroke [7].

Nutritional Interventions

In the management of malnutrition, interventions targeted at individuals may comprise one, or any combination, of the following strategies:

1. *Dietary counselling* where the patient and/or their carers are counselled to increase the frequency of food and/or fluid consumption and thus maximise energy and protein intake. Advice is tailored to a patient's preferences and lifestyle, taking into account any clinical conditions such as diabetes, hyperlipidaemia, or renal insufficiency.

2. *Food fortification* to increase the macro- and micronutrient density of food and/or drink, using energy and protein-rich ingredients such as milk powder, butter, and milk, or commercially available, prescribable powders and liquids, e.g. Procal (Vitaflo, Liverpool, UK) or Duocal (Scientific Hospital Supplies, Liverpool, UK).
3. The provision of prescribable *oral nutritional supplements* (ONS) (often known as sip feeds), e.g. Ensure (Abbott, Maidenhead, UK), Fortisip (Nutricia, Trowbridge, UK), or Resource (Novartis, Camberley, UK).
4. *Texture-modified diets* to meet the nutritional needs of those patients who are unsafe to swallow food and drink of normal texture.
5. *Tube feeding* to meet all, or a proportion, of nutritional needs in those patients with a functioning gastrointestinal tract who are unable or unsafe to meet their needs orally.

Dietary Counselling

The aim of dietary counselling is to improve the macro- and micronutrient intakes of individuals by providing patients and/or their carers with tailored advice and support, often accompanied by written information including suggested daily menus and recipe sheets. By tailoring advice to an individual's nutritional requirements, preferences, symptoms, and lifestyle it may be possible to achieve good compliance. Furthermore, on cessation of intervention, dietary habits may have changed sufficiently to ensure maintenance of any weight gain and/or functional benefits. Advice may be provided on a variety of topics including food choice and preparation, altered meal patterns, snacks, and nourishing drinks and may include advice on how to manage specific symptoms (e.g. dry mouth, taste changes) or how to overcome anorexia or specific eating difficulties. The effectiveness of dietary counselling will depend on many factors, and in patients who have had a stroke, confusion, altered consciousness, or limited comprehension may make it difficult for some patients to comply with dietary advice in the acute setting. On discharge, people recovering from a stroke may have some difficulties with shopping and food preparation, and multi-disciplinary team input may be required to address these issues in discharge planning. To date there are no studies evaluating the impact of dietary counselling in patients who have had a stroke [73].

Food Fortification

The aim of food fortification is to increase the nutrient density of food and drink without increasing portion sizes. Thus, this strategy might be particularly useful in individuals with a poor appetite or early satiety, symptoms that frequently accompany acute illness. Food fortification advice can be provided for individuals and/or their carers but can also be implemented at ward or unit level for vulnerable populations. Studies that have measured the impact of providing energy-dense meals and

snacks to hospitalised patients have reported increased energy and protein intakes [74–76], a significant increase in body weight [77], and a significantly shorter length of hospital stay in a subgroup of the intervention patients [78]. To date there are no studies that have investigated the impact of food fortification on other clinical outcomes or cost.

Oral Nutritional Supplements (ONS)

While the FOOD trial suggests there are no benefits in routine supplementation of stroke patients using ONS [24], there is evidence that ONS can be beneficial in terms of energy intake, weight gain, and functional status in other patient groups, in particular the elderly [78], if they are provided to those who are nutritionally at risk or malnourished [79]. Typically, ONS contain a mix of macro- and micronutrients and most provide around 300 kcal, 12 g protein, and a full range of vitamins and minerals per serving, although there is a wide range available. ONS are usually present in liquid form, but puddings and powders are also available. Like tube feeds, ONS are foods for special medical purposes (FSMPs), and as such their composition and labelling are regulated under the European Commission Directive 1999/21/EC. ONS can be prescribed in the community for the management of disease-related malnutrition (and a number of other indications) in accordance with the Advisory Committee on Borderline Substances (ACBS) guidelines. The cost of ONS in the community is, however, often a consideration, and recently there has been considerable emphasis on the use of care pathways to ensure their appropriate use, including the need for regular monitoring and follow-up [80].

Texture-Modified Diets

In patients with dysphagia, a texture-modified diet may be prescribed after a full swallow assessment, usually by a speech and language therapist. Several studies have reported that patients requiring thickened fluids are less likely to meet fluid requirements [81, 82] and that texture-modified diets are often nutritionally inadequate [83, 84]. Since people who are nil by mouth (or have minimal intake) for more than 5 days are considered nutritionally at risk, patients may require oral nutritional supplements and/or supplementary tube feeding in order to meet their nutritional requirements [7].

The aims of dysphagia management are as follows [81, 85]:

- Minimise risk of malnutrition
- Minimise risk of dehydration
- Minimise risk of aspiration pneumonia
- Maintain oral intake

It is considered good clinical practice to maximise the nutritional intake of patients on texture-modified diets, but currently there is a lack of evidence around

how best to achieve this [7]. In clinical practice it appears difficult to achieve consistent supplementation of texture-modified food and drinks, in part due to organisational constraints, but also due to issues around achieving the correct texture when adding thickeners at ward level, and the observation that people on these diets tend not to consume very much and frequently fail to meet their nutritional and fluid requirements [81–84]. Currently, it is not possible to discriminate between the impact of the food's unappetising appearance, diluted flavour, and altered texture; patient-specific factors such as poor appetite, impaired mobility, or depression; and organisational issues such as limitations on the provision of a choice of attractive meals of the correct texture.

Tube Feeding

In those with a functioning gastrointestinal tract, tube feeding should be considered not only for those who are nil by mouth due to unsafe swallow, but also for those who are unable to meet their nutritional needs by the oral route alone, especially if they are already malnourished [7]. It should be noted that even in stroke populations, dysphagia is not the only reason that people fail to meet their nutritional requirements by the oral route alone. In general, people should be fed via a tube into the stomach unless there is upper gastrointestinal dysfunction. Where there is evidence of upper gastrointestinal dysfunction, or an inaccessible upper gastrointestinal tract, post-pyloric (duodenal or jejunal) feeding should be considered. For people being fed into the stomach, bolus or continuous methods should be considered, taking into account patient preference, convenience, and drug administration [7]. Those requiring post-pyloric feeding should, however, receive continuous rather than bolus feeding [7]. People who are unable to swallow safely or take sufficient nutrition orally should have an initial 2- to 4-week trial of tube feeding, and those who require longer term support should be considered for gastrostomy feeding [7, 47].

For a full discussion of the role of tube feeding in the management of stroke please see below.

Mealtime Improvements and Optimising Nutritional Care

At any time on a stroke unit there is likely to be a high proportion of patients experiencing significant feeding difficulties, either as a result of their stroke or due to pre-existing malnutrition. In recognition of this, it would appear to be good clinical practice to ensure ward-based systems and procedures are implemented that maximise the dietary intake of all patients, rather than targeting only those who are already malnourished. A number of strategies have been recommended as good clinical practice (Table 7.2) by national and international organisations including BAPEN and the European Commission, and professional bodies including the Royal College of Nursing and the Royal College of Physicians, although currently

Table 7.2 Strategies to improve nutritional care at mealtimes and the mealtime environment

Strategy	
Protected mealtimes [86, 87]	Periods on a hospital ward or in a care home when all non-urgent clinical activity stops; people are made ready to eat and provided with a pleasant environment that encourages eating; provision of physical assistance with eating and drinking; verbal encouragement; observation and recording of meal completion
Red trays [88]	Patients requiring assistance with eating and drinking are identified, e.g. nutritional risk, confusion, poor vision; food is provided on a red tray to ensure those requiring assistance receive it
Feeding assistance [89, 90]	Patients are assisted to eat and drink, including provision of adapted crockery and cutlery if required; opening of packets; food is placed where patient is able to reach it easily; food may be cut up; patients may be fed if required; verbal encouragement
Improved dining environment [91, 92]	Family-style meals; communal eating in a homey room; table dressing; menu choice; quiet and pleasant environment; lack of distractions

there is a lack of good-quality evidence to support their use [65]. At ward level the provision of food and drink is considered a nursing responsibility; however, it could be argued that strategies that aim to improve the mealtime environment and the patient meal experience require support from clinicians and other health-care professionals at all levels if they are to be effective.

Monitoring and Evaluation

The main objective of monitoring is to ensure nutritional support is provided safely and effectively. Monitoring also permits clinicians to assess the extent to which nutritional goals have been met and to detect and treat clinical complications as early and effectively as possible. Should any complications occur, or nutritional goals not be met, monitoring and evaluation will allow clinicians to alter the type of nutrition support, or amend the regimen, to improve its effectiveness or to minimise or prevent complications. To achieve these objectives, monitoring protocols should include a variety of observations and measurements (Table 7.3) [7].

The type and frequency of monitoring will depend on the extent and severity of the stroke, the presence of any co-morbidities that might complicate nutritional management, e.g. diabetes, in patients receiving enteral tube feeding, whether previous results were abnormal, the type of nutrition support used, the setting of the nutritional care, and the expected duration of nutrition support.

While not currently recommended for use in routine clinical practice in hospitalised patients who have had a stroke, serial triceps skinfold thickness (TSF) measurements can be a useful way to measure changes in fat mass over time (weeks or months) in patients who are likely to be followed up in the long term, e.g. in outpatient clinic. Together with MAC (see previously), TSF measurements can be used to determine mid-arm muscle circumference (which provides an estimate of lean body

Table 7.3 Nutritional, anthropometric, and clinical monitoring

Parameter	Frequency	Rationale
Nutritional intake (from oral, enteral, or parenteral nutrition)	Daily initially, then twice weekly when stable	To ensure patient meets daily nutritional requirements
Fluid balance	Daily initially, then twice weekly when stable	To ensure patient meets daily fluid requirements (not over- or under-hydrated)
Weight	Weekly, then monthly (daily if there are concerns regarding fluid balance)	To monitor ongoing nutritional status and determine if nutritional goals have been met
Mid-arm circumference and triceps skinfold thickness	Monthly (if weight cannot be obtained)	To monitor ongoing nutritional status and determine if nutritional goals have been met
Gastrointestinal function, e.g. diarrhoea, constipation, abdominal bloating	Daily initially, then twice weekly	To ensure tolerance of feed and to determine potential causes of gastrointestinal dysfunction
Clinical condition, e.g. temperature, blood pressure, consciousness, swallowing ability	Daily initially, then twice weekly when stable	To ensure that the feeding route, methods, and goals of nutritional treatment remain appropriate
Drug therapy	Daily initially, then monthly when stable	To prevent/reduce drug nutrient interactions
Laboratory data	Daily initially, then twice weekly when stable	To monitor clinical status, fluid status, and assess for re-feeding risk
Psychological and social status	Daily initially, then twice weekly when stable	To determine potential impact on nutritional intake and/or status

Adapted from NICE 2006 [7]

mass), and thus regular measurements of both TSF and MAC over time can indicate changes in body composition, i.e. lean body mass and fat mass. In clinical practice, this can be useful if the aim is to measure the impact of nutritional intervention either alone or together with physical and/or other therapies, such as might occur during rehabilitation after stroke. Since both the measurements of MAC and TSF are prone to large inter- and intra-observer error, all such anthropometric measurements should be undertaken by the same skilled practitioner on each occasion [93]. Similarly, hand-grip strength can be used to measure the impact of nutritional interventions over time on skeletal muscle function [94].

Observational studies show that documentation regarding nutritional status, body weight, appetite, and food intake is generally poor [95–98], yet nutritional intervention cannot be managed safely or effectively without adequate standards of both monitoring and documentation [7]. This would seem particularly pertinent with the decreases in length of hospital stay observed in recent years. With average hospital stays as short as 4 or 5 days, it is perhaps unrealistic to expect that the full nutritional treatment plan will be implemented in time for the patient to be discharged. While it should be possible to ensure the patient undergoes nutrition

screening and assessment while in hospital, the full treatment plan may not be fully implemented prior to discharge. In such cases, post-discharge monitoring and follow-up arrangements to ensure the patient's nutritional status are evaluated effectively, and to measure the impact of nutritional intervention, are particularly necessary. However, evidence suggests that discharge documentation to GPs relating to nutrition is poor and that, as a result, only a small proportion of malnourished patients are followed up by a dietician [99]. The doctor's role in communicating relevant nutritional information between hospital and community health-care professionals is pivotal in ensuring effective discharge planning and safe transfer of care with respect to nutrition. This will be accomplished usually in collaboration with a dietician and other members of the multi-disciplinary team such as speech and language therapists and physiotherapists.

Since eating and drinking can remain problematic for many months post-stroke, and stroke may result in changes in social and/or psychological status that might impact on dietary intake and/or nutritional status, patients should be screened for nutritional risk status whenever they attend outpatient clinics, including at 6- and 12-month reviews in stroke clinic, or when they come into contact with community-based health-care professionals [7]. All those identified as malnourished or at risk of malnutrition in the community should be referred for a full nutritional assessment and intervention if required [7, 80].

Overweight and Obesity

Epidemiology

Obesity, i.e. excess body weight, in particular excess fat mass, is associated with an increased risk of several conditions that may lead to stroke, including hypertension, hyperlipidaemia, and diabetes mellitus.

Since 1980 the prevalence of obesity has nearly doubled worldwide. In 2008, more than 1.4 billion adults (35 %) aged 20 years and older were overweight, and of these, over 500 million (11 %) were obese [3]. Overweight and obesity are the fifth leading risk for global deaths, and at least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44 % of the diabetes burden, 23 % of the ischaemic heart disease burden, and between 7 and 41 % of certain cancer burdens are attributable to overweight and obesity [3]. By 2050 obesity is predicted to affect 60 % of adult men and 50 % of adult women in the UK, and the NHS costs attributable to overweight and obesity are projected to reach £9.7 billion, with wider costs to society estimated to reach £49.9 billion per year [100]. These factors combine to make the prevention of obesity a major public health challenge.

While it is recognised that overweight and obesity are associated with the incidence of first-ever stroke, it is still debatable whether or not this is an association with obesity alone or a reflection of the fact that overweight and obese individuals

are more likely to have other conditions such as hypertension, diabetes, and hyperlipidaemias, that in themselves increase the risk of stroke and cardiovascular diseases. Most studies seem to show that obesity is a modifiable risk factor for ischaemic stroke, but that it is highly mediated through other risk factors, i.e. diabetes, hypertension, and hyperlipidaemia [101].

Aetiology

The fundamental cause of obesity and overweight is an imbalance between energy (calories) consumed and energy expended, i.e. more energy is consumed than the body burns. The excess energy is stored as adipose tissue.

The exact cause of obesity is not clear, and in any individual likely arises from a complex combination of factors. The Obesity Systems Map [102] was developed to provide an insight into the multiple factors contributing to the high prevalence of obesity in the UK. It shows a complex web of often reinforcing causal factors that range from genetic predisposition and individual psychology and physiology, through the culture and economics of food production, food consumption, and the built environment; to education on food and nutrition, and attitudes towards physical activity and lifestyle. It is not within the scope of this chapter to consider all of these factors, but it is worth noting that eating habits, physical activity, and psychological issues are considered modifiable, and therefore are most often targeted in weight-loss interventions.

Detection

Body mass index (BMI) is a simple index of weight for height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of their height in metres (kg/m^2). BMI provides the most useful population-level measure of overweight and obesity, as it is the same for both sexes and for all ages of adults. It should be considered a rough guide however, since the same BMI may not correspond to the same degree of fatness or associated health risk in different individuals and populations. Acknowledging this, the World Health Organisation continues to recommend that using a standard definition allows for meaningful comparisons between individuals and populations and provides a firm basis for evaluating interventions [103].

Health-care professionals need to be aware, and inform their patients, that members of black, Asian, and other ethnic groups face an increased risk of chronic health conditions at a lower BMI than the white population (below BMI 25 kg/m^2) [104]. This has been demonstrated mainly in relation to risk of type 2 diabetes, and more research is needed to find out if the increased risk at lower BMI in different ethnic groups holds for first-ever stroke and/or stroke recurrence. Table 7.4 shows the BMI

Table 7.4 BMI thresholds for white European and Asian populations [104]

White European populations	Asian populations	Description
<18.5 kg/m^2	<18.5 kg/m^2	Underweight
18.5–24.9 kg/m^2	18.5–23 kg/m^2	Increasing but acceptable risk
25.0–29.9 kg/m^2	23.0–27.5 kg/m^2	Increased risk
≥30 kg/m^2	≥27.5 kg/m^2	High risk

Table 7.5 Waist circumference cut-offs for different ethnic groups

Population	Cut-offs	
European	Males	≥94 cm
	Females	≥80 cm
South Asian, Chinese, Japanese	Males	≥90 cm
	Females	≥80 cm
South and Central American	Use south Asian recommendations until further data available	
Sub-Saharan African	Use European recommendations until further data available	
Eastern Mediterranean and Middle East	Use European recommendations until further data available	

Adapted from International Diabetes Federation guidance [110]

thresholds for white European and other populations recommended by the World Health Organisation (WHO 2004) [104].

More recently, it has become evident that the distribution of fat around the body is associated with different health risks. Abdominal obesity (also known as central adiposity) is associated with an increased risk of metabolic and cardiovascular diseases than an even or peripheral distribution of fat around the body [103]. Abdominal fat can vary dramatically within a narrow range of total body fat and BMI, which suggests the need for additional measures to assess the health risks associated with overweight and obesity [103]. Indeed, abdominal obesity has been shown to be a stronger risk factor for stroke than BMI [105, 106].

To detect central adiposity, it is possible to measure waist circumference [107], although there is considerable debate around the potential impact of measurement site on risk categorisation [108]. Waist circumference (WC), measured at the midpoint between the lower border of the rib cage and the iliac crest, is a convenient and simple method considered a good surrogate of visceral adiposity across a wide age range. It provides a measure of fat distribution that cannot be obtained by measuring BMI alone. Waist circumference is not recommended as a routine measure but may be used to give additional information on the risk of developing other long-term health problems [109]. It should be noted that the waist circumference cut-offs are different for the sexes and for different ethnic groups (Table 7.5) [110]. Since metabolic and cardiovascular risk plateaus at higher BMIs, there is no benefit to measuring waist circumference in those with a BMI greater than 35 kg/m^2 [102].

To date there is a lack of evidence that weight reduction in overweight or obese individuals has an impact on the primary or secondary prevention of stroke [111].

However, being overweight or obese is associated with conditions that increase the risk of first-ever stroke, e.g. hypertension, diabetes, and hyperlipidaemia, and current guidelines therefore recommend that people who have had a stroke should be encouraged and supported to lose weight, at the same time as addressing other risk factors such as smoking, hypertension, diabetes, or physical inactivity [46, 47].

Assessment

Assessment should be focused on determining the degree of obesity, identification of risk factors for developing complications of obesity (cardiovascular disease and/or stroke), dietary intake, and contributing causes [109]. The degree of obesity can be established through measurements of weight and height to determine BMI, and the presence and extent of any central obesity may be established by a waist circumference measurement. Identification of other cardiovascular risk factors may be determined by blood pressure measurements [112] and through the biochemical assessment of blood glucose and a lipid profile. Other tests may be considered if appropriate, e.g. liver function tests or thyroid function tests.

Any medical conditions and co-morbidities that could increase the risk of developing complications of obesity should be discussed, e.g. family history of stroke and vascular disease, medical problems, medication, as should any psychological factors that might impact on, or be impacted by, obesity. An assessment of current dietary and alcohol intake should be made and should include an exploration of the patient's knowledge about diet, and any previous dietary changes they have made in an attempt to lose weight or decrease alcohol intake. The assessment should also include identification of any environmental factors, e.g. social issues, smoking, physical activity, and exercise, that might impact on the risk of developing complications of obesity [109].

Management

The level of intervention should be determined based on the degree of obesity, waist circumference, and the presence of relevant co-morbidities and risk factors [109, 113]. Interventions should be escalated from general advice on healthy weight and lifestyle, through diet and physical activity tailored to the individual (often in combination with psychological interventions), to consideration of drug therapy or surgery [109].

In the face of many misleading articles in the lay media, it is important to set realistic targets for weight loss at the outset and to manage expectations. People should be made aware of national sources of accurate information and advice, such as NHS Choices and Change4life, and should be advised to lose a maximum of 0.5–1.0 kg per week [109]. Guidelines [109, 113] recommend that people should be

advised to avoid "yo-yo" dieting (otherwise known as weight cycling), in which weight is repeatedly lost and regained over weeks, months, or years, since in some studies this has been shown to increase a person's likelihood of developing fatal health problems more than if the weight had been lost gradually or not lost at all. More recent evidence however, suggests the impact of "yo-yo" dieting on morbidity and mortality is not consistent [114].

People should be made aware that the more weight they lose, the greater the health benefits, particularly if they lose more than 5 % of their body weight and maintain this for life [109, 113]. Furthermore, people should be reassured that even preventing future weight gain can lead to health benefits [109, 113]. Clinicians should acknowledge the effort required to lose weight, prevent weight regain, or avoid any further weight gain, and to maximise the chance of achieving weight loss, should take into account the person's feelings about being overweight or obese, and their willingness and motivation to try to lose weight [109, 113].

Lifestyle Modification Programmes

Multi-component interventions are the treatment of choice [109], since dietary interventions are more likely to be successful in terms of reducing morbidity if they form one component of a lifestyle modification programme [109, 113].

Lifestyle modification programmes usually address dietary intake, physical activity, and behaviour change, and include input from a dietician, a physiotherapist, or qualified physical activity instructor and a psychologist. The focus of such programmes is on life-long lifestyle change and the prevention of future weight gain. Such programmes usually last at least 3 months, and sessions are offered at least weekly or fortnightly and include a "weigh-in" at each session. People attending lifestyle weight management programmes lose on average around 3 % of their body weight, but this varies considerably [109].

Dietary Intake

To date there appears to be no evidence to suggest that advice on losing weight while still in hospital following an acute stroke confers any benefits on overweight or obese individuals. The need to lose weight, however, is frequently addressed in outpatient clinics soon after hospital discharge following acute stroke.

The main requirement of a dietary approach to weight loss is that total energy intake should be less than energy expenditure. Dietary changes should be individualised, tailored to food preferences and lifestyle, and should allow for flexible approaches to reducing energy intake [109]. Diets that contain 600 kcal less per day than the person needs to stay the same weight are recommended for sustainable weight loss [115]. While low-calorie diets (1,000–1,600 kcal/day) may also be considered, they are less likely to be nutritionally complete [116]. Very low-calorie

diets (less than 1,000 kcal/day) may be considered for a maximum of 12 weeks continuously, or intermittently with a low-calorie diet (for example for 2–4 days a week), by people who are obese and have reached a plateau in weight loss [109]. Guidelines recommend that diets of less than 600 kcal/day should be used only under clinical supervision when there is an urgent need for weight loss [109, 113].

People are more likely to maintain a healthy weight if they reduce their consumption of energy-dense diets containing fatty and/or sugary food and drinks and follow a lower energy, high-fibre diet; consuming fewer take-away meals; eating more fruit, vegetables, and whole grains; minimising alcohol intake; and consuming less confectionery and fewer sugary drinks [117]. While there is considerable debate around which macronutrients (fat or carbohydrate) are most likely to result in excess weight gain, a recent large RCT with follow-up to 2 years concluded that reduced energy diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise [118].

People should be advised to avoid concentrating on reducing the intake of one or two foods, or one particular food group, e.g. fat or sugar, since this strategy is less likely to be successful in the long term than aiming to eat a well-balanced, varied diet including all food groups in the correct proportions [109, 113].

Different types of diets have been attempted in the prevention of cardiovascular disease and, to a lesser extent, stroke, e.g. Mediterranean diet, lipid-lowering diets, low-salt diets for hypertension. These diets were designed to alter macro- and micronutrient profiles to reduce risk factors and were not necessarily designed for weight loss. However, in controlling the intake of macronutrients, weight loss often accompanies any changes in risk factors such as reduced blood pressure and altered blood lipid profile [119].

Some people may prefer a commercial weight-loss programme such as Weight Watchers, although the effectiveness of these programmes is difficult to assess, since they vary widely in content, presentation, timing, and venues. Furthermore, drop-out rates can be very high [120]. However, programmes that emphasise realistic goals, gradual progress, sensible eating, and exercise can be very effective for some people [109, 113].

Physical Activity

There is consistent evidence that interventions combining diet and physical activity are more effective for weight loss than diet alone [109, 113]. People who have had a stroke should be encouraged to increase their physical activity as much as is safely possible, even if they do not lose weight as a result, because of the other health benefits physical activity can bring, such as reduced risk of type 2 diabetes and cardiovascular disease.

Recent guidelines [121] recommend that adults should be encouraged to do at least 30 min of moderate-intensity physical activity on 5 or more days a week. The activity can be in one session or several lasting 10 min or more. Moderate-intensity activity usually increases a person's breathing rate and heart rate and makes them

feel warm, and includes activities such as brisk walking, cycling, gardening, house cleaning, golf, and racquet sports.

To prevent obesity, most people should be advised they may need to do 45–60 min of moderate-intensity activity a day, particularly if they do not reduce their energy intake [121]. People who have been obese and have lost weight should be advised they may need to do 60–90 min of physical activity a day to avoid regaining weight [121].

Adults should be encouraged to build up to the recommended levels of physical activity for weight maintenance, using a managed approach with agreed goals. Any activity should take into account the person's current physical fitness and ability. While guidelines recommend that people should be encouraged to reduce the amount of time they spend in sedentary activities such as watching television or using a computer [109, 113], and should be supported and encouraged to try other activities that may be locally available, e.g. community walking groups, gardening schemes, or dog walking, there is currently a lack of evidence to support this strategy.

Behavioural Interventions

Evidence suggests the combination of behavioural interventions with diet and exercise results in an even greater weight reduction than either intervention alone, and thus weight management programmes should include behaviour change strategies to increase people's physical activity levels or decrease inactivity and improve eating behaviour with regard to the quality of the person's diet and energy intake [109].

Behaviour therapy usually focuses on what and how much a person eats and may involve asking the patient to keep a food diary to help them better understand the nutritional content of foods. It may also involve changing grocery-shopping habits, timing of meals, or advising the person to slow down the rate at which they eat. The behaviour programme may also explore how a person responds to food, in an attempt to understand what psychological issues may underlie a person's eating habits. For example, one person may binge eat when under stress, while another may use food as a reward. In recognising these psychological triggers, an individual can develop alternative coping mechanisms that do not focus on food. Involving family members (usually spouse/partner) in behavioural treatment programmes is generally more effective for weight loss than targeting the overweight individual alone [109].

Pharmacological Interventions

Drug treatment should be considered only after dietary, exercise, and behavioural approaches have been attempted and have failed to achieve the desired weight loss, or for those people who have reached a plateau on these interventions [109]. Currently, only one drug is specifically licensed for use in the treatment of obesity in the UK (Orlistat, Roche, Switzerland). A meta-analysis of 15 RCTs found that this drug, in combination with a weight-reducing diet, was more effective for weight loss maintenance than placebo and diet at 12 months. At the same time, use of

Orlistat was associated with small decreases in total cholesterol, %Hb1Ac and both systolic and diastolic blood pressure [109]. Since Orlistat reduces the absorption of energy-dense fat by inhibiting pancreatic and gastric lipases, it is associated with increased rates of gastrointestinal symptoms that are usually mild and transient.

When drug treatment is prescribed, arrangements should be made for appropriate health-care professionals to offer information, support, and counselling on additional diet, physical activity, and behavioural strategies, and information on patient support programmes should also be provided [109]. Regular review is recommended to monitor the effect of drug treatment and to reinforce lifestyle advice and adherence.

If there is concern about the adequacy of micronutrient intake, a supplement providing the reference nutrient intake for all vitamins and minerals should be considered, particularly for vulnerable groups such as older people (who may be at risk of malnutrition) [109].

Surgical Interventions

Overall mortality is 29–40 % lower in the 7–10 years after surgery in patients receiving bariatric surgery compared with BMI-matched subjects not receiving surgery [122]. Bariatric surgery is therefore recommended as a treatment option for people with obesity if all of the following criteria are fulfilled [109]:

- BMI $\geq$40 kg/m^2, or 35–40 kg/m^2 in the presence of other significant disease that have the potential to be improved by weight loss, e.g. type 2 diabetes or high blood pressure.
- All appropriate non-surgical measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months.
- The person has been receiving or will receive intensive management in a specialist obesity service and the person recognises the need for long-term follow-up.
- The person is generally fit for anaesthesia and surgery.

Regular, specialist postoperative dietetic monitoring is recommended [109], and should include information on the appropriate diet for the bariatric procedure; monitoring of the person's micronutrient status; and individualised nutritional supplementation, support, and guidance to achieve long-term weight loss and weight maintenance. Patients may also benefit from information on national or local patient support groups.

Monitoring and Evaluation

Weight loss is very difficult to achieve in the long term, therefore most patients will require medium- to long-term monitoring, encouragement, and support [123, 124]. Monitoring should include records of weight change and changes in waist circumference [109, 113] and may include measurements of changes in body composition,

e.g. fat mass and lean body mass, although current national guidelines do not recommend routine use of bioelectrical impedance analysis to achieve this [109]. An increase in physical activity level together with changes in diet will make it easier for people to alter their body composition in a positive way, i.e. increase lean body mass and decrease fat mass.

Perhaps more importantly, clinicians should monitor the impact of multicomponent interventions on changes in risk factors such as hypertension (may respond to dietary salt reduction), blood lipid profile (may respond to changes in diet although people are more likely to receive statins), and blood glucose (will respond to changes in diet).

Changes in dietary intake can be assessed using a variety of methods, including 24-h dietary recall, 5-day dietary diary, or weighed food intakes [58], although it should be recognised that each method has its strengths and weaknesses and requires specialist training in order to obtain an accurate assessment of intake. Clinicians should also remember that people who are overweight or obese are those who are most likely to under-report dietary intake, particularly the energy and fat components of the diet, as well as other nutrients they perceive to be "bad" [125].

The Obesity "Paradox"

In stroke populations it has been shown that those with low BMI (<20 kg/m^2) are more likely to suffer poor outcomes than those with a higher BMI, and indeed those who are overweight or obese have even better outcomes than those in the desirable range for BMI [126–129]. This paradoxical association between BMI and mortality after stroke is most effectively demonstrated in a large cohort study in Denmark using data collected as part of a national stroke registry [126]. In this study of 13,242 individuals, mortality was higher in underweight patients (i.e. BMI <20 kg/m^2) compared with those who were in the healthy range BMI (i.e. 20–25 kg/m^2), overweight (BMI 25–30 kg/m^2), obese (BMI 30–35 kg/m^2), or severely obese (BMI >35 kg/m^2) [126]. More recently, a prospective study of 543 patients designed to examine the impact of BMI on outcomes post-stroke showed that those with BMI less than 18.5 kg/m^2 (underweight) were more than twice as likely to die at 6 months than those who were overweight or obese [129]. In this study it was also shown that there were no significant differences in stroke recurrence rates between BMI categories at 6 months post-stroke (BMI <18.5 kg/m^2 = 3.7 %; healthy BMI = 3.8 %; overweight = 4.5 %; obese = 2.8 %; $p = 0.91$).

This better survival of overweight and/or obese patients (and increased mortality of underweight patients), observed in both ischaemic and haemorrhagic strokes, suggests that weight management strategies targeting the optimal BMI range used for the healthy population may require further evaluation and individualisation in the secondary prevention of strokes. In the future, it would be important to evaluate other indicators of nutritional status and distribution of body fat, such as waist circumference, in order to explore this paradox and its effect on stroke recurrence and mortality.

Dysphagia

Swallowing

The process of swallowing has been described as the most complex of "all or non-reflex" [130, 131]; however, although the pharyngeal swallow is a basic reflex, feedback regarding bolus size and viscosity emanating from afferents in the mouth and pharynx [132] regarding bolus size and viscosity via the cortex will modify timings of various components of the swallow.

A normal swallow is difficult to define, but essentially it is a series of sequential coordinated events that ensures a safe passage of food or liquid from the mouth to the stomach [133]. As food is brought from the plate or cup towards the mouth, preparation to swallow begins.

There are essentially three functions to the oro-pharyngeal swallow. These are bolus preparation, airway protection (trachea and nasal), and bolus passage through the pharynx to the oesophagus; and three swallowing phases: oral, pharyngeal, and oesophageal (relaxation of the upper oesophageal sphincter). The relationship between these phases of timing and duration is dependent to some degree on bolus characteristics.

Bolus Preparation/Oral Phase

The oral phase of swallowing is under volitional control, in that it is personal choice how long food is chewed before the bolus is gathered together and transferred to the back of the mouth; this will be influenced by bolus viscosity, texture, volume, and personal preference [134, 135].

As the bolus approaches the lips, the hyoid bone moves forward and up pulling the larynx up against the base of the tongue [136, 137]. Once the bolus has been placed in the oral cavity, lips are closed; the bolus is prepared for swallowing, by chewing and mixing with saliva in the case of a solid bolus (e.g. meat). When ready, the bolus is collected on the tongue and trapped between the tongue and the hard palate, such that in the antero-posterior view it is said to resemble a Viking long boat. The bolus is then propelled backwards to the pharynx by a rippling movement of the tongue from anterior to posterior.

Passage Through the Pharynx

Passage of the bolus through the pharynx is not straightforward. Once the bolus has left the back of the tongue, it moves momentarily into the valleculae, before passing over or around the epiglottis [138, 139]. The bolus then divides and passes through the lateral food channels (pyriform sinus), before reforming to pass through the upper oesophageal sphincter (cricopharyngeus), which is relaxed and opened.

The movement of the bolus is not a passive phenomenon, but an active process commencing with a push from the posterior tongue, and continued with a rippling of the lateral [140] and posterior pharyngeal wall (the pharyngeal stripping wave) [141].

Airway Protection

The pharynx is an anatomical structure/"tube" that is shared by both respiration and swallowing. To swallow safely, there needs to be an interruption to the respiratory cycle [142, 143]. As a consequence, during swallowing there is a period of apnoea, followed by expiration, but this is not invariable and certainly after sequential swallowing, inhalation may occur [139]. Where apnoea is not possible, e.g. lung fibrosis, COPD, or heart failure, swallowing may be a problem, resulting in dysphagia.

Protection of the airway commences at the beginning of the swallow, with upward and forward laryngeal movement. Concurrently the false vocal cords begin to come together, followed closely by the true vocal cords and then the epiglottis. The real protection of the airway is not the epiglottis but the vocal cords. It is possible to swallow without the presence of an epiglottis [144] and in sequential swallows the epiglottis is frequently upright [139].

As the bolus moves to the back of the oral cavity, the soft palate elevates to close off the nasal passages, aided by the forward movement of the posterior pharyngeal wall (Passavant's cushion) [133].

Commencement of the Pharyngeal Swallow

Original research had suggested that the pharyngeal swallow would commence once a bolus passed the base of the anterior faucial arches. Subsequent research has found that this is true in some cases, but for many others the swallow does not trigger until the bolus is in the pharynx itself [145, 146].

Neural Control of Swallowing

The pharyngeal swallow is triggered by the presence of the bolus in the pharynx. The exact point at which the swallow triggers is different in each person. Information regarding the bolus presence is referred to as the brainstem and cortex [147, 148] and a swallow is triggered. However, there is not one interneuron but a system of connections within the reticular formation of the medulla, near the inferior olive, which has an important role to play. At the same time, information regarding the bolus characteristics are conveyed via afferents (within cranial nerves V, VII, IX, X–XII) to the cortex, which then modulates the swallow to regulate how long the upper oesophageal sphincter remains open, the dimensions of the pharynx, and the control of respiration and airway closure [148].

Cortical control is complex and is detailed elsewhere [149], suffice to say that there is no single cortical or subcortical region that has ultimate control. The swallow is bilaterally, but asymmetrically, represented [150] within the cortex (motor cortex, supplementary motor cortex, amygdala, frontal cortex, and cerebellum). Two areas that appear to be critical for the coordination of swallowing are the nigrostriatal pathway and the anterior insula cortex. Within these areas are numerous neuro-transmitters including substance P, dopamine, and noradrenalin (see Fig. 7.1) [151, 152].

Swallowing Following Stroke

As a consequence of stroke, dysphagia will occur if the cortical pathways related to swallowing are interrupted anywhere along their path. Also, a lesion within the medulla or pons could similarly affect the ability to swallow [153, 154].

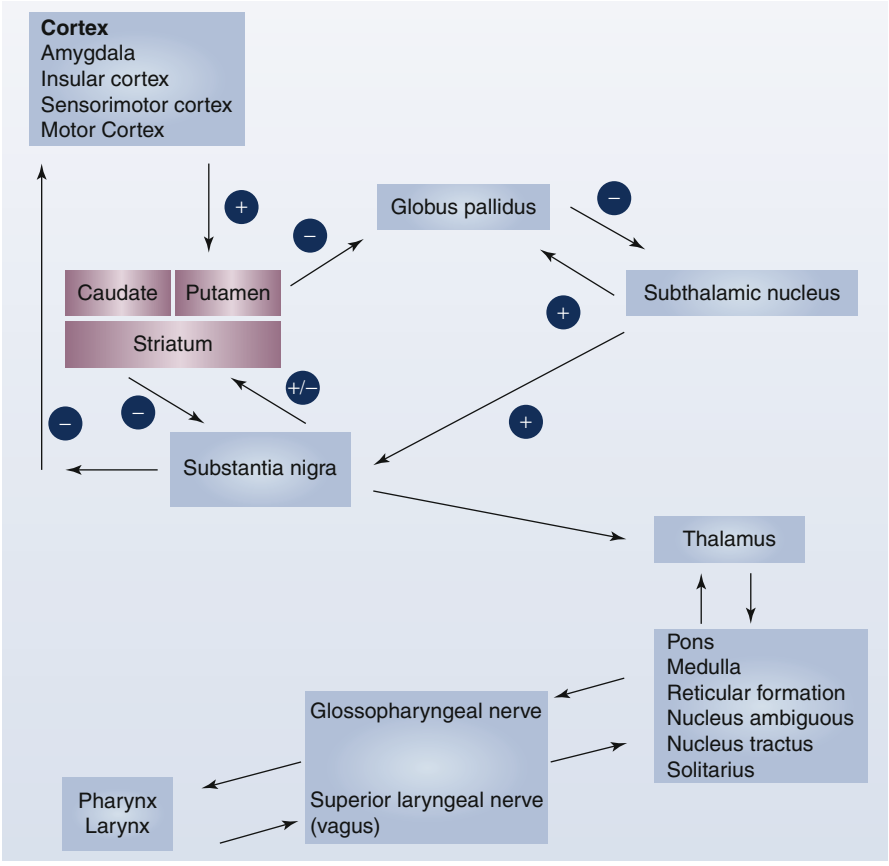

Fig. 7.1 Neural control of swallowing

Lesion Site

Dysphagia may follow a stroke in any area/lobe of the brain, as the pathways are complex and interdependent. The occurrence and recovery of dysphagia will frequently depend on the relative dominance between the affected and unaffected hemisphere for swallowing. There has been much research investigating the lesion location, but there has been no conclusive single cortical location identified as the most relevant. Stroke within the subcortical structures, cerebellum, and brainstem may be more likely to result in dysphagia, particularly because of the close proximity of many important pathways [152].

From a cortical perspective, the occurrence of dysphagia will depend on the side of the brain affected, i.e. if the hemisphere affected by stroke is the dominant hemisphere for swallowing, then dysphagia will occur. The particular problem that occurs will depend on which area of the brain is affected. The issue may be motor, sensory, or sensorimotor. There may be a problem of coordination (stages of swallow or with respiration) or dyspraxia.

Epidemiology

Abnormalities within the swallowing system are common following stroke, and some authors have suggested that the occurrence may be as high as 100 %; however, clinically relevant problems with swallowing or dysphagia are present in 28–65 % of people during the acute phase of stroke.

Globally, 15 million people suffer a stroke annually [154], of these up to 9,750,000 (65 %) will have dysphagia. Of these, about half (4,875,000) will be aspirating, and half of these (2,437,500) silently.

The number with dysphagia reduces significantly during the early days of stroke, such that by 14 days after the stroke 90 % of people will be swallowing safely [155–157]. However, a small proportion of people will have ongoing problems for some time [152]. Some of those who appear to have returned to a safe swallow after 3 months are found to have difficulties at 6 months [154–156]. If the swallow does not show any signs of recovery in the first 10 days, it is probable that the return of a safe swallow may take between 2 and 3 months.

Swallowing recovery is dependent on neural plasticity [158–160], with either the non-affected hemisphere enlarging [43], or other cortical areas taking over, or both. Failure of the non-affected hemisphere to enlarge will result in dysphagia persisting. Hamdy and colleagues have undertaken many eloquent studies to show this, using both fMRI and transcranial magnetic stimulation [153, 162].

Aetiology of Dysphagia Following Stroke

The ability to swallow safely may have many different aetiologies/co-morbidities (many predating the stroke) that interplay; compounded by the fact that some older

Table 7.6 Medications adversely affecting swallowing

Class of medication	Effect
Anti-psychotic (chlorpromazine, risperidone)	Dry mouth
Tricyclic antidepressants (amitriptylline)	Dry mouth
Antibiotics	Sore mouth, fungal infection
Opiates (morphine, codeine)	Dry mouth, sedation
Diuretics	Dry mouth, hypocalcaemia
Benzodiazepines	Sedation
Corticosteroids	Oral fungal infection
Metformin	Altered taste
Alpha blockers and calcium channel blockers	Dry mouth
Antiepileptic medication	Sedation
COX2 inhibitors/non-steroidal anti-inflammatory agents (naproxen)	Reduced cough

people will have presbyphagia, and a new physiological insult has led to a decompensation of their swallow. Frequently, medications will also have a negative impact on swallowing (Table 7.6) [163].

With increasing age, there are subtle but definite changes in swallowing, which frequently go unnoticed because of the slow onset and the gradual compensation strategies employed, i.e. smaller portions, softer consistency, or skipping courses. These changes are termed presbyphagia [164].

Many people may wear dentures or have a reduced number of teeth. Reduced numbers of teeth reduce chewing capacity, resulting in larger portions of food being swallowed [165], consequently when the swallow is compromised after stroke, this may lead to a high risk of aspiration.

For dentures to work, there needs to be good bone structure, muscle strength, and healthy gums. Many people do not wear theirs due to pain, either because the dentures do not fit (as a result of bone resorption or poor fitting), or because of infection in the gums. Following a stroke, with facial nerve palsy the muscle tone in the cheek is reduced, resulting in a failure to keep dentures in place, making hard food impossible to eat.

Many medications prescribed prior to or after stroke, such as antihypertensive medications or statins, have an anticholinergic effect [166–168]; these may result in a dry mouth, poor vision, or confusion. This may decompensate the swallow in those people whose physiological reserve is already limited. Other medications such as antidepressants, medication for incontinence (urologicals), and antipsychotic medication have strong recognised anticholinergic effects, resulting in much the same outcome, but also causing drowsiness. Drowsiness is the commonest cause of dysphagia. Any reduction of conscious level, including sleep, results in a reduction in the frequency of swallowing and on occasion the swallow reflex stops [166, 167].

Infections such as gum disease, abscess, salivary gland infections, or candidiasis in the mouth and possibly the oesophagus may make swallowing painful and difficult. This may manifest itself as food refusal rather than any particular aspect of swallowing itself, particularly in those people with communication difficulties.

Concomitant lung disease or cardiac diseases may be associated with dysphagia, particularly in those people where breath holding is not possible, such as stage III/IV cardiac failure or end-stage lung disease [169].

Detection

Initially there is a need to determine whether someone has dysphagia or not. A screening assessment is often undertaken by nursing and medical staff. The majority of these assessments are based on that initially described by Smithard et al. [151, 156, 170].

The assessment includes a series of questions followed by a simple swallow assessment using teaspoons of water, followed by a larger volume of water (50–90 ml). The sensitivities and specificities of all swallowing screens are similar. The main purpose of these screens is to permit those people to eat and drink who are considered to be safe. The majority of screens are able to rule out aspiration risk (NPV 90 %) [171] rather than rule it in. Therefore, a safe swallow on a screen probably is.

Ramsey et al. [171] investigated the addition of a chest radiograph to the standard bedside screen/assessment. The study did not provide any conclusive results, as not enough strokes with relevant pathology could be recruited.

If the swallow screen flags up a problem with the swallow, a referral should be made to a speech and language therapist for a formal assessment, or the swallow rescreened if it is at a time when speech and language therapists are unavailable.

Assessment

The assessment of dysphagia (as opposed to the screening assessment performed at the time of stroke) is a mixture of a clinical bedside assessment by a speech and language therapist or someone trained in dysphagia management (the actual professional may depend on the country), followed, where appropriate, by instrumental investigation [46, 172]. The most frequently used investigations are video fluoroscopy [173] and fibre-optic endoscopic evaluation of swallowing (or FEES) [174].

Video fluoroscopy provides the ability to see anatomy and physiology at the same time. It is generally widely available in most hospitals but does require the use of a radiology screening suit and a radiographer. Patients are exposed to radiation, equivalent to that of a chest radiograph. FEES, on the other hand, can be done at the bedside. It requires access to a nasal endoscope and training in its use. The advantage is that it can be performed at the bedside and does not expose the patient to radiation. The main disadvantage is that the passage of the bolus cannot be followed clearly, aspiration is only seem after the event, and the oesophagus is not seen at all.

Other assessments have been used including ultrasound [174], manometry [175], and scintigraphy [176]. Frequently more than one procedure will be used, usually in combination with a workstation that permits the “swallowologist” to review all the information together.

The major concern of dysphagia is the development of aspiration, and as a consequence a chest infection (see section "Complications of aspiration" below). The risk of aspiration increases with the increasing dependency of the patient. Those who are bed-bound and require feeding by others are more likely to develop pneumonia. The major reason for aspiration pneumonia is not food or liquid directly, instead it is frequently entry of oral pathogens into the airway, either with food or saliva or both [177–179].

Complications of Aspiration

- No obvious ill effects
- Recurrent cough
- Grumbling pyrexia
- Chest infection
- Asthma/COPD
- Food avoidance
- Weight loss
- Dehydration
- Cyanosis/hypoxia
- Hypoxic fit
- Airway obstruction
- Death

There is a debate in the dysphagia world as to whether detection of aspiration is important. Undoubtedly aspiration is important, but if someone has a clinically unsafe swallow, is it important to document aspiration? Bear in mind the long-term outcome in people with clinically documented dysphagia is similar to those with aspiration.

It has been suggested that the use of technology to investigate the swallow slows down the return to oral feeding. Clinicians can be too quick to refuse people food when previously they have been managing quite successfully.

Management

The management of dysphagia post-stroke has one aim only and that is to provide a method of safely providing adequate nutrition to the patient. Where possible, the oral route is used to provide nutrition, and if this is not possible, enteral feeding is used. On occasions both will be used together.

The ability to swallow will improve over time, with the swallow returning to many people within the first 2–10 days [155, 157]. Generally there is no need to consider any intervention over the first 24–48 h (except with intravenous fluids). If the swallow has not improved by that time, and it is not possible to resume oral feeding, a nasogastric tube should be passed, with all the usual caveats regarding naso-

gastric feeding. On occasion there may be a clinical need for an oral route for medication, and where oral feeding is not possible, and an alternative method of delivery (transcutaneous, buccal, rectal) is not available, then a nasogastric tube may be used.

Oral Nutrition

If oral feeding is considered appropriate, then there are essentially two ways of managing a poor swallow. The first is to alter what is eaten, by changing the texture, viscosity, taste, and size of the bolus. The second is to change the anatomy/physiology by monitoring breathing, turning the head, or tucking down the chin [180, 181]. Changing the viscosity/texture of the bolus is the commonest approach to managing the swallow. This is despite some counselling against the use of thickeners [182].

The role of the speech and language therapists (pathologist) is to reduce the risk of aspiration and improve swallowing function to allow a safe ingestion of food and liquid [183]. This is achieved by using posture changes (chin tuck, head turning) or swallow manoeuvres (breath holding, effortful swallow) to alter the physiology of swallowing.

Carnaby et al. compared usual care with three times weekly and daily swallowing therapy for 1 month [181]. Those with daily therapy were more likely to regain their swallow ($p=0.02$) and be eating a normal diet ($p=0.04$). The incidence of chest infection was reduced.

The literature supports the use of swallowing manoeuvres and postural movements for some patients [184, 185]. Head turning or chin tuck has shown benefit in 67 % and 77 %, respectively, reducing aspiration with some bolus consistencies [186] and increased the size of the bolus that could be swallowed [185]. Manometric studies have not been able to support the clinical findings [187]. McCullough and Kim, studying the Mendelsohn manoeuvre, noted some clinical benefit, but found that in stroke patients fatigue was a problem, particularly with older patients [187]. However, the evidence is limited due to the size of the studies, and that often studies are of mixed aetiologies [188, 189]. Similarly requesting change in eating or drinking speed may prove a problem, particularly in older patients, due to changes in oral sensorimotor function and in the ability to fully monitor the bolus characteristics [190].

Bolus Modification

The mouth and pharynx are full of sensory receptors that provide input into the cortex to modify the pharyngeal swallow. Bolus temperature, viscosity, volume, and taste can modulate the swallow [191], and hence can be used in the management of dysphagia.

Taste

Chee et al., studying healthy adults, suggested that the swallow is highly influenced by chemical-sensorial stimuli, with sweet and sour eliciting the shortest oral preparatory phase [191]. Sour taste may elicit a strong submental muscle contraction which could be beneficial with rehabilitation. Similarly bitter tastes produce a longer oral preparatory phase, which may provide longer for pharyngeal protection and should be explored in the realms of rehabilitation [191]. A study by Cola et al. has suggested that the use of (cold) sour tasting foods can shorten the duration of pharyngeal transit, though further work is still required in this area [192].

Rheology

Rheology is often interpreted as referring to the viscosity of a liquid; however, it is a term to describe the mechanical properties of liquid in its totality [193, 194]. Bolus size and consistency, with a normal swallow, is a major determinant on the duration of the swallow. Sensory feedback to the cortex via the mouth and pharynx regarding bolus characteristics will determine how long the larynx is elevated and the relaxation of the upper oesophageal sphincter [195, 196].

Oral/tongue deficits require, in many cases, a thicker bolus to promote bolus cohesiveness, whereas pharyngeal paresis/slow transit and pooling may require a thinner consistency. Clavé et al. found that increasing bolus consistency in those oral preparatory problems reduced the risk of laryngeal penetration and aspiration (39.5 % vs 26.3 %) [195]. Hamdy et al. examined the effect of bolus pH and temperature on the swallow [193]. Cold water with citric acid added slowed the swallow significantly. Although the texture and size of a bolus are frequently changed to support oral feeding in the clinical setting, little work has been done in anything other than water [197, 198].

Although increasing the viscosity of liquids with thickening agents (based on starch or guar gum) may reduce aspiration risk, due to their consistency and palatability, patients requiring thickened fluids are less likely to meet fluid requirements [82].

Modified-Texture Diets

As the rheology of liquid can affect the swallow, so can the consistency of food. The speech and language therapist may recommend following an assessment of the swallow, a change in the consistency of food and the rate that it is delivered to the patient.

Once the consistency of a food has to be changed, the palatability of the food may be reduced [199], and the nutritional content may be poor [83, 84, 199, 200]. It is not unknown for relatives/carers to provide people with pre-prepared baby food

with all the nutritional risks that this entails. Modern techniques involved with preparing food for people with dysphagia should bypass many of these problems and may markedly increase intake and hence nutritional status.

Tube Feeding

Enteral feeding, either by the nasogastric route or the gastrostomy route, does not prevent aspiration pneumonia occurring, as the most common reason is the aspiration of oro-pharyngeal secretions. As a consequence, good mouth care in the presence of enteral feeding is essential. Those fed via gastrostomy may suffer with reflux; this can be treated with either proton pump inhibitors and or pro-kinetic agents.

Nasogastric tubes are usually the primary route for enteric feeding used for short-term feeding (usually less than 4 weeks) in those who are either nil by mouth due to unsafe swallow, or who require supplementary feeding due to inadequate oral intake. Gastrostomy feeding is commonly used for long-term feeding following a stroke. A recent review by Gomes et al. for the Cochrane Library has suggested that percutaneous endoscopic gastrostomy (PEG) feeding is probably safer and more effective than nasogastric tube feeding in the longer term [198].

Nasogastric Tube

For a long time the consensus view has been that the presence of a nasogastric (or orogastric) tube inhibits a normal swallow [200–202]. This no longer holds true, and the use of such tubes may assist in rehabilitation due to the provision of nutrition [203].

Nasogastric tubes are frequently not tolerated [204] for a variety of reasons (see section "Complications of nasogastric tube placement" below). Where a nasogastric tube needs to be repeatedly replaced, a method of restraint may need to be considered, the most common of which is the nasal loop in the UK [205]. The use of constraints carries moral and ethical connotations which are discussed later.

Nasogastric tube placement is not a begin procedure, and the risk of complications has to be considered. The misplacement of a nasogastric tube is considered a never event by the Patient Safety Agency and as such, care has to always be exercised in its placement, as food in the wrong place could be fatal.

Complications of Nasogastric Tube Placement

- Recurrent placement
- Nasal ulceration
- Poor tube placement/wrong placement

- Food sticking to the nasogastric tube
- Increased pharyngeal secretions
- Feed failure
- Oesophageal reflux
- Placement in the lung
- Oesophageal perforation
- Aspiration
- Poor body image

Percutaneous Endoscopic Gastrostomy (PEG)

Over the last few years, PEG feeding has become the enteral feeding route of choice for long-term feeding, as there is more certainty over feed success and compliance with feeding regimens [206–208]. What is not certain is whether the use of PEGs improves the swallow, or that the swallow improves as part of the general improvement seen after their placement due to nutritional benefit [209, 210].

Gastrostomy tubes pass through the abdominal wall directly into the stomach. They are usually used for patients who require medium- to long-term feeding, or where passing and or retaining a nasogastric tube is difficult. The most common route for the placement of gastrostomy tubes is endoscopically (PEG) but they can also be placed radiologically or as a last resort, surgically. Many percutaneous jejunostomy tubes are placed endoscopically or radiologically via gastric puncture with an extension through the pylorus into the duodenum or jejunum (PEG-Jejunostomy).

Timing of Placement

The paper by Hussein suggests that if the swallow has not returned or is not returning within 10 days, it may take 70 days or longer for the swallow to return for oral feeding. As a consequence, a gastrostomy should be sited somewhere between 2 and 4 weeks post-stroke [46, 47, 208]. Gastrostomy placement is an operation that requires consent, and as such, the risks and complications have to be explained. Major complications are not common but can be serious and rarely fatal (Table 7.7).

Behavioural Techniques

Behavioural techniques often utilise biofeedback as part of the treatment package. Biofeedback may take many forms, but essentially they provide the patient and therapist with cotemporaneous information of their performance of the intervention task.

Table 7.7 Complications of PEG feeding

Major complications (Reported incidence 3–19 %)	Minor complications (Reported incidence 13–62 %)
Gastric haemorrhage	Tube displacement
Gastrocolic fistula	Tube obstruction
Gastric perforation	Tube leakage
Gastro-oesophageal reflux	Pneumo-peritoneum
Aspiration pneumonia	Skin excoriation/infection
Peritonitis	Cellulitis
Serious abdominal wall infection	Pain at tube site
Bowel obstruction	Buried bumper syndrome
Intussusception	Over-granulation of entry site
Oesophageal perforation	Diabetes control may be affected
	Nausea
	Diarrhoea

Biofeedback is used in conjunction with other methods of swallowing therapy. Logemann et al. reported a case study using indirect biofeedback with pharyngeal swallowing manoeuvres [211]. Over the years, different researchers have experimented with the use of biofeedback in conjunction with surface EMG [212, 213] and video endoscopy [214], accelerometry [215], and neck transducers [216].

Tongue Exercises

To move the swallow from the front of the mouth to the back relies on the movement of the tongue in relation to the palate and the pressures exerted during this procedure. Steele et al. have noticed that this is different between different viscosities and textures [217, 218]. With age, skeletal muscle quality may change and there may be a consequent reduction in isometric and swallowing tongue strength [219, 220].

Robbins et al. studied tongue strength in older people and found that an 8-week progressive resistance regimen improved swallowing pressures and increased muscle volume by 5 % [219]. Similarly, Lazarus et al. found that by using the IOWA Oral Performance Instrument there was a significant increase in tongue strength [220]. Clark et al. in a slightly larger cohort (39 adults) found similar results after 9 weeks directional training [221]. Robbins et al. found improvement in tongue strength and improved swallowing (timings and residue remaining) [222] and less aspiration in a small cohort (Martin-Harris et al.) of stroke patients with dysphagia.

Shaker Exercises

The Shaker exercise programme consists of a series of head-raising exercises whilst lying flat on the bed or floor. Three head raises are sustained and followed by a series of 30 repetitive head raises. The exercise strengthens the suprahyoid muscles,

resulting in improved upper oesophageal opening, laryngeal anterior excursion, and a reduction in post-swallow aspiration. In a small study of 27 people in 2002, Shaker and colleagues demonstrated that those in the treatment arm were able to resume swallowing; videofluoroscopy was the gold standard assessment [223]. Logemann et al., in a small multi-centre study (19 patients) that was beset with problems, noted that the Shaker and traditional therapy produced similar results but by different mechanisms [224]. They concluded that the traditional exercises (Mendelssohn Manoeuvre) should be used where there are neck problems. A further small study [225] of 11 patients showed that the Shaker exercise resulted in an increase of thyrohyoid shortening after 6 weeks compared to traditional exercises involving tongue exercises and swallow manoeuvres. Where it is not possible to perform the Shaker exercise, Yoon et al. have suggested that chin tuck against resistance offers the same benefits [226].

McNeill Dysphagia Training Program (MDTP)

The MDTP uses the act of swallowing as an exercise incorporating a hard swallow [183, 227]. The main thrust of the programme is to rebuild functional patterns of swallowing. During the programme, a patient is moved up or down the ladder of treatment of increasing resistive forces and alterations in movement velocities, timings, and movement specificity of the swallowing activity. Small case series have suggested that the MDTP is superior to standard therapy with sEMG. However, the studies are all a mixed case series and are not stroke specific [228, 229].

Surface Electromyography (sEMG)

sEMG is the recording of electrical activity within muscles. It has been advocated as an adjunct to swallowing therapy. Crary et al. reviewed the charts of 25 stroke patients who had dysphagia for a mean of 24.8 months and found that after a period of therapy that there was a 92 % increase in oral intake with a mean improvement of 2.96 on the Functional Oral Intake scale [228]. Bogaardt et al. found improvement in all 11 subjects to varying degrees [229]. Apart from a standard use of sEMG for varying periods of time (mean seven sessions), different swallowing therapy was used (Mendelsohn, Shaker exercises).

Faucial Stimulation

Lazzara et al. studied a mixed group of neurologically impaired individuals [230]. Results suggested that there was a decrease in the oral and pharyngeal transit times. Power et al., studying stroke patients only, were unable to replicate these findings, and instead noted that stimulation of the faucial arches at a frequency of 5 Hz increased the swallowing response time by 114 %, whereas 10 Hz inhibited the

swallow [231, 232]. This suggests that the relationship is far more complex than initially realised, which is borne out by the variability of the triggering of the swallow between individuals.

Neuromuscular Electrical Stimulation (NMES)

Neuromuscular electrical stimulation (NMES), usually trans-cutaneously, is of interest as it is potentially a non-invasive way of retraining the swallow. The whole basis of the treatment is to stimulate innervated healthy muscle recruiting fibres to cause a contraction. If the stimulation is used to augment a functional activity, then it is referred to as Functional Electrical stimulation. NMES in the case of swallowing involves the placing of electrodes on the skin over the larynx, and during the swallow and using the muscle stimulation of the hyoid muscles, to cause the larynx to elevate. There are many individual muscles in this area; intramuscular stimulation has noted that the thyro-hyoid is more closely related time wise to the laryngeal elevation than the myelo-hyoid [213, 233, 234].

Transcutaneous stimulation is unable to attain this degree of accuracy. In a meta-analysis of seven studies, Carnaby-Mann et al. found a small but positive effect for this intervention [213]. In 2009 Clark et al. recommended that further studies were required as no high-quality randomised trials existed [234]. Studies by Shaw and Bülow have noted positive effects with NMES [235, 236]. Permsirivanich et al., in a single-blind randomised study, compared rehabilitation swallowing therapy (diet modification, oral motor exercises, thermal stimulation, and swallowing manoeuvres) to NMES therapy (diet modification, oral motor exercises, and NMES) [237]. Both groups showed an improvement in swallowing using the Function Oral Intake score, by three to four levels; however, there was an absolute benefit in the NMES arm by 10 % (81 % vs. 91 %). The difference in mean change was significant at the $p<0.001$.

There is increasing evidence that NMES does have a place in swallowing treatment, but as Ludlow et al. noted in their review, it is beneficial for a small group of mild to moderate dysphagia rather than severe dysphagia [238].

Pharyngeal Stimulation

Swallowing, although reflexic, is highly dependent on sensory feedback [237, 239]. This feedback provides information regarding bolus characteristics. Fraser et al. and Hamdy et al. have shown that stimulation of the pharynx will produce changes in the cortex lasting up to 30 min [240]. However, the peak excitation of pharyngeal swallow is later than that usually produced by a volitional swallow, suggesting that the maximal benefit of pharyngeal stimulation would be achieved in conjunction with volitional swallowing exercises. Jayasekeran and colleagues further investigated this effect in people with acute stroke [241]. One treatment each day produced improved airway protection compared with controls ($P=0.038$). Active PES also reduced aspiration, improved feeding status [237, 239], and resulted in a shorter time to hospital discharge [242].

Pharmacological Interventions

Swallowing is complex, with several sites of intervention, including the cerebral hemispheres/lobes, brainstem, and topically. A topical theory is that depletion of substance P in the pharyngeal plexus as well as centrally results in a disordered pharyngeal swallow. Several papers [242, 243] have suggested that ACE inhibitors can reduce aspiration and the incidence of aspiration pneumonia. Capsaicin will act topically on the pharynx. Recent work by Rofes et al. has shown an increase in the vertical movement of the larynx with capsaicinoids by way of the TRPV1 receptor, reducing laryngeal penetration by 50 % ($p<0.05$) and pharyngeal residue by 50 % ($p<0.05$), and shortened the time of laryngeal vestibule closure ($p<0.001$), upper oesophageal sphincter opening ($p<0.05$), and maximal hyoid and laryngeal displacement [244]. Rofes et al., using Piperine acting via the TRPV1/A1 receptor in the pharynx, noted a 35 % (150 μM) to 57 % (1 mM) reduction in unsafe swallows (reduced time to laryngeal closure) and a consequent reduction in the severity score of the penetration-aspiration scale [245].

Perez et al. found improvements in pharyngeal transit times (a mean reduction of 1.34 s, 95 % CI −2.56, −0.11) and a reduction in swallow delay of 1.91 s (95 % CI −3.58, −0.24) using Nifedipine controlled release in a crossover design study [245–246].

These studies would suggest that the pharynx hosts an array of receptors, which can be utilised to assist in the recovery of the swallow. It is possible that all medications are acting via a final common pathway, which may be substance P, or calcium channels, or both.

Acupuncture

Li et al. and Zou et al. suggest that acupuncture following stroke may be beneficial in swallowing recovery [247, 248]. In the 2008 Cochrane review, Xie and colleagues concluded that there was not enough evidence to support the use of acupuncture for the treatment of dysphagia in acute stroke [249]. Long and Wu, undertaking a meta-analysis of 72 RCTs enrolling a total of 6,134 patients, report that the treatment with acupuncture with usual treatment was more effective than usual treatment (OR 5.17, 95 % CI 4.18–6.38) [250]. They do acknowledge that in the majority of the trials there were questions regarding methodology and randomisation, but conclude further studies are needed.

Orthoses

Selley and colleagues reported the use of a palatal training device, essentially a wire loop attached to the plate of a full denture, that supports the soft palate. In 37 stroke patients, of the 23 that survived, 22 were taking adequate oral diets [251].

Surgery

Surgical techniques for the management of aspiration are not new, with publications being prevalent in the 1970s. Brooks and McKelvie published a case review of a patient who underwent an epiglottoplexy for intractable aspiration [252]. This involves subtotal closure of the larynx by fixation of the epiglottis. The report suggests that the airway is maintained, speech preserved, and aspiration abolished. Cricopharyngeal myotomy has been suggested by some authors, where there is a lack of relaxation of the cricopharyngeus or upper oesophageal sphincter resulting in pooling. The results are mixed, though some have found good results [253].

Other surgical techniques such as laryngeal suspension, laryngeal closure, or diversions have been employed in the field of head and neck cancer. Total laryngectomy and tracheostomy have both been used in the past, and have limited or no role in the management of dysphagia following stroke, though may retain some use in neuromuscular disorders such as motor neuron disease.

Outcome Measures

The question that needs to be asked regarding swallowing studies: Are the right questions being asked, and are the right things being measured? It is always useful to know what the physiology is and whether an intervention improves this. But the end result is an improvement in swallowing, and hence quality of life. Changes to physiology do not matter if there is no change clinically.

The Dysphagia Outcome Severity Scale [254], SWALQOL [255], and Functional Oral Intake Scale [256] are useful measures in the clinical situation, as they permit the clinicians to speak a common language. All studies using patients should use these scales or a common scale so that results can be pooled. Researchers in the dysphagia field need to think about a common minimum data set, and there needs to be a push towards randomised trials. A common minimum data set would permit the combining of the results of similar studies to provide a more powerful answer than a single study alone.

Long-Term Outcome

Dysphagia is an independent predictor of outcome [157], including mortality, length of hospital stay after the acute event, and admission to long-term care. Smithard et al. found using the South London Stroke Register the largest effect exerted is in the first year, but that there is an increase in admissions to care homes at approximately 4–5 years [257]. Further work is needed to investigate the factors underlying this.

Ethical Issues

There are many difficult and contentious issues around the provision of nutrition. The main question is "whether to provide nutrition is appropriate or not"? Generally enteral nutrition is seen as a medical treatment. Consequently, it can be stopped and started along the lines of any medical treatment [258]. If there is doubt, a 2-week trial of enteral feeding should be attempted with outcomes monitored.

The question that needs to be asked: Is this long enough, and what improvements are expected in this time? What is clear is that no food equates, eventually, to no life. The decision to provide nutrition or not must not be taken lightly and must be done on an individual case-by-case basis after full discussion with all parties involved, including the patient if they are competent.

There are two further issues that frequently tax clinicians; first is that of the person who wants to eat and drink, but whose swallow is unsafe, putting them at high risk of aspiration. The compliance with instructions/advice may depend on the food consistency, with less compliance being demonstrated with thickened fluids [259]. Providing the patient is cognitively intact and is deemed to have mental capacity, and after explaining all the risks that eating and drinking entails, they should be allowed to eat and drink. If capacity is an issue, a similar discussion should be had with their representative/advocate.

The second scenario is of someone who is capable of swallowing and is able to meet their own needs but refuses to swallow. This case scenario is difficult and very burdensome on all formal and informal carers. Restraint and forced provision of nutrition will only work whilst it is being administered, with the original position rapidly returning. In a patient with mental capacity, this is not an option in some countries [260].

The use of restraints is not encouraged, as frequently they do not influence the long-term outcome or prognosis of the patient. Where restraint is being used, it should be used for the minimum period of time after seeking legal advice. Where possible, the person with swallowing difficulties should make the decision regarding swallowing and compliance, as part of the informed consent process, and capacity is autonomy. In short a competent patient has the right of self-determination, so long as no one else is harmed [261].

Who makes the decision and the appropriateness of a decision is always difficult. Although a proxy may have been appointed to make a medical decision, research has shown that their decision and that of the person they are acting for are, in the majority of cases, not congruent [262].

Whatever decisions are taken, it is essential that communication is paramount, to ensure that all carers (formal and informal) are aware of the plan of care; a framework may need to be implemented when the person and professionals do not agree on the best treatment.

Conclusion

Malnutrition and swallowing problems are common after stroke and frequently occur together. Failure to recognise their presence will result in increased morbidity and mortality. Patients admitted to hospital following a stroke may already be malnourished or at risk of malnutrition, and people often become more malnourished while they are in hospital. Recovery and rehabilitation will be slowed, infection risk may be elevated, and people will be more likely to end up in long-term care.

Since malnutrition and swallowing are associated with poor outcomes and can persist for many months post-stroke, monitoring of nutrition and swallowing status needs to be regular and consistent, and may need to continue into the care home environment and in those living at home. Consequently, the issues need to be raised with all care staff/professionals, and treatment of malnutrition and swallowing difficulties requires input from the MDT.

Patient Questions

Q. During admission to hospital with a stroke, weight loss may occur. What are the reasons behind this and what can be done to ameliorate any malnutrition?

A. Weight loss may be due to many reasons. An acute illness is often associated with an increase in metabolic rate and protein metabolism, but is also accompanied by a decrease in physical activity such that total energy expenditure is not usually elevated above that expected for a healthy person of the same age and gender. Malnutrition (accompanied by weight loss) can occur gradually over time, e.g. due to social reasons such as isolation, poverty, lack of support, or psychological reasons such as depression. Malnutrition can be caused, or exacerbated, by stroke, e.g. due to altered consciousness, anorexia (common in acute illness), oral pain due to infection, psychosis and mistrust, bland taste (food or medication), or the presence of swallowing problems. Malnutrition following illness can take many months to correct, especially if there are also social or psychological reasons why intake may be compromised.

The correct management is to identify the underlying problem and correct it. A dietician referral should be made whenever nutrition is poor, swallowing is a problem, or there is weight loss. A dietician can advise on the provision of the correct amount of nutrients (not just energy) using snacks, food fortification, oral nutritional supplements (also known as sip feeds), or supportive enteral feeding. If the underlying problem is dysphagia, this needs to be identified. A referral to the speech and language therapist needs to happen to determine the correct method of feeding and food consistency.

Q. What are the dangers associated with poor nutrition?

A. For any biological system to function, energy and other nutrients such as protein, vitamins, and minerals are required. The lack of adequate nutrition will eventually result in organ and system shutdown and failure. Lack of nutrition will result in muscle and protein loss, increased risk of infection, increased risk of pressure ulcers, weight loss, and eventually death. Re-feeding after a period of poor nutrition is associated with ion shifts, in particular potassium, calcium, and magnesium. These can result in cardiac arrhythmias and the risk of gastrointestinal dysfunction and epileptic fits. The key to avoiding re-feeding syndrome is prevention by ensuring nutrition is introduced slowly, together with daily monitoring of calcium, electrolytes, glucose, and magnesium.

For the individual there are adverse impacts on mobility, mood, quality of life, function, and activities of daily living. For health and social care providers, there is the added cost of managing malnourished individuals who are more likely to need to visit their GP, be hospitalised, and need care home placement or a package of care on hospital discharge.

Q. How do you assess whether someone is malnourished, **and its causes after stroke**?

A. A significant proportion of people admitted with stroke will be already malnourished. The aetiology of this may be as simple as someone on a diet, but may be associated with an underlying malignancy, pre-existing dysphagia, lack of teeth, medication causing a dry mouth, or sore mouth due to oral candidiasis.

Everyone admitted with stroke needs to be screened for nutritional risk using a validated nutrition screening tool. Anyone identified as at risk or malnourished should be referred for a full nutritional assessment by a nutrition specialist such as a dietician. The assessment will include the following components: body mass index, history of weight change, review of laboratory data, review of clinical condition (including ability to swallow safely), dietary assessment, and consideration of relevant environmental factors (whether in hospital, care home, or at home). Enquire about change of appetite, fatigue, and medication that may cause a dry mouth or change taste perception. Dysphagia may be assessed by using a bedside water screen or just observing someone eat and drink. Remember that a low conscious level is the commonest cause of dysphagia.

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Chapter 8
Urinary and Bowel Complications After Stroke

Zehra Mehdi and Mehool Patel

Abstract Urinary and bowel complications are fairly common after stroke. Post-stroke urinary incontinence is a prevalent condition up to 2 years after stroke. Short-term and long-term year stroke survival, disability, handicap, and institutionalisation rates are adversely influenced by post-stroke urinary incontinence. Bowel function is often affected following a stroke, resulting in complications of faecal incontinence and constipation. Communication and mobility difficulties resulting from stroke may further contribute to bladder and bowel problems. A proactive patient-centred approach to assessing and managing these problems is essential to improving stroke outcomes. Healthcare professionals should address these common complications and be aware of strategies to assess and actively manage them, with the aim of regaining continence, which is associated with better stroke outcomes. Good continence care has a multitude of benefits for stroke patients and their carers. Although continence may not always be restored, several interventions can be instituted to improve the patient's quality of life, which in turn may improve their engagement with stroke rehabilitation.

Keywords Urinary • Bowel • Stroke • Post-stroke • Incontinence

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Key Messages

- Bowel and bladder complications are common sequelae of acute stroke.
- Post-stroke urinary incontinence is widely recognised as an important predictor of poor functional outcomes, increased institutionalisation, and mortality rates.
- Bowel function is often affected following a stroke, resulting in complications of faecal incontinence and constipation.
- Communication and mobility difficulties resulting from stroke may further contribute to bladder and bowel problems.
- Healthcare professionals should address these common complications and be aware of strategies to assess and actively manage them, with the aim of regaining continence.

Introduction

Bladder and bowel problems occur frequently following a stroke. Urinary incontinence affects more than a third of stroke patients admitted to hospital, with up to a quarter of them remaining incontinent at 1 year, and up to 10 % at 2 years. Faecal incontinence is also a significant problem affecting 30–40 % of individuals immediately after stroke, and constipation is a common complaint on rehabilitation wards. These complications can have a devastating impact on the patient's physical, psychological, and social well-being, adversely affecting their ability to participate in stroke rehabilitation. A proactive patient-centred approach to assessing and managing these problems is essential to improving stroke outcomes. This chapter discusses the prevalence, natural history, causes, assessment methods, and management strategies of post-stroke bladder and bowel complications.

National Standards for Continence Care

Good continence care has a multitude of benefits for stroke patients and their carers. The UK National Clinical Guidelines for Stroke 2012 [1] present clear recommendations for managing bladder and bowel complications following a stroke during the acute and rehabilitation phases of care (Table 8.1). These guidelines specify "All wards and stroke units should have established assessment and management protocols for both urinary and faecal incontinence, and for constipation in stroke patients". The guidelines emphasise the importance of a documented active management plan for all patients with persistent problems. The implementation of these recommendations has been extremely variable across the UK.

The National Sentinel Stroke Clinical Audit 2010 [2] found that only 63 % of stroke patients with persistent bowel and bladder complaints had a documented plan

Table 8.1 National clinical guidelines for stroke 2012: continence care

	Recommendations
Acute phase	**A**. All wards and stroke units should have established assessment and management protocols for both urinary and faecal incontinence, and for constipation in stroke patients
	B. Patients should not have an indwelling [urethral] catheter inserted unless indicated to relieve urinary retention or where fluid balance is critical
Rehabilitation phase	**A**. All wards and stroke units should have established assessment and management protocols for both urinary and faecal incontinence, and for constipation in stroke patients
	B. Patients with stroke who have continued loss of bladder control 2 weeks after diagnosis should be reassessed to identify the cause of incontinence and have an ongoing treatment plan involving both patients and carers. The patient should:
	Have any identified causes of incontinence treated
	Have an active plan of management documented
	Be offered simple treatments such as bladder retraining, pelvic floor exercises, and external equipment first
	Only be discharged with continuing incontinence after the carer [family member] or patient has been fully trained in its management and adequate arrangements for a continuing supply of continence aids and services are confirmed and in place
	C. All stroke patients with a persistent loss of control over their bowels should:
	Be assessed for other causes of incontinence, which should be treated if identified
	Have a documented, active plan of management
	Be referred for specialist treatments if the patient is able to participate in treatments only be discharged with continuing incontinence after the carer [family member] or patient has been fully trained in its management and adequate arrangements for a continuing supply of continence aids and services are confirmed and in place
	D. Stroke patients with troublesome constipation should:
	Have a prescribed drug review to minimise use of constipating drugs
	Be given advice on diet, fluid intake, and exercise
	Be offered oral laxatives
	Be offered rectal laxatives only if severe problems remain

Adapted from Intercollegiate Stroke Working Party [1]

to promote continence. The audit also revealed the inappropriate use of urinary catheterisation in acute stroke patients: 20 % of patients were catheterised in the first week following stroke, and in 10 % of these cases there was no clear rationale for the insertion. These results demonstrate a failure by healthcare professionals to adequately assess and manage a significant number of stroke patients with continence problems. This may be the consequence of multiple factors such as inadequate education on bowel and bladder management amongst nurses and doctors, nursing staff shortages, time constraints, inadequate toilet facilities, and a lack of

moving and handling aids. It is vital that these factors are acknowledged as barriers to providing good continence care and are adequately addressed to improve the quality of care provided.

Post-stroke Urinary Incontinence

Epidemiology

The International Continence Society has attempted to standardise the terminology of lower urinary tract dysfunction. It has established the definition of urinary incontinence as "the involuntary loss of urine that is a social or hygienic problem", which has been further subdivided according to the patient's symptoms [3]. This terminology has been universally accepted for use in international consultation documents and National Institute for Health and Care Excellence (NICE) guidelines [3, 4].

It is widely recognised that post-stroke urinary incontinence is common, but there is considerable variation in the reported prevalence rates; this is due to several factors:

1. The use of different definitions of urinary incontinence
2. Different population samples (hospital versus community)
3. Measurement of prevalence at varying time intervals following acute stroke (at admission, 1 week, 1 year)
4. Different study designs
5. Failures to account for the presence of premorbid incontinence

In a review of nine hospital-based studies published between 1985 and 1997, Brittain et al. reported rates of post-stroke urinary incontinence at admission between 32 % and 79 % of patients [5]. In a population-based study conducted in 2001, Patel et al. found rates of post-stroke urinary incontinence of 40 % at 7–10 days following admission [6]. Data from the UK collected between 1998 and 2004 have also demonstrated urinary incontinence rates of 39–44 % at 1 week post-admission [7].

Comparatively, epidemiological trials such as the Leicestershire MRC Incontinence Study found that 34.2 % of adults over the age of 40 had urinary incontinence at times, with severity increasing with age [8]. This suggests that many stroke patients may have already experienced bladder problems prior to their stroke.

Natural History of Post-stroke Urinary Incontinence

Post-stroke urinary incontinence is a persistent condition, with significant numbers of patients remaining incontinent at discharge [6, 9]. Patel et al. explored the natural history of post-stroke urinary incontinence in 235 patients over a 2-year period [6].

Data for this study was acquired from the South London Stroke Register, a population-based register covering a population of over 230,000. Follow-up data was obtained using personal interviews with patients and their carers and through postal questionnaires [10]. The study reported urinary incontinence prevalence rates of 19 % at 3 months, 15 % at 1 year, and 10 % at 2 years [6]. Three further studies have demonstrated the persistence of urinary incontinence at 1 year, reporting prevalence rates ranging from 9 to 27 % [11–13]. Although all of these studies excluded patients with premorbid bladder problems, the definitions of urinary incontinence and assessment methods varied, which may account for the variation in prevalence rates reported.

Certain factors have been identified as independent predictors of persistent post-stroke urinary incontinence [13–17]:

1. Increasing age
2. Female sex
3. Stroke severity and size

Patients suffering from total anterior circulation infarcts were found to be less likely to regain continence at 3 months. Comparatively, patients who suffered a lacunar infarct had an odds ratio of 3.65 [95 %, CI: 1.1–12.2] for regaining continence [14]. These finding were supported by a prospective study investigating the association of bladder function with unilateral hemispheric stroke [15], which identified a significant positive correlation between large infarct size and the development of post-stroke urinary incontinence. The authors of this study concluded that such infarcts involving both cortical and subcortical regions of the brain were more likely to result in damage to neuro-micturition pathways (spinothalamic) and result in communication difficulties, both directly and indirectly contributing to incontinence.

Currently, there is no data to support a correlation between either the location of the stroke lesion or the aetiology of the stroke (haemorrhagic versus ischaemic) and the development of urinary incontinence, and further research is required in this area.

Effects of Urinary Incontinence on Stroke Outcomes

It is widely recognised that urinary incontinence following stroke is a strong and independent predictor of poor outcome [6, 11, 12, 14, 18, 19]. Persistent urinary incontinence at 3 months following stroke has been reported to be the single best predictor of moderate to severe disability in patients under the age of 75 [20]. A prospective observational study of 324 patients was conducted in 2001 investigating the impact of persistent urinary incontinence at 3 months on stroke outcome [14]. On multiple logistic regression analysis, persistent post-stroke urinary incontinence was independently associated with a greater rate of institutionalisation of 27 %

compared to 9 % in the group who regained continence. They also investigated the impact on post-stroke disability using the Barthel Index and the Frenchay Activities Index [FAI] and found disability to be significantly worse in those patients who remained incontinent at 3 months. Another population-based study reported even higher rates of institutionalisation—45 % at 1 year, which was four times greater than in those who regained continence [11].

Post-stroke urinary incontinence is also independently associated with higher mortality rates [12, 21]. A study in 2011 reported significantly higher mortality rates in the incontinent group at time intervals of 1 week, 6 months, and 1 year [12]. The authors highlighted that regaining continence within the first week following stroke was associated with a better prognosis, which was similar to those with normal bladder control.

There are many reasons why persistent urinary incontinence is associated with worse outcomes:

1. *Interference with the ability to participate in stroke rehabilitation*. Physical and psychological factors may impact on the patient's ability to participate in rehabilitation [22]. Urinary incontinence may lead to low morale and poor self-esteem, resulting in apathy and a reduced desire to participate in rehab. Stroke patients who have a poor response to rehabilitation are more likely to have a poor functional outcome, increased length of hospitalisation, and a greater mortality rate [22, 23].
2. *Psychological impact*. Urinary incontinence may be extremely distressing for both the patient and their carer. This condition may result in a significant impact on the patient's quality of life, interfering with social activities, sleep patterns, and personal relationships, resulting in feelings of embarrassment and guilt. On multivariate analysis, Brittain et al. demonstrated that depression after stroke was more than twice as likely in patients suffering from incontinence compared to those without bladder problems [24].
3. *Marker of stroke severity*. Persistent urinary incontinence is associated with larger strokes and has been related to coma states [14, 25]. Extensive brain damage may impair toileting skills due to altered sensorium.
4. *Increased risk of falls*. Patients suffering from urge incontinence may attempt to ambulate to the bathroom in a rush, and this has been associated with an increased risk of falls, which may lead to fractures and subsequent increased hospitalisation [26].

Pre-existing urinary incontinence has also been associated with poor outcomes following stroke. Studies analysing this relationship have found higher mortality rates amongst this group. Jawad et al. reported that 79 % of patients who died prior to their 6-month functional review suffered from premorbid urinary incontinence [27]. Similar findings were demonstrated in another study, which reported that of the 16 patients with pre-existing incontinence, 19 % died within the first week, 44 % died within 3 months, and 25 % died within 2 years [7].

Neural Control of Micturition

In order to determine the cause of urinary incontinence following a stroke, it is important to consider the factors controlling normal micturition. Complex neural mechanisms located in the brain, spinal cord, and peripheral ganglia are responsible for ensuring bladder filling and voiding occurs in a coordinated manner [28]. These mechanisms control smooth and striated muscle activity of the following anatomical structures:

- Urinary bladder and bladder neck
- Urethra
- Urethral sphincter
- Pelvic floor muscles

Figure 8.1 illustrates the different structures and neural mechanisms involved. The spinobulbospinal pathway mediates the voiding reflex and it is believed that this reflex operates as a switch, being either completely "off" during bladder filling or "on" during voiding [28, 29].

Bladder-Filling Cycle

During the filling cycle, stretch receptors within the bladder detrusor muscle signal low intensity afferent impulses to the spinal cord via the pelvic nerves (S2–S4) and then via the spinal cord (lateral spinothalamic tracts) to the pontine micturition centre and the frontal cortex. This results in three processes:

1. Inhibition of the parasympathetic innervation of the detrusor muscle of the bladder via the *pelvic nerves*, resulting in bladder relaxation.
2. Stimulation of the sympathetic outflow in the *hypogastric nerve*, resulting in contraction of the bladder outlet (bladder neck and urethra).
3. Stimulation of the sympathetic outflow in the *pudendal nerve* via neurons in the Onuf's nucleus, resulting in contraction of the external urethral sphincter.

These spinal reflexes are collectively known as the "guarding reflex" allowing one to remain continent. Furthermore, several studies have suggested that a region within the lateral pons of the brain known as the "pontine storage area" may contribute to this process by stimulating striated urethral sphincter activity [28–30].

Bladder-Voiding Cycle

The bladder is usually able to hold approximately 500 ml of urine before needing to empty. At a critical level of bladder distention, the afferent impulses in the pelvic nerves intensify to the spinal cord, switching the spinobulbospinal pathway to

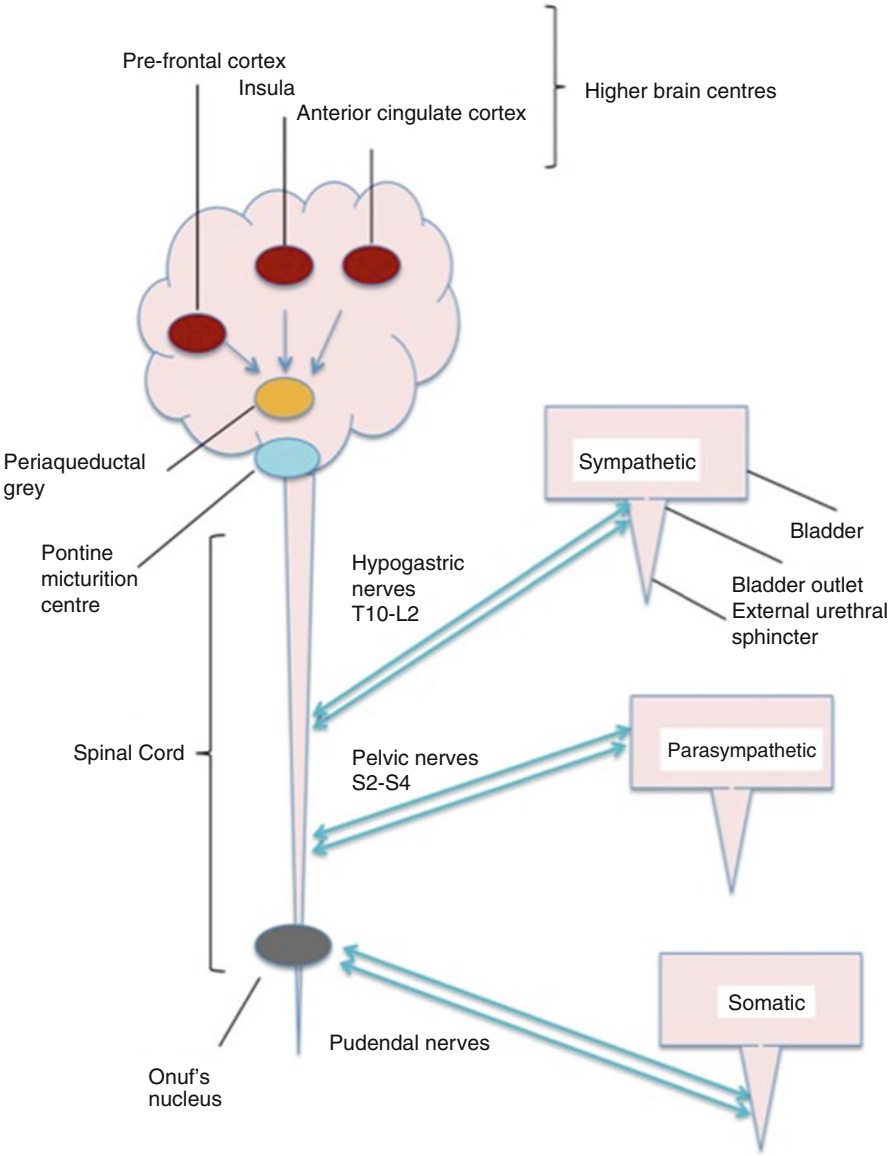

Fig. 8.1 The neural control of micturition (From Mehdi et al. [80]. © 2013 John Wiley & Sons Ltd. With permission from John Wiley and Sons)

maximal activity [28]. These signals are relayed from the spinal cord to the pontine micturition centre of the brain via the periaqueductal grey. Activation of the pontine micturition centre results in the following:

1. Inhibition of sympathetic outflow in the hypogastric and pudendal nerves, resulting in bladder outlet and urethral sphincter relaxation.
2. Stimulation of parasympathetic outflow to the bladder, resulting in detrusor muscle contraction.

Voluntary Control

Voluntary voiding is under strict control from higher brain centres, which have been identified using functional magnetic resonance imaging. These include the prefrontal cortex—in particular the right inferior prefrontal gyrus—the anterior cingulate cortex, the thalamus, the caudal hypothalamus, and the insula [28, 30]. The periaqueductal grey plays a pivotal role in relaying signals to and from these higher brain centres to control primary input into the pontine micturition centre. This process ensures that voiding only takes place when it is considered to be socially desirable to do so and effectively suppressed at all other times [28–31].

Types of Post-stroke Urinary Incontinence

Several different processes may account for the development of post-stroke urinary incontinence. Figure 8.2 illustrates the various types of urinary incontinence that may occur following a stroke.

Direct Damage to the Neuromicturition Pathways: Urge Incontinence

This is the most frequently reported cause of post-stroke urinary incontinence [15, 32, 33]. The stroke lesion itself may directly disrupt the neuromicturition pathways within the brain, resulting in uninhibited detrusor contractions. The consequence of detrusor overactivity is often a sudden urge to void that is difficult to postpone, and subsequently may result in the involuntary leakage of urine. The strength of the contractions will determine the degree of urinary leakage, with stronger ones resulting in complete bladder emptying. Conversely, weaker contractions lead to frequent small-volume leakages and ineffective bladder emptying, which results in large residual volumes of urine [>100 ml]. Thus, patients with urge incontinence also complain of symptoms of urinary frequency and nocturia [33]. Detrusor overactivity is also referred to as detrusor hyper-reflexia and can be demonstrated using urodynamic studies; however, this investigation is not routinely required. Studies using urodynamic evaluation of stroke patients have reported a wide variation in

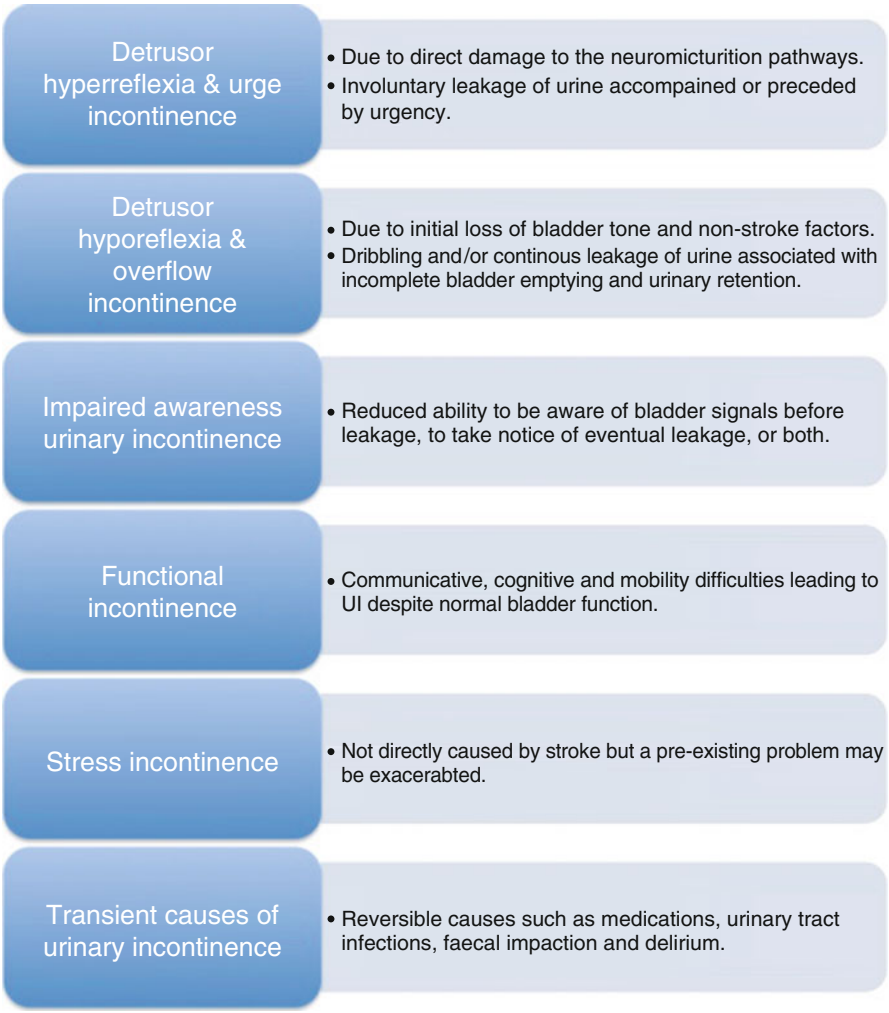

Fig. 8.2 Schematic diagram representing the causes and types of post-stroke urinary incontinence (From Mehdi et al. [80]. © 2013 John Wiley & Sons Ltd. With permission from John Wiley and Sons)

prevalence rates of this condition, ranging from 37 to 90 % [15, 34, 35]. There is inconclusive data associating the site of the stroke lesion and the development of urge incontinence; however, lesions in the frontal lobe have been suggested [34, 36].

Detrusor Hyporeflexia with Overflow Incontinence

This type of post-stroke incontinence has been reported in various studies, with prevalence rates ranging from 21 % to 35 % [15, 17, 32, 37]. It has been postulated that detrusor hyporeflexia may occur after an acute stroke because of an initial loss

of bladder tone. However, in most of these studies, non-stroke factors were also present such as use of anticholinergic medications or diabetic polyneuropathy, which can affect bladder tone and result in overflow incontinence [15]. Detrusor hyporeflexia results in the incomplete bladder emptying, resulting in large post-void residual urine volumes (>100 ml) and subsequent symptoms of dribbling and/or continuous leakage of urine. The resultant urinary retention may occur acutely, and is usually very painful, or it may be chronic, developing over a longer period of time, in which case it is usually painless. In all cases of urinary retention, constipation must be excluded as a causative factor.

Impaired-Awareness Urinary Incontinence

A few prospective hospital-based trials have explored the concept of impaired awareness of urinary incontinence in acute stroke patients [36, 38, 39]. This type of incontinence has been defined as "Urinary incontinence with reduced ability to be aware of bladder signals before leakage, to take notice of eventual leakage, or both" [39]. In a cohort of 65 patients, more than half were found to have impaired awareness of their symptoms, ranging from slight unawareness to anosognosia. The authors reported that this type of incontinence appeared to be an independent risk factor for poor outcome both at 3 months and 1 year following stroke [38, 39]. When compared to patients with urge incontinence, it was found that those with impaired awareness had a greater frequency of parietal stroke lesions and, less frequently, frontal lesions. This finding was consistent with the known role of the parietal and temporal lobes in correctly identifying and validating signals in a given social circumstance, compared to the volitional role of the frontal lobe structures in the conscious recognition of afferent bladder signals.

Functional Incontinence

Stroke-related factors, such as cognitive, communicative, or mobility difficulties, may impact indirectly on the patient's ability to maintain effective toileting skills despite normal bladder function [5, 7, 15]. The resulting "functional" incontinence has been significantly associated with aphasia and/or cognitive impairment [15]. In another study, the following stroke-related factors were reported on multivariate analysis to be significantly associated with initial urinary incontinence: visual field defects, dysphagia, motor weakness, and age over 75 years.

Stress Incontinence

This type of incontinence does not occur as a direct consequence of stroke; however, stroke-related factors might aggravate a pre-existing condition. Stress incontinence occurs upon exertion (standing, coughing, and sneezing) and it is primarily the consequence of weakness of the pelvic floor muscles [4]. Reduced pelvic

muscle tone and motor weakness resulting from an acute stroke can lead to greater exertional efforts in toileting, exacerbating pre-existing stress incontinence. Acute stroke can also be complicated by aspiration pneumonia, and the resulting cough may also aggravate this type of incontinence [40].

Transient Causes of Urinary Incontinence

These transient causes are potentially reversible and, if present, it is imperative that they are adequately addressed. The pneumonic "DIAPPERS" illustrates these causes [41]:

- **D**elirium
- **I**nfection—urinary tract or chest infections
- **A**trophic urethritis/vaginitis—thin, sore skin may be contributing to the incontinence
- **P**harmaceuticals—antimuscarinics, diuretics, sedatives
- **P**sychiatric
- **E**xcess urine output—large fluid intake, caffeinated drinks
- **R**estricted mobility—arthritis pains, fear of falling
- **S**tool impaction

Assessment of Post-stroke Urinary Incontinence

Initial Assessment at Admission

All stroke units should have an agreed protocol for the assessment of urinary incontinence. Firstly, all patients admitted to hospital following an acute stroke should undergo a basic assessment of their bladder function to identify any problems. This initial assessment can be carried out by nursing staff and should include a urine dipstick to identify the presence of a urinary tract infection. If bladder problems are identified, then a full continence assessment should be undertaken to identify the type of urinary incontinence and any contributing factors.

Comprehensive Assessment of Continence

This should be undertaken as soon a bladder problem such as urinary incontinence is identified. It is important to appreciate that this is a personal assessment regarding a potentially sensitive topic, which requires both time and privacy. Although there are very few studies evaluating the different assessment processes used, Table 8.2 outlines a framework for the assessment of urinary incontinence. This assessment should guide the development of a suitable treatment strategy tailored to the individual patient's needs.

Table 8.2 Assessment strategy to identify and evaluate post-stroke urinary incontinence

Assessment	Rationale
Basic nursing assessment within 24 h of admission	To identify those patients who are incontinent of urine
History taking	
Onset and duration of symptoms? Urgency? Dribbling? Are symptoms related to a specific activity? e.g. coughing, sneezing Pre-existing incontinence? Associated bowel symptoms? Medications (diuretics, anticholinergics, oestrogens, sedatives, antidepressants) Fluid intake? Medical history—diabetes, recurrent urinary tract infections, and dementia Cognitive abilities? Functional capacity: dexterity, mobility, and aids Effect on quality of life?	To determine the type of urinary incontinence To plan appropriate management strategies To determine problems caused by UI and/or contributing to it
Clinical assessment	
Clinical examination: neurological and abdominal examination, rectal and pelvic examinations Urinary frequency and volume charting for 5–7 days Fluid intake charting Bowel chart	To assess for a palpable bladder suggestive of urinary retention, constipation and/or any prolapse, atrophy, or signs of infection To assess current pattern of voiding and bladder capacity To determine if symptoms are worse at particular times of the day—to plan schedule for prompted voiding To assess number and types of drinks To assess for constipation
Functional capacity of toilet skills [17]	To assess ability to get to a toilet or request for help
	To assess ability to manage clothing and maintain appropriate posture to allow micturition
Initial Investigations	
Urinalysis Post-void residual volumes using a bladder scanner	Evidence of urinary tract infection Evidence of incomplete emptying and urinary retention
Transient causes of UI	
Pneumonic: DIAPPERS [58] **D**elirium **I**nfection **A**trophic urethritis/vaginitis **P**harmaceuticals **P**sychiatric **E**xcess urine output **R**estricted mobility **S**tool impaction	To identify and address any reversible causes
Consideration of non-neurological causes of UI	Consider causes such as chronic chest infections leading to continual strain on the urethral sphincter due to coughing, or polyuria in diabetes, for example

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Detailed Bladder History

Table 8.2 illustrates the key components of the clinical history, which must be ascertained in all patients with urinary incontinence. It is essential to establish whether there were any pre-existing bladder problems prior to the stroke. Any previous gynaecological or urological procedures undertaken must also be noted, as they may impact on the current bladder complaints. Co-existing conditions such as diabetes, multiple sclerosis, spinal injuries, and dementia may also contribute to urinary incontinence. A full medication history must also be sought, as several drugs have been associated with bladder problems, including the following: antimuscarinic agents (urinary retention and constipation), diuretics (polyuria), sedatives (mobility problems and confusion), calcium channel antagonists (urinary retention and constipation), opiates (urinary retention, constipation, confusion, and reduced mobility), and cholinesterase inhibitors (increase bladder contractility). In addition to the questions outlined in Table 8.2, specific bladder-related questions should be included in the history to identify the presence of the following symptoms:

- *Urgency:* is there an insuppressible desire to void and difficulties reaching the toilet in time?
- *Frequency:* how often does the patient need to urinate in a period of 24 h?
- *Nocturia*: how often does the patient need to urinate overnight?
- *Hesitancy:* is there any difficulties initiating urine flow?
- *Poor stream:* is the flow of urine weak and slow or intermittent?
- *Straining:* does the patient need to strain to empty their bladder?
- *Symptoms of incomplete bladder emptying:* any dribbling of urine or a continuous leakage?
- *Dysuria:* any pain on passing urine?
- *Leakage of urine on exertion:* any incontinence upon coughing, sneezing, laughing?

These questions will help to determine the type of urinary incontinence, the severity, and pattern of the symptoms and will enable the healthcare professional to plan an appropriate treatment strategy.

Finally, social and environmental factors must also be assessed, although this could be done in the latter stages of the patient's admission, closer to the time of discharge. These factors include the impact of incontinence on the patient's social activities, work life, and sexual relationships.

Clinical Assessment

Clinical assessment of a patient with urinary incontinence should include the following:

1. *Abdominal examination:* to assess for the presence of a palpable bladder, indicating urinary retention, masses, and relevant surgical scars.
2. *Neurological examination:* to assess the severity of functional impairment resulting from the stroke and how this will impact on the patient's toileting abilities.

3. *Pelvic examination:* to assess for the presence of any vaginal prolapse, the general skin condition of the groin/perineum, and the presence of any atrophy.
4. *Rectal examination:* to assess for faecal loading suggesting constipation, which may contribute to incomplete bladder emptying and subsequent urinary retention.

Functional Assessment of Toileting Skills

A patient's ability to actually use a toilet may be affected by stroke, and therefore an evaluation of this is imperative as part of the continence assessment. Both physical and cognitive difficulties may contribute, and these should be formally assessed using validated standardised tests such as the Mini Mental State Examination [42]. Key components of this assessment should include the following information:

- Ability to physically mobilise to and locate the toilet or use hand-held urinals
- Ability or motivation to request for assistance to use the toilet if this is required
- Ability to independently remove clothing once toilet is reached
- Ability to maintain an appropriate posture to allow micturition to occur

Frequency and Volume Charting (Bladder Diaries)

This assessment method is very important for all patients suffering from urinary incontinence. It involves recording the frequency and volume of all fluid intake and of all urine output over a minimum of 3 days. The optimum duration that a bladder diary should be kept is unclear from clinical studies; however, this assessment method is useful in determining the best schedule for bladder training strategies [4]. The chart should inform the healthcare professional regarding the following:

- Number and types of drinks
- The timing of fluid intake
- Voiding patterns: frequency, volume, timing, nocturia
- Bladder capacity

This information also provides a useful baseline against which to measure improvements after interventions have been initiated. Patients should be encouraged to take responsibility for completing their own chart; however, this may not be possible due to manual or cognitive difficulties.

Investigations

Urinalysis

Urine dipstick testing is essential in all patients with urinary incontinence, especially to detect the presence of a urinary tract infection. The current NICE recommendations on interpreting urinalysis findings suggest that treatment should be

definitely initiated if the patient is symptomatic and both leucocytes and nitrites are positive. If either leucocytes or nitrites are positive then treatment with an appropriate antibiotic should be considered if the patient is symptomatic. A midstream urine specimen should always be sent [4]. Other findings such as glycosuria may indicate the presence of other contributing conditions such as diabetes.

Bladder Scan

This is a non-invasive accurate method of estimating post-void residual urine volumes. Post-void residual urine is associated with various complications, such as an increased risk of urinary tract infections and with urinary incontinence. A cut-off value of >100 ml of post-void urine has been suggested as a trigger to prompt further investigations and consider interventions, especially in symptomatic individuals [43, 44].

Treatment Strategies to Promote Continence

Interventions to promote continence in stroke patients can be labour intensive, requiring a proactive structured approach by the multidisciplinary team. Even before a full systematic continence assessment is undertaken, healthcare professionals should ensure the following measures are available to acute stroke patients:

- Easy access to a nurse call bell or picture cards
- Access to hand-held urinals for individuals who are unable to mobilise to the toilet
- Be offered absorbent pads if unable to hold a urinal, which may help with confidence and provide comfort; however, the use of pads should be promptly reviewed on full continence assessment.

Realistic aims must be discussed with the patient, and although treatment plans should be directed to achieve continence, this may not be possible in all cases. The term "dependent continence" has been used to describe the process of achieving dryness with containment devices such as absorbent pads or appliances, medications, or with toileting assistance using commodes, bedpans, or hand-held urinals [45].

Evidence-Based Interventions

There is a paucity of good-quality clinical trials evaluating the effectiveness of interventions in post-stroke urinary incontinence. A recent meta-analysis described 12 randomised controlled trials with a total of 724 patients, investigating treatment strategies of urinary incontinence following stroke [46]. The main findings from these trials have been summarised in Table 8.3; however, conclusions are limited by small sample sizes with wide confidence intervals and failures to account for

Table 8.3 Randomised controlled trials of interventions to treat post-stroke urinary incontinence

Study	Subjects and study design	Results	Conclusions
Behavioural interventions			
Lewis et al. (1990) [47] $n=23$	Comparison of sensory-motor biofeedback plus timed voiding in 11 patients versus timed voiding alone in 12 patients. All subjects suffered from urge urinary incontinence	Fewer incontinence episodes in the intervention group [WMD 2.20, 95 % CI 0.12–4.28]	Larger trials are needed to evaluate the effectiveness of this intervention
Gelber et al. (1997) [48] $n=18$	Comparison of timed voiding in 8 patients versus voiding on request [interpreted as usual care] in 10 patients	Data obtained were too few for any useful analysis	No conclusions could be drawn as insufficient data was obtained
Tibaek et al. (2007) [49] $n=26$	Comparison of the impact of an intensive pelvic floor-training programme in 26 women with mixed stress/urge UI versus usual care [general rehabilitation]	No significant difference found on either the mean number of incontinence episodes [WMD −1.00, 95 % CI −2.74–0.74] or on impact on quality of life as measured by the mean score on the SF36 Health Survey Questionnaire	Insufficient evidence to advocate the use of pelvic floor training in mixed stress/urge UI post-stroke
Specialised professional input			
Wikander et al. (1998) [50] $n=34$	Hospital-based prospective comparison of patients randomly allocated to a ward using conventional methods of rehabilitation [$n=13$] or to a ward practicing rehabilitation based on assessment using the Functional Independence Measure [FIM] [$n=21$]. All patients were assessed on admission and on discharge	Twenty patients in the intervention group regained continence before discharge compared to 3 in the control group [$p<0.01$] Greater improvement in functional well-being in the intervention group compared to the control group [$p<0.01$]	Rehabilitation based on use of FIM may reduce rates of urinary incontinence and enhance functional well-being better than conventional methods of rehabilitation [although small sample size and lack of blinding of outcome measures]

(continued)

Table 8.3 (continued)

Study	Subjects and study design	Results	Conclusions
Brittain et al. (2000) [51] $n=232$	Community-based prospective comparison of care by a Continence Nurse Practitioner of 152 patients including assessment and treatment versus usual care provided by the General Practitioner of 80 patients	Rate of incontinence lower in the intervention group [40/73 vs. 31/48 RR 0.85 CI 0.63–1.14] Reduced number of urinary symptoms in the intervention group at 3 months [$p<0.01$] and at 6 months [$p=0.06$]	Specialised input and individualised care plans may reduce the number of urinary symptoms [although confidence intervals were wide, not fully reported and wide definition of UI used]
Complementary therapy			
Chu et al. (1997) [52] $n=60$	Comparison of scalp acupuncture in 30 patients versus usual care [which included receiving acupuncture combined with nursing care] in 30 patients	A reduction in urinary frequency and incontinence in 90.3 % in the intervention group [p 0.05–0.001]. No results reported for the control group	Insufficient results reported to draw conclusions
Zhou et al. (1999) [53] $n=80$	Prospective comparison of the use of eye and scalp acupuncture in 40 patients versus no acupuncture in 40 patients	Lower rates of UI reported in the intervention group [18/40 vs. 32/40]	Acupuncture may be an effective intervention in post-stroke UI; however, quality of study is questionable as minimal methodological detail is reported
Zhang et al. (2002) [54] $n=60$	Comparison of acupuncture in 36 patients versus usual care using mannite and other unspecified medicines in 28 patients	Lower rates of UI reported in the intervention group [6/36 vs. 26/28]	Acupuncture may be an effective intervention in post-stroke UI; however, the quality of study is questionable as minimal methodological detail is reported
Liu et al. (2006) [55] $n=75$	Comparison of ginger-salt partitioned moxibustion plus routine acupuncture in 39 patients versus routine acupuncture in 36 patients	Significant difference reported in the intervention group on mean voiding frequency [WMD −5.57, 95 % CI −7.00 to −4.14] and on mean nighttime voiding frequency [WMD −3.18, 95 % CI −3.95 to −2.41]	This may be an effective intervention however the quality of study is questionable as minimal methodological detail is reported

Pharmacotherapy			
Judge et al. (1969) [56] $n=13$	Cross over trial comparing the use of oestrogen [quinestradol 0.25 mg 4 times a day] against placebo in 13 females admitted to long-stay geriatric hospitals	Results reported separately for patients with mild or severe incontinence. Combined results were not statistically significant [paired samples means −3.88 95 % CI −8.42–0.66]	Insufficient evidence to support use of this intervention in post-stroke UI
Gelber et al. (1997) [48] $n=19$	Comparison of timed voiding in 10 patients versus the use of Oxybutinin in 9 patients. All subjects were reported to have urinary incontinence and bladder hyper-reflexia	Data obtained were too few for any useful analysis	No conclusions could be drawn as insufficient data was obtained
Zhu et al. (2003) [57] $n=80$	Hospital-based study comparing the use of meclofenoxate plus salvia miltirrhiza in 40 patients versus salvia miltirrhiza alone in 40 patients	Fewer patients were reported to have urinary symptoms in the meclofenoxate group [9/40 vs. 27/40, RR 0.33, 95 % CI 0.18–0.62]	There may be a role for this intervention in post-stroke UI; however, larger studies are required

patients' pre-existing urinary incontinence in nine of the trials [47–57]. The authors of the meta-analysis concluded that there was insufficient data from these trials to guide practice; however, there was some evidence that adopting a structured approach to assessment and management and specialist continence nursing input may be beneficial. This structured approach using individually tailored interventions has been supported by the findings of several other studies [58–61]. One such trial demonstrated a 67 % success rate in regaining continence within 30 days of stroke [58].

As there is limited stroke-specific research to guide continence care after stroke, universal principles in managing different types of urinary incontinence may be adopted [3, 4].

Scheduled Voiding Regimens

Scheduled toileting regimens are a form of behavioural therapy used in management of urge, functional, and mixed incontinence [61]. They include the following voiding programmes:

- Bladder training
- Habit training
- Prompted voiding
- Timed voiding

The effectiveness of these voiding programmes has been evaluated in multiple studies, and overall they have demonstrated reduced episodes of incontinence and improved bladder-function control [61–63]. Table 8.4 outlines the approach for each of these schedules and highlights suitable patients for which they may be appropriate.

Table 8.4 Scheduled voiding regimens

Voiding regimen	Technique	Suitable patients
Bladder training [63]	Gradually increase intervals between voiding until an acceptable interval is reached	Urge incontinence/detrusor overactivity
		Patient must be motivated and cognitively able to participate in this regimen
Habit training [68]	Voiding intervals are based on the patient's own habits and planned at times prior to the patient's incontinence episodes	Functional incontinence
		Useful in patients with cognitive impairment
Timed voiding [67]	Fixed voiding schedule, every 2–4 h, which remains unchanged and ensures regular bladder emptying	Functional incontinence
		Impaired awareness urinary incontinence
Prompted voiding [65]	The patient is prompted to void at regular intervals; however, they are only assisted to the toilet if there is a positive response	Functional incontinence

Management of Urge Incontinence and Detrusor Overactivity

Several strategies have been suggested to improve symptoms of urgency and frequency associated with detrusor overactivity. The following interventions may be employed to manage this type of incontinence:

Bladder Training

There is evidence indicating that this voiding schedule is beneficial in patients with urge incontinence [4, 62]. It is dependent on high levels of motivation in both the patient and the healthcare professional, and the patient must be cognitively intact. Information is obtained regarding the patient's voiding behaviour using a baseline frequency and volume chart. This is used to design a voiding schedule that involves gradually increasing the interval between voiding, initially by 15–30 min only. This interval is gradually increased further until a satisfactory pattern is reached, with the patient remaining dry and holding on for 2- to 3-h intervals. Ongoing frequency and volume charting can be used to formally monitor progress using this technique. Current guidelines advocate that this technique should be attempted for at least 6 weeks prior to considering other measures [4].

Medications

If bladder-training techniques alone do not produce a satisfactory response, then a combined approach using an antimuscarinic agent should be considered. These drugs inhibit the neurotransmitter acetylcholine, which interferes with the parasympathetic innervation of the detrusor muscle, reducing the frequency of involuntary contractions. Current NICE guidelines recommend the following agents as first line:

1. Oxybutynin (immediate release)
2. Tolterodine (immediate release)
3. Darifenacin (once-daily preparation)

The lowest recommended dose should be administered, and the patient should be aware of potential side effects such as dry mouth, constipation, blurred vision, and urinary retention [4]. Therefore, it is important that a post-void bladder scan is undertaken prior to commencing this medication to ensure that problematic incomplete bladder emptying (>100 ml residual) is not already present. All patients should be reviewed after 4 weeks to evaluate if there has been any benefit in using these agents [4].

Lifestyle Changes

Excess caffeine intake and citrus fruit may exacerbate urge incontinence, and therefore some patients may benefit from limiting or excluding these substances from their diet. Clinical evidence supporting this theory is, however, limited [64].

Management of Functional Incontinence

The management of this type of incontinence must be directed by the outcome of the functional assessment of toileting skills (see previous section). The stroke may have caused physical, communication, and/or cognitive impairment, which may be contributing to incontinence. Strategies should be adopted to address these impairments and their impact on toileting skills. Key components of managing functional incontinence include:

- *Mobility issues*. Strategies used to facilitate access to the toilet include use of a wheelchair or a walking aid. Hand-held urinals are available for both men and women, and absorbent gels can be used within the urinal to prevent spillage if dexterity is an issue. Clothing that is easy to remove such as Velcro fly fastening or loose trousers should be incorporated into the treatment plan.
- *Cognitive/communications/visual issues*. Picture cards, large sign posting, and colour codes are examples of strategies that could be adopted to help patients recognise the location of the toilet.
- *Voiding schedules*. These include the following:
  - *Prompted voiding*. This involves prompting the patient to void at regular intervals; however, they are only assisted to the toilet if there is a positive response to the prompt, i.e. a request for help [65].
  - *Timed voiding*. This is a fixed voiding schedule, every 2–4 h, which remains unchanged and ensures regular bladder emptying. This is particularly useful in patients with impaired-awareness urinary incontinence [66].
  - *Habit training*. A voiding schedule is created based on the patient's own habits, using information derived from the frequency and volume chart. Voiding intervals are planned at times prior to the patient's incontinence episodes. This voiding schedule is particularly useful in patients with cognitive impairment [67].

Management of Detrusor Hyporeflexia with Overflow Incontinence

As previously described, the main consequence of detrusor hyporeflexia is incomplete bladder emptying, leading to urinary retention. This may occur acutely or chronically, and both situations need to be urgently addressed. In the case of acute retention, an in/out catheterisation technique to drain the bladder could be used. Regular bladder scanning should then be undertaken to monitor for recurrence. If retention of more than 400 ml of urine occurs, catheterisation should be repeated [40].

Intermittent Catheterisation

This can be useful in patients suffering from chronic retention of urine. It requires the patient or their carer to intermittently insert a urinary catheter into the bladder to ensure urine volumes are maintained below 500 ml [21]. The required frequency to achieve this will vary from individual and can be determined by using a frequency and volume chart. This technique should only be used if post-void residual volumes as determined by bladder scanning are greater than 100 ml. If residual volumes fall consistently below 100 ml, then this technique should be abandoned. Intermittent catheterisation may be inappropriate in the following cases: urethral trauma, pain issues, distorted anatomy, or if the technique is unacceptable to the patient or their carer.

Long-Term Catheterisation

As previously discussed, the results of the National Sentinel Stroke Audit (2010) revealed that many patients are catheterised unnecessarily without a clear reason indicated. Urinary incontinence alone is NOT an indication for an indwelling catheter. Urinary catheters are associated with a number of complications [68]:

1. Catheter-associated urinary tract infection
2. Urethral damage—urethritis, erosions, creation of a false passage, urethral fistulas
3. Encrustations—mineral deposition within the catheter biofilm, which can lead to catheter blockage
4. Bladder stones

In some cases, however, a long-term catheter (more than 14 days) is required. This is usually made of silicone, hydrogel-coated latex, or silicone elastomer-coated latex [40]. Patients must be educated on how to manage the catheter at home and when to seek help. In some cases it may be appropriate to use a catheter valve as an alternative to free drainage. This allows some stimulation of the bladder by allowing it to fill in the usual manner. Although the evidence is limited, it has been suggested that catheter valves can improve bladder tone and capacity and are useful in patients who have the ability to manipulate the valve and empty the catheter regularly [69].

Management of Stress Incontinence

Treatment strategies for stress incontinence are focused around improving pelvic floor muscle strength and tone [4, 70]. Not all patients will be able to partake in a pelvic floor exercise programme and a continence specialist must individually assess this.

Containment Devices

Unfortunately, despite the above measures, some patients remain incontinent, and in this group of patients the aim of therapy should be to achieve dryness-dependent continence. Containment devices can significantly help to improve a patient's quality of life. They include the following:

- Absorbent pads: the correct size and the most suitable variety used (e.g. all in one, pull-ups, inserts) [40].
- Penile sheaths are also an option for men.

Implications for Further Research

There is insufficient evidence to guide clinical practice regarding which treatment strategies work best for the various types of post-stroke urinary incontinence. Robust clinical trials are needed in this area to allow evidence-based protocols to be developed specifically for the stroke patient population. A large multi-centre randomised trial, ICONS: Identifying Continence Options after Stroke, is currently in progress evaluating the effectiveness of a systematic voiding programme for the management of urinary incontinence after stroke [71]. The voiding programme includes interventions such as bladder training, habit training, timed voiding, prompted voiding, and pelvic floor muscle exercises. The results of this study are awaited and will hopefully enable evidence-based management protocols to be developed for post-stroke urinary incontinence.

Bowel Complications

Bowel problems such as constipation and faecal incontinence are usually the result of functional impairment following stroke rather than direct neurological damage. Bowel problems can be extremely distressing and may result in social isolation.

Epidemiology

It is widely recognised that bowel dysfunction is common problem following stroke [18, 72–74]. One study demonstrated that constipation affected 60 % of patients admitted to a stroke rehabilitation ward [18]. Faecal incontinence is also a significant problem affecting 30–40 % of individuals immediately after stroke, 11 % at 3 months, 10–19 % at 6 months, 11 % at 1 year, and around 15 % at 3 years [18, 72, 73]. Faecal incontinence has been associated with worse outcomes following stroke.

In one study of over 800 stroke patients, faecal incontinence at 3 months was associated with an increased risk of institutionalisation and greater mortality rates within 1 year [74].

Causes of Bowel Problems Following Stroke

Post-stroke bowel complications are usually due to functional impairments affecting toileting abilities rather than direct effects of the stroke lesion [73]. In one study investigating the natural history of post-stroke faecal incontinence, it was found that requiring assistance to use the toilet was the strongest predictor for the development of faecal incontinence at 3 months following stroke [73]. Other stroke-related functional risk factors include the following: mobility issues, impaired manual dexterity, vision problems, communication difficulties due to speech disturbances, cognitive problems, and depression [73–75]. Overflow faecal incontinence may also occur in stroke patients resulting from constipation and faecal impaction. Interestingly, there is some evidence to suggest that post-stroke faecal incontinence may be a transient condition. In one large clinical trial, 35 % of patients incontinent at 3 months regained continence at the 1-year time point [73].

Constipation may occur due to delayed colonic transit times as a result of reduced mobility [18]. Other functional impairments and psychological factors may also contribute. A community-based study showed that use of anticholinergic agents was independently associated with the development of post-stroke faecal incontinence [73].

Assessment of Post-stroke Bowel Problems

The assessment of bowel problems can be potentially embarrassing for the patient, and therefore the subject must be addressed in a sensitive manner. An initial assessment of bowel function is essential for all stroke patients in identifying a potential problem. If a bowel complication is found, a comprehensive assessment is then required to address the following issues:

1. Identify the type of problem: constipation, faecal incontinence, or both
2. Identify the underlying cause
3. Identify any contributory factors

Detailed History of Bowel Habits

It is important to identify the presence of any pre-existing bowel problems such as constipation. The healthcare professional should enquire about the patient's "normal" bowel habits and this should be used as a baseline of normal bowel

function for that individual. A medication history is also important, especially the use of laxatives, anticholinergics, and nonsteroidal anti-inflammatories, which have been associated with an increased risk of faecal incontinence.

Clinical Assessment

The following examinations may be helpful in assessing stroke patients with bowel complaints:

1. Abdominal examination—palpation may reveal signs of constipation
2. Digital rectal examination—this will identify rectal loading, faecal impaction, and stool consistency, although an empty rectum does not exclude constipation
3. Perineal and groin examination—observe for rectal prolapse, irritable perineal skin, anal fissures, and haemorrhoids

A functional assessment of the patient's toileting skills is also important in a similar manner to that previously described for urinary incontinence.

Bowel Habit Diary

A bowel diary should be kept for all stroke patients recording information on frequency, colour, and consistency of the stool. The Bristol stool scale is a useful tool for assessing the type and consistency of the stool [76]. A food and fluid chart are also useful assessment measures to identify contributory factors such as a lack of fibre intake.

Treatment Strategies

The most likely cause of bowel complications in stroke patients is due to functional impairments as a consequence of the stroke. It is thus necessary for an individually tailored treatment care plan to be formulated, taking into consideration the patient's specific disabilities. Education of patients and their carers is paramount in managing this disabling condition.

Faecal Incontinence

There is limited clinical evidence for the use of specific strategies in the management of post-stroke faecal incontinence. Universally accepted treatment measures can thus be adopted to manage functional faecal incontinence following stroke [77, 78]:

1. Environmental factors: Ensure privacy by assisting patient to the toilet, either walking if possible or wheeling them on a commode.

2. Prompted toileting and, if this is unsuccessful, then scheduled toileting should be tried based on the patient's bowel habits diary.
3. If behavioural techniques fail, then a combination of loperamide and enemas may achieve bowel control.

Additionally, current guidelines recommend that individuals suffering from faecal incontinence should be offered the following containment devices: disposable body-worn pads, disposable bed pads, anal plugs (for patients who can tolerate them), skincare advice (cleansing and barrier products), advice on odour control and laundry, and disposable gloves [78].

Constipation

The treatment strategy employed to manage this complication in stroke patients will vary according to the severity of constipation. The following measures should be considered:

Positioning and timing. The morning gastro-colic reflex facilitates bowel movements, and thus patients should be encouraged to utilise the toilet during the morning, especially after a hot drink [40]. Privacy should be maintained and correct toilet positioning should be adopted. Some patients may require support from a handrail or a foot rest to maintain a sitting balance. In patients who are unable to maintain a sitting position, if possible they should be hoisted into a sitting position over a bed pan rather than left lying flat.

Dietary factors and mobility. An appropriate diet with adequate fibre and fluid intake should be maintained. Patients should be encouraged to mobilise as much as possible.

Laxatives. There are four main types of laxatives, which have different mechanisms of actions:

(a) Bulk forming (e.g. Fybogel, Normacol): These laxatives are taken with fluids and work by adsorbing liquid and swelling. The resultant bulk causes increased peristalsis, thereby reducing colon transit times. They may not be the best choice for stroke patients who may be suffering from swallowing difficulties.
(b) Stimulant (e.g. Senna, docusate, glycerol): These laxatives work within 6–12 h by stimulating the intestinal lining of the colon, which results in increased peristalsis and fluids secretion lubricating the stool. They should only be used short term, as prolonged use can lead to reduced muscle tone in the colon, potassium depletion, and dehydration.
(c) Osmotic (e.g. Movicol, Lactulose): These laxatives work by drawing water into the bowel and allow easier passage of stool. Movicol is commonly used in stroke patients as it is generally well tolerated [79].
(d) Softeners (e.g. docusate, arachis oil): These are emollient laxatives, which work by coating the stool with a layer of oil, helping it to retain water and therefore keeping it soft.

General measures that will minimise constipation include ensuring adequate hydration of patients and minimising the use of pharmaceutical agents that can precipitate constipation.

Conclusion

Bladder and bowel complications following a stroke are common, complex, and multifactorial in nature. Not only is there a strong association between these complications and worse stroke outcomes, but also they can have a devastating impact on the patient's quality of life. Although the stroke lesion itself may be contributing to the problem, it is resulting functional impairments which compound the situation further. Healthcare professionals should be aware of these complications and must be trained on assessment methods and treatment strategies. Any underlying reversible causes must be promptly addressed. It is imperative that the multidisciplinary team, in collaboration, formulates an individually tailored care plan with the patient to promote continence. This personalised care plan should outline realistic goals and be periodically reevaluated and altered according to the patient's needs. Although continence may not always be restored, several interventions can be instituted to improve the patient's quality of life, which in turn may improve their engagement with stroke rehabilitation.

Patient Questions

Q. Why am I incontinent of urine following my stroke?

A. It is fairly common following a stroke to be incontinent due to various reasons. Stroke itself can cause incontinence, and mobility and communication issues can result in what is known as functional incontinence. Other co-existing conditions such as urinary tract infection and constipation can also cause your incontinence. Your medical team should assess your condition and prescribe an appropriate plan to manage your condition.

Q. Will my incontinence get better?

A. It depends on the underlying cause for your incontinence as well as your general recovery from your stroke. If the incontinence is due to a specific issue such as infection or poor mobility, then treating the infection or improving your mobility would help you recover from incontinence. If it is due to the stroke itself, the extent of your overall recovery from stroke will determine your recovery from incontinence.

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Chapter 9
Positioning and Pressure Care

Mark McGlinchey, Nicole Walmsley, and Gill Cluckie

Abstract Positioning and pressure care are important components of post-stroke management and require a consistent approach over a 24-h period to be considered effective. When resting in bed, patients should be positioned in a range of different positions, including supine lying, side lying, and sitting upright in bed. When sitting out of bed, patients should have appropriate seating provided based on their clinical presentation to enable early mobilisation and facilitate the rehabilitation process. In all positions, careful attention to pressure care, including the use of pressure-relieving equipment, is required to reduce the development of pressure sores and other complications associated with immobility, such as contractures and pain. As there is a lack of evidence regarding optimal positioning, seating, and pressure care for patients post-stroke, more research is required to guide clinicians in these aspects of care.

Keywords Positioning • Bed positioning • Seating • Wheelchairs • Pressure care • Pressure sores • Post-stroke management

Key Messages

- There are a number of recommended strategies to optimise positioning of patients post-stroke that may facilitate the rehabilitation process and prevent or reduce complications associated with poor positioning.
- All patients after stroke should be considered at potential risk of pressure sore development and should be assessed for their individual risks and an appropriate action plan should be put in place.

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Introduction

Positioning is considered to be an important component of post-stroke care and requires a consistent approach over a 24-h period to be considered effective [1]. As such, all members of the stroke multi-disciplinary team have a responsibility to ensure that optimal positioning occurs in order to facilitate the rehabilitation process and to prevent complications arising from poor positioning, which may affect functional outcome [2]. Whilst there are many factors to consider when positioning patients, one key element that requires multi-disciplinary involvement is attention to pressure care. This chapter will focus on positioning and pressure care of the stroke patient and will be divided into four sections. The first section will provide an overview of positioning, including the benefits of correct positioning and the complications of poor positioning. The second section will focus on the positioning of patients in bed, covering positions such as supine, side lying, and sitting upright in bed. The third section will focus on positioning when seated and review some of the more commonly used seating systems. The fourth section will provide an overview of pressure care for stroke patients, including the prevention and management of pressure sores in stroke patients. This chapter will conclude with suggestions for further research into positioning and pressure care post-stroke.

Positioning Post-stroke

It is accepted that stroke unit care results in improved mortality and functional independence compared to general ward care [3]. Patients on a stroke unit are more likely to have greater therapeutic contact with staff, spend less time lying down, and more time sitting out of bed as well as being better positioned than patients on general wards [4]. Despite these differences in stroke unit and general ward care, stroke patients can spend a considerable amount of time being inactive during their day. In the first few weeks post-stroke, studies have suggested that stroke patients may only be active for as little as 27 min and up to 2.8 h per day, and upper limb therapy performed during therapy sessions can be as little as 4–11 min per session [5, 6]. Additionally, immobility arising from stroke-related impairments, such as reduced attention, muscle weakness, sensory loss, and tonal changes, can make it difficult for stroke patients to move their limbs and adjust their position. As such, patients may require assistance to move into and maintain different positions in order to prevent complications associated with a lack of or incorrect positioning. Correct positioning of stroke patients is therefore suggested as an important component of post-stroke care [1, 7].

Benefits of Correct Positioning

There have been a number of reported benefits of positioning described in the literature [7–9], which are listed in Table 9.1. However, there is limited evidence to support the efficacy of positioning in achieving these benefits. The perceived benefits of positioning

Table 9.1 Reported benefits of correct positioning

Promote functional recovery	Prevent complications	Physiological	Cognitive/ psychological	Social
Encourage functional recovery of the affected limbs Modulate muscle tone Experience normal posture Support and stabilise body segments Encourage compensatory movements of the unaffected limbs Increase sensory input	Pressure sores Contractures Oedema Chest infections Damage to the affected limbs or vulnerable brain	Improve respiratory capacity Improve circulation Prevent postural hypotension	Increased spatial awareness Provide comfort	Promote opportunities for socialisation/ communication Achieve safe swallow/feeding

as well as the suggested positions for stroke patients have been derived mostly through consensus opinion amongst clinicians caring for stroke patients [7–9]. A survey of United Kingdom (UK) physiotherapists highlighted 28 aims or benefits of positioning, with 14 aims identified by a minimum of 50 % of survey respondents [7]. Other studies have identified the most commonly recommended positions for conscious and unconscious stroke patients—sitting in an armchair and lying on the non-affected side, respectively—amongst nurses, physiotherapists, and occupational therapists, although a lack of consensus amongst the different professional groups with respect to supine lying, sitting upright 30°, and lying on the affected side was reported [8, 9]. However, these consensus-based studies all highlighted the benefit of regular position changes and that different positions should be adopted for different clinical reasons.

More recently, a number of studies have evaluated the effect of positioning on a range of impairments, such as contractures and pain, as well as patient function [10–14]. These trials evaluated the effect of sustained stretches, ranging from 20 to 30 min performed either two or three times per day, between 5 and 7 days per week for at least 4 weeks on contracture formation in addition to conventional stroke unit care. Due to their small sample sizes, a meta-analysis of these randomised controlled trials was conducted to evaluate the effect of sustained positioning on shoulder external rotation range of motion, which was the only impairment included in all studies [15]. The results of this meta-analysis failed to demonstrate the benefit of positioning to prevent or reduce shoulder external rotation contracture after stroke. The only study which demonstrated a significant reduction in shoulder external rotation contracture development between control and experimental groups enrolled patients within the first 2 weeks post-stroke [11], whereas the other studies recruited patients from 3 to 12 weeks post-stroke. As soft tissue shortening can develop within the first few weeks

post-stroke [15], it may suggest that earlier positioning post-stroke is more beneficial in maintaining joint range of motion than late-stage positioning. As well, the meta-analysis suggested that the dosage of 20–30 min two to three times per day may not be sufficient to prevent or reduce contracture formation and therefore more research is required to determine the optimal dosage for contracture prevention.

In terms of seating, current clinical guidelines highlight the importance of sitting patients upright, including sitting patients out of bed [16–18]. There is increasing evidence to suggest that patients who undergo early mobilisation demonstrate improved functional outcomes post-stroke [19, 20]. Documented benefits of providing specialist postural support in seating include improved mental arousal due to activation of the ascending reticular formation [21], improved upper limb function [22, 23], enhanced communication, reduced fatigue, and improved energy conservation [24], and positive psychological benefits for patients [25].

The lack of sufficient evidence to demonstrate the benefits of positioning in bed and in the seated position highlights the importance of conducting a detailed assessment of the patient's clinical presentation and implementing positioning and seating strategies based on these assessment findings and the specific needs of the patient.

Complications of Incorrect Positioning

It has been reported that complications post-stroke can impede rehabilitation, increase hospital length of stay and the direct cost of patient care, as well as negatively affect functional outcomes [2]. As such, strategies to reduce the occurrence of complications post-stroke should be readily implemented. There are a number of potential complications that can arise from limbs being immobilised in poor alignment for prolonged periods of time as well as positions being sustained that may affect physiological parameters. These potential complications described in the literature are listed in Table 9.2 [26–39]. As pressure care will be discussed later in this chapter, this section will focus on the musculoskeletal and physiological complications arising from incorrect positioning.

One of the consequences of immobility imposed by the different impairments post-stroke is that the resting positions of different body regions can place muscles in shortened positions [26]. For example, the upper limb resting on the patient's thigh in sitting upright results in shoulder adduction and internal rotation, elbow flexion, forearm pronation, and wrist and finger flexion and places these muscle

Table 9.2 Reported complications of poor positioning

Musculoskeletal	Skin	Respiratory	Cardiovascular	Digestive
Contracture formation Pain, including hemiplegic shoulder pain	Pressure sores	Hypoxia	Changes in blood pressure Changes in intracranial pressure	Difficulty in swallowing (increased risk of aspiration)

groups in shortened positions compared to their antagonist muscles. Muscles adapt to this enforced immobilisation through loss of sarcomeres [27], resulting in muscle shortening, as well as changes in the viscoelastic properties of the surrounding connective tissues, including an increase in the ratio of collagen to muscle fibre [28]. These adaptive changes result in less compliance when passively stretched and manifest clinically as increased resistance on passive ranging. These adaptive changes have been demonstrated to occur within days of immobilisation [27] and could lead to more permanent soft tissue shortening, known as a contracture, if not effectively managed. Contractures are a common complication post-stroke, occurring in up to 60 % of patients within the first year post-stroke [2]. As upper limb function is more likely to be comprised with greater restrictions in joint range [11], strategies to prevent or slow down the development of contractures should be implemented. Whilst most studies have demonstrated that currently used positioning strategies have limited effect on contracture development [15], positioning patients early post-stroke may slow down the development of contractures [11].

In addition, positions or postures that do not provide adequate support to weak and hypotonic body regions may contribute to the development of other musculoskeletal abnormalities and pain. The shoulder joint is particularly vulnerable to these complications as it derives most of its stability from muscular support, which is often reduced or lost post-stroke [29]. If the upper limb is unsupported against gravity, the shoulder joint capsule and surrounding ligaments can stretch over time, which can result in inferior glenohumeral joint subluxation [29, 30]. Whilst subluxation itself may not be painful, it is strongly associated with hemiplegic shoulder pain [31], which can be a significant clinical problem resulting in poor recovery of arm movement and upper limb function. In addition, external and uncontrolled forces applied to the weak and hypotonic upper limb can lead to sub-acromial impingement, rotator cuff injury, and bicipital tendonitis [30]. Subluxation, soft tissue damage, and pain may be minimised if the upper limb is well handled and supported in different positions [29–31].

There are a number of respiratory and cardiovascular physiological changes that can arise in different positions, which may have clinical implications if patients maintain these positions for prolonged periods of time. Oxygenation may be lower in the supine and flat side lying positions compared to sitting upright at least 45° post-stroke [32, 33]. However, there may be no difference in oxygenation between side lying with the head of bed elevated at 45° compared to sitting upright in bed at 70° [34]. Blood pressure changes have been noted between supine and sitting upright positions, though results have been mixed [35–37]. Studies have also investigated the effects of positioning on cerebral blood flow and perfusion [37–39], which may have important consequences in ensuring that penumbral tissue post-stroke is sufficiently perfused. Again, results have been mixed due to small sample sizes, but more authors suggested that the supine position may result in improved cerebral blood flow and perfusion compared to sitting upright positions [37, 39]. Due to the inconclusive results from these studies, it is important that the patient is monitored closely for physiological changes arising from changes in positioning. It also supports the notion that patients require regular position changes due to the benefits of adopting different positions.

Positioning in Bed

Immediately following a stroke, patients can demonstrate a range of impairments that will limit their ability to engage in rehabilitation [40]. Muscle weakness and flaccidity, due to decreased descending inputs on spinal motor neurons, as well as somatosensory impairments, can make it difficult for patients to move their limbs and adjust their position. Cognitive impairments, such as reduced attention, as well as decreased nutritional intake arising from dysphagia, can make it difficult for patients to participate in rehabilitative activities for sustained periods of time. As such, patients may spend a considerable amount of time in bed in the initial period post-stroke. Therefore, correct positioning of stroke patients in bed is important to prevent complications arising from poor positioning, which may influence the rehabilitation process and affect functional outcome [2].

Positioning of stroke patients in bed is not just confined to the initial period post-stroke. All patients will spend time in bed for sleeping, and patients who are able to sit out will need to return to bed at some point in order to rest and relax. As well, the initial period post-stroke may be followed by the emergence of abnormal posturing of the different body regions, due to muscle imbalance, soft tissue shortening, and increased tone [1, 40]. Common abnormal postures described in the literature [1] are listed in Table 9.3. The suggested positioning strategies for supine, side lying, and sitting upright in bed described in the literature and reported in this section are designed to counteract the effect of this abnormal posturing, which may result in secondary musculoskeletal complications if not prevented. Whilst these abnormal postures and suggested positioning strategies to counteract these postures have been well described in the literature [1], the actual presence of these postures in patients post-stroke has been inferred mostly from observations of clinical practice rather

Table 9.3 Typical posturing post-stroke

Body region	Position
Head	Laterally flexed to affected side; rotated away from affected side
Scapula	Depressed, retracted
Shoulder	Adducted, internally rotated
Elbow	Flexed
Forearm	Pronated
Wrist	Flexed
Fingers	Flexed
Trunk	Side flexed to affected side
Pelvis	Retracted on affected side
Hip	Extended, adducted, and internally rotated
Knee	Extended
Ankle	Plantar flexed
Sub-talar joint	Inverted
Forefoot	Supinated
Toes	Dorsiflexed

than through direct scientific evaluation. In addition, the suggested positioning strategies to counteract anticipated abnormal postures arising from stroke are based on the assumption that all patients experience these postures. However, there is no direct evidence to confirm this assumption. As such, these suggested positioning strategies should not supersede the findings from an individualised patient assessment. Instead, the strategies should provide guidance to assist clinicians in the optimal positioning of patients.

As positioning is considered to be most effective when applied consistently over a 24-h period [1], the use of diagrams or photographs taken with patient consent can be used in the clinical setting to demonstrate individual positioning strategies and use of equipment to convey to all members of the multi-disciplinary team how to optimally position patients (Fig. 9.1a–d).

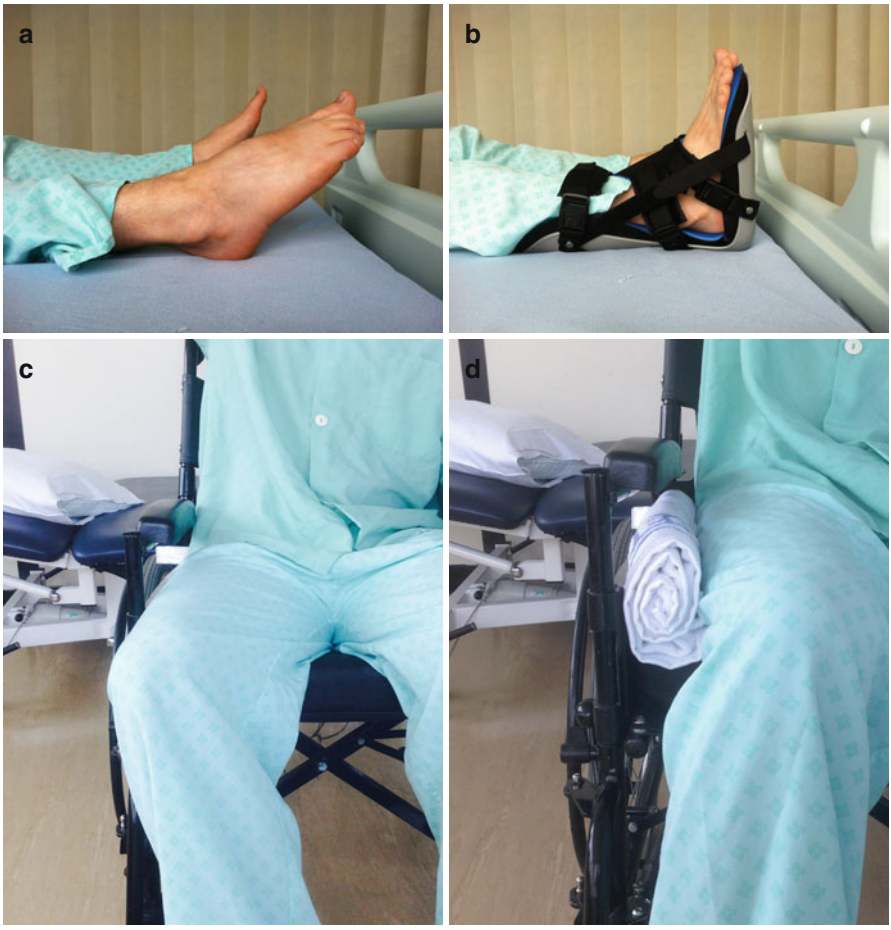


Fig. 9.1 (**a–d**) Use of photographs to demonstrate equipment use

For the following positions and unless otherwise stated, the reported joints refer to the joints on the affected side of the body, i.e. the side of the body presenting with the most impairments as a direct result of the stroke.

Supine (Fig. 9.2)

- Key components
  - Neutral head, neck, and trunk alignment (may use a pillow under the head)
  - Upper limb supported on a pillow
    - Scapular protraction
    - Shoulder abduction and external rotation
    - Elbow extension
    - Forearm mid-pronation or supination
    - Wrist and finger neutral or slight extension
    - Thumb abduction

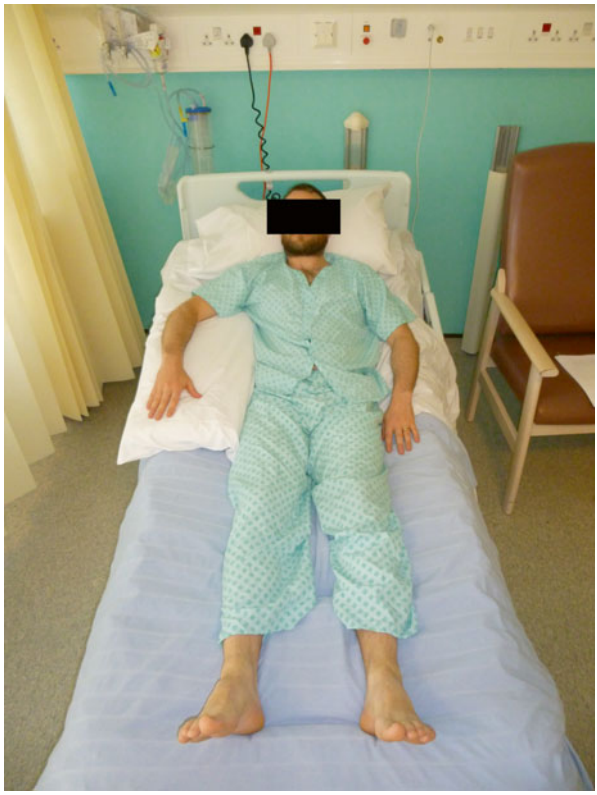


Fig. 9.2 Supine lying

  - Neutral hip position (may use pillows or a blanket on the lateral aspect of the thigh to prevent hip external rotation)
  - Knee extension (or slight knee flexion with a rolled blanket under the knee to prevent knee hyperextension)
  - Neutral ankle position, or ankle plantargrade (may use resting foot splints or a blanket against the sole of the foot to prevent ankle plantarflexion)

Supine is one of the least recommended bed positions for stroke patients [7–9]. Whilst cerebral perfusion may be enhanced in the position [37, 39], patients in supine lying are more likely to demonstrate hypoxia compared to more upright postures [32, 33]. In addition, supine lying can make social interaction difficult for patients and is considered an unsafe position for swallowing due to the increased risk of aspiration [8, 9]. Therefore, supine with slight head-of-bed elevation (approximately 30°) is generally recommended over supine with no elevation amongst nurses and therapists [8, 9].

Side Lying: Lying on the Affected Side (Fig. 9.3)

- Key components
  - Neutral head, neck, and trunk alignment
  - Scapular protraction
  - Shoulder flexion and external rotation
  - Elbow extension
  - Forearm mid-pronation or supination
  - Wrist and finger neutral or slight extension with thumb abduction
  - Hip and knee extension (and hip and knee flexion for the non-affected side)
  - Ankle plantargrade

Lying on the Non-affected Side (Fig. 9.4)

- Key components
  - Neutral head, neck, and trunk alignment
  - Upper limb supported on pillow
    - Scapular protraction
    - Shoulder flexion and external rotation
    - Elbow extension
    - Forearm mid-pronation or supination
    - Wrist and finger neutral or slight extension with thumb abduction
  - Hip and knee flexion (and hip and knee extension for the affected side)
  - Ankle plantargrade

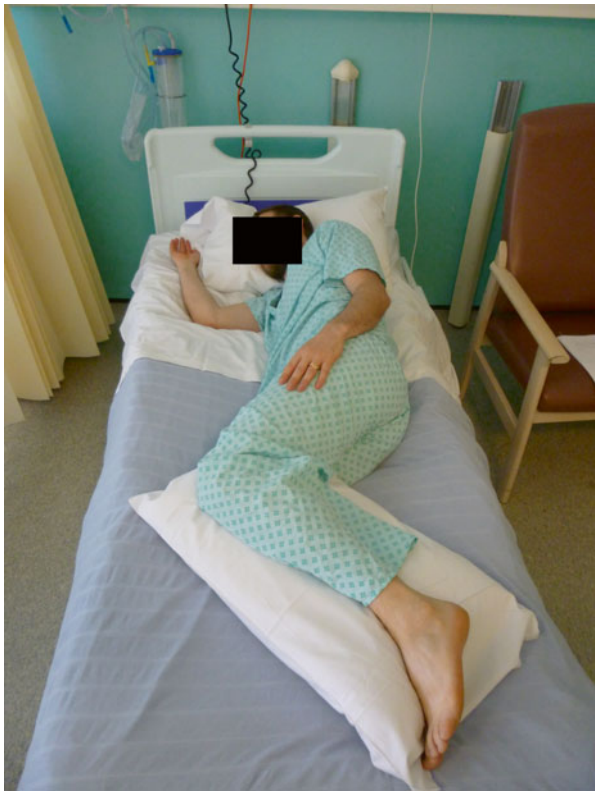


Fig. 9.3 Lying on the affected side

Side lying is more recommended than supine amongst nurses and therapists for stroke patients when resting in bed [7–9]. Lying on the non-affected side is especially recommended as one of the preferred bed positions for both conscious and unconscious stroke patients amongst nurses and therapists [8, 9]. The affected side is more easily positioned in this position and there is the potential for patients to use their affected side when uppermost. When patients lie on their affected side, careful attention is required to ensure that the affected side is well aligned, as reduced sensation and weakness may make it difficult for patients to sense areas of discomfort and adjust their position accordingly. There has been no comparison of physiological differences between side lying with and without head-of-bed elevation. Therefore, both positions could be considered when positioning patients on their sides.

Sitting Upright in Bed (Fig. 9.5)

- Key components:
  - Neutral head, neck, and trunk alignment (consider rolled towels on the lateral aspect of the head to prevent rotation and lateral flexion)

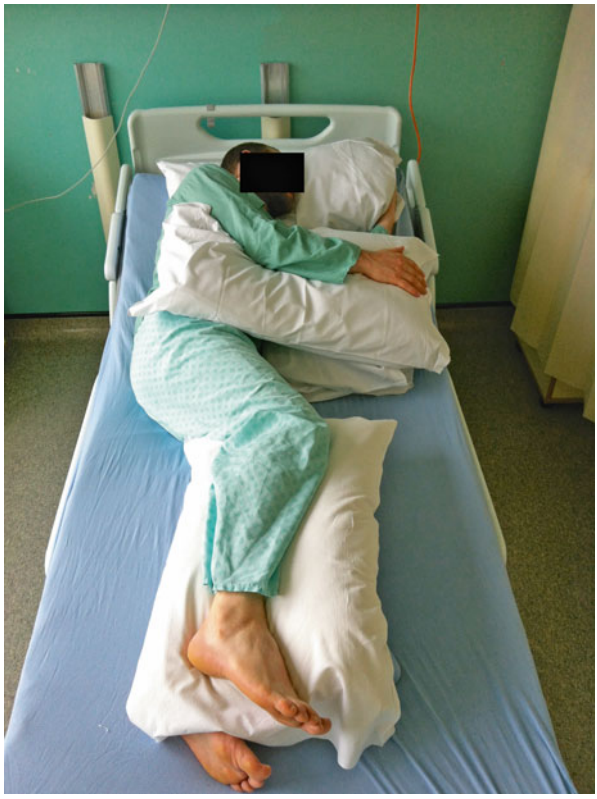


Fig. 9.4 Lying on the non-affected side

– Upper limb supported on a pillow
  - Scapular protraction
  - Shoulder flexion, abduction, and external rotation
  - Elbow extension
  - Forearm mid-pronation or supination
  - Wrist and finger neutral or slight extension
  - Thumb abduction
– Neutral hip position (may use pillows or a blanket on the lateral aspect of the thigh to prevent hip external rotation)
– Knee extension (or slight knee flexion with a rolled blanket under the knee to prevent knee hyperextension)
– Ankle plantargrade (may use resting foot splints or a blanket against the sole of the foot to prevent ankle plantarflexion)

Whilst there is no consensus regarding the optimal head-of-bed elevation when resting in bed, there may be no difference in oxygenation when patients are sitting upright at 45° elevation compared to 70° elevation [34]. As such, the optimal head-of-bed elevation may be more dependent upon patient preference and comfort.

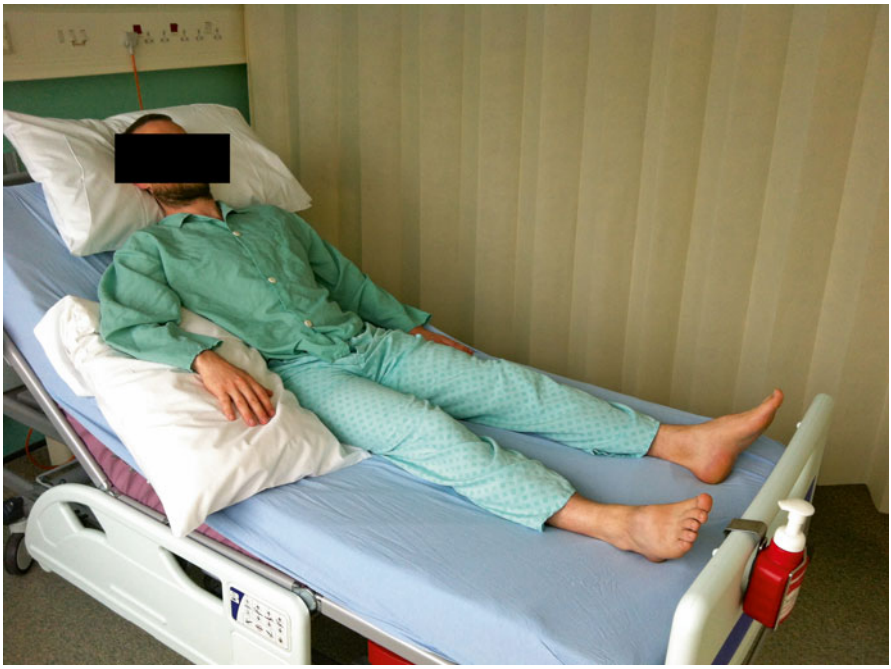


Fig. 9.5 Sitting upright in bed

Studies looking at cerebral perfusion post-stroke have only looked at head-of-bed elevations from 0 to 45° [37–39] and most report that cerebral perfusion is reduced with more upright postures [37, 39].

Sitting upright is considered the safest bed resting position for effective swallowing and therefore reduces the risk of aspiration [7–9]. Sitting upright also enables the patient to eat, drink, and socially interact more easily than more recumbent positions.

Positioning and Seating

Why is seating important? Following damage to the central nervous system by a stroke, a patient's ability to sit independently and unsupported can be affected [40]. Some stroke patients will demonstrate difficulty sitting unsupported in the short term or the acute phase of stroke recovery, whereas other patients will present with more significant impairments and require more long-term and complex postural management support. Being able to sit independently is integral to most, if not all, functional daily life tasks [40]. Therefore, ensuring that patients are positioned correctly in the seated position is seen as an essential part of the rehabilitation process to regain sitting balance and is pivotal to a patient's recovery. Due to the limited evidence available to guide clinicians regarding correct seating post-stroke, providing appropriate seating

for patients after stroke can be challenging and requires a multi-disciplinary approach involving nursing, physiotherapy, and occupational therapy. As such, it may be worthwhile to review the typical sitting postures adopted by stroke patients, and subsequently discuss the optimal seating positions in stroke rehabilitation.

Typical Sitting Posture Post-stroke

There are many reasons why a patient is unable to sit independently after a stroke. A patient's ability to sit is affected by motor, sensory, and cognitive impairments after a stroke [41]. These can include the following:

- Motor
  - Contralateral trunk (and upper limb) weakness
  - Increased or reduced muscle tone
  - Fatigue and reduced physical endurance
- Sensory
  - Contralateral proprioceptive and/or sensory loss
- Cognitive
  - Reduced consciousness
  - Attention deficits, including sustained attention and inattention of the affected side
  - Spatial awareness and perception of midline impairments
  - Behavioural impairments

As a result of these impairments, patients post-stroke typically adopt a characteristic asymmetrical sitting posture (Table 9.4, Fig. 9.6) [41].

These postures are often reinforced or highlighted due to the sustained effect of gravity upon the different body segments whilst the patient attempts to maintain an upright position [42]. A consequence of these postures is that the patient sits in poor alignment with altered weight distribution. In addition to the previously described complications associated with poor positioning, such as soft tissue shortening, pain, and pressure sores, a lack of appropriate seating support may result in the patient sliding out of the chair, which may increase the risk of falling. A detailed assessment of posture will determine the appropriate seating required to ameliorate these observed postures and reduce the risk of secondary complications.

Optimal Seating Posture

As reported in the "Positioning in Bed" section, commonly described positioning strategies, including those used in sitting, have limited evidence to support their efficacy. The optimal seating position has been reported as being "erect,

Table 9.4 Typical sitting posture of a stroke patient

Body region	Position
Head	Laterally flexed towards the affected side; rotated away from the affected side
Scapula	Depressed, retracted
Shoulder	Adducted, internally rotated
Elbow	Flexed
Forearm	Pronated
Wrist	Flexed
Fingers	Flexed
Trunk	Laterally flexed towards the affected side +/- rotated
Pelvis	Retracted on the affected side and posterior tilt, resulting in unequal weight bearing through the ischial tuberosities
Hip	Abducted and externally rotated
Ankle	Inverted and reduced foot contact with the floor

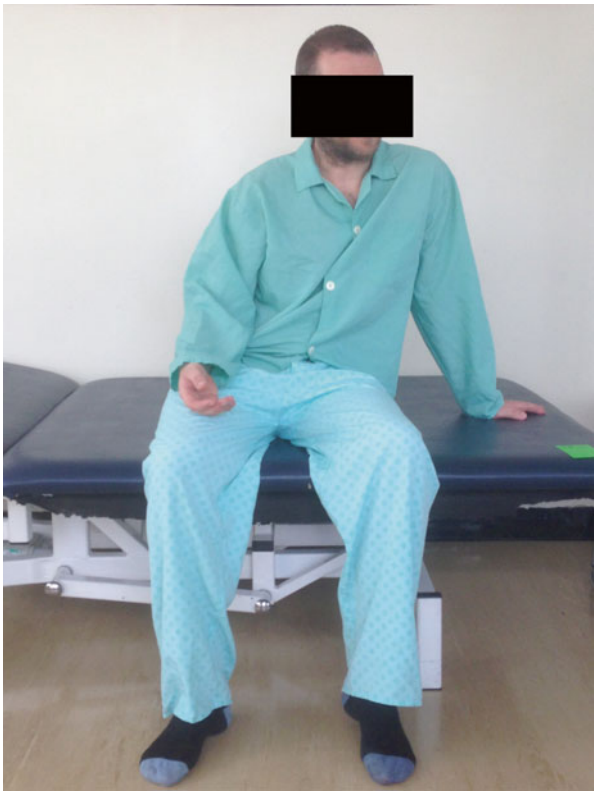


Fig. 9.6 Typical sitting posture of a stroke patient

symmetrical, and aligned" [43]. This is derived from ergonomic theory that says that adopting this position prevents the development of complications and supports the natural anatomical structure of the body. The suggested optimal sitting position described in the literature [1] is reported below (Fig. 9.7):

- Neutral or midline head, neck, and trunk alignment
- Upper limb
  - Scapular protraction
  - Shoulder flexion, abduction, and external rotation, though there is a lack of consensus regarding the exact degree of positioning
  - Elbow either flexed or extended—there is a lack of consensus as to the optimal position
  - Forearm pronation
  - Neutral wrist position
  - Finger extension
  - Thumb abduction
- Neutral pelvic alignment
- Hips and knees at 90° flexion
- Feet flat on the floor

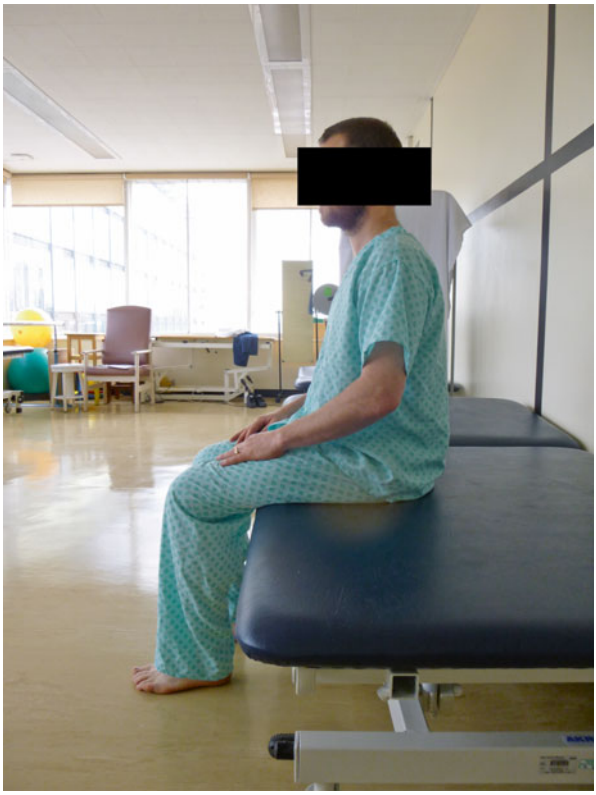


Fig. 9.7 Optimal sitting position

It should be noted that maintaining this optimal seating position may be difficult due to the previously described post-stroke impairments as well as a patient's attempt to readjust their position. As such, clinicians need to be realistic regarding how long a patient is likely to maintain this optimal position.

Seating Options

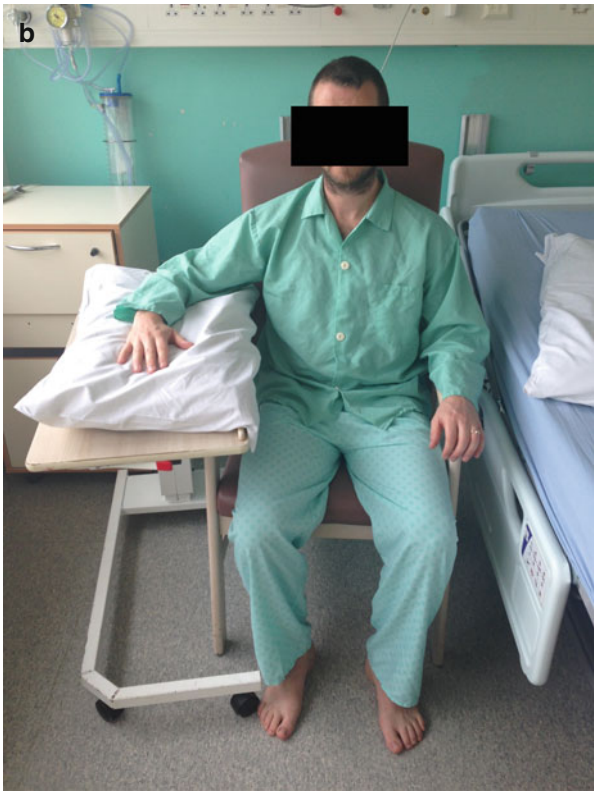
As patients post-stroke demonstrate a range of impairments that can change over time, a number of seating options to address different seating requirements are reviewed below. It is important to note that as the patient's clinical presentation changes, a review of their seating needs will be required.

Standard Armchair

For most patients, a standard armchair with a pillow or table to support the patient's affected upper limb will suffice (Fig. 9.8a, b). This may be considered for patients who demonstrate independent sitting balance but may still need some extra support for their affected upper limb.

Fig. 9.8 (**a**, **b**) Positioning in a standard armchair (**a**) with a pillow for support; (**b**) with a pillow on a table for support

Fig. 9.8 (continued)



Wheelchairs

Wheelchairs are another seating option for patients post-stroke which, as well as providing transport for the patient, can provide more adjustable seating settings (Fig. 9.9). This may be considered for patients who need some additional support or equipment to maintain an aligned and upright sitting posture. This can include lateral supports to maintain neutral trunk alignment in the chair as well as lumbar rolls that can be used to maintain a patient's lumbar lordosis and anterior pelvic tilt (Fig. 9.10). There are also alternative back rests that provide more trunk support than the standard canvas of a wheelchair, which tend to encourage a slumped posture. Upper limb supports, such as the Bexhill arm rest, can be fitted onto most wheelchairs to provide additional support to the affected shoulder and upper limb, as well as facilitate optimal positioning (Fig. 9.11).

Specialist cushions will be required for patients who are unable to relieve their own pressure, which can increase the risk of skin breakdown. They can also give additional support to position the pelvis where there is poor pelvic alignment, such as pelvic obliquity or posterior tilt. There is some evidence that contoured cushions can provide more postural stability in sitting compared to air or flat cushions, though this research only involved a small sample of nine paraplegic patients [44].

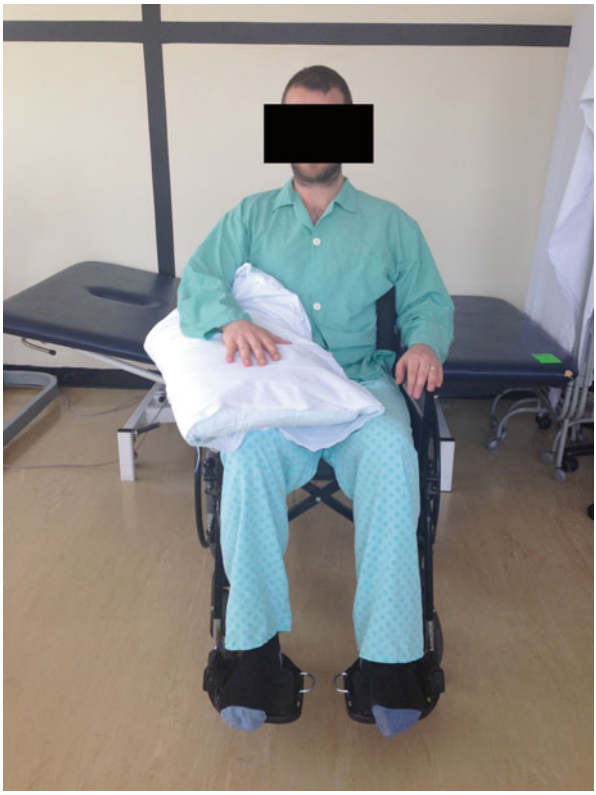


Fig. 9.9 Wheelchairs provide transport as well as more adjustable seating settings for patients post-stroke

Fig. 9.10 Lateral supports

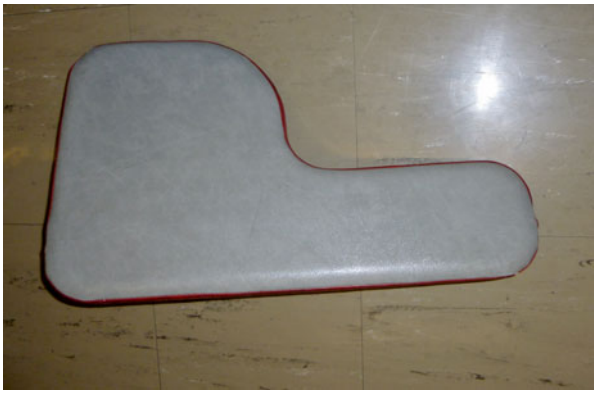


Fig. 9.11 Upper limb supports

Complex Seating Systems

Specialist seating systems are designed for patients who are unable to maintain or achieve an aligned and upright sitting posture with a standard armchair, or in a wheelchair with the previously described supportive equipment. This occurs most commonly in patients with more severe strokes, who require maximal assistance to maintain sitting balance. In these situations, they should be provided with a wheelchair or armchair that has a gravity-assisted mechanism, also known as a "tilt-in-space" chair (Fig. 9.12). This seated position allows the experience of sitting in a symmetrical position, with gravity assisting the maintenance of a balanced symmetrical posture. It also enables the patient to experience sitting in an upright position in a graded fashion, by gradually decreasing the angle of recline towards 0°. This can be achieved over a few days or weeks post-stroke. However, some patients with more severe impairments will need this level of support long term. There are both static (armchair) and wheelchair options for tilt-in-space seating.

There is a lack of consensus regarding which chair is the most appropriate for patients with more severe impairments. Patients may tolerate sitting in a chair for longer periods of time if sat in a wheelchair with more support, whereas they may only tolerate a shorter period of sitting in a standard wheelchair with less support [42]. In these situations, careful consideration needs to be given to the actual goal of seating. There is some research to suggest that use of a tilt-in-space chair improves skin perfusion, particularly when tilted to 35° and pressure is directed through the ischial tuberosities rather than the sacrum [45–47], though this evidence has been derived from small patient samples.

Powered Wheelchairs

A powered wheelchair should be considered for those patients who are likely to be long-term wheelchair users. A powered wheelchair allows a patient who has upper limb weakness and is unable to self-propel independently to move themselves around in an environment. This can lead to an improved sense of independence and control. There are

Fig. 9.12 Tilt-in-space seating

both indoor (Electrically Powered Indoor Chair–EPIC) and outdoor versions (Electrically Powered Indoor Outdoor Chair–EPIOC) and they can also be fitted with postural support mechanisms, such as lateral supports and tilt-in-space options. Powered wheelchairs may minimise a patient using their non-affected lower limb to propel themselves forward, informally known as "punting", which may result in an asymmetrical sitting posture.

Careful consideration needs to be given to the cognitive ability of the patient to learn the wheelchair's controls and manage the chair spatially in a changing and unpredictable environment, such as on a ward or in the community. However, there is case study evidence to suggest that patients with severe spatial neglect can learn to use a powered wheelchair if given intensive daily training [48].

Common Challenges to Seating After Stroke

Pusher Syndrome

Pusher syndrome (also known as ipsilateral pushing and contraversive pushing) is a clinical disorder that is characterised by the patient using the non-affected side of their body to push towards their affected side and resisting attempts at passive

correction (Fig. 9.13) [49]. Pusher syndrome results from a misrepresentation of the patient's sense of verticality [50], determined by visual and postural means, with most patients generally perceiving their postural midline towards the contralesional side [51, 52]. This syndrome is seen in approximately 10 % of all stroke patients and pusher behaviour usually resolves within the first 6 months post-stroke for the majority of stroke patients with pusher syndrome [50, 53, 54]. Although seen in left- and right-hemisphere lesions, there is an increased incidence in right-hemisphere lesions [55, 56] and it is often associated with other neurological impairments, such as spatial neglect in right-hemisphere lesions and aphasia in left-hemisphere lesions [50]. A number of anatomical regions have been implicated in the development of pusher syndrome [57]; however, it is most commonly seen in lesions of the posterolateral thalamus, insular cortex, and post-central gyrus [50].

Ensuring appropriate seating for patients with pusher syndrome is crucial to their rehabilitation as this syndrome is evident when a patient is in a sitting (or standing) position, and therefore cannot be treated in bed in the lying position. As patients may demonstrate greater pushing behaviour if they feel their balance is challenged [49], seating should position the patient in midline alignment in a safe and supportive manner. Midline positioning may also assist in the reorientation of the patient's

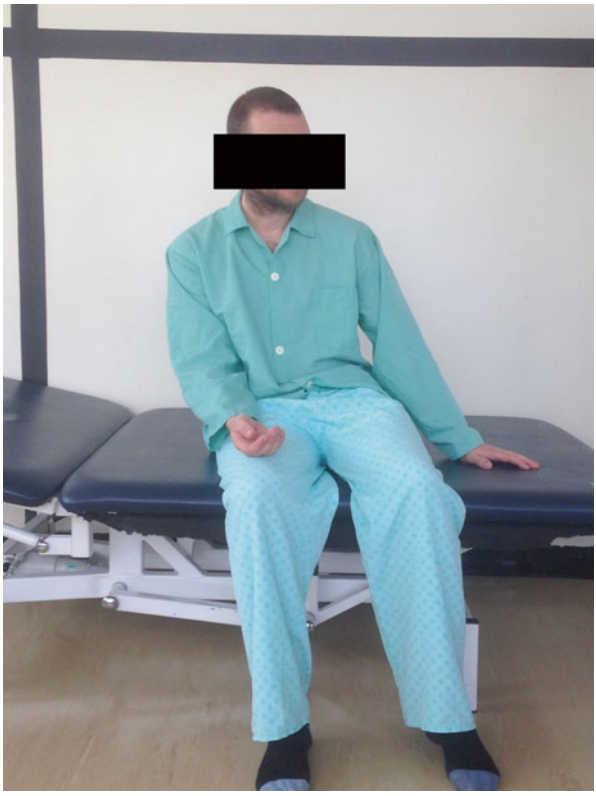


Fig. 9.13 Pusher behaviour in sitting

sense of verticality. As patients with pusher syndrome usually demonstrate intact visual processing of their sense of vertical [50], encouraging patients to align their body with the midline position using visual cues (e.g. doorframes) is considered an important treatment strategy in the management of pusher syndrome [54]. Therefore, ensuring the patient is sitting in midline whilst visually exploring their environment may also assist in the management of pusher behaviour. As such, patients may require a tilt-in-space wheelchair or armchair and the use of accessories such as lateral, pelvic, and head supports may be needed to maintain midline and provide a stable base of support.

Cognition and Behaviour

Approximately 35 % of stroke patients experience cognitive impairments and behavioural changes post-stroke [58]. Seating patients with cognitive and behavioural impairments, such as disorientation, fluctuating attention, impulsivity, and poor insight, can be challenging for clinicians. Patients may attempt to move or adjust their position, either by standing up or attempting to transfer from bed to chair, without the required physical ability and therefore can be at risk of falling or causing injury. It may also be difficult for these patients to maintain the optimal positioning strategies in a chair for any length of time and therefore may not gain the benefits of being positioned in a seated position. Therefore, clinicians need to balance the therapeutic value of sitting a cognitively and behaviourally impaired patient in a chair versus the potential safety risks associated with being in a seated position.

In clinical practice, these patients may benefit from frequent and shorter periods of sitting in a chair rather than prolonged periods of sitting. These patients may also need supervision to sit out safely, although this has staffing implications. Cognitive or behavioural impairments can often be managed when a person is sat out with behavioural management plans including activities for distraction or sensory stimulation [59].

In addition to supervision, a number of accessories and equipment can be considered when seating cognitively and behaviourally impaired patients. The use of seating accessories, such as pelvic straps, seat belts, and lap trays are one option, although their use is ethically controversial as it may be interpreted as a form of physical or technological restraint [60]. If accessories need to be implemented for these patients, the four-quadrant approach is a helpful framework for the ethical analysis of situations involving potential restraint [60]. This approach facilitates ethical analysis by considering four elements—indications for intervention, patient preference, quality of life, and contextual feature. Wheelchair or armchair accessories, including tilt-in-space chairs, should not be used with the primary intention of restraint. Wander guards, or bed and chair alarms, can also be considered to minimise risk when patients attempt to move in the absence of supervision.

Pressure Care

Pressure sores are a significant problem in healthcare causing discomfort and distress to patients, extended hospital stays, and increased health costs. In the UK, it has been estimated that pressure sores account for up to 4 % of all NHS expenditure and an annual cost of £1.4–2.1 billion [61]. In addition to the costs for healthcare, pressure sores can have a significant impact on patients' quality of life [62, 63].

What Are Pressure Sores?

Pressure sores can be defined as "A new or established area of skin and/or tissue discolouration or damage which persists after the removal of pressure and which is likely to be due to the effects of pressure on the tissues" [64]. A number of factors have been identified which increase the risk of skin breakdown. These include the following:

- Reduced mobility [65, 66]
- Sensory impairment [67, 68]
- Neurological impairment [69]
- Acute illness [70]
- Reduced conscious level [65, 71]
- Age [72, 73]
- Vascular disease [65]
- Terminal illness [74, 75]
- Malnutrition [72, 76]
- Dehydration [77]
- Incontinence [65, 78]

Pressure sores can develop on many areas of the body, particularly on the bony prominences such as the sacrum, heels, malleoli, shoulders, hips, and elbows. However, any area of the body which is exposed to pressure forces for a prolonged period of time is at risk.

There are three specific types of skin damage that can account for skin breakdown: pressure, shear, and friction.

Pressure

The pressure of the patient's own body weight compresses the skin and underlying capillaries between the patient and the surface, e.g. bed, chair. When this pressure is applied over a long period of time without relief, capillary damage occurs. Healthy capillary pressure is 20–40 mmHg but this is often lower in patients with vascular disease, potentiating the risk of pressure sore development [79].

Shear

As a result of movement, skin layers are wrenched in opposite directions; the epidermis remains static but the underlying tissue is forced forward, thereby damaging the capillaries. The capillary damage leads to tissue ischaemia. Shear is an important factor for patients in the semi-recumbent position in a bed or chair where they may be at risk of sliding out of position. Shear forces are then experienced on the sacrum, heel areas, and potentially the shoulder prominences.

Friction

The skin rubs against another surface, leading to the epidermis being stripped away and the development of small, shallow blisters. This can be caused by uneven surfaces, such as wrinkles in bed sheets or clothing.

Grading of Pressure Sores

Once tissue damage has occurred, pressure sores are graded according to their depth and the level of skin layers which are affected. They are graded from grade 1, indicating redness without tissue breakdown, to grade 4, with damage to muscle, bone, or tendon (Table 9.5) [80]. The use of a standardised scale can ensure that different professionals are using the same standards to assess and treat pressure sores.

Pressure Sores in Stroke Patients

Since 2000, 17 studies have reported the frequency of pressure sores in stroke patients across a range of healthcare settings and have investigated risk factors in this population (Table 9.6).

These studies indicate that pressure sores are a persisting problem throughout the post-stroke period and that increased levels of dependency predict an increased risk of pressure sores [2, 81–83]. Those patients admitted with pressure sores to a rehabilitation setting may have pre-existing pressure sores but during the rehabilitation phase, the risk of skin breakdown persists [83]. For stroke patients, body areas at particular risk appear to be the sacrum, malleoli, and heels [84, 85]. For those patients with severe disability, there appears to be an increased risk of developing grade 4 pressure sores with full-thickness skin damage [82].

With the exception of the study by Suttipong and Sindhu [86], which included severely disabled older stroke patients in a rural area of Thailand, it is notable that there has been a reduction in pressure sore incidence in acute units since 2000. The introduction of stroke units and the increased use of specialist mattresses and cushions may go some way to explaining these changes.

Table 9.5 Grading of pressure sores [80]

Category/ stage	Title	Description
I	Non-blanchable redness of intact skin	Intact skin with non-blanchable erythema of a localised area, usually over a bony prominence. Discolouration of the skin, warmth, oedema, hardness, or pain may also be present. Darkly pigmented skin may not have visible blanching. *Further description:* the area may be painful, firm, soft, warmer, or cooler as compared to adjacent tissue. Category/stage I may be difficult to detect in individuals with dark skin tones. May indicate "at-risk" persons
II	Partial-thickness skin loss or blister	Partial-thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanguineous filled blister. *Further description*: Presents as a shiny or dry shallow ulcer without slough or bruising. This category/stage should not be used to describe skin tears, tape burns, incontinence-associated dermatitis, maceration, or excoriation
III	Full-thickness skin loss (fat visible)	Full-thickness tissue loss. Subcutaneous fat may be visible but bone, tendon, or muscle is *not* exposed. Some slough may be present. *May* include undermining and tunnelling *Further description*: the depth of a category/stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput, and malleolus do not have (adipose) subcutaneous tissue and category/stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep category/stage III pressure ulcers. Bone/tendon is not visible or directly palpable
IV	Full-thickness tissue loss (muscle/bone visible)	Full-thickness tissue loss with exposed bone, tendon, or muscle. Slough or eschar may be present. Often include undermining and tunnelling. *Further description*: the depth of a category/stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput, and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/stage IV ulcers can extend into muscle and/or supporting structures (e.g. fascia, tendon, joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable

Risk Scoring

There are a number of risk prediction scores to identify those patients at increased risk of pressure sores. The three most commonly used are the Waterlow, Norton, and Braden scores.

The Waterlow score has ten variables: weight, continence, skin type, mobility, age, sex, nutrition, neurological deficits, surgery/trauma, and medication [87]. A higher score is indicative of higher risk. A high-risk score is 15–20 and very high-risk score is above 20. The Norton score has five variables: general physical

Table 9.6 Summary of studies investigating pressure ulcers in stroke patients

Study	Number of stroke patients	Follow-up period	Care setting	Frequency of pressure sores by grade and/or time	Factors increasing pressure sore risk
Langhorne et al. (2000) [81]	311	Median follow-up 7 weeks	Mixed–hospital and community	In-hospital – 21 % 6 months – 8 % 6–18 months – 8 % 18–30 months – 11 %	Increased pressure sore risk with increased dependence (as measured on FIM)
Westergren et al. (2000) [82]	123	Not reported	Rehabilitation	Grade 1–4.1 % Grade 2–4.9 % Grade 3–3.3 % Grade 4–2.4 %	Increased pressure sore risk with dependent eating (Katz ADL)
Roth et al. (2001) [83]	1,029	Mean follow-up 28 days	Rehabilitation	8 % on admission 4.3 % during rehabilitation	Increased pressure sore risk with greater stroke severity (as measured on NIHSS)
Evans et al. (2001) [107]	304	Follow-up 3 months	Acute	8 % on stroke unit	Not reported
Doshi et al. (2003) [108]	140	Not reported	Rehabilitation	0.7 %	Not reported
Kwan et al. (2004) [109]	351	Mean follow-up 10 days	Acute	3 %	Not reported
Bae et al. (2005) [110]	579	Median follow-up 11 days	Acute	1.38 % during hospital admission	Not reported
Saxena et al. (2006) [84]	200	Mean follow-up 34 days	Rehabilitation	Sacral redness – 6.5 % Malleolar redness – 1.5 % Sacral sore – 1.5 % Ankle sore – 1 %	Not reported

Capon et al. (2007) [85]	201	Single data collection point–no follow-up reported; 53.4 % >1 year post-stroke	Long-term units	27 %	Not reported
Sackley et al. (2008) [2]	122	Follow-up to 12 months	Mixed–rehabilitation and community	Whole study period – 22 % 3 months – 17 % 6 months – 13 % 12 months – 18 %	Increased likelihood of all complications including pressure sores with increased functional dependence (Barthel Index)
Suttipong and Sindhu (2012) [86]	168	Single data collection point–no follow-up reported; post-stroke period 1–240 months	Community	47.6 % Grade 1–15.5 % Grade 2–25 % Grade 3–0.6 % Grade 4–6.5 %	Increased pressure sore risk with skin moisture, friction/shear forces, poor mobility, low activity level, and poor nutrition
Hong et al. (2008) [111]	1,254	Follow-up to 3 months	Acute	3.3 %	Pressure sore relationship with poor functional outcome (as measured on mRS)
Indredavik et al. (2008) [112]	244	Follow-up to 3 months	Acute	0.6 %	Not reported
Ingeman et al. (2010) [113]	8,024	Not reported	Acute	0.25 % vs. 1.4 % (comparing 2 registries)	Not reported
Ingeman et al. (2011) [114]	13,721	Follow-up 30 days and 1 year	Acute	1.2 %	No association with pressure ulcer and 30 day mortality
Kuptniratsaikul et al. (2013) [115]	214	Follow-up 1 year	Mixed–rehabilitation and community	2.6 %	Not reported
Rahman et al. (2013) [116]	647	Follow-up of 5.7–4.7 days	Acute	2.19 % Grade 3 and 4–0.43 %	Increased pressure sore risk with each additional year of age and with additional co-morbidities

mRS modified Rankin Score, *NIHSS* National Institute of Health Stroke Severity score, *FIM* functional independence measure, *LOS* length of stay

condition, mental state, mobility, level of activity, and incontinence [88, 89]. This tool was developed in elderly hospitalised patients. The scale ranges from 5 to 20, with lower scores indicating higher risk. A score of 12 or below indicates high risk.

The Braden risk assessment indicator has six variables: sensory perception, moisture, activity levels, mobility, nutrition, and exposure to friction or shear forces [68, 90]. The tool was developed in nursing home patients. The scale ranges up to 23, with lower scores indicating higher risk. A score of 12 or less indicates high risk.

The Waterlow score has been found to have the highest sensitivity of these tools whilst the Norton score had the highest specificity [91]. A further study found that the Waterlow score plus serum albumin levels were significant predictors of pressure sore development [92]. However, risk assessment tools themselves have a number of drawbacks and are not designed to take account of preventative measures already in place. Staff should also use their clinical judgement and, in addition to using a risk assessment score, reflect on a regular basis if the preventative strategies used in practice are effective [93].

Strategies to Prevent Pressure Sores in Stroke Patients

Pressure-relieving surfaces are designed to reduce or relieve the pressure on the skin and tissues of the patient from the weight of their body and a surface such as a bed or chair. Such devices are static (e.g. foam mattress), dynamic (with varying pressure under the patient, such as an alternating pressure air mattress, as shown in Fig. 9.14), or rotating (with a tilting mechanism on the bed to laterally rotate patients without manually rolling them).

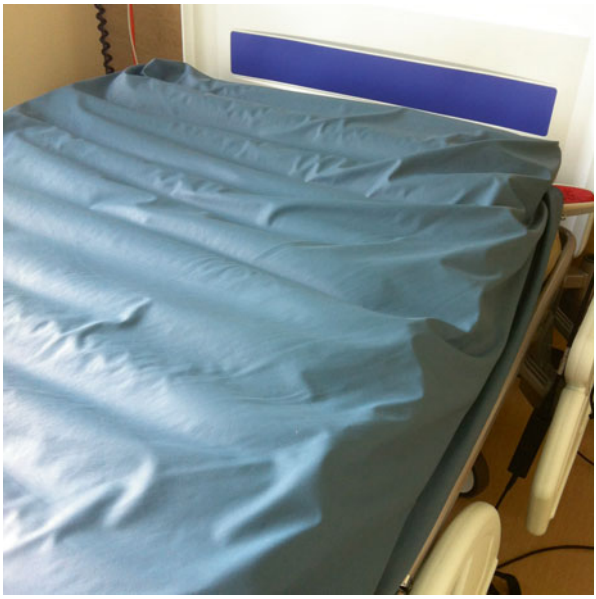


Fig. 9.14 Pressure air mattress

Goals for pressure sore prevention have been identified as:

- Identify at-risk individuals and specific factors placing them at risk
- Maintain and improve tissue tolerance to pressure in order to prevent injury
- Protect against the adverse effects of pressure, shear, and friction
- Improve the outcome for patients at risk of pressure damage through educational programmes to healthcare providers, patients, and family [94]

Interventions to Prevent Pressure Sores

Three specific interventions can be considered to prevent pressure sore development: interventions for impaired mobility, for impaired nutrition, and to improve skin health.

Interventions for Impaired Mobility

In a systematic review of evidence in preventing pressure sores, 51 RCTs evaluated interventions for impaired mobility [95]. These results suggested that overlay mattresses in operating theatres were likely to be beneficial in reducing pressure sores. However, dynamic mattresses were likely to be as effective as overlay mattresses but were likely to be more cost effective in inpatient settings. Both mattresses were superior to static hospital mattresses. In terms of repositioning, one study found that repositioning patients every 4 h with a specialised foam mattress reduced the incidence of pressure sores compared to every 2 h on a standard hospital mattress [96]. However, this study did not directly compare different repositioning frequencies on the same specialised mattress, and therefore it is difficult to support a standard of four hourly repositioning based on this single trial. In the UK, a recently published guideline recommends repositioning at least every 6 h, or 4 h for those patients at high risk [97].

In a further review by the Cochrane Collaboration in 2011 [98], foam mattresses were found to be superior to standard hospital mattresses in preventing pressure sores, and medical-grade sheepskins were found to be effective in reducing pressure sores. There was insufficient evidence to demonstrate whether patients at high risk of pressure sores require alternating or static pressure mattresses, though both pressure mattresses may be superior to the standard hospital mattress for pressure sore prevention. However, one study suggested that alternating pressure mattresses were more cost effective than alternate pressure overlays [99].

For stroke patients identified at high risk of pressure sores, either dynamic or overlay air mattresses should be considered as soon as possible following admission. Repositioning is likely to be required at least every 4 h but should be tailored according to the patient's skin condition and risk assessment.

Interventions for Impaired Nutrition

A systematic review identified five RCTs for impaired nutrition [95] and one of these included studies found that oral nutritional supplements in patients over 65 years resulted in reduced pressure sore risk [100]. However, the benefits of routine oral nutritional supplementation in stroke patients have been proven to be ineffective following the results of the FOOD trial [101]. Whilst it remains clinically important to ensure adequate nutrition for patients, including for the prevention of pressure sores, routine nutritional supplementation is not recommended for stroke patients.

Interventions for Impaired Skin Health

A systematic review identified three RCTs that investigated methods of improving skin health, typically with topical applications to the skin [95]. The studies were inconclusive in whether specific topical treatments could be effective in reducing pressure sore risk.

Despite national and international guidelines on the prevention of pressure sores and the widespread availability of risk-scoring tools for pressure sores, there remains uncertainty as to how frequently these are used in clinical practice [102–104]. Healthcare professionals involved in the care of stroke patients need to be aware of their role to ensure that adequate attention is paid to prevent the potentially damaging effects of pressure on patients' skin, the rehabilitation process, and quality of life.

Management of Pressure Sores in Stroke Patients

Once a pressure sore develops in a stroke patient, it is crucial that an appropriate management plan is developed that incorporates the whole multi-disciplinary team. There is a risk that the rehabilitation plan will be at risk and the patient's level of independence may change. The occupational therapist will be crucial to ensure any cushion provided for the patient's wheelchair is appropriate to their pressure sore risk whilst also maintaining their safety and position. The physiotherapist will be crucial to ensure that patient positioning is optimised to prevent complications and facilitate recovery. The nursing staff have a key responsibility to make a treatment plan for management of the pressure sore, including selecting appropriate dressing types, reviewing mattress and cushion provision, repositioning schedules, and seeking advice from the tissue viability specialists. Often there is an increase in the amount of time that patients spend in bed once a pressure sore has developed, and this may have a significant impact on independence, mood, and physiology [105]. There is no evidence that bed rest is necessary and it is more appropriate to use an

individual care plan for each patient that limits time spent in any one position. The patient must still be encouraged to participate actively in rehabilitation, which ultimately will aim to improve their mobility, thereby preventing pressure sore risks for the future. As it has been reported that stroke patients spend around 46.4 % of their time sitting out of bed, pressure care management is imperative to consider alongside positioning, seating, and postural management [106].

Summary

The prevention of pressure sores is a vital component of good stroke care. Their development, and therefore also their prevention, is multi-faceted and requires a multi-disciplinary approach. As reported, pressure sores can develop throughout the patient pathway—from acute care to rehabilitation and into long-term care. Therefore, the strategies used to prevent pressure sore development must also continue for as long as the patient remains at risk, regardless of their care setting. The use of specialised mattresses and cushions, according to their risk, is only one element of a prevention strategy. Repositioning, improving skin care, ensuring adequate nutrition, and rehabilitation to improve functional independence must also be part of a pressure sore preventative strategy for stroke patients.

Conclusion

This chapter has focussed on positioning and pressure care of patients post-stroke. It has discussed the benefits of correct positioning and complications associated with poor positioning and suggested possible strategies to position patients optimally when resting in bed and when seated. It has also discussed pressure care management in the stroke population, including the use of tools to identify patients at risk of developing pressure sores as well as strategies to prevent and manage pressure sores.

Whilst there is some evidence regarding optimal positioning, seating, and pressure care for patients post-stroke, more research is required to guide clinicians in these aspects of care. With regard to positioning and seating, there is a need to establish the optimal dosage of positioning strategies as well as the effect of different postural seating systems on patient outcome; with regard to pressure care, there is a need to establish the effect of different pressure-relieving systems. In the absence of definitive evidence regarding correct positioning and pressure care, the importance of delivering care on a detailed assessment of the patient's clinical presentation and implementing appropriate strategies based on these assessment findings cannot be underestimated.

Patient Questions

Q. What is the best position for a stroke patient when resting in bed?

A. There is no one ideal or recommended position for stroke patients, as each position has benefits and limitations and the choice of position is dependent upon the underlying goal of adopting that particular position. It is recommended that a range of positions are used in order to gain the benefits of that position and to reduce the likelihood of developing complications associated with maintaining positions for prolonged periods of time.

Q. What can affect a patient's ability to sit in a chair following a stroke?

A. Following a stroke, there are multiple factors that can affect a patient's ability to sit in a chair, including cognitive, physical, and sensory impairments. A full assessment should be completed by an occupational therapist and physiotherapist to identify a patient's impairments and to determine the extent to which these impairments may impact on sitting in a chair safely. This should be reviewed as the patient's progresses.

Q. How should the risk of pressure sores be assessed?

A. It is important to assess every stroke patient for the factors known to increase the risk of pressure sores developing, such as immobility and incontinence. Use of a standardised assessment tool, such as the Waterlow, Braden, or Norton score, may help with the assessment but should not replace clinical judgement of other factors considered to increase the patient's risk. Risks and any care plans to reduce the risk of pressure damage should be reviewed regularly and after any significant change, such as acute illness.

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Chapter 10
Management of Spasticity

Jonathan Birns and Tehmina S. Irani

Abstract Spasticity is one of the many components of the upper motor neurone syndrome; the other components including exaggerated reflexes, clonus, clasp-knife phenomena, flexor and extensor spasms, spastic dystonia, and Babinski's sign. Spasticity is a symptom that is not isolated and can cause pain, stiffness, and spasm, resulting in a massive impact on a person's physical and emotional lifestyle. The management of spasticity requires a multidisciplinary approach incorporating nurses, physicians, physiotherapists, occupational therapists, and orthotists working together to provide a variety of treatments tailored to the needs of the individual patient.

Keywords Spasticity • Tone • Upper motor neurone • Stroke • Post-stroke

Key Messages

- Spasticity is one component of the upper motor neurone syndrome that is characterised by increased tone, exaggerated reflexes, weakness, and contractures.
- Spasticity can cause pain, stiffness, and spasm, resulting in a massive impact on a person's physical and emotional lifestyle as well as carer burden.
- The management of spasticity involves a multidisciplinary team approach to direct treatment tailored to the needs of the individual patient.
- A variety of non-pharmacological and pharmacological treatment options for spasticity exist.
- The management of spasticity is integral to the aims of rehabilitation involving re-education of movement and promotion of independence.

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Introduction

The most common definition used for spasticity is a motor disorder characterised by "a velocity dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome" [1]. With its increased tone and exaggerated tendon jerks, spasticity may be a significant cause of disability and pain and, if untreated, may lead to contractures. It is one component of the complex clinical picture that results from the upper motor neurone syndrome that includes weakness, loss of dexterity, fatigability, and muscle spasms [1]. The extent and type of spasticity can fluctuate widely according to position, fatigue, stress, and drug use. It is a dynamic phenomenon and requires continued multidisciplinary assessment and management.

Epidemiological studies have shown spasticity to affect 17–38 % of stroke patients and for it to occur usually within the first few weeks or months following stroke [2, 3]. However, the onset of spasticity is highly variable and can occur in the short-, medium-, or long-term post-stroke period [4]. Spasticity presents in a variety of ways depending on the size, location, and age of lesion. Epidemiological studies have demonstrated spasticity to affect primarily the elbow (79 % of patients), the wrist (66 %) and the ankle (66 %) [5]. In the upper limbs, the most frequent pattern of arm spasticity is internal rotation and adduction of the shoulder coupled with flexion at the elbow, the wrist, and the finger [6, 7]. In the lower limbs, adduction and extension of the knee with equinovarus foot is the most observed pattern.

Pathophysiology of Spasticity

Spasticity is one of the positive features of upper motor neurone syndrome and arises from upper motor neurone lesions involving the corticoreticulospinal system in the brain, brainstem (most importantly, those arising in the bulbopontine tegmentum), or spinal cord, and the clinical syndrome depends on the lesion's location, extent, and the time since it occurred [8]. These lesions disturb the balance of supraspinal inhibitory and excitatory inputs, producing a state of net disinhibition of the spinal reflexes. These include proprioceptive (stretch) and nociceptive (flexor withdrawal and extensor) reflexes [9]. The increased spinal cord excitability and impaired inter-neuronal systems result in increased muscle tone, hyper-reflexia, muscle overactivity, and antagonist muscle co-contraction.

Most of the important upper motor neurones controlling spinal reflex activity arise in the brainstem. However, the ventromedial reticular formation, the origin of the main supraspinal inhibitory tract (dorsal reticulospinal pathway), is under cortical control (Fig. 10.1). A lesion in the path of these corticobulbar fibres, either in the cortex or in the internal capsule thus results in reduced inhibitory drive and net excitation of spinal cord activity. An appreciation of this neuronal pathway explains

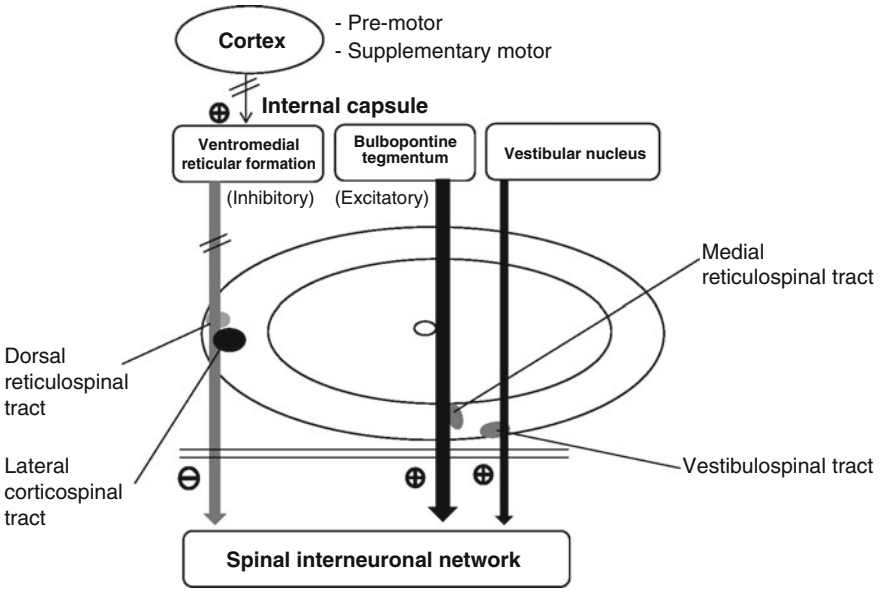

Fig. 10.1 The majority of descending pathways controlling spinal reflex excitability. (Inhibitory fibres are shown in grey and excitatory fibres are shown in *black*)

why spasticity secondary to stroke is usually less marked than that due to a spinal cord lesion, with less severe upper motor neurone features [10].

There are two main contributory factors to resistance to movement in the context of post-stroke limb spasticity: a neurogenic component (overactive muscle contraction) and a biomechanical component (stiffening and shortening of the muscle and soft tissues). If left untreated, a vicious cycle occurs in which unopposed contraction due to spasticity of affected muscle groups leads to abnormal limb posture, resulting in soft tissue shortening and further biomechanical changes in the contracted muscles. This, in turn, prevents muscle lengthening and perpetuates further tonicity and formation of contractures [11].

Effect on Lifestyle

People with spasticity often feel embarrassed and frustrated with its limiting effect on daily activities [10, 12]. Severe pain and stiffness, in addition to loss of function, can have a devastating effect on the patient, and problems with sleep due to spasms can lead to fatigue and depression. Spasms in the limbs may also result in problems with positioning and pain that may, in addition, affect sexual relationships. Maintaining hygiene may prove difficult adjacent to areas with increased tone, and patients with spasticity are also at a high risk of developing pressure ulcerations [13]. The patient's emotional and psychological state can be in constant turmoil,

with a strain on their social life, and referral to appropriate specialist agencies may be of benefit [14]. For some patients, spasticity may not only be distressing and painful, but an expensive cause of disability in terms of increased carer burden and reduced rehabilitative progress.

It may be seen, therefore, that secondary complications arising due to spasticity include impaired movement, hygiene, and self-care; poor self esteem, body-image, and sleep patterns; low mood; deformity; weakness; pain; contractures; and pressure ulcers. Patients with spasticity are also more likely to live in institutional care than in their own home, and are significantly more functionally impaired than those without spasticity.

Assessment

Spasticity assessment includes both identifying which muscles or muscle groups are overactive, and also determining the effect of spasticity on all aspects of patient function, including mobility, employment, and activities of daily living. Furthermore, factors such as cognition and deficits of sensation, attention, and vision (that may exacerbate spasticity) need to be evaluated. A systematic approach to assessment is required by a multidisciplinary team involving medical specialists (often from rehabilitation medicine or neurology disciplines), nurses, and allied healthcare professionals including physiotherapists, occupational therapists, orthotists, and rehabilitation engineers.

Formal assessment of tone may be measured using clinical scales such as the modified Ashworth and Tardieu scales (Table 10.1), or using techniques such as

Table 10.1 Modified Ashworth and Tardieu scales

Modified Ashworth scale	
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder of the range of movement
2	More marked increase in muscle tone through most of the range of movement, but affected parts easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected parts rigid in flexion or extension
Modified Tardieu scale	
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of the passive movement, with no clear catch at precise angle
2	Clear catch at precise angle, interrupting the passive movement, followed by release
3	Fatiguable clonus (<10 s when maintaining pressure) occurring at precise angle
4	Infatiguable clonus (>10 s when maintaining pressure) occurring at precise angle

electrogoniometry to measure range of movement across a joint or quantitative neurophysiology [15, 16]. Whilst the latter two techniques are not widely available or practical in routine clinical practice, the clinical scales require no instrumentation, are quick to carry out, and have good inter- and intra-observer reliability [17–19]. The modified Ashworth scale is most widely used but its validity, reliability, and sensitivity are acknowledged to have limitations [20]. A number of scales also exist to assess patients' self-reported health status including pain, comfort, mobility, continence, and fatigue [21, 22]. Since pain and stiffness are important and troublesome symptoms in relation to spasticity, visual analogue, and verbal rating scales are often usefully employed to record objective change following treatment. In those who have communication deficits or who lack numerical skills, pictoral rating scales may be used. In people with severe cognitive deficits and problems with communication, tools such as the AbilityQ may be used to test an individual's ability to use different types of scales and thus help present questions in an appropriate format [23].

In patients with selective, underlying, voluntary movement in limbs with increased tone limiting "active" function, functional assessments are helpful tools to guide rehabilitative progress. Examples include the Action Research Arm, Frenchay, and nine-hole peg tests for the upper limbs; the Functional Ambulation Category, 10-m walking time, and 6-min walking distance tests for lower limbs [11]. Passive function can also be assessed using verbal or visual analogue ratings of "ease of care", timed-care tasks (for example, the time taken for washing and dressing), or formal scales that measure dependency or carer burden (such as the Barthel's index of activities of daily living).

First introduced in the 1960s, goal setting and its attainment has developed into a crucial element of spasticity assessment [24]. The attainment of goals following interventions varies amongst patients, and a single outcome measure is not always able to capture all domains. The Goal Attainment Scale (that involves simple recording of treatment goals achieved) has proved useful in terms of being suitable for patients with health problems, who need a multidimensional but individualised approach to treatment planning and outcome [25].

Purpose of Treatment

The management of muscle tone is an integral part of therapy for patients suffering from spasticity. Muscle tone is a dynamic, complex process that is part of an overall pattern of posture and movement. Appropriate management of tone is one of the fundamental principles of the Bobath method of facilitative physiotherapy, which gives priority to normalisation of tone and improving symmetry even at the cost of postponing standing or walking. However, this pre-occupation with normalisation of tone is not supported by evidence, and there are several other approaches which combine early mobilisation with active muscle tone management during rehabilitation [26].

The management of abnormal tone and spasticity is difficult, as it depends on achieving the right balance between hypo- and hypertonia between different muscle

groups. The problem is compounded by the fact that spasticity varies between different groups of muscles and times of the day, and is affected by the emotional state of the patient, activity being undertaken, limb posture, and the timing of medication. Inappropriate exercise can result in inappropriate tone patterns, to the ultimate detriment of the patient. If not managed correctly, spasticity leads to poor gait patterns, contractures, and loss of function.

Spasticity should be considered in relation to other impairments, and in the context of therapy goals, because interventions directed solely at reduction of spasticity are unlikely to result in significant functional gains. The therapeutic management of spasticity is closely related to the aims of rehabilitation; these include avoidance of complications, restoration of movement, re-education of movement and gait, development of self-dependency, and social integration, improving self-esteem and overall body image, as well as promoting new neurophysiological dynamics and neural plasticity. A further aim of treating spasticity is to relieve pain and other distressing symptoms that have a detrimental effect on quality of life.

There should be a multidisciplinary team approach to spasticity management, through which realistic goals and expectations of the patients, families, and caregivers can be established. It is important that treatment be tailored to the individual patient, and factors that may aggravate spasticity, including inter-current medical illness, medications that increase muscle tone, and emotional stressors, should be managed in the first instance [27, 28]. It should also be borne in mind that some patients may be able to use their increased tone to aid with function and maintaining postural control and ambulation, and so global reduction of tone may be destabilising. Appreciation of the differing treatment options for focal versus global spasticity is important, as is the awareness that treatment of spasticity may ameliorate weakness in affected limbs.

Non-pharmacological Approaches

Prevention of Aggravating Factors

In addition to causing pain and discomfort, pain and discomfort themselves and other nociceptive stimuli aggravate the symptoms from spasticity. As such, a multidisciplinary approach to identifying any aggravating factors and treating them is crucial to management of spasticity. Besides pain and discomfort, the other common aggravating factors are constipation, infection, tight clothing, and poor postural management.

Education and Psychological Support

All members of the multidisciplinary team should provide education to patients and carers about the causes and nature of spasticity and, if needed, strategies should be employed to reduce emotional stress. Patients and carers should be provided with

verbal and written information, including information leaflets, to help them understand how spasticity affects day-to-day function and how to avoid any triggers. Patients need to be made aware of how visceral and cutaneous stimuli may affect their spasticity.

Involvement of Physiotherapy/Occupational Therapy

Treatment of abnormal tone is initiated by physiotherapists, who can offer a range of interventions including physical therapy, attention to posture and seating, and orthotic devices [29–31]. Correct positioning is a critical aspect of management in order that the patient is in a balanced and stable posture that is comfortable and maximises function. Optimal seating is planned and implemented by occupational therapists and physiotherapists, and this may involve the use of a variety of seating adjustments such as foot straps; knee blocks; and head, neck, and trunk supports [32]. Occupational therapists and physiotherapists also are responsible for application of casts and splints to minimise spasticity and prevent contractures [33]. Implementation of planned seating and positioning strategies by nurses and carers throughout the day and night is crucial to management of spasticity and prevention of its complications.

Physiotherapists and occupational therapists should complete their assessments over a period of time and in conjunction with other members of the patient's multidisciplinary team, including the patient's carers and nurses, in order to optimise management strategies. It is essential that such strategies attain the correct balance between movement and positioning and continuity of care, particularly across the interfaces of primary and secondary care, involving community rehabilitation teams and care agencies, facilitates the appropriate choice and timing of any management intervention [21].

Pharmacological Treatments

Drug therapy is generally initiated at low dosages and then gradually increased in an attempt to avoid adverse effects [21, 28]. Optimal therapy is the lowest effective dosage. Drug treatments should be contemplated early in severe cases of spasticity, where secondary problems often develop and combination therapy using oral medications and focal injections of botulinum toxin or other chemodenervating agents may allow for the best control of spasticity with the least side effects [34].

Oral Medication for Treatment of Global Spasticity

Baclofen, tizanidine, diazepam (that act centrally) and dantrolene (that acts peripherally on skeletal muscle) are the most widely used drugs in patients with global spasticity. Other agents such as gabapentin, clonazepam, clonidine, and cyproheptadine have also been used for the management of spasticity, but in fewer patients.

Baclofen

This is the most widely used anti-spastic drug whose clinical benefits mainly relate to reducing muscle spasms and hyper-reflexia [35]. Baclofen is structurally similar to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid) and increases inhibition both pre-synaptically and post-synaptically by selectively binding to GABA-B receptors [36]. The common starting dose is 5 mg three times daily that then may be titrated up to a maximum daily dose of 60–100 mg in divided doses. Side effects are predominantly from central depressant properties including sedation, ataxia, weakness, and fatigue [35]. Tolerance to the medication may develop, and baclofen must be slowly weaned to prevent withdrawal effects such as seizures, hallucinations, and increased spasticity. Limitations of baclofen use include its lowering of seizure threshold and patients' intolerance of side effects at higher doses.

Tizanidine

This is an imidazoline central alpha-adrenoceptor agonist that has been confirmed to be a useful anti-spastic agent. It is a short-acting drug with dose-dependent linear pharmacokinetics and larger inter-patient variability compared with other anti-spastic agents [37]. Patients report less muscle weakness from tizanidine than baclofen or diazepam, but side effects include drowsiness, fatiguability, dizziness, dry mouth, and gastrointestinal disturbance [37–39]. There is a small incidence of abnormal liver function tests and these should be monitored at intervals during therapy [40]. Tizanidine may be combined with baclofen, presenting the opportunity to reduce the dosage of both drugs, but additive adverse effects, including sedation, may occur.

Diazepam

This was one of the first anti-spastic agents, but in view of its potential to cause significant fatigue and drowsiness, is only recommended for relieving painful nocturnal spasms [35, 41]. Midazolam, another benzodiazepine, is sometimes useful to help distinguish between patients with active spasticity and contractures.

Dantrolene

This is a useful anti-spastic agent that has a similar range of side effects to baclofen, but is less likely than the other agents to cause drowsiness, confusion, and other central effects because of its mechanism of action. Dantrolene has been shown to decrease muscle tone, clonus, and muscle spasm, but since its action is not selective for spastic muscles, it may cause generalised weakness, including weakness of the respiratory muscles [36]. It can also cause hepatitis, and so periodic monitoring of liver function tests is advised [42, 43].

Gabapentin

Gabapentin interacts with voltage-sensitive calcium channels in cortical neurons and increases the synaptic concentration of GABA, enhances GABA responses at non-synaptic sites in neuronal tissues, and reduces the release of mono-amine neurotransmitters. It is generally used as an anticonvulsant and analgesic for neuropathic pain. The most common side effects include dizziness, fatigue, drowsiness, weight gain, and peripheral oedema. In a randomised, double-blind, placebo-controlled study involving 30 patients with upper motor neurone spasticity secondary to a pyramidal tract lesion, Formica et al. showed Gabapentin in doses of 2,700–3,600 mg/day to provide significant improvement in Ashworth scores but no change in spasm frequency [44].

Focal Treatments, Intrathecal Baclofen, and Surgical Techniques

Patients who are unresponsive or intolerant to conservative spasticity treatments may benefit from referral to a specialist service for consideration of other therapeutic modalities [45].

Focal Treatments

Spasticity is often focal in origin and it may be more appropriate only to reduce spasticity in the affected muscles [34]. Focal pharmacological treatments should be combined with non-pharmacological therapies, including stretching programmes and physiotherapy assessments, in order to obtain optimal benefits. The aim is to improve function, mobility, and dexterity; ease pain and decrease spasms; allow orthotic wearing; and improve body image in terms of cosmesis.

Botulinum Toxin

Botulinum toxin is a powerful neurotoxin produced by Clostridium botulinum. There are seven distinct subtypes (A–G) and the most commonly used one in spasticity is Type A botulinum toxin. Botulinum toxin prevents presynaptic release of acetylcholine resulting in neuromuscular blockade. The multicentre, randomised, controlled BoTULS (Botulinum Toxin for the Upper Limb after Stroke) trial, involving 333 stroke patients with upper limb spasticity and reduced arm function, demonstrated botulinum toxin injection (in addition to a 4-week therapy programme) to improve muscle tone, upper limb strength, basic arm functional tasks of hand hygiene and facilitation of dressing, and pain, compared with therapy alone [46]. There was no significant difference, however, in achievement of improved arm

function between groups using the Action Research Arm Test at 1 month as a primary outcome measure. The ongoing PrOMBIS (Predicting Outcome and Measuring benefit from Botulinum therapy In Stroke) trial may provide more information regarding the potential for botulinum toxin to improve the functional ability of stroke patients with spasticity.

Botulinum toxin is injected intramuscularly with an onset of action within 12 h and its clinical effect, in terms of reduction in spasticity, is visible over a course of 4–7 days from the time of injection. The total duration of the effect lasts for approximately 10–12 weeks with the maximal effect seen at 3–4 weeks. Repeat injections may be necessary but are not recommended within 3 months. Some patients may become resistant to botulinum toxin as a result of antibody formation [11]. Side effects are uncommon with licensed and recommended doses, but induction of excessive weakness of the injected muscle, pain, flu-like symptoms, and rash exist. If larger doses are employed, neuritis, dysphagia, and respiratory compromise may occur [11, 47].

Post-botulinum toxin injection, it is important for the multidisciplinary team to review the ongoing care of the injected muscle, the achievement of goals, and the measurement of functional outcomes with the patient and their carers. Splinting and orthosis usage, in addition to botulinum toxin, provides prolonged stretch to the muscle injected and aims to improve muscle length, correct and prevent contractures, and maximise function. Pre-existing splints should be reviewed and, if required, new ones applied 7–14 days post-injection when maximal clinical effects of botulinum toxin are clinically apparent [11]. At the same time, it is important to make sure that the weakened muscles are not overstretched, as that can end up in tearing of the stiffened muscle fibres, resulting in intramuscular haematoma. In addition, ongoing patient education on stretching regimens and guidance on participating in activities is useful. Functional electrical stimulation may also be combined with botulinum toxin therapy to improve symptoms and function [48, 49].

Phenol Nerve Block

Phenol (carbolic acid), in concentrations more than 3 %, acts as a neurolytic agent and it is this neurolytic effect that is responsible for reducing spastic muscle innervations, and hence spasticity. In addition, phenol has a local muscle relaxant property and patients experience a transient muscle relaxation within an hour of phenol nerve blocks. Phenol nerve blocks produce a dramatic and instant effect, but the technique may be time-consuming, provide variable duration of symptomatic relief, and there is a risk of painful dysaesthesia and neural damage following the procedure [29, 50, 51].

Phenol injections are generally used for regional lower limb spasticity in individuals who are intolerant of systemic muscle relaxant therapies. They are also occasionally used for large muscles of the lower limbs (e.g. the quadriceps and hamstrings) that may require doses of botulinum toxin too high to be safely used for the individual. Side effects are not very common, but include those local to the

injection site such as erythema, pain, discomfort, and sometimes local haematoma, infection, abscess formation, muscle fibrosis, or nerve causalgia. Very rare side effects include vascular injury and systemic side effects of arrhythmia, pulmonary fibrosis, confusion, and renal impairment [52].

Intrathecal Baclofen Therapy

This consists of long-term delivery of baclofen to the intrathecal space from a programmable pump surgically placed just below the skin in the abdomen [35]. Meythaler et al. showed this to be an effective treatment modality in a randomised study of 21 stroke patients with "intractable" spasticity for more than 6 months with significant reductions in Ashworth scores [53]. The ongoing multicentre, randomised, controlled SISTERS trial of intrathecal baclofen versus best medical treatment in patients with generalised spasticity post-stroke, who have not reached their therapy goals with currently available treatment options, will help to identify further benefits of intrathecal baclofen for patients with post-stroke severe spasticity. Side effects are less common when baclofen is administered intrathecally, because the drug does not circulate throughout the body, but it may still be associated with drowsiness, nausea, and headache.

Surgery

This is the last option to treat spasticity, and surgical interventions can be divided into peripheral ablative procedures, such as rhizotomy or peripheral neurectomy, more central ablative procedures such as cordectomy, myelotomy, and stereotactic procedures [54], or procedures like tendon release, lengthening and transfer, tenotomy and myotomy that require referral to orthopaedic surgeons. These procedures are considered in individuals who are refractory to medical treatments, and the benefits of surgery always need to be weighed carefully against its risks. Bollens et al. recently completed a randomised controlled trial of selective neurotomy versus botulinum toxin in 16 patients with spastic equinovarus of the foot after stroke and showed tibial neurotomy to produce a higher reduction in ankle stiffness, but no difference in ankle kinematics during gait, muscle weakening, or patient activity or quality of life [55].

Conclusion

Assessment for spasticity needs to be individualised towards a person's needs. Care should be managed in a multidisciplinary format allowing for treatment options to be considered and chosen regularly. Effective management should be seamless, incorporating continuous education, support, and treatment in both primary and

secondary care, and involvement of rehabilitation teams and care agencies in the community. The effects of spasticity are likely to change over time, and therefore continuous assessment and review is integral to the successful management of spasticity.

Patient Questions

Q. How should post-stroke spasticity best be managed?

A. The management of spasticity requires a multidisciplinary approach incorporating nurses, physicians, physiotherapists, and occupational therapists working together to provide a variety of treatments tailored to the needs of the individual patient. There should be arrangements for targeted therapy and this should include a programme of stretching and physical therapy intervention. Therapists, along with carers and relatives, help in planning 24-h postural management programme.

Q. Will botulinum toxin injection to my "spastic" fingers make them work again?

A. No. If the multidisciplinary team consider it to be appropriate treatment, its aim is to relieve the increased stiffness and associated symptoms, but it will not have an effect on the already decreased power. In fact, the muscles into which the injection is undertaken may have less apparent use by virtue of the botulinum toxin induction of decreased tone. It is important to have ongoing therapy-directed stretching exercises in addition to optimisation of splinting to maintain muscle and soft tissue length across joints.

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Chapter 11
Falls and Osteoporosis Post-Stroke

Frances Dockery and Peter Joseph Sommerville

Abstract Falls are a common and serious, but potentially preventable, problem after stroke. Avoiding falls requires balance, which is a fluid and dynamic physical skill. There are a number of perceptual, neurological, and mechanical mechanisms underlying our ability to balance, and they are complex and heterogeneous. Depending on where strokes occur in the brain, balance may be affected in different ways. It is important to identify stroke patients who are at risk of falls in order to optimize prevention, and a number of stroke-specific risk factors have been identified, but the available assessment scales have only limited sensitivity and specificity. If management of falls risk in stroke is to be effective, assessments have to identify the precise and individual mechanisms underlying balance problems, and then specific management has to be targeted at these deficits. The consequences of falls after stroke can be severe and include loss of confidence and loss of independence, as well as serious injury including fractures. Stroke patients are at greater risk of osteoporosis, particularly on the hemiplegic side, which occurs rapidly following paresis. Management of falls risk post-stroke should also include timely assessment of bone health and the associated fracture risk.

Keywords Falls • Fear of falling • Exercise • Fracture • Osteoporosis • Bone mineral density

Key Messages

- Following a stroke, falls risk is increased over and above the falls risk associated with ageing.
- The assessment of stroke patients who are at risk of falls should be multidisciplinary, so too should the delivery of interventions designed to prevent them.
- Bone density is lost rapidly in the hemiparetic limb following a stroke, with resultant increased fracture risk.
- Along with osteoporosis drug treatment, exercise, nutrition, and addressing falls risk are important strategies to reduce fracture risk.

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Incidence of Falls After Stroke

Epidemiology

Falls are common at all stages after stroke. Studies have reported that between 22 and 39 % of people with stroke fall at least once during their inpatient stay in rehabilitation units, and that falls rates in stroke patients are between 3.4 and 17.8 falls per 1,000 patient days [1–5]. This compares with average fall estimates of between 2 and 7 falls per 1,000 patient days in the general inpatient population. At first glance, these numbers may seem surprisingly high. One possible explanation for this is that inpatient stays for stroke patients are of relatively long duration and the accumulated day-by-day risk over time leads to these high incidences. However, analyses of falls rates over time in inpatients lend support to the notion of added extra risk attributable to stroke. The risk of falls in stroke is not restricted to a hospital setting. At 6 months, the incidence of falls has been observed to be between 37 and 73 % [6–9] and studies that assessed falls rate in patients who had a stroke over a year previously have found higher incidences compared with non-stroke controls (36 % vs. 24 % in one study and 23 % vs. 11 % in another) [10, 11].

Circumstances of Falling

The existing literature on falls in stroke has, in many cases, taken care to analyse what people were doing and where and when they fell. Studies in inpatient acute and rehabilitation care settings [1, 4, 5, 12–14] have reported that falls commonly occur beside the bed or in the toilet/bathroom area. This may be because people spend much of their time in these areas while they are inpatients. However, these are also places where people often make transfers. Broadly similar patterns have been observed in community settings [6, 10, 11, 15, 16]. After discharge from hospital, falls occur most often during the day, and most often in the home. The lounge, bedroom, and garden are the places where falls occur most frequently and the most likely activities at the time of falling are walking or transferring.

Why Strokes Lead to Falls

Falls are common in the frail older person. Since 75 % of stroke patients are older than 65 years of age, many reasons for older people to fall impact on stroke survivors falling. Examples include generally decreased muscle strength and postural reflexes, impaired sensory systems such as vision, less dynamic blood pressure responses to changes in posture, joint disease, cognitive impairment, reduced reaction time, and incontinence. However, strokes can lead directly to falls because of

the vital role almost every part of our brain plays in maintaining our balance. Balance itself is a highly complex and dynamic skill. Even when standing still, there is a constantly activated feedback loop that keeps us upright—a simple observation that underlines this fact is that everyone, when standing, exhibits a certain degree of natural postural sway. In some this is barely noticeable, and in others it is more marked (measurements of sway have been reported as a predictor of falls in older people) [17]. As we stand, our sway is continuously registered by our proprioceptive, vestibular, and visual systems. Next, the information is processed by our central nervous system. Finally, small and accurate compensatory movements occur, in particular in the muscles of the lower legs and feet, to correct the sway and restore the centre of balance to a central position.

The problem of balance as we locomote around and interact within the world is greater still. Walking and not falling is a skill that takes years to learn because it is so complex. In order to walk in a balanced way, multimodal sensory information about speed, direction, limb position, and body tilt must be combined in the brain with information about the environment, including the surface underfoot and obstacles in our way. This information is then used by the brain to produce a motor response—this has to be smooth, fluent, and precise so that as our centre of gravity pitches to and fro with every step, our legs provide just the right amount of force in exactly the right direction to keep us moving forward in an upright position. The same considerations apply to every movement we have learnt to make, from walking up a step and rising out of a chair, to getting into a car. To balance we must also be able to compensate for the unexpected—whether catching a toe on a floor-level obstacle or being pushed by an impulse at the shoulder, we can only stay on our feet by rapid and accurate corrective movements. To avoid falls we must also use our memory and executive abilities, for example: To navigate a familiar environment in poor lighting conditions such as a nocturnal visit to the bathroom, we must use spatial memory about the location of obstacles and room layout to plan the safest route.

Anterior Circulation Strokes

Hemiplegia is the most common result of a stroke in the motor cortex. If a limb is too weak, it is less likely to be able to compensate when called upon to provide a crucial extra impulse in response to an unexpected change in the centre of gravity. A weak leg is less likely to be able to maintain extension during the stance phase of walking, which can lead to buckling at the knee and a loss of stability. Decreased foot clearance during the swing phase, whether from weakness at the hip, knee, or ankle can result in tripping. A weak arm may not generally impede normal locomotion, but if someone uses a walking aid, they are recruiting their arm into helping to provide a larger base on the floor. The weaker the arm, the less stable the base and the less tolerance to unexpected forces. In a near-fall situation, it is often the arm that steadies balance, whether on a piece of furniture or a hand rail. A weak arm, in this situation, is less likely to save a person from falling.

Frontal lobe strokes may affect the prefrontal cortex and may affect executive function and lead to poor planning and initiation of movement, which would lead to unsafe mobilization and risky decisions. Also within the frontal lobe, the premotor and supplementary motor cortices have an important role in representing complex sequences of movements. If the premotor or supplementary motor cortices are affected by stroke, it could lead to an inability to execute the complex movements involved in gait and lead to instability. Gait apraxia is sometimes seen in these patients, which may also contribute to falls risk.

A stroke affecting the sensory cortex could cause problems with joint position sense on one side. If proprioception in a limb is affected, it is unlikely to be able to sense the subtle dynamic changes in joint position which must be called upon to inform our balance mechanisms. This might be especially problematic if there is an unexpected obstacle underfoot. Proprioception in the upper limbs is also important for balance because patients often need to use their arms to help with transfers, to use walking aids, or to reach out to steady themselves if they overbalance.

Strokes affecting the posterior parietal cortex can often lead to visual or sensory inattention or neglect. A patient neglecting one side is more likely to encounter unseen obstacles on that side and may trip and fall. In addition, neglect of one side can cause problems with recognition of a problem on that side, which makes rehabilitation, and the re-learning of balanced gait, difficult. Posterior parietal strokes can lead to topographical disorientation, or topographical agnosia, as the systems underlying the mental map of the environment break down. These patients may not be able to represent accurately the layout of environments, especially if they are unfamiliar. They will then be more vulnerable to falls as they encounter unfamiliar or unexpected obstacles.

Strokes affecting the deep brain structures, such as the basal ganglia, can also interrupt sensory or motor pathways, causing problems with proprioception and hemiplegia as described, or may result in extra-pyramidal symptoms of bradykinesia, stiffness, and tremor leading to a decreased ability to compensate during dynamic movements.

Posterior Circulation Strokes

If the occipital cortex is affected, or indeed any of the optic radiation, visual field deficits may result. This causes patients not to see obstacles in an aspect of their visual field; often one quadrant or one half. They may be able to compensate for this to varying degrees, partly dependent on the attention they are able to pay to the affected side. More profoundly affected may be patients with bilateral occipital cortical damage, which can result in an inability to see anything at all (although some movement perception may be preserved). This phenomenon is known as cortical blindness. These patients self-evidently will have problems seeing where they are going and be more at risk of falls. The visual pathway takes information from the optic nerves to the posterior occipital lobe, and then back into “higher order” visual processing areas in the so-called ventral and dorsal streams. The dorsal stream, which includes the superior occipital and posterior parietal lobes, is particularly involved in the perception of depth and movement. Strokes in this area can lead to impaired depth

perception—these patients may have increased difficulty staying balanced in physical tasks that involve a representation of how far away something is. Examples would include stepping over an obstacle, climbing a step or over-/under-shooting a handle or bannister.

Brainstem lesions may cause hemiplegia or hemisensory loss from their interruption of ascending or descending pathways, or may cause gaze palsies resulting in difficulty tracking motion, increasing falls risk. A patient with diplopia will have problems forming the unified visual image and this may impair depth perception with an effect on falls risk as outlined above. However, the brainstem is also the centre for the integration of vital information from the vestibular system. Neurones in the vestibular portion of the eighth cranial nerve synapse at four vestibular nuclei in the superior medulla and inferior pons. From these nuclei, some motor neurons travel in the lateral vestibulospinal tract to modulate postural adjustments in a descending reflex arc. Meanwhile, many neurons travel directly to the inferior cerebellum to reach the flocculonodular node for the integration of vestibular information for eye and head control, as well as control of axial muscles for balance. Some neurones from the vestibular nuclei link directly to oculomotor nuclei to mediate the vestibulo-ocular reflex (causing our eyes to move in the opposite direction to our head to keep our visual percept stable). A stable visual percept is very important in balance as we rely heavily on "optic flow" (the expansion, contraction, or translation of an optical image on our retina) to obtain information about the movement of our head relative to the environment [18]. Patients with strokes affecting these pathways may have balance problems and exhibit saccadic abnormalities.

It may be seen, therefore, that strokes in the brainstem and cerebellum can be particularly ruinous to balance, with interruption of spinocerebellar, cerebrocerebellar, and/or vestibulocerebellar pathways leading to ataxia, incoordination, and falls.

Muscle Tone

Following a stroke, the tone in muscles may change. Too little tone, and a limb is less able to support the weight put upon it, which may lead to postural instability. Patients with low tone in a limb may not be able to provide the firm, quick impulse of a stumble, required to correct an unexpected shift of the centre of gravity. On the other hand, too much tone results in a stiff limb which cannot exercise the dynamic changes in power required to mediate balance. In addition, the postural reflexes may be affected, and there may be too strong an efferent impulse in response to stretch.

Environment

The falls risk after stroke goes beyond particular physical impairments. Very often, stroke patients are hospitalized and may spend some days in bed. During this time and despite best efforts, they may suffer deconditioning and so when

they mobilize again they are less strong and less steady. Very often after a stroke, the usual environment of people changes, whether that is because they are in hospital and unused to the physical layout, or they have been moved to different rehabilitation centre, or their home has been adapted in response to their changed care needs, or in some cases because they have had to go into residential care. They may have to use equipment, such as commodes, which they have not used before. The unfamiliar environment presents new physical challenges, and these may lead to falls, particularly at a time when motor functions are being re-learnt.

Psychological Factors

Good balance and falls avoidance after stroke depend on patients maintaining a certain level of mobility and pushing themselves to learn or re-learn motor skills. Doing these things requires a certain level of psychological health, but depression is common after stroke, and depressed patients may be less inclined to take on these challenges. Another psychological consequence of stroke may be fear of falling, which can itself lead to falls in the manner described below.

Drugs

Many of the conditions associated with stroke are treated with medications that can increase patients' falls risk. Examples include antihypertensives that can induce cerebral hypoperfusion, often worse with standing, which can lead to light-headedness and balance problems; antidepressants such as tricyclic antidepressants (TCAs) that have been associated with clinically significant orthostatic hypotension, cardiac rhythm disturbance and drowsiness; and antipsychotic drugs, used to treat agitation, that predispose to psychomotor slowing and extrapyramidal symptoms [19].

Incontinence

Urinary incontinence is common after stroke, as detailed in Chap. 8, and is a recognized risk factor for falls. This may be simply because underlying severe disability can lead to both incontinence and falls. However, if patients need to get up to go to the toilet frequently, or rush to avoid accidents, or have to change wet clothes too often, they may be at risk of falls. Further detail on this is discussed in the relevant chapter.

Assessment of Falls Risk

It is useful to be able to predict which patients are likely to fall and quantify individuals' falls risk. By identifying such patients, targeted falls prevention interventions can be undertaken to help reduce risk. A number of studies have examined which patient factors are associated with falls (Tables 11.1a, b, c and d). The studies vary in methodology, findings, and conclusions and there is a dearth of randomized studies. Overall, it appears that in terms of impairments, visuospatial neglect and cognitive impairment seem to be most reliably associated with falls. Depression as a complication also seems to be an important factor. Fallers have consistently worse balance in the studies covered, and there is some data to suggest they walk slower. The data showing increased falling with lower functional performance indicates that patients' disabilities may be more important that their impairments when it comes to falls prediction.

These observations have led some researchers to devise tools that can be used to predict falls risk based on observable patient characteristics (Table 11.2). In general, no test has been found to have excellent sensitivity and specificity for falling, but low Berg Balance scores have been found to be fairly good predictors of falling in the community (especially when combined with a history of falls) [8] and in hospital [29]. Rapport et al. [32] reported that when a falls questionnaire was combined with neuropsychological tests of impulsivity, falls could be predicted in 80 % of cases of male right middle cerebral artery territory stroke survivors in a rehabilitation setting. Nyberg et al. [34] give a scoring system that is based on the data observed in their study which correlated significantly with the fall risk, but this has not been independently validated. Part of the difficulty in devising a test to predict falls in stroke patients lies in the fact that so many different factors may contribute to falls risk. A simpler test is likely to ignore important variables, whereas a more complex one may be unwieldy.

Mitigating Falls Risk

The most compelling reason to understand and assess falls risk after stroke is to prevent people from falling. In the community-dwelling general elderly population, there is an established, evidence-based acceptance that certain interventions are effective in reducing falls. These include exercise programmes, prescribing modification programmes, interventions for visual impairment, and home safety interventions, as well as multifactorial assessments and interventions [35]. As described below, there is less evidence, however, supporting such interventions in the stroke patient population [36].

Table 11.1a Cross-sectional studies assessing the relationship between different characteristics and falls

Study	Subjects	Methods	Findings
Ugur et al. (2000) [20]	293 stroke patients discharged from an inpatient unit. 52 % male	A standard questionnaire was posted to the patients or their relatives to obtain information about falling, and patients were asked to fill out Montgomery and Asberg rating scale and Barthel Index (BI) functional status forms to evaluate their mood and functional status. Other information about stroke type, severity, and risk factors were screened from hospital records	Falls associated with older patients, right hemispheric aetiology, depression, low BI score, and the absence of heart disease. No association found between falls and diabetes, hypertension, trauma, and gastrointestinal disease
Hyndman et al. (2002) [15]	41 community-dwelling people with stroke. Mean age 69.7 years old. 63 % male. Time from stroke onset 3–288 months	Patients were visited at home, and their demographic characteristics and falls history obtained using Stack and Ashburn's falls assessment questionnaire. Cognition was assessed with the Middlesex Elderly Assessment of Mental State test, mobility was assessed using the Rivermead Mobility Index, functional status was assessed using the Nottingham Extended activities of daily living (ADL) scale, functional arm movement was assessed with the Rivermead Motor Assessment (RMA) and anxiety and mood were assessed using the Hospital Anxiety and Depression score	Those who had had two or more falls had significantly reduced arm function and ADL ability. Repeat fallers had significantly higher depression scores than non-fallers with no near falls. On average, repeat fallers had their stroke more recently than non-fallers. Differences across faller vs. non-faller groups in stroke side, age, gender, and number of medications were not statistically significant
Hyndman et al. (2003) [21]	48 community-dwelling stroke patients. 62.5 % male. Mean time since stroke 46 months	Patients were interviewed about falls history, adaptive equipment, medication, and co-existing diseases. Attentional capacity was assessed using four subtests of the Test of Everyday Attention, visual attention was assessed using the Star Cancellation Test, balance was assessed with the Berg Balance Scale (BBS), and functional abilities were assessed with the Nottingham Extended ADL scale	Impaired attentional ability in both tests of sustained and divided attention correlated with falls, poor balance, and reduced ADL ability

Belgen et al. (2006) [22]	50 community dwelling stroke patients recruited from support groups and via advertisement. Participants could walk 10 m with no physical assistance and follow three stage commands. Mean age 59.9 years old. 62 % male	A questionnaire recorded information about demographic characteristics and medical and stroke history. Participants were interviewed about their falls history including fear of falling, living situation, and functional abilities. Falls related self-efficacy scale measurements were undertaken, motor function was assessed with timed sit-to-stand, timed up-and-go, Fugl-Meyer Assessment (lower limb) and BBS. Mood was measured with the mood and emotion subscore of the Stroke Impact Scale	Patients with any falls history were more likely to have a fear of falling, had less falls-related self efficacy and more depressive symptoms. Multiple fallers had poorer balance, more fear of falling and used a greater number of medications than never- or single- fallers. Age, gender, the use of an assistive device, alcohol history and stroke side were not significantly associated with falls
Souyer et al. (2007) [23]	100 cognitively intact, ambulant community dwelling patients with a stroke at least 6 months prior. Only 45–60 year olds were recruited	Patients were interviewed to determine demographic characteristics, falls history, and medical and stroke history. Function was measured using the Functional Independence Measure (FIM) instrument. Joint position sense was measured using a computerized 2-inclinometer system. RMA was used to assess motor ability, tone was measured using the Ashworth scale and functional evaluations of balance and gait were determined using Tinetti Assessment	Significant differences between multiple fallers, one time fallers and never-fallers with respect to functional status, functional balance and gait. Multiple fallers had significantly worse knee proprioception than the other groups. Fallers were more likely to use a walking aid. Ordinal analyses suggested that as spasticity, general disability, and functional disability in gait and balance increased, so did falls risk. Falls were not associated with age, gender, stroke side or aetiology, or ankle joint position sense

Table 11.1b Retrospective cohort studies assessing the relationship between different patient characteristics and falls

Study	Subjects	Methods	Findings
Sze et al. (2001) [14]	677 patients admitted to a Chinese stroke unit approximately 1 week after stroke. 53 % male	Analysis of medical and falls history for the duration of the inpatient admission from the medical notes. Cognition was measured using the Abbreviated Mental Test score (AMTS) and function was assessed with BI. Data on falls was also obtained from a form filled in by staff in the event of a fall	11.5 % fell during their admission. Falls were associated with low BI, urinary incontinence, dysphasia, and hemiplegia. No association found between falls and previous stroke, diabetes, hypertension, ischaemic heart disease, cognition, and sensory impairment in univariate analyses
Teasell et al. (2002) [3]	238 consecutive admissions to a stroke unit who were judged to have potential to eventually go home after their stroke. Mean age 72.1 years old. 49.8 % male	Data including demographic and medical characteristics and stroke impairments were collected from medical notes. Balance was assessed using the BBS, function was assessed with the FIM score, and motor recovery was assessed with the Chedoke-McMaster Stroke Impairment Inventory. Other stroke impairments such as cognitive impairment or aphasia were measured from reports of relevant therapists. Falls were observed during patients' stay of inpatient rehabilitation	37 % of patients experienced at least one fall; 19 % of patients experienced at least two falls. Fallers were more likely to have impaired balance and lower functional abilities with their affected arm, leg, and foot. Fallers were more likely to be apraxic and cognitively impaired. Repeat fallers had lower functional independence. Age, the presence of aphasia, homonymous hemianopia, neglect, depression, and seizure history were not associated with falls
Suzuki et al. (2005) [4]	256 patients admitted to a stroke rehabilitation unit	Data including demographic information, clinical and falls history extracted from medical records. Function and cognition were measured using FIM scores	47 % of patients fell at least once during their inpatient stay. Falls were significantly associated with lower measures of functional independence and lower cognitive performance
Schmid et al. (2010) [24]	1,269 patients admitted to four hospitals over a 5-year period. Mean age 71 years old. 56 % male	All medical, demographic, falls- and stroke- specific data were collected in a review of medical notes and charts (including data on mood and anxiety). Stroke severity was measured using National Institutes of Health Stroke Scale (NIHSS). Dependence was recorded for any patient who was reported to need help with any ADL	5 % of patients fell during their admission. Greater stroke severity was associated with falls, as was a history of anxiety. Factors that were not associated with falls were age, gender, ethnicity, the presence of gait abnormality, hemiparesis, sensory impairment, aphasia, brainstem stroke; or a history of hypertension, depression, diabetes, seizures, syncope, urinary tract infection, or Parkinson's disease. Falls in this study were independently associated with a loss of function even after adjusting for stroke severity, age, gait problems, and previous stroke

Table 11.1c Prospective longitudinal studies assessing the relationship between different patient characteristics and falls

Study	Subjects	Methods	Findings
Forster et al. (1996) [6]	108 community stroke patients at discharge from inpatient rehabilitation who were over 60 years of age and were resident at home with residual disability	Questionnaire-based interview to obtain falls history, demographics, and medical history at discharge. Further falls history taken at 8 weeks and 6 months. Carers were also interviewed including a 28-point questionnaire about well-being. Function was measured with BI, cognition was assessed with the AMTS, balance and functional movement were assessed with the Motor Club Assessment, social activity was assessed with the Frenchay activities index, and perceived state of health was assessed with the Nottingham health profile. Neglect was measured using Albert's test. Walking speed was measured	73 % of patients fell during follow-up. Fallers were significantly less active at 6 months and had lower measures of gait and balance and functional ability. Even though fallers and non-fallers had no significant gait speed difference at the beginning of the study, at 6 months fallers were significantly slower. Patients who had fallen at least twice were less socially active at 6 months. Carers of fallers were significantly more stressed. Falling was not significantly associated with age, cognitive impairment, or other co-morbidities such as diabetes, chronic obstructive pulmonary disease, hypertension, or poor eyesight
Jørgensen et al. (2002) [11]	111 patients in the community who suffered a stroke, on average, 10 years previously. Mean age 67 years old. 57 % male	Demographic and medical historical data collected in a questionnaire at the beginning of the study. Functional ability was assessed using the BI, motor function of the arms and legs was assessed with subscores of the Scandinavian Stroke Scale, vision was assessed with Printer's Point Score test, mood and anxiety were assessed with the Montgomery-Asberg Depression Rating scale, and cognition was assessed with the Mini Mental State Examination (MMSE). Patients kept a 'falls calendar' to record falls index for a mean of 112 days	23 % of stroke patients fell during the period of follow-up. Falls were significantly associated with depression, but not decreased leg function or epilepsy. Depression was also associated with decreased leg function

(continued)

Table 11.1c (continued)

Study	Subjects	Methods	Findings
Yates et al. (2002) [25]	280 community-dwelling stroke survivors identified from admission records of 12 facilities. Mean age 68.3 years old. 50 % male	Clinical evaluation within 14 days of stroke onset, including assessments of leg function with Fugl-Meyer lower limb score, and other stroke deficits with NIHSS. Follow-up at 1 month, 3 months, and 6 months to determine fall status	51 % of subjects fell in the follow-up period. Risk of falling was greater for subjects with motor impairment and motor + sensory impairment. In multivariate analysis, the motor + sensory + visual impairment group were less mobile, and fell significantly less
Andersson et al. (2006) [26]	162 patients admitted to a stroke unit. Mean age 73 years old. 55 % male	Clinical evaluation at a mean of 8 days post-stroke. Demographic information, medical and drug history, including history of visual impairment, was obtained by structured interview and reference to medical notes. Cognition was assessed with MMSE, stroke deficits were assessed with NIHSS, motor function was assessed with the Birgitta Lindmark motor assessment scale, neglect was assessed with the Behavioural Inattention test and Baking Tray test, tone was assessed with the modified Ashworth scale, balance was assessed with BBS. The 'Stops Walking While Talking' and 'Timed up and go' tests assessed global mobility with extra attentional demands and against the clock. Alternate patients were followed up either at 6 or 12 months by interview to establish falls history	43 % of patients fell at least once during follow-up. Fallers were significantly more likely to have functional motor impairment, have visual impairment, or take sedative medication. Falls were not associated with age, gender, stroke side or severity, spasticity, cognitive impairment, neglect, or antidepressant or diuretic usage

Mackintosh et al. (2006) [8]	55 patients from a community rehabilitation centre. Mean age 68 years old. 45 % male	An initial interview established cognitive performance (using the Orientation-Memory-Cognition test), falls risk factors medication, and falls history. Hemianopia was assessed using visual confrontation, hemi neglect was assessed with the Star Cancellation ratio and the Baking tray test. Muscle strength was tested using the Nicholas Manual Muscle Tester, balance was assessed with the BBS and Step Test, tone was assessed with the Tone Assessment Scale, fear of falling was assessed with the Falls Efficacy Scale, depression was assessed with the Geriatric Depression Scale, and activity levels were assessed with the Human Activity Profile. Patient then kept a diary to record falls for 6 months	45 % of patients fell during the study period. Fallers were more likely to have hemi neglect, low quadriceps strength, a low BBS, a low step test score, a slower gait speed, have lower activity levels, and be taking multiple medications. No significant association was found between falling and age, gender, hemianopia, strength of dorsiflexors or hip abductors, spasticity, use of psychotropics, fear of falling, or depression
Czernuszenko et al. (2007) [27]	353 inpatients at a stroke facility	Assessment from medical notes of demographic data, falls risk factors, and medical history. Function was measured with Modified Rankin Score and BI. Stroke severity was measured with the Scandinavian Stroke Scale. Data on falls was recorded as they occurred throughout the inpatient stay, which had a mean length of 28 days	10 % of patients suffered falls. Fallers were more likely to have unilateral neglect, have more functional disability, and have more severe stroke impairments

Table 11.1d Randomized controlled studies assessing the relationship between different patient characteristics and falls and examining different rehabilitation interventions

Study	Subjects	Methods	Findings
Tilson et al. (2012) [28]	408 subjects with stroke within the last 45 days, residual paresis, slow walking but needing no more than one person's assistance. Mean age 62 years old. 54.9 % male. Subjects were drawn from the wider Locomotor Experience Applied Post-Stroke (LEAPS) study	Demographic characteristics and information pertaining to medical history and stroke risk were obtained at randomization. Gait speed was measured and 6 min Walk test was administered. Motor function was tested with Fugl-Meyer assessment scale, balance was assessed with BBS and Activities Specific Balance Scale, cognition was assessed with MMSE and Trail-Making tests. Depression was tested with Patient Health Questionnaire nine-item depression scale, disability was assessed with the Stroke Impact Scale, and physical function was assessed with the Short Form −36	Across groups, falls were positively associated with age at onset, a history of alcohol abuse, Fugl-Meyer total motor upper limb and lower limb scores, low walking speed, 6 min walk distance, low BBS, the use of an assistive device, and increasing Modified Rankin scales. No other significant relationships found, including with depression and cognitive impairment
		Subjects were randomized either to early locomotor training programme (LTP) at 2 months, late LTP at 6 months, or early strength and balance exercises in the home (HEP) at 2 months	There was no difference across the three arms in overall fall rate
		Patients kept a falls diary and were followed up by phone at 2 and 12 months	Early-LTP in severely slow walkers was associated with more falls than late-LTP or HEP. Late LTP group was significantly less mobile

Table 11.2 Validity indices for different tests in falls prediction over the duration of different studies

Clinical test	Investigator	Study period	OR	Sens (%)	Spec (%)	PPV (%)	NPV (%)
History of previous falls	Mackintosh et al. (2006) [8]	6 months	28	92	72	48	97
Berg Balance Score <50	Mackintosh et al. (2006) [8]	6 months	20	92	65	42	97
Berg Balance Score <50 + history of inpatient fall	Mackintosh et al. (2006) [8]	6 months		83	91	71	95
Berg Balance Score <45	Andersson et al. (2006) [26]	6–12 months		63	65	58	69
Berg Balance Score <30	Maeda et al. (2009) [29]	Mean 83 days		80	78	NR	NR
STEP test score <7	Mackintosh et al. (2006) [8]	6 months	20	92	64	42	97
STEP score <7 + history of inpatient fall	Mackintosh et al. (2006) [8]	6 months		83	86	63	95
Slow gait <0.56 m/s	Mackintosh et al. (2006) [8]	6 months	6	58	81	47	88
Hemineglect	Mackintosh et al. (2006) [8]	6 months	3.8	50	79	40	85
STRATIFY score at baseline	Smith et al. (2006) [30]	6 months	NS	11	89	25	76
STRATIFY score at discharge	Smith et al. (2006) [30]	6 months	NS	16	86	38	66
Downton index >2	Nyberg et al. (1996) [31]	Median 48 days	2.9	91	27	NR	NR
Fall assessment questionnaire + behavioural impulsivity	Rapport et al. (1993) [32]	NR	NR	NR	NR	80	NR
"Stops walking when talking"	Hydman et al. (2004) [33]	6 months		53	70	62	62
"Stops walking when talking"	Andersson et al. (2006) [26]	6–12 months		15	97	78	61
Timed up and go >14 s	Andersson et al. (2006) [26]	6–12 months		50	78	59	72

OR Odds ratio, *Spec* Specificity, *Sens* Sensitivity, *PPV* positive predictive value, *NPV* negative predictive value, *NR* not recorded

Physical Therapy and Exercises

Most stroke patients receive some form of physiotherapy and most stroke specialists would agree that physiotherapeutic interventions are key to restoring mobility and balance. After a stroke, ways of coping with deficits have to be learnt, and it is unquestionable that in many patients supervised practice of physical skills will provide benefits. Physiotherapy helps to identify impairments in dynamic function as

well as the ways in which patients physically compensate for the deficits. Sometimes falls may result from the deficits themselves and sometimes from the compensatory mechanisms (e.g., over-reliance on unaffected limbs to the extent that balance is affected, known as "pusher syndrome"). Physiotherapists can help teach patients adaptive and balanced ways of mobilizing so that they can reduce their falls risk.

Physiotherapists and occupational therapists both have an important role to play in determining what patients can and cannot do safely. This is vital to prevent falls in both inpatient and community settings. By setting guidelines about what patients should be doing on their own, and what they should be doing with supervision, what aids they should be using, and what mobilisation techniques they should employ, therapists can help ensure that the falls risk is minimized as long as patients are operating on a day-to-day basis within their recommended safe levels of function. Of course, if falls do occur it is mandatory to determine whether patients were operating within these recommended safe levels, or whether they were doing something over and above what had been recommended. In the case of a patient who falls despite following recommendations, further assessments may be warranted to determine if there was another unrecognized cause of the fall. In some cases, discussion may need to take place about whether the previously agreed safe levels of function are actually still safe. Sometimes new, lower levels may need to be set, but of course this may compromise the independence of patient. The decision to do this would have to take place as part of a wider analysis of the patients' goals and wishes as well as the overall direction of rehabilitation. Conversely, the management of a patient who falls after "giving it a go" with a risky and unrecommended manoeuvre is very different. The reasons that the patient has for taking the risk need to be sought in order to determine the approach to take. On the one hand, the patient may not be aware of the risk and require an explanation; alternatively, they might acknowledge the risk but go ahead anyway because of an urge for independence. In all these cases, an individualized approach needs to be taken, in order that the management plans can be tailor-made for each patient. In many cases, there is also a difficult balance to be struck between independence and safety.

A number of randomized controlled trials have addressed the question of whether falls can be reduced in stroke patients undergoing specific physiotherapeutic or exercise regimens. A small trial on early rehabilitation after stroke randomized 56 patients to normal care or an intervention group that were mobilized in the first 24 h post-stroke [37]. This intervention proved no less safe than normal care, but the rates of falls over the following year were no different. As previously discussed, falls are commonly seen while transferring. A study of 48 patients compared usual inpatient rehabilitation with a group who received extra sit-to-stand practice [38]. Although the intervention group's sit-to-stand performance and quality of life improved, their falls rate remained unchanged. Another research group [39] gave patients a rehabilitation programme that included sit-to-stand training as well as training with a biofeedback device aimed at improving postural symmetry. Out of their 54 participants, they found that the intervention group suffered significantly fewer falls than the controls who underwent a conventional rehabilitation programme (42 % vs. 17 %, $p<0.05$).

A larger study [40] randomized 146 patients with mobility problems over a year after a stroke to receive either community physiotherapy or no intervention. At 6 and 9 months, the intervention group had slightly better mobility and gait speed than the control group, but around 20 % of patients in both groups had fallen by these time points. Another community study [41] randomly assigned 61 patients to receiving either supervised agility training or Tai-Chi like stretching and weight-shifting practice. Even though the agility group fell less than the stretching/weight-shifting group (25 falls vs. 75 falls), this difference did not reach significance ($p = 0.2$). The agility group, whose training involved experimenter-induced standing perturbations, suffered significantly fewer falls on an unexpectedly moving platform. Yelnik et al. and Duncan et al. independently showed that falls were not reduced by a multi-sensorial approach to rehabilitation that included visual deprivation during exercise or by employing body-weight supported treadmill practice in place of home exercise including balance training [42, 43]. The latter study did, however, find significantly fewer falls in severely slow walkers who had balance training at home.

Medications

As previously discussed, commonly prescribed medications such as antihypertensives, antidepressants, sedatives, and other psychoactive drugs can predispose to falls. Some medications, however, may actually help decrease risk. Studies have demonstrated reduced falls rate and risk with vitamin D provision to patients with low vitamin D levels [44]. This may be mediated by the effect that vitamin D has on increasing muscle protein synthesis and thereby enhancing muscle strength. A further study showed an even greater reduction in falling from alendronate therapy compared with vitamin D therapy [45]. These findings have not however been replicated, and the putative mechanisms of a falls risk reduction with bisphosphonates are not clear [46, 47].

Interventions for Visual Impairment

Whilst randomized controlled trial data is lacking, there are a range of possible interventions for patients with visual field defects, diplopia, or other eye movement abnormalities after stroke [48]. Some are proposed to work by restoring the visual field (restitution); these aim to take advantage of the fact that patients with so-called cortical blindness can sometimes see moving objects in their affected field. Other strategies compensate for the deficit by changing behaviour, such as by training patients to scan across the visual field. Others still aim to substitute for the visual field defect by using a device or extraneous modification such as a prism. Finally, eye patches may be useful in patients who have diplopia.

Environmental Interventions and Equipment

A number of different environmental interventions are possible to try to help reduce falls risk with stroke patients. In the inpatient setting, chair alarms are sometimes used to alert nurses to patients getting up who may not be very safe to mobilize independently. Other strategies involve identifying patients at risk using alert badges at "board rounds" or alert wristbands. Inpatient environments should be well-lit with non-slippery floors and handrails that are easy to see.

Meanwhile at home, occupational therapy assessments are a key intervention in optimizing the environment to minimize falls risk. People's homes may be messy with potential obstacles strewn on the floor. There may be slippery carpets or mats. The route to the toilet may be circuitous with bulky furniture in the way. These are things that are usually straightforward to fix. At the same time, balance may be improved with the provision of hand rails in opportune locations. Devices such as stair or bath lifts may help people who might otherwise fall at these locations. A convenient commode may also reduce long and risky trips to the bathroom. A range of other pieces of equipment usually recommended by physiotherapists may also help people's balance after stroke. Some, such as sticks or orthoses, aid mobility and increase the physical area of people's support base. The evidence-base for these therapy-directed interventions is extrapolated from interventions to prevent falls in older people in the absence of stroke-specific data [35, 49].

Social Environment

People who are at risk of falls may have the risk attenuated to some extent by the presence of other people to help them. For example, a common time for falls to occur is during transferring. If people have the right help and supervision at these times, whether from friends and family or formal carers, falls can be avoided.

Urinary Incontinence

Since urinary incontinence is associated with falls, and the relationship may be partly causal, it follows that managing the incontinence can help manage the falls risk. This will firstly involve assessments to uncover the precipitating factors leading to incontinence and, secondly, specific management strategies aimed at ameliorating or removing those factors. Of course, the management of incontinence, as much as the management of falls, is multidisciplinary, and very often physiotherapists and occupational therapists are invaluable in devising and practising toileting regimens to avoid incontinence after stroke.

Summary

A comprehensive evidence base from which to recommend particular interventions to reduce falls risk after stroke is lacking. It may be, however, that the evidence-based approach to falls reduction in the general older population can also be applied, to an extent, to stroke patients. This seems especially true of multifactorial interventions that are based on multifactorial risk assessments. However, not all strokes occur in older age and the stroke population has specific, separate problems and deficits that should be assessed and managed differently.

It is, however, fair to say that the first step in the management of falls risk after stroke is to identify the antecedent factors that contribute to the falls risk in that particular patient. There are many such factors and especially in stroke, different members of the multidisciplinary team have complementary roles in bringing these factors to light, according to their specialty. Just as the assessment of risk is multidisciplinary, so is its management. Patients at risk of falls after stroke will benefit from a coordinated approach to determine the most appropriate individualized interventions which can be applied by members of the different disciplines.

Consequences of Falls

Falls, when they do occur, can have severe consequences. Some are psychological, such as the development of a fear of falling, which can lead to its own complications. Others are due to injuries sustained at the time of fall, such as fractures or bleeding. People who fall and cannot get up for a long time may be at risk of hypothermia, dehydration, pressure sores, or rhabdomyolysis. There is a burden on carers of patients who fall and falls may lead to more stress for carers. Falls can lead to patients restricting the activities they do, and a resultant loss of independence. This can lead to reduced quality of life.

Fear of Falling

Fear of falling is increasingly recognized as an important determinant of morbidity after falling. It refers to anxiety about falling that may have been caused by a fall that actually occurred, or may just be a result of a general sense of imbalance. It affects people in a number of different ways. Firstly, there is the psychological burden of the anxiety. However, the mental state itself can also cause physical problems. If someone is afraid of falling they are less likely to attempt to mobilize; their mobility and balance then deteriorates, and, as a consequence, their fear of falling increases and becomes more justified.

Fear of falling often has functional consequences as well. People with fear of falling (or indeed with falls regardless of their emotional response) may try to do less around the house, with a resulting loss of independence. They may go out less and give up previously enjoyed activities or lose touch with their social network. These changes may have a profound impact on a patient's quality of life. There is a possibility this could lead to poorer mental health and depression (although studies have only established a correlation and not a causal link between fear of falling and depression).

In stroke research, studies have shown correlations (again, not causal relationships) between fear of falling and indices of quality of life, depression, and anxiety [50]. Fear of falling can also hamper rehabilitation. Patients with anxieties about balance and falling may be less willing to try new compensatory mechanisms or practise recovering their mobility. This mandates an approach to stroke rehabilitation that includes consideration of patients' psychological states, particularly with regard to their physical function. Cognitive behavioural therapy may be an invaluable tool to allow patients to learn to tackle their fear and has been shown to be effective in non-stroke patients who have fear of falling [51]. Meanwhile, exercise may have the dual benefit of increasing mobility and improving psychological health [52].

Bleeding Risk After Falling

A number of injuries can result from falling and, depending on the mechanism of the fall, bleeding may result. Such bleeding will be potentiated by the antithrombotic medications commonly prescribed to patients after ischaemic stroke. Many patients are prescribed anticoagulants for secondary stroke prevention but, despite the benefit, clinicians may be reluctant to prescribe them in patients at risk of falling because of worries about contributing to bleeding, including traumatic subdural or intracerebral haemorrhage. A number of key studies have addressed this clinical dilemma. Man-Song-Hing et al. [53] analysed data from 49 different studies examining falls, anticoagulation, and intracranial haemorrhage in non-stroke patients and calculated that a person with atrial fibrillation (AF) on warfarin would have to fall 295 or more times a year to make warfarin more risky than beneficial. This probably cannot be usefully extrapolated to stroke patients, however, as it relies on assumptions about the rates of falls which are based on non-stroke patients, and the authors only used traumatic subdural haemorrhage in their analysis of factors that would count against warfarin. Gage et al. [54] retrospectively analysed records of 1,245 Medicare beneficiaries with AF and found that patients treated with warfarin (around half) were no more likely to suffer intracranial haemorrhage, but if they did, it was more likely to be fatal. However, because of the reduction in stroke rates in the warfarin group, warfarin protected patients overall from a composite endpoint of stroke, intracranial haemorrhage, myocardial infarction, and death. It is difficult, however, to draw robust conclusions about the efficacy and safety of warfarin in

fallers from this study as there is a selection bias in that patients in the study were only on warfarin because their physician thought that it would be safe and beneficial enough to prescribe and there was no standardized way of assessing falls risk; whether patients were at risk of falls or not was taken from remarks written in the notes. The BAFTA trial [55] randomized 973 over-75-year-olds with AF to either warfarin or aspirin. Patients were recruited from 200 English GP practices, but excluded if their GP found, there were clinical reasons to chose warfarin over aspirin, or vice versa. There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin. These data support the notion that warfarin is not associated with a high excess bleeding risk in the elderly. It should be noted that the sample in the BAFTA study is likely to have excluded some patients at high risk of falls, if their GPs used these patients' falls risk as a reason to prefer aspirin. Donze et al. [56] studied 515 patients discharged home on warfarin for AF and found that while patients at high risk of falls (determined using a screening questionnaire) had a higher annual rate of major bleeding than those at lower risk (8 % vs. 6.8 %), this was not significant. These studies perhaps argue that extra major bleeding rates with warfarin are overestimated.

Osteoporosis and Fractures Post-Stroke

Epidemiology

Several studies have noted the higher incidence of fragility fracture (mainly hip fracture) in stroke survivors, as well as a higher prevalence of stroke history amongst series of hip fracture patients than matched controls [57–60]. Studies vary considerably in age ranges, ethnicity, methodology, and confounders, but almost all have demonstrated a risk ratio of hip fracture in stroke survivors of between 1.5 and 4 times that of the general population [57–61]. Hip fracture risk is most apparent in younger-aged stroke patients (though absolute fracture numbers are lower), with a large Swedish study from national hospital data finding an 8- to 12-fold higher risk of hip, as well as all fragility fractures, in stroke survivors under 60 years versus the age-matched general population [59]. A similar series from Scotland also found the highest odds ratio (fivefold) amongst younger female stroke survivors [60].

Apart from the devastating event of a hip fracture in any individual, younger stroke patients in particular seem to have a greater loss of independence from baseline and a greater mortality risk than similar-aged hip fractures without a prior stroke [62]. The morbidity ratio following hip fracture seems less influenced by a stroke history in older age, though remained higher than in those without [60, 63, 64]. Hip fracture is already a grave event for any older individual, with a consistent 25–30 % 1-year mortality seen in most large series [65]. The well-known female preponderance of osteoporosis and fracture risk in the general population is less

striking post-stroke, with a narrowing of the gender gap in fracture prevalence [59, 60, 66]. Reasons for this are explained further below, given the specific fracture risk factors in stroke survivors, which are common to both genders. Fracture risk is highest in the early days post-stroke, waning over subsequent years [59, 60, 66]. Factors likely to contribute to this are firstly, there is a rapid decline in bone mineral density (BMD) in the immediate aftermath of a stroke, notably in the hemiparetic side, and secondly, falls risk is notably higher in the early days post-stroke.

Reasons for Increased Fracture Risk Post-Stroke

Falls

As discussed earlier in the chapter, stroke survivors are prone to frequent falls, and a fall is the leading contributor to fragility fracture post-stroke [60].

Bone Mineral Density (BMD) Reduction

Low BMD has been associated with a higher stroke risk in later life, meaning the stroke patient might already be predisposed to a higher fracture risk for reasons that are not entirely understood, but may involve shared risk factors for vascular calcification [67]. What is clear, however, is that there is a rapid and substantial decline in BMD following an acute stroke, as is the case following spinal cord injury and as seen in astronauts [57]. A key factor seems to be the sudden loss of weight-bearing stress on the skeleton, causing "disuse osteopenia." Mechanical forces on bone are applied through both muscle forces and ground reaction forces, and loss of bone mass occurs very rapidly in their absence. From measures of BMD, bone turnover markers, and bone biopsy studies, bone loss begins almost immediately following stroke (probably due to the loss of muscle tone), progresses until 3–4 months later, and continues at a reduced pace until 1 year [57, 68–70]. There are no prospective studies looking at changes in BMD beyond 12 months, however. Any data beyond this time point comes from cross-sectional studies, but extrapolation from spinal cord-injury patients suggests that a stabilization of BMD is reached thereafter [71].

Available studies have used different modalities to measure BMD and have included patients with varying degrees of disability, making comparisons difficult [57]. Despite this, the consensus is that generally as much as 17 % of BMD is lost in the first year after a stroke vs. a usual bone loss (after peak growth) in adults of about 1–2 % per year [57, 69, 72]. Moreover, in hemiparesis, as much as 2 % of the BMD loss occurs in the first month. The degree of bone loss relates to motor disability, with those who are ambulant immediately following a stroke showing a much lesser fall in BMD [73–75]. Bone density reduction occurs predominantly on the paretic side, and upper limb is affected more than lower, due to its usually greater degree of paresis. It is the case though, that the dynamic changes in bone metabo-

lism following hemiplegia have local as well as generalized effects on the skeleton, with an up to 4 % BMD loss seen on the non-paretic side [68, 74, 75]. Peripheral quantitative CT has gained an increasing role in looking at bone microarchitecture and has potential to overcome the deficits of dual energy X-ray absorptiometry (DXA) BMD scanning in fracture risk prediction [76]. A prospective study using this modality is currently underway in stroke survivors that may give further insight into the pathophysiology of post-stroke bone loss [77].

Loss of Mechanical Loading Effects on Bone Mass

The skeleton is constantly remodelled through life, through a balanced process of osteoblastic bone formation and osteoclastic bone resorption, which allows skeletal growth in childhood, healing following fractures, and adaptation of bone size and strength to mechanical force. This finely balanced process is influenced by numerous factors such as age, hormones, and mechanical loading. Uncoupling of the remodelling process of bone formation and resorption leads to increased resorption, development of osteoporosis, and increased fracture risk. Given that mechanical unloading is a key contributor to post-stroke osteoporosis, it is important to understand the pathophysiology in order to consider therapeutic strategies.

Though the precise mechanism of this uncoupling following removal of usual loading forces remains elusive, important scientific advances have been made in recent years. It is the osteocyte rather than the osteoblast or osteoclast that senses the mechanical load [78]. Osteocytes account for at least 90 % of bone structure throughout the skeleton and are formed from mature osteoblasts. There are numerous membrane-spanning channels within the osteocyte known as gap junctions, which allow osteocytes to connect directly with one another from deep within bone tissue, allowing rapid transmission of signals. These channels are formed by the linkage of membrane protein complexes; connexin43 (Cx43) being the most predominant one in bone. Cx43 is an important regulator of the ability of bone cells to respond to mechanical stimuli, through controlling calcium oscillations which occur in the osteocyte following mechanical loading [79, 80]. These loading forces also drive interstitial fluid through the unmineralized matrix surrounding osteocytes, enhancing flow and therefore transport of nutrients, waste, and signals between cells. The osteocyte is activated, in turn, through the actin cytoskeleton of its dendritic processes [80, 81].

The subsequent pathways that translate into altered bone mass are also not fully elucidated, but apart from calcium oscillations occurring, numerous substances are released by the osteocyte in response to mechanical loading such as nitric oxide and prostaglandins. These have an anabolic effect on osteoblast activity and may inhibit osteoclast activity [81]. The latter occurs by suppression of a cytokine produced by osteoblasts called receptor activator of nuclear factor kappa-B (RANK) ligand, which is a potent stimulator of osteoclast function. Mice lacking RANK ligand in osteocytes are protected from bone loss induced by hind-limb unloading [82], and the monoclonal antibody denosumab that is a RANK ligand inhibitor has shown significant clinical efficacy in post- menopausal osteoporosis.

Another important discovery in more recent years is of the Wnt gene signaling pathway, which has allowed much greater understanding of bone homeostasis in general, as well as in the context of mechanical loading effects [83, 84]. The term Wnt stems from a combination of "integration site 1" gene and a homology gene known as "wingless." The Wnt gene signaling pathway has a central role in regulating development of many body organs and tissues. In bone, it is the major driver of osteoblast activity and of bone mass [85]. A Wnt protein is produced by the osteocyte and binds to a number of co-receptor complexes such as "Frizzled receptor" and low-density lipoprotein receptor-related protein (Lrp)5 located on the osteoblast. This complex, through a cytoplasmic protein called B-catenin, results in nuclear transcription of target genes for osteoblast proliferation and function. The role of inhibitors of Wnt signaling antagonists seems crucial to the development of disuse osteopenia. One such, named sclerostin, is produced by the osteocyte and prevents the formation of the Wnt complex, by competitively binding with Lrp5, thereby leading to greatly reduced osteoblast activity and bone formation. In animal studies, when osteocytes sense a mechanical load, they reduce the expression of sclerostin, whereas mechanical unloading causes decrease of Wnt signaling activity accompanied by upregulation of the Sost gene encoding for sclerostin production [84, 86]. Transgenic sclerostin-deficient mice were protected from bone loss stimulated by hindlimb suspension, implicating sclerostin as an important factor in the dramatic bone loss that occurs when weight-bearing ceases, such as in the hemiparesis setting [86]. Sclerostin levels have been measured in humans but show an inconsistent relationship with BMD. One study in women with post-stroke osteoporosis noted elevated levels, however, which were associated with low BMD [83]. The Wnt pathway is the target of several novel osteoporosis drugs in development, such as the sclerostin inhibitor rosozumab, which shows promising results in phase II trials [87].

Vitamin D/PTH/Calcium Imbalance

Vitamin D deficiency is widespread in the general population, particularly in older and housebound people. Stroke survivors with impaired mobility are more prone, as they may spend less time outdoors getting sunlight exposure [88]. The early, marked increase in osteoclastic activity following loss of mechanical load after a stroke leads to a significant increase in calcium release into the circulation, which may not be detected unless measured by serum ionized calcium or by urinary calcium excretion [57, 89]. Suppression of parathyroid hormone (PTH) then occurs in response to this, which leads to reduced renal production of 1,25 hydroxy Vitamin D (1,25 OHD3) which may further deplete Vitamin D levels in an already deficient patient. Although PTH and 1,25 OHD3 may have a role in modulating the bone response to unloading, the relationship is complex and remains unclear [90].

Nutritional Deficiencies

Apart from vitamin D and calcium, there are several other vitamins and trace elements which play a role in bone homeostasis but no clear evidence implicates them or their deficiency in osteoporosis and fracture risk in the general population other than mention of the following:

Vitamin K is essential for the carboxylation of two substances called matrix gla protein and osteocalcin, which are important components of healthy bone [91]. Vitamin K is stored in the liver, and stores are depleted by periods of fasting of as little as 3 days and in one small study in stroke survivors, levels were independently related to low BMD [92, 93]. In a large prospective study, women with baseline Vitamin K deficiency had higher risk of subsequent osteoporosis and hip fracture, which could be a potential contributor to post-stroke osteoporosis in a deficiency setting [94].

Vitamin B12 and folate deficiency lead to elevated homocysteine levels, which are associated with increased fracture risk, though low B12 and folate have not been causally associated with low bone mass or fracture risk [95]. Despite this, one small placebo-controlled study of B12 and folate supplementation in a group of very disabled stroke survivors seemed to reduce fracture risk after 2 years, but a larger trial in a less-dependent stroke population did not [96, 97]. Assessment for B12 and folate deficiency would be prudent in stroke patients, however, with bone health as well as general health in mind.

Iatrogenic Factors

Following a stroke, a patient is most likely to be prescribed a concoction of new medications, which have clear evidence of benefit for reducing future vascular risk. Not all these are without potentially harmful effects on bone health. Warfarin, being a vitamin K antagonist, may impair bone density and has a plausible biological mechanism to do so. Observational data in various cohorts, including stroke survivors, have linked warfarin with increased bone loss and fracture risk [98, 99]. More recently, however, a large prospective series of warfarin users refuted this finding [100]. The gains of warfarin therapy for stroke prevention in AF will certainly outweigh any potential fracture risk, particularly when the association is not entirely clear. The novel oral anticoagulant drugs (NOACs) do not have this inhibitory effect on the vitamin K cycle and therefore should not have this adverse effect. Unfractionated heparin, though now rarely used, leads to increased fracture risk; low molecular weight heparins seem largely free of this effect, though again are seldom used following stroke [101].

For the patient with epilepsy post-stroke, anticonvulsants are implicated in osteoporosis, mainly through impairment of vitamin D metabolism, and this largely applies to older agents such as phenytoin and carbamazepine. Newer anticonvulsants

may be free from this effect but this is not entirely clear from the few studies to date [102, 103]. Proton pump inhibitors, often co-prescribed with aspirin prophylactically, are also associated with a higher fracture risk, possibly through impaired calcium absorption which is stomach acid-dependent [104, 105]. Numerous other medications relevant to the stroke patient have also been implicated as contributors to alerted bone mass and fracture risk. These include selective serotonin re-uptake inhibitor (SSRI) and serotonin/noradrenaline reuptake inhibitor (SNRI) antidepressants, antipsychotics, anxiolytics, statins, and glitazones [106]. Polypharmacy in the post-stroke setting is common and, though necessary, warrants evaluation of risk/benefit ratio in a population already at high risk of fracture.

Post-Stroke Osteoporosis Management

It is clear that in the aftermath of a stroke, the skeleton undergoes marked dynamic changes leading to accelerated loss of bone mass and increased fracture risk. Acknowledging this and addressing reversible risk factors should be part of routine, early post-stroke care, though a few international stroke guidelines make this specific recommendation [107].

Assessment

The traditional gold standard investigation for fracture risk assessment is a DXA bone density scan. In recent years, several fracture risk assessment tools have been developed to overcome the limitation of a DXA scan, given that the greatest proportion of fragility fractures occur in those who are osteopenic rather than osteoporotic. Low BMD, though a major fracture risk factor, is only one of many, including age and prior fracture, as we have discussed. FRAX® is the most commonly used risk assessment tool worldwide, but doesn't account for stroke or immobility in its risk assessment. QFracture® is another tool that does, as a single category of prior stroke/TIA/myocardial infarction, acknowledging the association of vascular disease with increased fracture risk, but there is no specific inclusion of hemiparesis or immobilization [108]. Despite differences between the two tools, they have been shown to perform similarly at a population level [109]. Fracture risk assessment tools have limitations, in older age in particular, and none have been assessed in a stroke population specifically [110].

Interventions

Interventions can be divided into factors addressing falls risk and factors addressing bone health directly. The former is dealt with in detail in the previous section on falls post-stroke. Strategies to improve bone density include exercise, nutrition, and pharmacotherapy.

Exercise

Immobility is a leading contributor to post-stroke osteoporosis; therefore importance of weight-bearing exercise where possible is essential. In a detailed review on all post-stroke exercise regimens, three controlled trials were identified that investigated the effect on BMD [107]. There seems to be some benefit in early physiotherapy and weight-training exercise in maintaining bone density and structure on the paretic side, though more dedicated research on this area is needed. Whole-body vibration induces osteogenesis in animal studies and has shown some beneficial effects on bone in older adults, but one trial specifically in chronic stroke patients showed no beneficial effects on bone turnover markers [111].

Nutrition

Vitamin D status should be evaluated following stroke for those with paresis, given the rapid skeletal metabolic changes that occur with immobilization, as well as the likely sunlight deprivation that may follow. This practice may reduce falls as well as fracture rates [112]. Dosages and preparations of vitamin D supplied to deficient patients varied in studies, but in line with osteoporosis guidelines in general, replacement with 800–1,000 units of colecalciferol is advised, +/− calcium supplementation, bearing in mind the immobilization hypercalcaemia that may occur and existing dietary calcium intake. There have been recent concerns of increased cardiovascular risk from supplemented calcium where dietary intake is adequate, though this remains controversial [113, 114]. However, expert bone societies do advocate estimation of dietary calcium intake before supplementation [115, 116]. Single high-dose boluses of vitamin D should be avoided, as they have been linked to possible increased falls and fracture risk [117].

Vitamin deficiencies such as B12 and folate should be replaced only if low, as is usual practice. Vitamin K is rarely measured routinely and sufficient intake can be obtained from a balanced diet. Though one study from Japan found that vitamin K administration led to improved BMD in chronic stroke patients, there was no comparator group in this small cohort [118]. Soy proteins have mildly oestrogenic effects and can reduce osteoclastic and increase osteoblastic activity. Sato et al. studied the effect of the synthetic soy protein ipriflavone in hemiplegic stroke patients [119] and found it to prevent BMD decline to a greater degree than vitamin D3 or placebo. However, the study was small ($n = 30$ per arm), looked at metacarpal rather than axial BMD, and included both males and females. Since then, a larger placebo-controlled trial of ipriflavone in a postmenopausal population over 4 years found no beneficial effect on BMD [120] and it is not routinely recommended for fracture risk reduction, even in the post-stroke setting.

There are numerous other nutrients that may influence bone metabolism such as copper, zinc, vitamin C, and protein, but there is no firm evidence that supplementation of any will influence bone mass, even in the general population [121]. Particular attention to nutrition in the stroke survivor to achieve a healthy balanced intake is prudent for multiple reasons, including bone health.

Medication Review

In prescribing for the stroke patient who has a hemiparesis and/or immobility, it should be borne in mind the ability of certain drugs to impair bone density as mentioned above. For example, in post-stroke epilepsy, choosing a newer anticonvulsant may be wise. The need for proton pump inhibitors and SSRI antidepressants should be reviewed at regular intervals. In treating hypertension, thiazides may have a beneficial effect on the skeleton by reducing urinary calcium excretion and can enhance osteoblastic calcium uptake [122]. Frusemide, on the other hand, is associated with increased fracture risk, possibly through urinary calcium loss [122]. However, both agents may increase falls risk by reducing blood pressure, as mentioned earlier.

Bone-Sparing Pharmacotherapy

A number of bisphosphonates have been evaluated in stroke survivors. Etidronate, alendronate, and zoledronate have demonstrated attenuation of BMD reduction following hemiparetic stroke [57, 68, 123]. Risedronate has also shown to reduce hip fracture risk in Japanese male and female stroke patients [46, 47], but fracture numbers were in single figures only. No randomized trials have been conducted in Caucasian or Afro-Carribean cohorts. The anti-resorptive monoclonal antibody denosumab is a potent agent for fracture prevention in post-menopausal women, but has not so far been trialled in stroke or immobilized patients specifically. Given the marked failure of bone formation in the stroke setting, an anabolic agent such as the PTH analogue teriparatide, along with the even more potent sclerostin inhibitor rososuzamab, currently in phase III trials, has theoretical benefits in the hemiplegic stroke patient but this remains to be determined beyond animal data at present [124, 125]. Meanwhile, in stroke survivors, standard age-related osteoporosis treatment guidelines should apply, with bisphosphonates being first-line therapy until further data emerges on optimal therapeutic agents in the post-stroke setting.

Conclusion

Falls and fractures are an important cause of morbidity following a stroke. Patients are at risk of falls, both in the immediate aftermath of their illness and, subsequently, in the community. Because the control of balance and locomotion depend on the functioning of separate neuronal pathways, strokes in different locations can cause falls in a number of different ways. Falls are also caused by the complications of stroke, as well as the medications prescribed to stroke patients. The identification, assessment, and management of patients who may fall involves a multidisciplinary approach, taking into account known risk factors, performing assessments of function and disability, and providing a patient-centred approach to the mitigation of risk.

Fractures are common following a stroke because of the increased falls risk and decreased bone loading on the paretic side. The osteocyte appears to have an important role to play in mediating the changes of hemiparetic bone loss, and there are promising advances in the identification of the cellular mechanisms underlying their action. Following a stroke, patients should be assessed for their risk of osteoporosis, including identification of their co-morbidities, medications, and metabolic abnormalities that constitute risk factors for the condition. Treatment of osteoporosis is multifactorial and includes exercise, nutrition, review of medications, and bone-sparing pharmacotherapy.

Patient Questions

Q. Since being discharged home after my stroke, I feel very unsteady when I walk around. What can I do to reduce my risk of falling?

A. Reducing your falls risk involves assessments and interventions from several different members of the stroke multidisciplinary team. The physiotherapist can evaluate your gait and balance, and give you rehabilitation and exercises to improve your strength and balance. They may provide you with walking aids and, if necessary, help you with spasticity. The occupational therapist can assess you in your own home and may make recommendations to improve your safety there. Meanwhile, your doctor can help tailor your medications to reduce your risk of falling.

Q. I have been prescribed warfarin because of my atrial fibrillation, but I have had a fall and I am worried about the risk of bleeding. What should I do?

A. Decisions about taking warfarin are always difficult if someone has a fall. The multidisciplinary team can help assess your falls risk and may be able to intervene to reduce your chances of falling. For many people, even if they have had a fall, the benefits of warfarin in reducing the chance of another stroke are greater than the risks of bleeding, but it is important to come to an individual decision that is right for you, in conjunction with your doctor.

Q. What can be done to reduce my risk of a fracture if I fall, after a stroke?

A. Interventions to reduce risk of falls should also help reduce your risk of a fracture but it is also advisable that bone health is addressed separately, soon after a stroke. This will take the form of addressing your other risk factors for a fracture, such as reviewing your medications and nutritional status, and may include conducting a bone density scan. The latter may need to be repeated within a year, because bone density can decline quite quickly following a stroke, especially where there is residual limb weakness. If you are found to have osteoporosis or to have a particularly high fracture risk, there are a number of medications available which your clinician may prescribe for you to help reduce this risk.

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Chapter 12
Post-Stroke Cognitive Impairment

Bhavini Patel and Jonathan Birns

Abstract Cognitive impairment is common after stroke and its recognition is crucial, as it impacts on rehabilitation. Deficits may affect specific cognitive domains such as language or may be more global. In this chapter, we review the literature studying the neuroanatomy and the clinical presentation of major types of cognitive deficit, and discuss which neuropsychological tests are appropriate for each cognitive domain. Pharmacological treatment options are limited, but several studies are analysing the effects of secondary stroke prevention and specific biological products and their role in preventing, altering, or reducing cognitive decline.

Keywords Cognitive impairment • Aphasia • Delirium • Executive function • Attention

Key Messages
- Commonly used screening tools may miss impairments other than memory problems.
- Post-stroke delirium can remain in up to 30 % of patients and is associated with increased risk of institutionalisation and mortality.
- Executive function problems are a hallmark of cerebral small vessel disease and should be evaluated using appropriate tests, such as the trail-making test.
- Trials are ongoing studying the benefits of controlling risk factors for stroke on cognitive impairment.

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Introduction

Post-stroke cognitive impairment falls under the umbrella term of vascular cognitive impairment, encompassing all forms of cognitive loss associated with cerebrovascular disease and ischaemic brain injury. Cognitive impairment related to stroke may be in association with cortical and/or subcortical haemorrhage or infarction, strategic haemorrhage or infarction, that produces an abrupt onset of cognitive impairment often without additional focal neurologic deficit and/or "silent" haemorrhage or infarction (without overt clinical decline at the time). A number of different domains of cognitive function may be affected, often depending on the structural location of the stroke. These include memory, language, orientation, attention, and executive function. Whilst the site, size, and depth of the lesion will impact significantly on the cognitive effects of the stroke, "distance effects" of diaschisis and disconnection syndromes will also be contributory. Diaschisis refers to the depression of activity in areas of the brain distant to the stroke, often confined to relatively discrete functions, and is supported by reduced blood flow and EEG abnormalities being demonstrated in non-infarcted brain areas. In younger individuals these effects commonly recover, but in older patients chronic diaschisis may result in a disconnection syndrome involving the loss of brain function by an intact area of brain at some distance from the stroke.

Epidemiology

Data from 1,618 patients of the South London Stroke Register suggest that the prevalence of cognitive impairment 3 months after a stroke is 22 %, as defined by abnormal mini-mental state examination (MMSE) or abbreviated mental test (AMT) scores [1]. After 5 years, 22 % of patients followed up remained impaired, and after 14 years, 21 % were affected. The prevalence was higher in patients with total anterior circulation strokes (50 %) but there was a stepwise deterioration in patients with lacunar stroke and small-vessel disease (SVD) [1]. In a Singaporean population of 252 patients with a transient ischaemic attack (TIA) or non-disabling ischaemic stroke, within 6 months of the event, only 56 % of patients were "cognitively intact," 40 % were "cognitively impaired but not demented," and 4 % were "demented" (using DSM [Diagnostic and Statistical Manual of Mental Disorders]-IV criteria). At 1-year follow-up, 31 % of those who were "cognitively impaired but not demented" improved to "cognitively intact", 10 % of the "cognitively intact" group deteriorated to "cognitively impaired but not demented," and 11 % deteriorated from "cognitively impaired but not demented" to "demented" [2]. Longitudinal observational studies such as these are limited by the lack of comparison with a non-stroke population under similar circumstances, the inclusion of a heterogeneous stroke population, and patients being lost to follow-up. Losing patients to follow-up introduces bias, as the severely disabled are more likely to drop out (from death or

inability to attend), and therefore the actual prevalence at 5 years may be higher than that quoted. The aforementioned studies may also be limited by the use of cognitive assessment tools lacking sensitivity for the different cognitive domains affected after a stroke. More recently, the Secondary Prevention of Small Subcortical Strokes (SPS3) triallists undertook comprehensive neuropsychological evaluation of 1,636 patients within 6 months of suffering a lacunar stroke and found 47 % to have mild cognitive impairment (classified as z scores [converted from raw scores using published norms] being ≤−1.5 in memory and/or non-memory domains) with the largest deficits seen on tests of episodic memory, verbal fluency, and motor dexterity. Younger age (odds ratio [OR] per 10-year increase: 0.87), male sex (OR: 1.3), less education (OR: 0.13–0.66 for higher education levels compared to 0–4 years education), post-stroke disability (OR: 1.4) and impaired activities of daily living (OR: 1.8) were independently associated with mild cognitive impairment [3].

Rabadi et al. reported that post-stroke patients with cognitive impairment had more severe strokes with greater disability and delayed admission into rehabilitation compared with cognitively intact patients. However, the authors demonstrated that patients with cognitive impairment had significant improvements in their functional scores with rehabilitation [4]. Zinn et al. showed post-stroke cognitive impairment to be associated with poorer recovery to independence of activities of daily living despite similar rehabilitation opportunities [5]. In a Belgian study of 532 stroke patients, cognitive impairment, in addition to atrial fibrillation, age, and diabetes, was an independent predictor of mortality [6].

Pathophysiology

Vascular cognitive impairment is heterogeneous, and the pathophysiology of post-stroke cognitive impairment is unlikely to be explained by a single process. The supratentorial brain exhibits a number of distinct patterns of vascular supply, each particular to a peculiar zone, offering relative protection from and vulnerability to circulatory changes [7]. The basal ganglia and thalamus are supplied by long arterioles and muscular arteries from adjacent sources at the base of the brain; the cerebral cortex and corpus callosum (excluding the splenium) are supplied by short arterioles; and the subcortical association bundles or U-fibres are supplied by the terminal twigs of the longest cortical arterioles and by the earliest branches of the long medullary arteries and arterioles. For a given sector of the U-fibres, these two types of afferent vessels usually arise from different points on the brain surface, constituting a dual supply, and in the immediate subcortical region their terminal arterioles often appear to interdigitate. The external capsule area is supplied by the same two types of vessels as in the U-fibre area and, in addition, by lateral rami of the lateral striate arteries, thus constituting a triple blood supply. The terminal arteriolar territories of these three sources have also been shown to interdigitate [7]. The centrum semiovale is supplied by long, penetrating arteries and arterioles (20–50 mm in length and 100–200 μm in original diameter) originating from the pial

network located on the brain surface. These penetrating vessels arise, close to each other, at right angles from the subarachnoid vessels, run through the cortical layers perpendicular to the brain surface and enter the white matter along the course of myelinated fibres [8]. The vessels penetrate to different depths, with the longest converging centripetally toward the angles of the lateral ventricles. These carrying vessels do not arborise but give off perpendicularly oriented short branches that irrigate the white matter, each of which provides the blood supply to a cylindrically shaped metabolic unit [9].

In addition to the aforementioned centripetal white matter blood supply, van den Bergh described cerebral arteries originating from choroidal and striate arteries which, after travelling toward the frontal horn, body, and posterior horn of the lateral ventricle and reaching a subependymal location, turned back into the white matter away from the ventricle, thus delineating a centrifugal or ventriculofugal supply (i.e. away from the centre of the brain or away from the ventricle). In this white matter region between the cortical and ventricular surfaces, ventriculopetal and ventriculofugal arteries have been said to form "a three-dimensional border area between the centripetal network surging from the periphery and a centrifugal network, dependent from well-defined branches". [10]. Anastomoses between these networks are either scarce or absent [8] and this pattern of vascularisation has led to the theory that the subcortical white matter harbours an arterial border zone, or watershed, that is particularly susceptible to being injured as a result of systemic or focal decreases in cerebral blood flow [11].

The subcortical white matter may therefore be considered a distal irrigation field prone to injury in the face of impaired blood flow. In contrast to the cerebral territories described with interdigitating blood vessels providing dual or triple blood supply, the centrum semiovale, basal ganglia, and thalamus have no such interdigitating supply and are more vulnerable to ischaemia and are the most common sites for lacunar infarcts [12]. Furthermore, the supplying blood vessels themselves are subject to the changes of arteriosclerosis and the arrangement of white matter metabolic units is such that, although anastomoses do exist at the precapillary level, one distributing vessel irrigates only one metabolic unit [9].

Cerebral Small Vessel Disease

Cerebral arterioles and small penetrating arteries supplying subcortical structures, both of diameter less than 400 μm, undergo physiological, age-related, and arteriosclerotic changes, which may then be accelerated by disease states such as chronic hypertension and diabetes mellitus. The changes in the blood vessels include intimal atheroma formation, medial smooth muscle hypertrophy, and subsequent hyaline deposition in the walls [13]. Consequently, the vessel wall becomes rigid and the lumen becomes narrow, impeding blood flow. In addition, there is a general tendency to increasing tortuosity of cerebral arterioles with ageing, compounding any reduction in blood flow [14].

Reduced blood flow or complete occlusion of a single small artery (due to local arterial wall pathology or emboli) may produce necrosis in an artery's territory of supply, with destruction of all of the cellular elements and subsequent removal of the necrotic tissue by a standard inflammatory response [13]. Such lacunar infarctions, whose size range from 1 to 20 mm in diameter, account for a quarter of ischaemic strokes and are the most common abnormality found in human brains at post-mortem examination [15].

Lipohyalinosis and Microatheromatosis

In autopsy studies, two types of vascular pathology underlying occlusion of perforating arteries causing lacunar infarction have been distinguished: lipohyalinosis and microatheromatosis [16, 17]. Lipohyalinosis refers to a continuum of arteriolar alterations, from the earliest thickening of the vessel wall to progressive narrowing, poststenotic dilatation, thrombosis, and fibrinoid necrosis, and was present mainly in patients with small, multiple, asymptomatic lacunes. Microscopically, the muscle and elastic laminae are replaced by collagen with a generalised increase in subintimal hyaline material. As a result of the histopathological continuum also including microaneurysm formation in association with impaired vessel wall integrity, this same lipohyalinotic pathology has also been implicated to be the driving force behind deep brain haemorrhage of subcortical origin. In contrast, microatheromatosis refers to a small atheromatous plaque narrowing or occluding a small artery proximally at its orifice and was found mainly in patients with single, larger lacunes [17].

Leukoaraiosis

Many ischaemic episodes are insufficiently prolonged to produce true infarction but may damage vulnerable tissue elements. Different cell types have varying degrees of vulnerability to ischaemia, with neurons being more vulnerable than oligodendrocytes, which themselves are more vulnerable than astrocytes [13]. Individual cells may undergo apoptosis involving the generation and sensation of signals that continued cell survival is no longer advantageous, the transduction of these signals by activation of a cascade of proteases, and subsequent cleaving of the genomic DNA into small fragments, thus terminating cellular viability. In this way, cells are removed without an accompanying inflammatory response and the rest of the tissue remains intact [18]. However, many combinations of neuronal and glial damage, that are intermediate between the extremes of focal neuronal loss and infarction, occur producing varying degrees of loss of myelin and axons, reactive astrocytosis, and tissue rarefaction falling short of cavitation [19]. The radiological correlate of these pathological changes is leukoaraiosis demonstrated by hypointensities on CT scanning or hyperintensities on T2 weighted and FLAIR MRI scanning. Quantitative perfusion MRI studies have shown that cerebral blood flow is reduced in the

periventricular areas in patients with leukoaraiosis, and the degree of hypoperfusion correlates with the severity of leukoaraiosis [20].

Leukoaraiosis has been associated with impaired blood-brain barrier function, with endothelial cell retraction, increased vascular permeability, and greater susceptibility to white matter injury for relatively small insults [21]. One study has demonstrated intravenously injected contrast agent to leak into the brain, particularly in the territory of the perforating arteries, more in those with white matter hyperintensities on brain MRI than in controls [22]. Iwata et al. observed a small area of enhancement in the thalamus on contrast MRI 24 h before the development of a lacunar infarct at that location, leading the authors to suggest that breakdown of the blood-brain barrier may be the initiating event in lacunar infarction [23].

Cerebral Large-Vessel Disease

Large-vessel disease appears to be the fundamental process underling the aetiology of cortical ischaemic stroke. Atheroma mainly affects the large (aortic arch) and medium-sized arteries (carotid bifurcation, vertebral artery origins, and the basilar artery)—with hypertension, diabetes mellitus, hyperlipidaemia, and cigarette smoking being the major risk factors for its development. Atheromatous plaques consist of early deposition of lipid in the artery wall, buildup of fibrous material, necrosis, inflammatory cell infiltration, and calcification with subsequent haemorrhage leading to ulceration and platelet-fibrin thrombus formation on the plaque surface. Atherosclerotic plaques are in a dynamic process, becoming active and unstable or remaining dormant. It is unclear what mechanism is involved in mediating the plaque instability and subsequent rupture, but an exogenous antigen such as low-grade infection or an inflammatory response may be important. Thrombus on the plaque surface may become incorporated into the plaque with subsequent endothelialisation, obstruct the arterial lumen, be lysed by natural fibrinolytic mechanisms, and/or embolise to occlude a distal artery. Emboli consist of a combination of platelet aggregates, cholesterol debris, and fibrin. Hence, atherosclerosis may result in ischaemic stroke through insufficient blood flow caused by acute in situ thrombotic arterial occlusion, low flow distal to a severely narrowed or occluded artery, and embolism of atherosclerotic plaque or thrombus from a large vessel to occlude a smaller intracranial artery. Emboli may also arise from thrombi of cardiac origin as a result of atrial fibrillation, causing intra-atrial stasis and thrombus formation in the left atrial appendage, valvular heart disease, or a dyskinetic left ventricle due to ischaemic or non-ischaemic cardiomyopathy, causing thrombus formation in the left ventricle.

Endothelial Dysfunction

The normal cerebral endothelium plays a crucial role in the regulation of cerebral blood flow and the blood-brain barrier and, in addition, presents an anticoagulant phenotype to blood. However, under stimulation by numerous agents, the

endothelium may be activated to undergo a number of changes including loss of vascular integrity, cytokine production, expression of leukocyte adhesion molecules, and a change in phenotype from antithrombotic to prothrombotic [24]. A number of separate lines of evidence suggest that chronic endothelial dysfunction plays an important role in the pathogenesis of cerebrovascular disease [25]. These include histopathological evidence of endothelial cell activation and retraction with increased vascular permeability and increased circulating levels of leukocyte adhesion molecules (shed from the surface of activated endothelial cells) and markers of coagulation activation (including thrombin-antithrombin complex and prothrombin fragments$_{1+2}$) in patients with cerebrovascular disease compared with controls [25–28].

Cerebral Amyloid Angiopathy

Cerebral amyloid angiopathy is characterised by the deposition of amyloid B-protein in the walls of the leptomeningeal cerebral vessels [29] and can lead to intracerebral haemorrhage, after vessel wall rupture, and less commonly cortical microinfarcts [30]. Haemorrhages caused by amyloid angiopathy are typically lobar and at the border of grey and white matter of the cerebral hemispheres [31]. Initially the disease affects leptomeningeal and neocortical vessels, and then progresses to the hippocampus, entorhinal and cingulate cortex, amygdala, hypothalamus, and the cerebellum [32]. The main risk factors identified are advancing age and concomitant Alzheimer's disease [33].

Post-Stroke Cognitive Assessment

Whilst neuroimaging assesses structural brain damage, neuropsychological examination provides precise and sensitive indices of a patient's mental efficiency [34]. Cognitive tests are standardised techniques that yield quantifiable and reproducible results that are referable to the scores of normal persons of an age and demographic background similar to those of the individual being tested [35]. Table 12.1 lists some of the cognitive tasks used in clinical practice. The most ideal test battery for cognitive impairment should be as short as possible to reduce the burden on the patient, but should be sensitive at detecting the common cognitive domains known to be affected in the disease process. A screening tool should be something that can be used in a typical clinic, whereas more precise cognitive batteries can be used by neuropsychologists to assess impairment in more detail. Most dementias are due to progressive neurodegenerative processes and therefore the cognitive tests should be sensitive to change over a defined period.

National Institute for Health and Care Excellence (NICE) quality standards state that all stroke patients should be screened within 6 weeks for cognitive impairment using a validated tool [36]. This should then allow for the best treatment for the individual patient. In general, simple tests that elicit discrete responses are

Table 12.1 Cognitive tasks description

Cognitive domain	Test	Description
Memory	Five-item recall/ repetition	Recall five items told at different points
	Digit span forwards	Repeat a string of numbers
	Digit span backwards	Repeat a string of numbers backwards
Executive function	Trail making	Patient asked to join alternate letter and number sequences (e.g. 1-A-2-B) as fast as possible
	FAS verbal fluency	Say as many numbers beginning with F then A then S in 1 min each
	Wisconsin card sorting test	Participant is told to match the cards, but not how to match
	Digit symbol	Match the symbol to the digits (e.g. 1 with ρ)
	Letter number sequencing	A task that requires the reordering of an initially unordered set of letters and numbers
Attention/orientation	Stroop test	Show a sequence of names of colours written in a different colour. Ask patient to say the written colour not the actual colour
	Serial 7s	Subtract 7 from 100, 93, 86, 79, and 72
	Recite months of the year backwards	December through to January
Aphasia	Frenchay Aphasia Screening Test (FAST)	Test of comprehension (e.g. pointing at objects in a scene, verbal expression [describe the scene]), reading, and writing
	Ullevaal Aphasia Screening Test (UAST)	Expression, comprehension, repetition, reading, reproduction of a string of words, writing, and free communication

valuable in determining focal brain damage. On the other hand, multidimensional tests, being dependent upon several aspects of cerebral function, tend to be non-specific but are very sensitive to changes in general intellect and mental efficiency [34]. The MMSE (range 0–30) was designed to be a screening tool for dementia and has been used widely as a cognitive assessment test in a variety of clinical genres, including stroke. It is short and easy to administer, which has made it popular worldwide. It covers temporal and spatial orientation, memory, attention, language and visuospatial assessment with a maximum score of 30° points. A cut of score of 24/30 provides a reliable score for diagnosing dementia with high specificity and sensitivity [37]. However, evidence suggests that the MMSE has many limitations as it misses mild cognitive impairment and does not test for executive dysfunction. It also cannot detect changes in the severely impaired patients towards the end stages of disease. It is also criticised for repetition bias in mild cognitive impairment [38]. As a test of global cognitive dysfunction in stroke patients, the MMSE has been somewhat superceded by the Montreal Cognitive Assessment

(MOCA). This also has a range of 0–30, but has been shown to be superior to the MMSE as a cognitive assessment tool in patients with cerebrovascular disease and, as such, is recommended in current guidelines [39–42]. In one study, the MOCA identified cognitive impairment in 67 % of stroke patients and 48 % of TIA patients with normal MMSE scores [43]. More recently, however, the MOCA has been shown to lack accuracy in post-stroke patients with cognitive problems not affecting memory [43].

In patients with subcortical infarction and cerebral SVD, in whom episodic memory is typically preserved, O'Sullivan et al. designed a clinical battery which took 20 min to administer [44] and had a high sensitivity and specificity. This battery included the digit symbol, FAS verbal fluency, digit span backwards, and trail-making tests. It was effective for determining deficits in patients with SVD and discriminating them from the normal ageing population, and it showed that bedside cognitive screening is possible in SVD [44]. Recently, the Brief Memory and Executive Test battery (B-MET) has been designed, which lasts 10 min and in a small group ($n=45$), had a sensitivity of 91 % and specificity of 85 % for differentiating SVD patients with cognitive impairment from patients with Alzheimer's disease. As a comparison, the MMSE had lower sensitivity (63 %) and specificity (62 %) [45]. The B-MET includes the five-item repetition, letter-number sequencing, five-item recall, and five-item recognition tests and an awareness assessment, analysing the patient's awareness of how well they performed. The B-MET has a short assessment for memory and orientation but increased assessment for executive function and information processing speed. Therefore it may miss impairment in memory while identifying more executive dysfunction.

The Birmingham Cognitive Screen (BCoS) is a screening test designed to assess different forms of praxis in patients with spatial neglect and aphasia [46]. Because many patients with stroke have neglect and aphasia, it is a useful test to identify such higher cognitive deficits. It is a short screen including the Florida Apraxia Screening Test for pantomime, gesture recognition test, movement imitation test, and multiple object use test, and in conjunction with tests of activities of daily living, it allows one to review the effect of the apraxia on their daily functioning. A very well-known test used for decades to assess visuospatial and executive functioning and praxis is the Clock Drawing Test. It is quick to administer and as a screening tool can be valuable to identify hemi-neglect, apraxia, and episodic memory [47]. It may predict future decline in cognition, although more data is required to confirm this.

Post-stroke cognitive impairment may sometimes be clinically silent, but relatives and carers may report abnormal behaviour resulting from lack of strategic planning, reduced speed of cognitive processing, and personality changes including apathy and irritability. As such, assessment of behaviour and function may be crucial to ascertain the impact of cognitive dysfunction on patients' ability to undertake complex, goal-directed, purposeful activities, which form part of daily life, such as cooking, dressing, shopping, and housework. Various scales have been derived to assess disability and have been verified in stroke. The most commonly used scales are the modified Rankin Scale [mRS] and Barthel index. Carers need to be educated about the impact of cognitive impairment and recognise that it can vary over time [48].

Cognitive Impairments After Stroke

Memory

Memory is the process in which information is encoded, stored, and retrieved. In simple terms, memory is divided into short-term memory (working memory) and long-term memory. Working memory, which refers to holding in and manipulating new information, is defined as memory duration of 15–30 s, and is closely associated with attention. An example is remembering a telephone number and may be assessed by the digit span test. The prefrontal cortex, which receives information from visual and auditory sensory cortices, as well as the hippocampus, plays an important role in working memory. Long-term memory is further divided into explicit and implicit memory. Explicit memory is divided into episodic memory (relating to events and experiences) and semantic memory (relating to facts and concepts). Long-term memory relies on the parahippocampal and perirhinal cortices. These brain regions receive information from the parietal and temporal cortex and then project to the entorhinal cortex and hippocampus. Synaptic changes in the hippocampus allow memory storage, which then reinstates the pattern of cortical activation, allowing learning. Damage to the hippocampus affects recent memories only as older memories are consolidated in the cortex. Implicit memory is the unconscious procedural memory, e.g. how to drive a car or emotional memory, e.g. fear of a known trigger. The neuroanatomy of implicit memory is not fully understood but is likely to involve a complex circuit. Lesional studies suggest that the hippocampus is not involved [49, 50].

Pure amnesic strokes are rare, as patients are likely to have focal neurologic deficits from their stroke. Akiguchi et al. described acute amnesic syndromes due to unilateral infarcts in 26 patients [51]. Eight had an anteromedial thalamic stroke and 18 had a medial temporal lobe plus hippocampal stroke. Prolonged recent memory loss was associated with new learning disabilities of verbal memory in left-sided lesions and non-verbal and visuospatial memory in right-sided lesions [51]. Careful neuropsychological testing may help identify patients with amnesia. Szabo et al. described hippocampal infarcts in 11 of 57 patients to be initially associated with prominent aphasia, but more detailed testing revealed more problems with verbal and non-verbal episodic memory loss [52].

Whilst the general screening tools (MMSE and/or MOCA) have been shown to be good screens for memory impairment, more detailed tests of memory exist. These include the Adenbrooke's Cognitive Examination-Revised (ACE-R) [53], Test Your Memory [54], Raven's Coloured Progressive Matrices, [55] and Sheffield Screening Test for Acquired Language Disorders [55]. Many patients can have transient amnesia immediately after the stroke such that testing of memory often improves with time.

Language

Dysphasia is the most common language disturbance caused by a stroke, affecting approximately one-third of patients. The most common types are expressive (affecting language formulation) and receptive (affecting comprehension and understanding). It is well accepted that expressive dysphasia is usually caused by a stroke in Broca's area (inferior frontal gyrus) and receptive dysphasia is usually caused by a stroke in Wernicke's area (superior temporal gyrus), both usually in the left hemisphere. Language is predominantly lateralised to the left hemisphere of the brain, with disconnection of left hemispheric brain regions having been shown to impair word generation in patients with cerebrovascular disease [21]. Other forms of dysphasia include transcortical sensory (where a patient has poor comprehension and naming with fluent spontaneous speech with paraphasias), anomic (inability to name objects), and conduction (fluent, paraphasic speech with poor speech repetition). Conduction dysphasia occurs when the connection between the Broca and Wernicke areas has been broken due to a lesion in the arcuate fasciculus. Dysphasia may also occur after damage to the insula or to deep brain structures such as the thalamus, again, as above, usually in the left hemisphere. Mutism is associated with large fronto-putaminal lesions [56].

Various language assessment scales have been used to assess the presence and degree of aphasia. The Frenchay Aphasia Screening Test (FAST) is the most popular and reliable screening test for patients with aphasia [57]. It has a specificity of 87 % and sensitivity of 80 %. The Ullevaal Aphasia Screening Test (UAST) has also been shown to be accurate for identifying aphasia with a sensitivity of 75 % and specificity of 90 %.

Orientation

Orientation forms a part of a global attentive process alongside concentration, exploration, and vigilance. It should be the beginning of all neurological and cognitive examination. Time orientation should include the year, season, month, date, and day of the week, while place orientation should include the building, floor, town, county, and country. These form the first section of the MMSE; however, only six of these ten items are included in the MOCA. Using the MMSE on 177 patients who had stroke, Desmond et al. [58] showed that 40.7 % of patients were disorientated 10 days after their stroke and 22 % remained disorientated at 3 months. The persistence of disorientation was associated with stroke severity, but not stroke location or subtype. Orientation has a significant impact on rehabilitation, with a reduction in Barthel Index scores, even after 6 months [59]. It affects activities of daily living and social function, and therefore limits recovery after a stroke.

Attention

Attention has been described as the foundation of other cognitive functions that allows an individual to select relevant information and filter out irrelevant information. Most studies have implicated the frontal and parietal lobes in the control of attention, more commonly in the right hemisphere. Post-stroke, attention is impaired in 46–92 % of patients, mainly due to neglect or inattention [60]. Deficits in attention impact on learning motor skills and are associated with falls and balance problems [60].

Hemispatial neglect is a special form of inattention when the patient is unaware of one side of their body or the world. This can be visual or sensory, but sensation and visual pathways are usually intact. Neglect is related to lesions in the temporoparietal lobes. Most often the lesion is in the right hemisphere, as there is redundant processing of the right visual fields by both hemispheres. The right hemisphere can compensate for left hemisphere neglect, whereas the left cannot compensate for right hemisphere lesions. In the early phase of recovery, neglect impacts greatly on rehabilitation, with more severe neglect associated with less improvement in limb paresis [61].

There are various tests of attention such as serial 7s, digit span, spelling "WORLD" backwards and reciting the months of the year backwards. Of all these, the digit span test is regarded as a relatively pure test of attention but it is impaired in global and focal brain damage and, therefore, is not specific. The normal median (forward) digit span for an educated 60- to 74-year-old person is 8 ± 1 and over 75 years is 6 ± 1 [62].

Executive Function and Information Processing Speed

Executive function is a term used to describe complex cognitive processes required to achieve a particular goal. It enables planning complex tasks, switching attention, and selection of appropriate responses, and relies on working memory [63]. Information processing speed is a cognitive function involving the ability to perform fluently and effectively a relatively simple task automatically, and it relies on the skill to process information automatically and speedily without intentionally thinking through the task. Impairments of executive function and information processing result from cortical-subcortical and cortico-cortical disconnection, due to white matter tract disruption, compromising the integration of information from large-scale neural networks [64]. A number of distinct fibre systems have been described, and these include dorsolateral prefrontal-subcortical circuits mediating volition, planning, purposive action, and effective performance; orbitofrontal-subcortical circuits providing frontal inhibition of the limbic system, preventing impulsivity and uninhibited behaviour; and anterior cingulate-subcortical circuits whose interruption results in apathy and abulia [65].

Since executive function requires intact functioning of frontal cortices and their connections via association fibres and short U-fibres, and information processing speed is dependent on the integrity of subcortical neural circuits, they are both impaired early in cerebral SVD. In the Rotterdam Scan Study, whilst strategic lacunes in the thalamus were associated with memory impairment, non-thalamic lacunes were associated with the impairments of information processing speed [66]. The Leukoaraiosis and Disability study showed thalamic lacunar infarcts to correlate with motor speed and executive dysfunction, and lacunes in the putamen and pallidum correlated with memory and motor speed [67]. In patients with a clinical lacunar stroke, Benjamin et al. showed the number of lacunes and the volume of tissue destroyed by the lacunes to correlate with worse executive function and information processing speed and showed thalamic lacunes, especially, to be associated with impaired information processing speed [68].

Several neuropsychological tests have been used to assess subcortical executive cognitive deficits such as verbal fluency, trail making, digit symbol, and stroop tests, although in general, trail making and digit symbol tests are the most sensitive, and specific individual tests to identify cognitive impairment in people with mild cognitive impairment due to SVD who have normal MMSE scores [69].

Post-Stroke Delirium

Delirium is an acute and fluctuating confusional state characterised by altered consciousness, cognitive impairment, and perception. It can present as agitation associated with increased motor activity, or reduced motor activity and lethargy. It occurs in 13–48 % of stroke patients, although the aetiology is poorly understood [70].

Delirium is more common after an intracerebral haemorrhage and large hemispheric infarcts [71]. Patients with delirium have a poorer prognosis, with worse disability and increased chances of nursing home placement [72]. They also have a higher mortality and length of hospital stay [70]. Increased age and metabolic disturbances increase the risk of post-stroke delirium [73]. Whilst EEG studies have shown generalised cortical dysfunction, the pathogenesis of delirium is still unknown, although various neurotransmitter disturbances such as excess of dopamine or lack of cholinergic transmission have been suggested [74]. This theory is supported by studies showing that atypical antipsychotics, which act on D2 dopaminergic receptors, are effective in treating delirium [75]. Evidence for cholinergic medications is still lacking, however, but with the advent of biomarkers, pharmacological trials in this field are likely to increase [76].

There are no specific tools designed to diagnose delirium after stroke. The two most commonly used tools for diagnosing delirium are the Confusion Assessment Model (CAM) [77] and the Delirium Rating Scale (DRS) [78]. There have been no studies looking at the treatment of delirium specifically after a stroke. However, guidelines from the Royal College of Physicians outline basic measures, including treating the cause (e.g. infection), nursing in a well-lit room, and only using sedation

sparingly [42]. If sedation is required, haloperidol is the drug of choice despite weak evidence of its superiority.

Managing Cognitive Impairment After Stroke

Non-pharmacological Therapies

Lifestyle modification has been associated with reduced cognitive decline in observational studies, and in a small randomised study ($n=38$), aerobic exercise has been shown to improve post-stroke cognitive function and sensorimotor learning [79, 80]. Smoking cessation is also associated with improved cognition in normotensive patients [81]. There is, however, a paucity of randomised controlled trial evidence to suggest cognitive training activities benefit post-stroke cognitive impairment [82].

Memory Improvement

Only two trials assessing post-stroke interventions to improve memory were identified in a Cochrane review, with a total of 18 patients between them. Both provided intervention in groups rather than individual therapy. A trial on 12 patients randomised to six memory strategies versus pseudo-treatment "drill and practice" control group showed that, after 4 weeks, the treatment group improved significantly on the Name-Face Paired Associated Memory Test. There was no difference, however, in 15 Words, Oxford Recurring Faces, or Memory Questionnaire tests [83]. Another study using imagery-based mnemonics for 10 weeks showed an improvement in delayed recall of day-to-day events [84]. However, there was no improvement in memory function overall, and the positive results may have been due to short term learning effects.

Occupational therapists are predominantly involved in cognitive rehabilitation. In the absence of a strong randomised controlled trial evidence base of interventions to target post-stroke memory impairment, they teach simple techniques such as association (i.e. associate the new information with something one already knows), visualisation, repetition, rehearsal, and compensation (e.g. write it down) in a pragmatic fashion.

Language Therapy

Speech and language therapy is the mainstay of post-stroke language rehabilitation with treatment being individualised to maximise the patient's ability to communicate via verbal, written, or non-verbal means. Whilst the ACTNOW study, including 170 post-stroke patients, showed 4 months of speech and language therapy did not have any benefit on speech recovery compared to regular communication [85, 86],

a meta-analysis of 39 randomised controlled trials, involving 2,518 participants, demonstrated speech and language therapy to result in significant benefits to patients' functional communication and receptive and expressive language [87]. More recently, promise has been shown for very early intensive rehabilitation of dysphasia post-stroke, with patients receiving twenty 1-hour rehabilitation sessions over 5 weeks after their stroke recovering better than patients who received standard therapy [88].

Technological advances may improve the outcome of speech and language therapy further. Transcranial magnetic stimulation (TMS) is a non-invasive technique that causes depolarization or hyperpolarization of a region of the brain via weak currents. A coil is placed against the scalp and a short pulse is applied through the skull. This stimulates the desired region of the brain, and repetitive TMS over Broca's area has been shown to improve scores on language and mood scales in a small randomised controlled trial ($n = 30$) [89]. A computer-based software program called Fast Forword language has also been developed and has shown some improvement in comprehension scores compared with traditional one-to-one treatment over the same period of time [90]. Such techniques need to be tested on larger groups with different deficits to assess their use in clinical practice.

Managing Disorientation

We could not find good evidence for any specific technique being effective for treating disorientation. From a pragmatic viewpoint, therapists suggest simple techniques to help patients who are disorientated after their stroke, such as prompting aids, writing down information, and associating the surroundings with memorable things. All these enable the patient to manage the disorientation, although may not treat it per se.

Attention Training

Attention process training (APT) is a theoretically based, hierarchical, multi-level treatment, which involves sustained, selective, alternating and divided attention, typically administered by therapists. In traumatic brain injury patients, APT has been shown to improve attention significantly and, in some cases, improved other cognitive functions too. Barker-Collo et al. randomised 78 stroke patients with impaired attention to APT or standard care and demonstrated APT to result in significantly greater improvement in attentional performance (as measured by integrated visual auditory continuous performance test full-scale attention quotient) compared with standard care. Differences on other measures of attention and broader outcomes were not significant, however [60].

A time pressure management (TPM) strategy has been investigated in stroke patients with mental slowness, and Winkens et al. conducted a randomised controlled trial in 37 patients across 8 rehabilitation centres. Ten hours of treatment, teaching

patients a TPM strategy to compensate for mental slowness in real-life tasks, resulted in improved speed of performance on everyday tasks, but did not affect other elements of mental attentional capacity [91]. Eye-Search is a novel rehabilitation tool for patients with visual inattention and neglect to use at home that has been shown to improve patients' ability to navigate safely and reduce collisions with their surroundings.

TMS can be used to analyse the inter-hemispheric inhibition hypothesis, which implies that the non-damaged cerebral hemisphere becomes hyperactive after a stroke, leading to excessive cross-hemispheric inhibition of a damaged right hemisphere. TMS has been studied in patients with visual inattention and hemispatial neglect, to assess if the inter-hemispheric inhibition hypothesis is plausible. Repetitive TMS and sham control stimulation of the unaffected hemisphere in six patients with post-stroke visual inattention showed repetitive TMS significantly improved performance in an attentional tracking task [92]. Stimulation of the affected side did not change performance compared to sham. Seven patients with hemispatial neglect receiving 10 days of repetitive TMS prior to occupational therapy performed better at the line bisection test compared to seven patients who received routine behavioural therapy [93]. TMS is a promising non-invasive technique, but its long-term effects are unknown. Longitudinal data is required in larger sample groups to assess the overall benefit of TMS post-stroke.

A number of computer-assisted attentional training programmes aimed at restoring attentional capacity post-stroke have been investigated in small randomised trials. Sturm et al. showed such training to provide significant learning effects for a number of attention functions (excluding vigilance) in patients with lateralised cortical lesions [94], and Westerberg et al. demonstrated statistically significant training effects and a decrease in symptoms of cognitive problems with such training [95]. It is interesting to note that in Sturm et al.'s study, training effects were less pronounced in patients with right-sided lesions compared with patients with left-sided lesions [94]. Computer-based and indeed Internet-based systems have been very well accepted by patients and their relatives, who showed high levels of motivation to use them regularly [96].

A Cochrane review of six randomised controlled trials, involving a total of 223 participants, with a mean age of under 65 in all but one trial, investigating non-pharmacological interventions aimed to restore attentional capacity post-stroke found improvement in divided attention immediately following treatment (standard mean difference [SMD] 0.67, 95 % confidence interval [CI] 0.35–0.98, $p < 0.0001$), but no impact on other attentional domains (e.g. alertness, selective attention, sustained attention; all $p > 0.05$) [97]. There was no impact on psychometric test scores in any attentional domain at long-term follow-up (defined as 3 months post intervention), nor was there was evidence that interventions for attention deficits improved functional abilities, mood, or quality of life either immediately or late after treatment. All included studies had small sample sizes (range 18–78) and treatment duration (3–11 weeks), and most trials employed computer-assisted interventions [92, 95, 97–100].

Treating Executive Dysfunction

There are no trials focusing specifically on executive function rehabilitation after stroke. A Cochrane review of five studies on post-stroke patients did not show any benefit of cognitive rehabilitation on executive function [101].

Pharmacological Therapies

Currently, there are no definitive pharmacological treatment options for cognitive impairment after a stroke. This is partly due to the heterogeneity of stroke and of cognitive impairment. Indeed, the cognitive benefits of stroke secondary prevention therapy and the use of specific drugs for dementia and neuronal recovery in post-stroke patients remain controversial.

Stroke Secondary Preventive Treatments

The role of hypertension in the aetiology of vascular disease and the beneficial effects of antihypertensive treatment in preventing stroke are well established. There is evidence to suggest that antihypertensive treatment may reduce vascular risk, even in normotensive individuals [102–104]. In contrast, the cognitive effects of blood pressure lowering remain a subject of considerable controversy [105]. Hypertension accelerates arteriosclerotic changes in the brain, predisposing to atheroma formation in large-diameter blood vessels and arteriosclerosis and arteriolar tortuosity of small vessels of the cerebral vasculature [106]. These vascular changes, incorporating medial thickening and intimal proliferation, result in a reduction of luminal diameter, increased resistance to flow, and decline in perfusion [107]. As we have described previously, such hypoperfusion can produce discrete regions of cerebral infarction and diffuse ischaemic changes in the periventricular and deep white matter (leukoaraisosis), causing vascular cognitive impairment, and also contribute to the pathogenesis of Alzheimer's disease by destabilising neurons and synapses [108–110]. Furthermore, accelerated arteriosclerotic changes of non-communicating perforating arteries supplying deep subcortical white matter circuits may not be reversible by blood pressure reduction once these changes are established [105]. Indeed, episodic or sustained hypotension, and possibly excessive treatment of hypertension, may induce cerebral hypoperfusion, ischaemia, and hypoxia that may in turn compromise neuronal function and eventually evolve into a neurodegenerative process [111–113].

Cross-sectional studies investigating the relationship between blood pressure and cognition have shown conflicting relationships with positive, negative, and J- and U-shaped associations, whilst the majority of longitudinal studies have demonstrated elevated blood pressure to be associated with cognitive decline [114]. Observational studies may demonstrate associations but do not determine causality;

the latter only being shown by intervention studies. Despite a large number of patients being studied ($n = 19{,}501$), only a small number of completed randomised placebo-controlled clinical trials of blood pressure-lowering agents have reported the effects of treatment on the risk of cognitive impairment, and a meta-analysis of their results demonstrated a heterogeneous effect of blood pressure lowering on different aspects of cognitive function, with improvement in global cerebral function and memory tasks, but impaired performance on perceptual processing and learning capacity tasks [114, 115].

Two completed large randomised trials have investigated the effects of blood pressure lowering in a post-stroke patient population. The PROGRESS study randomised 6,105 people with prior stroke or TIA to either active treatment with perindopril ± indapamide or matching placebo(s). After a mean follow-up of 3.9 years, cognitive decline (as measured by MMSE score decline by three or more) occurred in 9.1 % of the treatment group and 11.0 % of the placebo group (relative risk reduction of 19 %, $p = 0.01$) [101]. The SPS3 trial randomised 3,020 patients with MRI-defined symptomatic lacunar infarction to a systolic blood pressure target of 130–149 mmHg or <130 mmHg and showed no difference in cognitive decline (as measured by the Cognitive Abilities Screening Instrument) between the two groups at 1 year or 3 year follow-up [116, 117]. A further, small, 1-year follow-up study of 25 patients with cerebral SVD with baseline systolic blood pressure >120 mmHg and <160 mmHg and diastolic blood pressure <100 mmHg randomised to blood pressure reduction by ≥12/5 mmHg or no additional anti-hypertensive treatment also showed no significant difference between intervention and control groups in cognitive measures, including those of executive function [110]. Whilst a preliminary, 9-month follow-up, open trial of nimodipine in 31 patients presenting with cognitive impairment, progressive bilateral motor dysfunction, and leukoaraiosis on brain imaging showed a significant improvement in total Sandoz Clinical Assessment Geriatric scale scores [118], more recent studies have suggested that short-term benefits of nimodipine in the area of vascular cognitive impairment do not justify its use as a long-term anti-dementia drug [119]. Ongoing studies, including PODCAST [120], PRESERVE, and SPRINT-MIND, are investigating further the effects of lowering blood pressure on cognition in post-stroke patients.

Whilst anti-thrombotic and lipid-lowering treatments have been shown to reduce significantly recurrent ischaemic stroke, there is no randomised controlled trial evidence promoting their use in reducing post-stroke cognitive impairment. Several community-based, prospective studies and a cross-sectional study have suggested an association of aspirin treatment with the preservation of episodic memory and global cognitive performance, but further studies have contradicted these results, with long-term use of aspirin providing no benefit for cognition among generally healthy women aged 65 years or over, and suggesting potential for increasing the risk of development of cognitive impairment [121]. Furthermore, a substudy of the SPS3 trial showed antiplatelets not to prevent cognitive decline over an average of 2.8 years [117]. The Heart Protection [122] and PROSPER studies [123] also showed no overall benefit of statins, as lipid-lowering agents, on cognitive decline. Whilst the biological plausibility of anti-thrombotic and

lipid-lowering treatment strategies is recognised, the negative results for cognitive outcomes from randomised trials may be due to a heterogeneity of cerebrovascular disease load, vascular risk profile, and cognitive performance in included subjects, varying methods of neuropsychological assessment, and insufficient trial durations to see a treatment effect. Studies are ongoing to investigate these issues further, including the ENVIS-ion study investigating aspirin for the prevention of cognitive decline [121].

Homocysteine is a sulphur-containing amino acid that has been shown to cause acute and chronic endothelial dysfunction, to stimulate vascular smooth muscle cell growth and collagen synthesis, and to have procoagulant activity [124–126]. Cross-sectional studies examining the role of homocysteine in cerebrovascular disease have revealed it to be independently related to silent brain infarction and leukoaraiosis [127–129], and case-control studies have demonstrated hyperhomocysteinaemia to be an independent risk factor for SVD. Randomised controlled trials have not shown lowering plasma homocysteine to prevent cerebrovascular disease [130–132] and there is, similarly, no good evidence that lowering homocysteine levels improves cognitive function after a stroke.

Drugs Used in Dementia

Three cholinesterase inhibitors, donepezil, galantamine and rivastigmine, and memantine, an NMDA receptor antagonist, are approved as treatment options for dementia of the Alzheimer type. All have been investigated in patients with vascular cognitive impairment, with varying results. A Cochrane review of two large-scale, randomised, double-blind, parallel-group, placebo-controlled trials of donepezil in 1,219 people, with up to 24-week follow-up, with mild to moderate cognitive decline due to probable or possible vascular dementia (according to the NINDS/AIREN criteria and the Hachinski Ischaemia Scale) showed patients treated with donepezil to have a significantly better performance than the placebo group on the MMSE, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), Clinical Dementia Rating, and activities of daily living [133–135]. Subsequent to this meta-analysis, Roman et al. conducted a multi-centre, 24-week, randomised, placebo-controlled trial of donepezil in 974 patients with probable or possible vascular dementia and showed patients treated with donepezil to have a significant improvement from baseline to end point on the Vascular-Alzheimer Disease Assessment Scale-Cognitive Subscale, but not on the Clinician's Interview-Based Impression of Change. Patients with hippocampal atrophy who were treated with donepezil demonstrated stable cognition versus a decline in the placebo-treated group; in those without atrophy, cognition improved with donepezil versus relative stability with placebo [136]. An 18-week study of donepezil in 168 patients with CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy), a single-gene disorder producing a phenotypic presentation of cerebral SVD, had a neutral result but showed benefit in executive function measures in secondary analyses [137].

There have been two randomised, double-blind, parallel-group, placebo-controlled trials of galantamine in 1,380 participants, each with 6-month follow-up. The GAL-INT-6 trial included 592 patients with vascular dementia diagnosed according to recognised criteria, and with Alzheimer's disease and coincidental radiographic findings of cerebrovascular disease, and showed statistically significant treatment effects in favour of galantamine compared with placebo in cognition, activities of daily living, and behaviour. The GAL-INT-26 trial involving 788 patients with vascular dementia diagnosed using standard criteria showed statistically significant benefits favouring galantamine over placebo in assessments of cognition and favouring placebo compared with galantamine in assessments of behaviour [138].

Three trials have investigated the effect of rivastigmine on vascular cognitive impairment but in view of differing methodologies, including patient inclusion criteria, results have not been able to be pooled [139]. One trial included 40 participants with subcortical vascular dementia (age range 40–90 years) with a mean MMSE score of 13.2 and showed no significant difference on any outcome measure relevant to cognition, neuropsychiatric symptoms, function, or global rating between rivastigmine and placebo after 26 week follow-up [139]. Another trial included 710 participants with vascular dementia, including subcortical and cortical forms (age range 50–85 years; mean MMSE score of 19.1), and showed statistically significant advantage in cognitive response (but not with global impression of change) with rivastigmine treatment after 24 week follow-up [139]. Narasimhalu et al. conducted a 24-week, randomised, controlled, placebo-controlled trial of rivastigmine in 50 ischaemic stroke patients, and showed patients in the rivastigmine group to have significant improvement of verbal fluency but not of clock drawing or trail-making test performance [140].

Two studies, involving 900 patients, have investigated the efficacy and safety of memantine in patients with vascular dementia. The MMM 300 study showed a significant improvement in mean ADAS-cog and MMSE scores in 321 patients with probable vascular dementia, and a baseline MMSE score of 12–20 randomised to memantine relative to placebo over a 28-week period, but did not show a significant change in the global Clinician's Interview Based Impression of Change primary outcome measure [141]. The MMM 500 study similarly showed a significant improvement in mean ADAS-cog scores in 579 patients with probable vascular dementia and a baseline MMSE score of 10–22 randomised to memantine relative to placebo over a 28-week period, but did not show any change in the Clinical Global Impression of Change primary outcome measure [142].

Whilst cholinesterase inhibitor and memantine therapies have been approved for Alzheimer's disease, in patients with vascular dementia they have failed to achieve regulatory approval in light of the aforementioned trial outcome data [143]. Reasons include only modest benefit on standard cognitive measures, which under-sampled executive functioning, inconsistent benefits in global and daily function, which are difficult to evaluate when physical deficits with stroke co-exist, and trials often including patients with a "possible" or "probable"

vascular aetiology for dementia [143]. Whilst Narasmihalu et al. investigated a patient population, all of whom had suffered an ischaemic stroke and demonstrated rivastigmine to have a positive impact on verbal fluency, other executive-function measures were not significantly affected positively and the trial had a small sample size [140]. Multidisciplinary working parties have suggested that, in the future, case selection and outcomes should use updated clinical criteria, more sensitive executive function measures, and advanced imaging biomarkers that better quantify atrophy and vascular brain injury, including diffusion tensor and perfusion imaging, and possibly amyloid labelling or cerebrospinal fluid markers to detect concomitant Alzheimer pathology [143].

Antidepressant Drugs

It has been suggested that antidepressants may modulate cortico-striato-pallido-thalamo-cortical pathways [144] and may facilitate the reorganisation of neural circuitry by their activity on brain-derived neurotrophic factor [145]. Based on these theories, the cognitive effects of antidepressants on patients with cerebrovascular disease have been studied. Narushima et al. conducted a 12-week, randomised placebo-controlled study of fluoxetine or nortriptyline antidepressant treatment in 47 patients who had a stroke during the prior 6 months. Whilst no significant group effect was found at the end of treatment, 21 months after the end of treatment, the placebo group showed deterioration of executive function, whereas the active treatment group showed clear and significant improvement independent of depressive symptoms [146]. More recently, Royall et al. reviewed 35 open-label sertraline trials for executive impairment in ischaemic cerebrovascular disease, with outcomes including performance on clock-drawing, Executive Interview (EXIT25), Geriatric Depression Scale, and MMSE assessments and found only EXIT25 scores to improve significantly [147].

Biological Substances

Some studies are now involving biological substrates to treat cognitive impairment after stroke. Citicoline is an intermediate in the generation of phosphatidylcholine from choline that has been shown to slow down apoptosis and neuronal degeneration within the hippocampus in rats with induced Alzheimer's disease. In an open-label, randomised, parallel study of citicoline versus usual treatment in 347 patients 6 weeks after suffering a stroke, citicoline significantly improved attention, executive function, and temporal orientation in the 199 patients followed up at 1 year [148]. Only 37 subjects [10.7 %] discontinued treatment, with no difference between the two treatment groups (10.5 % citicoline vs. 10.9 % control). The triallists commented that citicoline appeared to be a promising agent to improve cognitive recovery after stroke, with larger clinical trials being needed to confirm the net benefit of this therapeutic approach [148].

Cerebrolysin is a biological substrate from pig intestine with neuroprotective and neurotrophic properties that may stimulate the growth of neurons. In a study of 242 patients with vascular dementia, cerebrolysin significantly improved cognitive function after 24 weeks of treatment [149]. A Cochrane review of six randomised control trials in vascular dementia suggested cerebrolysin may have a positive effect on cognitive function, but the trials had different treatment durations and there is no long-term data to suggest sustained improvement [150]. As such, cerebrolysin is not currently recommended for routine use.

Conclusion

Cognitive impairment is a common sequela of stroke that is often overshadowed by focal neurologic deficits. There are various neuropsychological tests available to assess the specific cognitive domains necessary; however, the optimal screening battery has not been agreed. Accurate diagnostic tools are being established that may help to improve assessment and treatment in the future. Current guidelines state cognitive impairment should be routinely tested in all stroke patients and, if impaired, rehabilitation methods should be pursued. Aside from secondary prevention of further stroke, there is no available drug treatment to target post-stroke cognitive impairment. More studies are required to assess pharmacological and non-pharmacological options specifically for vascular cognitive impairment.

Patient Questions

Q. How should cognitive impairment after a stroke be managed?

A. The most important aspect is to identify accurately which area of cognitive function is affected. For example, if it is mainly memory-based problems, then the occupational therapy team can help by teaching you to use techniques to jog your memory or modify your home environment to makes things easier. If the problem is mainly language-based, then the speech and language therapists have a range of techniques to help re-develop speech, depending on the exact type of problem. The problem needs to be managed by a multidisciplinary team, as cognitive impairment may affect the response to therapy of other functional impairments after the stroke.

Q. Will my memory remain poor in the long term?

A. In a small group of patients, the cognitive impairment observed after a week of the stroke recovered reasonably well by 3 months. However, for most patients there is some deficit, depending on the sensitivity of the tests used to assess the impairment. The aim of rehabilitation is to help patients cope with any mild deficits remaining.

Q. Are there any drug treatments for my cognitive problem?

A. Currently there are no recommendations for medicines in cognitive impairment after a stroke. There is some weak evidence for drugs used in Alzheimer's disease, but this is not enough to allow us to give the drug to all patients with cognitive impairment after their stroke. Ongoing research is currently looking for drugs that may help to slow down the process of cognitive decline after a stroke.

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Chapter 13
Post-Stroke Pain

Pippa Tyrrell and Anthony K.P. Jones

Abstract Pain is a common and often distressing complication of stroke, which can have a negative impact on rehabilitation and recovery. It most commonly affects the shoulder and upper limb and is usually classified as either central post-stroke pain (CPSP) or post-stroke shoulder pain. Pre-morbid pain conditions, sometimes exacerbated by immobility, tension-type headaches, spasticity-related pain, and widespread pain syndromes, may contribute to the pain experience following stroke. Careful clinical assessment is needed to ascertain the underlying cause(s) and instigate appropriate treatment and monitoring. All members of the multidisciplinary team, both in hospital and after discharge, need to be aware of the problems associated with post-stroke pain and the need for specialist referral where necessary.

Keywords Pain • Pain syndromes • Neuropathic pain • Stroke • Central Post Stroke Pain

Key Messsages

- Pain is a common and troublesome problem following stroke and can interfere with rehabilitation. Pain in the affected shoulder and upper limb is most common.
- Clinicians should know how to distinguish different types of pain (neuropathic, regional) as management differs. The SLANSS scale is easy to use in practice and helps identify neuropathic pain.
- The entire multidisciplinary team needs to be aware of the problem of pain following stroke and the need for rapid assessment and treatment. Pain in people with impaired level of consciousness or communication difficulties may be particularly challenging to recognise and may only become apparent during therapy or nursing procedures.

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- Management of pain after stroke requires a holistic approach, including appropriate positioning, mobilisation, and pharmacological management.
- Pain usually improves with time, particularly when managed promptly, but sometimes develops late. Clinicians should always ask about pain at post-stroke follow-up and ensure that people are referred rapidly for appropriate management.
- National clinical guidelines, such as the UK InterCollegiate Guidelines for Stroke, give detailed advice on management. Pain can usually be managed by the stroke team, but it is important to refer people with pain that is proving difficult to manage to appropriate pain specialists early.

Introduction

Post-stroke pain is a troublesome and disabling condition. Early reports in the literature tended to focus on post-stroke neuropathic pain (sometimes called central post-stroke central post-stroke pain (CPSP) or thalamic pain) with accounts of people presenting late to neurologists with unilateral, usually upper-limb, intractable pain with abnormal and often very distressing sensory disturbance. More recent literature has emphasised the importance of distinguishing types of post-stroke pain to ensure appropriate treatment and the importance of early intervention to ensure the best chance of recovery. Everyone treating people with stroke, both in hospital and the community, should be aware of the different types of post-stroke pain and how to help people access appropriate treatment rapidly.

Incidence

Post-stroke shoulder pain is reported to occur in 9–40 % of patients following stroke, depending on study design and patient selection [1, 2]. The temporal pattern of post-stroke pain varies. In some patients, it develops early and resolves over time; 80 % of people in one study with any type of pain at 2 months post-stroke had almost resolved or completely resolved symptoms by 6 months [2]. A study of shoulder pain after stroke showed that while it resolved in most patients, some who had not had pain at 4 months post stroke had developed it a year later [3]. A study of all types of pain in patients in the Lund Stroke [4] Register found that 60 % of people with pain at 4 months post stroke had upper limb pain, 35 % had pain [5] in lower limbs or elsewhere, and 7 % had headache.

Types of Post-stroke Pain

Musculoskeletal Pain

Musculoskeletal pain, most frequently affecting the back and hips [6], is the most common cause of pain in people with stroke, reflecting partly its frequency in the general population, particularly in older people who are at higher risk of stroke. It may pre-date the stroke and may be particularly troublesome following stroke, when it may be exacerbated by immobility or impaired movement.

Regional Shoulder Pain

This is the most common cause of pain occurring following stroke and may occur immediately following stroke or develop over time. It is more common in people with weakness of the upper limb [7]. It may be present at rest but may more commonly be associated with movement, particularly shoulder abduction or rotation. It may be associated with shoulder subluxation and/or spasticity of the upper limb, but shoulder subluxation is not always associated with pain. It is sometimes associated with ipsilateral sensory loss.

Central Post-stroke Pain (CPSP)

CPSP is characterised by its unpleasantness and is often described as being unlike any pain experienced previously. Patients may describe it as unpleasant burning, numbness, or coldness and use bizarre descriptors such as ‘clawing my arm from the inside’ or ‘a red-hot poker in my muscles’ [8]. The intensity of pain can be exacerbated by stress or cold and alleviated by warmth or distraction. Pain is very burdensome, even when of low intensity, [9] interferes with sleep, [10] and impacts significantly on quality of life. It is often associated with allodynia (defined as pain that is evoked by a stimulus that is not normally painful; e.g., brushing or light touching) and dysaesthesia (an unpleasant abnormal sensation that may occur with or without a physical stimulus) [11]. Patients may describe pain or unpleasant sensations associated with light touch from clothing or bed clothes, from cold, or occurring spontaneously. This description of CPSP is not unique to stroke and is common to other types of central deafferentation pain, including those caused by demyelination, syringomyelia, and traumatic brain injury.

Complex Regional Pain Syndrome

This is a severe neuropathic type of pain occurring at an extremity in association with vascular/autonomic changes that may initially be associated with hyperaemia but subsequently may be associated with reduced blood flow and atrophic changes. Although this is well described in textbooks, in the authors' experience it is rare in association with stroke. Early mobilisation in patients with stroke may explain why this is now rarely seen.

Headache Post Stroke

Headache following all types of stroke is common but is particularly associated with some stroke syndromes at onset, particularly subarachnoid or intracerebral haemorrhage, cervical artery dissection, migraine-associated stroke, and cortical venous sinus thrombosis [12, 13].

Spasticity Pain Post Stroke

As described in Chap. 10, spasticity is a common complication of upper motor neuron lesions such as stroke, and even with best practice physiotherapy may be a troublesome complication, causing limitation of movement, functional impairment, or pain. In one longitudinal study of people with first-ever stroke and upper limb weakness, almost half of the patients assessed developed some degree of spasticity in the first year [14].

Management of Post-stroke Pain

Musculoskeletal Pain

Many people with stroke have pre-morbid musculoskeletal pain that is exacerbated by stiffness and immobility. Careful clinical assessment, together with optimisation of moving and handling techniques to avoid pain, are essential. Simple analgesia taken regularly is helpful.

Shoulder Pain

Post-stroke shoulder pain can be extremely troublesome. It is made worse by movement of the shoulder, particularly abduction or rotation, and so impacts on activities of daily living such as washing and dressing and rehabilitation. There is little

evidence that shoulder strapping or wheelchair attachments (to support the upper limb) prevent subluxation, reduce pain, or improve function [15] although these may be used to make it clear to carers that the shoulder is at risk of damage from incorrect handling or positioning. Many people find supporting the affected arm on a pillow while sitting makes it more comfortable. There is insufficient evidence to support electrical stimulation for regional shoulder pain, [16] although it may prevent post-stroke shoulder subluxation [17]. Although subacromial injection of corticosteroids has been used clinically and anecdotally may provide rapid relief, there is no good evidence to support its use [18]. Simple analgesia should be offered regularly.

Central Post-stroke Pain (CPSP)

The evidence for efficacy of drug therapy in CPSP is based on quite small numbers of clinical trials, some of which were on mixed neuropathic pain syndromes. Current practice is therefore based partly on specific trial evidence on CPSP and partly on management of other causes of neuropathic pain. There is specific controlled trial evidence for efficacy of amitriptyline, [19] pregabalin, gabapentin, [20] and opioids [21] in central neuropathic pain, although generally opioids are not used as first-line management because of the potential side effects, particularly constipation.

Recent NICE guidelines for the management of neuropathic pain [22] suggest that a choice of amitryptiline, duloxetine, gapabentin, or pregabalin should be offered as initial treatment. (Nortryptiline is another alternative that is often better tolerated than amitryptiline.) NICE guidelines advocate that if initial treatment is not effective or not tolerated, then one of the remaining three agents should be offered, with further switching if the second and third drugs are not effective or tolerated. Tramadol is recommended to be considered by NICE only as acute rescue therapy, and capsaicin cream is recommended to be considered by NICE in individuals with localised neuropathic pain who wish to avoid or who cannot tolerate oral treatment. The Royal College of Physicians' National Clinical Guideline for Stroke [23] gives details of dose titration for amitriptyline, gabapentin, and pregabalin, but clinicians should always check with an up-to-date national formulary before prescribing. Patients need regular clinical reviews of progress to consider alterations in treatment (including treatment withdrawal) and referral to a specialist pain service if necessary. Rarely, patients who do not respond to drug therapy may be referred for transcranial magnetic stimulation, motor cortex stimulation, or deep brain stimulation of the thalamus or brainstem, which are available in a few specialist units [24].

Complex Regional Pain Syndrome

The main treatment is as for other types of post-stroke pain, in addition to maintaining as much movement as possible of the affected limb.

Headache

Understandably, patients in the recovery phase of stroke may find headache particularly distressing, worrying that it may be a sign of a further stroke. Careful clinical assessment followed by reassurance where appropriate and assurance of adequate hydration together with simple analgesia and distraction may be helpful.

Spasticity

As described in Chap. 10, when pain is present together with spasticity following stroke, then both the pain and the spasticity need to be addressed simultaneously employing passive stretching, antispasmodic therapy including botulinum toxin, splints, and analgesia. There is no evidence for benefit of passive stretching together with neuromuscular electrical stimulation [25] for either spasticity or pain. Early recognition of spasticity, together with physiotherapy and occupational therapy techniques to reduce it, is important, as the spasticity may exacerbate post-stroke pain.

Multidisciplinary Team Approach to the Management of Post-Stroke Pain

The management of pain after stroke can be challenging. Patients may be medically unstable, which makes diagnosis and management particularly difficult. Cognition and communication difficulties can make it difficult to assess the presence, nature, and severity of pain, and co-morbid illnesses and concurrent medication may complicate pharmacological approaches to management. The entire multidisciplinary team needs to be aware of the problem of pain and the importance of prompt assessment and treatment. If pain only occurs on movement, it may only be nursing and therapy staff who are aware of the patient's pain, which may only be communicated by facial expression, groaning, an increase in pulse or respiratory rate when being moved, or other non-specific signs of distress. Post-stroke shoulder pain typically occurs or worsens with shoulder abduction and so may only become apparent when the patient is being dressed or washed. Pain may make a patient reluctant to engage in therapy or impact on sleep patterns, leaving him or her too tired to do so. It has a significant impact on mood, which in turn has a negative effect on rehabilitation. It may delay discharge and transfer of care and can make life at home more difficult and distressing.

Some patients with post-stroke pain may be psychologically distressed, which may contribute to the post-stroke pain, particularly if associated with sleep disturbance. Although there is no evidence for the benefit of cognitive behavioural therapy for post-stroke pain, this may be beneficial in certain patients who are able to engage with this.

Clinical Assessment of the Patient with Post-Stroke Pain

A careful history is essential to the assessment of pain. If the patient is unable to communicate, then it is important to take a history from family and friends, the general practitioner, and other members of the multidisciplinary stroke team who have had the opportunity to observe the patient at different times of day or engaged in different activities. Specifically, the clinician should ask about pre-morbid pain or painful conditions (such as arthritis or a previous fracture), use of analgesics or other pain-relieving strategies, and any pre-morbid mood disturbance such as depression or anxiety. Asking the patient to describe the pain in their own words may elicit the bizarre descriptors that are associated with central neuropathic pain. In addition, some patients may describe a very unpleasant sensation that they feel is not 'true pain' but may be as unpleasant as clearly defined pain. In the authors' experience, it is best to treat such sensations as pain, as they can be as disabling. Exacerbating and relieving factors, intensity, and associated symptoms such as sleep disturbance should also be ascertained. A full musculoskeletal and neurological examination is required to assess the patient completely. Neurological examination includes careful assessment of the extent and distribution of sensory loss (including light touch, temperature, and pinch) and of motor deficit. Musculoskeletal examination includes an examination of the affected joints both at rest and on passive and active movements.

Distinguishing neuropathic pain from musculoskeletal pain is important in order to start the right treatment early. The SLANSS scale [26] is a self-reported questionnaire that is designed to identify pain of neuropathic origin and is useful in patients who can communicate. For those with communication disorders, the use of communication charts may be helpful.

Pain may continue to be a problem or may worsen or occur for the first time weeks or months following stroke. Best practice is for all patients to receive a 6-month post-stroke assessment, [27] which should include an assessment of pain symptoms. The Greater Manchester Stroke Assessment Tool (GM-SAT) [28] is one example of a structured 6-month assessment and includes the SLANSS scale to guide treatment. GM-SAT also has an easy access version [29] that may be helpful for people with communication difficulties. Once the problem of post-stroke pain has been identified, it is important that people have access to appropriate services in primary and secondary care so that pain can be assessed and managed.

Prognosis

Prognosis of post-stroke pain following diagnosis is variable. CPSP can sometimes, particularly with prompt treatment, resolve quite quickly on relatively small doses of medication, although it can become extremely troublesome and difficult to manage. Expert specialist pain management is then necessary. Post-stroke shoulder pain

generally improves if upper limb movement improves but again can affect activities of daily living and disrupt sleep. As with stroke recovery itself, post-stroke pain may continue to improve slowly over months to years; so in the authors' opinion, patients should never be told that their pain will not improve at any stage. Headache following stroke generally settles over time with reassurance and simple analgesia. Prognosis of complex or multiple pain problems remains extremely difficult, requiring intensive multidisciplinary team input.

Conclusion

All members of the multidisciplinary team need to be aware of the importance of pain following stroke. Careful observation of the patient at rest and when engaged in activities, together with a detailed history, is necessary to ensure prompt recognition and diagnosis. Pain is not always at its worst at onset and frequently develops after an interval of time, so repeated assessments may be required. Treatment depends on the type of pain. Rapid recognition and appropriate management by the entire multidisciplinary team is necessary to ensure the best possible outcome.

Patient Questions

Q. What is the best way to manage pain after stroke?

A. Management of pain after stroke depends on the cause. The commonest type of pain is shoulder pain, affecting the weak arm, with pain around the shoulder and upper arm. It is worse on movement and can make activities such as washing and dressing very uncomfortable. Supporting the shoulder by careful positioning such as resting the weak arm on a pillow and not allowing it to hang down can help prevent and alleviate pain. Simple analgesics such as paracetamol may be helpful. One sometimes troublesome cause of pain is called central post-stroke pain and is due to abnormal processing of sensations such as touch and temperature by the brain. This pain can be very distressing, as apparently ordinary sensations are perceived as very painful. There are a variety of drugs for this type of pain, and the earlier treatment is started, the better.

Q. Does pain after stroke get better?

A. Pain after stroke nearly always gets better if the right treatment is started promptly. Patients need to know that if they get pain following stroke, even after they have gone home, they need to see someone who can assess the pain, diagnose the cause, and ensure the appropriate treatment is started. Some people need the skills of specialists such as a rheumatologist or the pain team, but the key is early treatment without delay.

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Chapter 14
Post-Stroke Fatigue: Common but Poorly Understood

Toby B. Cumming and Gillian Mead

Abstract Fatigue is experienced by the majority of stroke survivors and often persists even after other symptoms of stroke have resolved. Post-stroke fatigue has important negative effects on a person's quality of life and their social connectedness. The research literature on post-stroke fatigue is still in its infancy, and our understanding of why it develops is based more on potential associates than definitive causal explanations. The factors most strongly associated with fatigue after stroke include physical disability and depression, but there are many other potential contributors. Fatigue is multi-dimensional, and any explanatory model must include a wide range of contributing factors, many of which have bi-directional associations with fatigue. Several interventions aimed at reducing post-stroke fatigue have been trialled in small-scale studies, with only limited success. There is great scope for improvements in treatment. Many factors that are relevant to fatigue are modifiable (e.g., sleep quality, physical activity levels), and there are lessons to be learned from approaches used in other models of fatigue (e.g., multiple sclerosis, cancer). Before we can hope to identify effective interventions, however, we need a more detailed understanding of not only why fatigue occurs after stroke, but also why it persists.

Keywords Fatigue • Stroke • Prevalence • Quality of life • Depression • Sleep • Physical activity

Key Messages
- Post-stroke fatigue is common, persistent, and has a negative impact on the lives of stroke survivors.
- Fatigue is not just tiredness or boredom or sleepiness, it is a lack of mental or physical energy that is not overcome by rest.

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- Stroke-related factors, including alterations in neural connectivity, perfusion, and inflammatory markers, may be linked to fatigue but consistent evidence is lacking.
- Physical disability, depression, and cognitive impairment have been strongly linked to post-stroke fatigue, and it is likely that these relationships are bi-directional.
- Sleep and physical activity are modifiable behavioural factors that can influence fatigue.
- An explanatory model of post-stroke fatigue should acknowledge that fatigue in the early stage might be a normal, adaptive response to acute stress.
- Interventions should target not only the initial development of fatigue, but also the factors behind its persistence in the longer term.

Introduction

The feeling of fatigue is familiar to us all. Think of the times that you've sat on the couch and could not summon the energy to get up, even just to walk to bed. Think of the times that your brain seemed lethargic, when even simple problem solving required substantial effort. Often these feelings can be traced to specific triggers, whether it is a long day at work, a head cold, jet lag, an exercise session, a hangover, or an infection. These feelings of fatigue typically don't last long and rarely impact greatly on our activities of daily life. Fatigue after stroke may not be qualitatively different to the subjective feeling of fatigue experienced in the broader population. What distinguishes post-stroke fatigue is its high prevalence, its persistence long after the acute event, and the major impact it has on independence and quality of life. The aim of this chapter is to outline a comprehensive account of post-stroke fatigue, including prevalence, definition and measurement, impact, contributing factors, explanatory models, interventions, and clinical management.

Fatigue Prevalence and Time Course

Of the wide range of symptoms and negative outcomes experienced after stroke, fatigue is one of the most prominent. Naturally, estimates of prevalence vary according to factors such as the fatigue definition used, characteristics of the patient sample, and time point post-stroke. Nevertheless, analysis of large prevalence studies reveals a consistent pattern: the majority of stroke survivors experience fatigue. Three important large studies into post-stroke fatigue have contributed much to our understanding of prevalence and time course [1–3]. A Danish study of 165 first

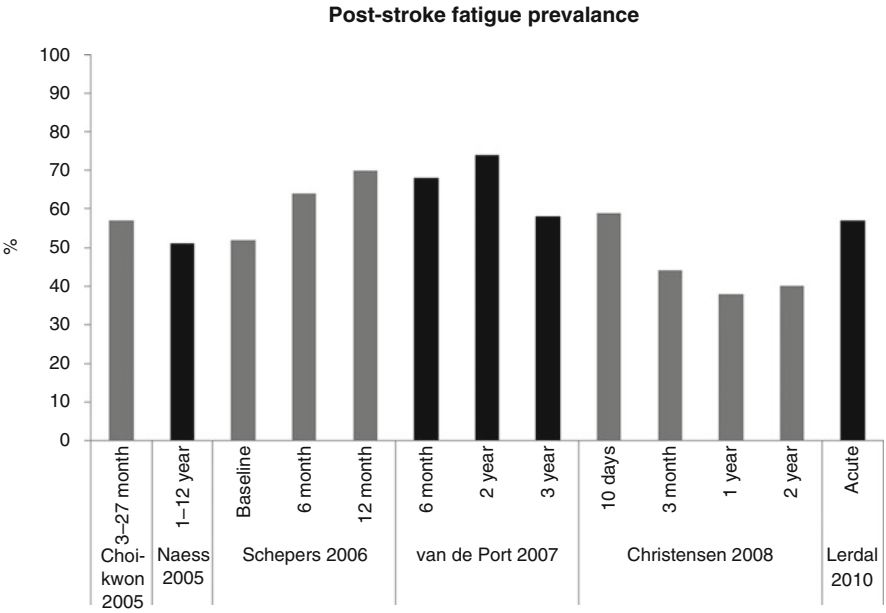

Fig. 14.1 Data on prevalence of post-stroke fatigue in selected large studies (>100 patients)

stroke patients identified fatigue in 59 % at 10 days post-stroke [2]. A Dutch study in 167 first stroke patients admitted for rehabilitation reported that 70 % had fatigue at 1 year post-stroke [3]. In South Korea, 57 % of the 220 patients assessed at 15 months post-stroke had fatigue [1]. Figure 14.1 outlines prevalence rates reported in six studies that were selected for their large sample sizes and use of accepted fatigue assessment scales. A small number of studies have reported lower prevalence rates, but there are reasons to believe that these estimates are not reflective of the general stroke population. Park and colleagues reported a prevalence of 30 %, but this was in a small group of 40 patients who were assessed for fatigue a long time (average of 33 months) after their stroke [4]. Tang and colleagues reported a fatigue prevalence of 23 %, but people with post-stroke depression were excluded from their sample [5]. Given the relationship between depression and fatigue after stroke, this prevalence is undoubtedly an underestimate.

The onset of fatigue after stroke typically occurs early, during the acute hospital stay. In the South Korean study cited above, onset of post-stroke fatigue was within a week of stroke in 77 % of those affected, while only 10 % reported fatigue onset beyond 6 months [1]. In the Danish study that reported fatigue prevalence of 59 % at 10 days, only 9 % of patients developed fatigue beyond 3 months [2]. This is not to say that the acute stroke event is the trigger of fatigue in all cases. A number of people have already experienced fatigue before their stroke [1], and we return to the issue of pre-stroke fatigue in the discussion of contributing factors to post-stroke fatigue below. Nevertheless, it is likely that the causes of fatigue can be traced back to the stroke event itself, or to factors present in the first week post-event, or both.

It is notable that fatigue is persistent over time after stroke, despite marked improvements in neurological and physical impairments. Duncan and colleagues conducted a systematic review of longitudinal studies, in an attempt to map the natural history of fatigue after stroke [6]. They identified nine studies that assessed fatigue at multiple time points (up to 3 years post-stroke), finding that the frequency of fatigue declined over time in seven studies and increased over time in two studies. The overall picture, though, was that fatigue remained common even in the longer term. In the Danish study, fatigue was found in 59 % at 10 days, 44 % at 3 months, 38 % at 1 year, and 40 % at 2 years [2]. In the Dutch study, fatigue was identified in 52 % at baseline, 64 % at 6 months, and 70 % at 1 year [3].

The stroke event need not be severe for fatigue to manifest. In a study of 76 patients with minor stroke—independent in self-care and with no major cognitive impairments—56 % had fatigue at 6-month follow-up [7]. At this 6-month time point, the group was completely independent in activities of daily living, with a median score on the Barthel index [8] at the ceiling of 20. Another study included 99 functionally active, young (<70 years old) patients with a non-disabling first stroke (NIH Stroke Scale score <6). Of these patients, 35 % reported fatigue at 12-month follow-up [9]. In a similar cohort of younger, mild stroke survivors, 72 % experienced fatigue at 12 months post-stroke [10]. On the basis of these three studies, we can conclude that fatigue is experienced by the majority of mild stroke survivors.

To put these prevalence figures in context, it is important to consider the prevalence of fatigue in non-stroke control populations. Many studies have not included control samples, so the data here are more difficult to source. One comparison of 90 stroke survivors and 50 age-matched controls demonstrated that a significantly larger proportion of the stroke group than the control group (51 % versus 16 %) experienced severe fatigue [11]. The same fatigue prevalence of 51 % was identified in a younger group of ischaemic stroke patients (mean age 48), while fatigue prevalence in controls in this study was 32 % [12]. One well-designed study compared levels of fatigue in groups of patients with stroke, patients with chronic heart failure, and healthy controls [13]. Fatigue levels were similar in the stroke and heart failure groups. In adjusted multivariate analysis with the controls as the reference group, stroke patients were at six times greater risk (odds ratio = 6.18, 95 % CI 3.31–11.55) and heart failure patients were at eight times greater risk (odds ratio = 8.03, 95 % CI 4.63–13.94) for fatigue. The Danish study cited above included a reference group from the population; 32 % of these controls reported fatigue [2]. This group, however, was a mix of those with and without health complaints and was poorly matched to the stroke group. When the stroke group was compared with an age-, gender-, and living arrangement-matched subgroup of controls, fatigue was significantly higher in the patients at 10 days post-stroke (59 % versus 39 %), but the prevalence in the stroke group dropped back towards the control level over time. Together, these studies clearly indicate that stroke increases the likelihood of fatigue, but there is also a substantial number of people in the general population (perhaps around a quarter to a third of people) who experience fatigue.

Defining Post-Stroke Fatigue

In 2001, Staub and Bogousslavsky published a review titled "Fatigue after stroke: A major but neglected issue" [14]. Their paper brought much-needed attention to post-stroke fatigue. A remarkable feature of the review, and an indication of just how neglected the issue was, is the reference list of only 35 studies. Staub and Bogousslavsky defined subjective fatigue as "a feeling of early exhaustion developing during mental activity, with weariness, lack of energy and aversion to effort" [14]. Fatigue has been characterised as a state of weariness unrelated to previous exertion levels, and it is not usually overcome by rest [15]. We contend that the concept of fatigue should encompass physical as well as mental fatigue and not necessarily be brought on by periods of activity. To reflect this, a definition of fatigue borrowed from the multiple sclerosis (MS) literature is apt: "*a subjective lack of physical or mental energy (or both) that is perceived by the individual to interfere with usual or desired activities"* [16].

A systematic approach to developing a more formal case definition of post-stroke fatigue has been undertaken [17]. The definition reads: "*Over the past month, there has been at least a 2-week period when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities.*" A similar, slightly modified definition was outlined for hospital inpatients. The structured interview that was formulated to classify fatigue emphasizes lack of energy and need to rest, and not lack of motivation, boredom, or sleepiness.

It is important to consider what fatigue is *not*. Fatigue should not be thought of as physical tiredness brought on by sustained exercise. A pertinent example of this in the stroke literature was provided by Tseng and colleagues [18]. They found that aerobic fitness was a strong predictor of the fatigue level reported immediately after exercise, whereas the strongest predictor of chronic fatigue was depression. "Exertion fatigue" may well be an important construct and is probably related to the broader notions of lack of physical and mental energy, but it is not what is meant when we refer to post-stroke fatigue. The same applies to mental fatigue: this should not be thought of simply as cognitive tiredness brought about by excessive mental effort.

Outside of stroke, some have drawn the distinction between pathological and non-pathological fatigue [19]. Fatigue is considered non-pathological if it is of short duration and has an identifiable cause (e.g., exercise, flu-like illness, endocrinopathy). Pathological fatigue has a greater intensity, longer duration and causes severe impairments to an individual's functional ability and quality of life. This distinction can be usefully applied to the stroke setting: whether fatigue after stroke is considered pathological will depend on the timing and the impact on everyday life. Post-stroke fatigue can occur in the acute stage (which may be a normal, restorative response) or in the chronic stage (which is likely to be pathological). Pathological long-term fatigue is the greatest concern.

Another distinction that has been posited is the pathophysiological difference between central and peripheral fatigue [20, 21]. Central fatigue occurs when there

is a failure to transmit motor impulses in the central nervous system, resulting in heightened perception of effort and reduced endurance in physical and mental activities. This failure has been localised to a network comprising the basal ganglia and its interconnected regions, including the thalamus and dorsolateral prefrontal cortex [22]. Peripheral fatigue is related to muscle fatigability and is characterised by failure to sustain the force of muscle contraction. The different roles of central and peripheral mechanisms underlying fatigue have not yet been explored in the context of stroke.

Measuring Post-Stroke Fatigue

Fatigue, as defined above, is a subjective experience, and therefore its measurement must include a phenomenological dimension. The most common approach to quantifying fatigue is via self-report assessment scales. Performance-based measures of fatigue can also be employed, with the realization that these measures reflect a narrower physiological conception of fatigue. For example, muscle fatigue can be evaluated by measuring the ability to perform muscle contractions over time [23]. Performance-based measures of mental fatigue have also been proposed, such as the use of a sustained attention task to assess cognitive fatigue [24]. In their review on fatigue in neurological conditions, Chaudhuri and Behan [20] outlined many techniques for identifying fatigability and its underlying causes. These included the Jolly test for identifying myasthenic disorders, single fibre electromyography, oxygen saturation of venous blood, muscle biopsy, neuroimaging to exclude demyelinating lesions, autonomic tests for orthostatic intolerance, and polysomnography. These physiological assessments offer attractive objectivity, but cannot be seen to encompass the concept of fatigue that was outlined earlier. The extent to which muscle fatigability and other physiological markers correlate with self-reported experience of fatigue after stroke is an interesting question that has not been addressed in the research literature.

Many of the self-report fatigue scales have been developed for and tested in MS. The similarities between these assessments are striking, both in item content and response scales, with only small differences in terms of focus on different aspects of fatigue. They are widely used in stroke populations, even though none have been developed specifically for this purpose (Table 14.1). One of the most commonly used measures in stroke is the fatigue severity scale [25]. It contains 9 items and responses to each item are made on a 7-point likert scale. The scale contains no specific reference to mental or cognitive fatigue; items are more focused on physical fatigue. A mean score >4 is considered to represent severe fatigue, though there is no strong rationale for this, and others have used ≥5 [26]. The fatigue assessment instrument is a predecessor of the fatigue severity scale, with a larger set of 29 items [27]. Another widely used tool is the fatigue assessment scale [28]. This 10-item measure uses a 5-point likert scale and covers both mental and physical aspects of fatigue. The fatigue impact scale is a 40-item tool, [29] with a

Table 14.1 Self-report assessment scales for fatigue used in stroke populations

Assessment	No. of items	Dimensions	Original target population	Stroke studies
Fatigue severity scale	9	–	MS, lupus	[1, 3–5, 12, 26, 38–48]
Fatigue assessment instrument	29	Global fatigue, situation-specific, consequences, responsive to rest	MS, chronic fatigue, Lyme disease, lupus, dysthymia	[9]
Fatigue assessment scale	10	–	Workers	[17, 49]
Fatigue impact scale	40 (short-21)	Cognitive, physical, psychosocial	MS, chronic fatigue	[1, 50, 51]
Multidimensional fatigue inventory	20	General fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity	Cancer, chronic fatigue	[2, 31]
Fatigue scale for motor and cognitive functions	20	Mental, physical	MS	[52]
Checklist of individual strength	24	Subjective fatigue, concentration, motivation, physical activity	Chronic fatigue	[11, 53]

modified version that contains 21 items on a 5-point likert scale. The shorter version consists of an 11-item cognitive subscale, a 7-item physical subscale, and a 3-item psychosocial subscale. The multi-dimensional fatigue inventory contains 20 items that are evenly distributed between the five dimensions of general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity [30]. Each item is scored from 1 to 5, with higher scores indicative of greater fatigue. Use of the total score is not recommended; those who want a single fatigue score are advised to use the general fatigue subscale score, and a cut-off of $\geq$12 on this subscale has been used to indicate fatigue [31]. A more recently developed tool is the fatigue scale for motor and cognitive functions [32]. The 20 items are evenly divided into mental and physical subscales, with responses on a 5-point likert scale. The checklist of individual strength also consists of 20 items, divided into the 4 subscales of subjective fatigue, concentration, motivation, and activity [33]. Suggested cut-offs are based on the subjective fatigue subscale, with <27 considered normal, 27–35 elevated, and >35 severe. While it is a broad health survey rather than a specific fatigue assessment, the Short Form-36 contains a vitality (or energy/fatigue) subscale of 4 items that is often used to measure fatigue [34]. Some have used the fatigue-inertia subscale from the Profile of Mood States assessment [35]. Brief visual analogue scales and single items have also been employed to identify fatigue, either in isolation ("Do you feel tired") [36] or taken from other scales, such as depression screening tools [37].

Assessing the criterion validity of these scales in stroke is not practical, as there is no accepted reference standard to evaluate them against. One attempt to evaluate the strengths and weaknesses of fatigue scales in stroke has been published: a comprehensive assessment of five common fatigue scales, chosen for their face validity in stroke [49]. Interestingly, the widely used fatigue severity scale was not one of them. Test-retest reliability (with a 3-day gap between assessments) was only moderate, with most scale items showing agreement between 0.40 and 0.60. Inter-rater reliability was generally very good, with agreement levels around 0.80–0.90. Attempting to move beyond reliability in evaluating fatigue scales is difficult. Demonstrating convergent validity of fatigue scales against each other only serves to illustrate what we already know—the items used are very similar. In terms of internal consistency, a lower Cronbach's alpha is not necessarily a negative; this may simply reflect that a scale covers some of the broader aspects of the multidimensional concept that is fatigue.

The Importance of Post-stroke Fatigue

Stroke patients who are fatigued have lower quality of life than those without fatigue. Large studies in Norway [44], Hong Kong [45], and The Netherlands [47] have demonstrated that post-stroke fatigue is significantly related to quality of life, even after adjusting for age, disability, and depression. This is important as the quality of life is the closest thing we have to a central and universally important health-outcome measure. Quality of life incorporates not just physical, but also psychological and social domains of health and well-being [54, 55]. As healthcare has moved from the traditional medical model (with humans as biological organisms) to a more humane model (people as integrated, feeling beings), quality of life has become viewed as the endpoint most relevant to the individual [56]. It follows that any factor that has an independent effect on quality of life—such as post-stroke fatigue—constitutes an important target for intervention.

In a study of more than 4,000 Swedish stroke survivors, fatigue was independently associated with dependence in activities of daily living and with having to move into an institution following stroke [36]. Other studies have failed to identify an effect of fatigue on activities of daily living, even in the context of reduced quality of life [47]. This raises the prospect of simple self-care and household tasks that require low-level energy expenditure being unaffected by fatigue, but other activities that require more exertion and that are pivotal to quality of life being affected. Persistent fatigue documented at 2 years' post-stroke was independently associated with a lower likelihood of returning to paid work (odds ratio = 0.29, 95 % CI 0.11–0.74).

Qualitative studies have shed light on the phenomenology of post-stroke fatigue. Fatigue matters to stroke patients, with 40 % reporting fatigue as their worst or one of their worst symptoms [50]. It limits participation in everyday life. One qualitative study reported that fatigue and the constant feeling of being tired ("It is just too much effort to do everything for myself") was a primary reason for not engaging in activities [57]. In spite of reasonable objective recovery of physical function, fatigue

in community-dwelling stroke survivors can be disabling [58]. Even in patients with low levels of physical disability, fatigue has debilitating effects on social participation, return to work, driving, reading, and sleeping [59]. Many patients reported feeling unprepared for the fatigue and struggling to adapt to it. Looking at the impacts reported here, it is easy to see how fatigue may influence quality of life (e.g., less social interaction, limited employment opportunities) without having a major effect on independence in activities of daily life.

It is likely that fatigue can have profound effects on stroke rehabilitation and inability to fully participate in rehabilitation may be a mediating factor behind many of the deleterious effects of fatigue. Unfortunately, there are very few data on this issue. One review was titled "Fatigue associated with stroke and other neurologic conditions: Implications for stroke rehabilitation," [15] yet this paper did not identify any studies on the effect of post-stroke fatigue on rehabilitation. Michael [60] suggested that fatigue can impede participation in rehabilitation, but this paper was based on anecdotal evidence from a single clinical case and a discussion of fatigue models, rather than results from an original data set. Morley and colleagues addressed the question in a pilot study of 20 stroke rehabilitation inpatients, with data reported briefly in a letter to the editor [61]. Eight of the 20 patients were assessed as having fatigue on the fatigue severity scale. Information from physiotherapists on whether fatigue interfered with rehabilitation was available for 16 patients; it had interfered in 6 of the 16, but only 3 of these 6 were fatigued according to the scale. So while it makes intuitive sense that fatigue can hamper rehabilitation after stroke, and therefore impact on recovery, there is very little supporting evidence for this relationship.

Several studies have raised the prospect that fatigue after stroke is related to an increase in mortality. Three years after stroke, patients with fatigue had a higher case fatality rate than those without fatigue [36]. In a UK study of more than 1,000 stroke patients, presence of fatigue was associated with shorter subsequent survival [62]. In a group of young stroke patients (mean age 48), Naess and colleagues reported that, adjusting for age and sex, fatigue was associated with mortality across the 12-year follow-up [43]. There is also evidence that post-stroke fatigue confers a higher risk of suicidality [46]. Therefore, reduction in levels of fatigue may result in not only better quality of life, but also longer life for stroke survivors. These findings do not necessarily imply that fatigue is a direct cause of death; it is likely that the fatigue-mortality relationship is mediated by other factors. In the Naess study, the significant relationship between fatigue and mortality disappeared when the multivariate regression included not only age and sex, but all variables associated with mortality in univariate analyses (alcoholism, myocardial infarction, and unemployment).

Potential Causes of Post-stroke Fatigue

As fatigue is a major contributor to the burden of disease following stroke, we need to understand what factors predispose patients to ongoing fatigue. There is not a long history of investigation into post-stroke fatigue, and we still have very limited

understanding of the mechanisms behind it. Of the studies that do exist, most have been observational and cross-sectional. We might yearn to identify causal factors for fatigue, but the bulk of our current information is at the level of association, not causation. There are published reviews of post-stroke fatigue that have made valuable contributions to summarising the existing literature [63, 64]. In the following discussion, we will split the variables that are potentially associated with the development of fatigue into three areas: pre-existing and stroke-specific factors, co-existing and bi-directional factors, and modifiable behavioural and environmental factors.

Pre-existing and Stroke-Specific Factors

Demographic Factors

There are conflicting results regarding the influence of age and sex on post-stroke fatigue. Older age was related to a greater likelihood of fatigue at 1 year [3] and at 15 months [16] post-stroke. Conversely, other studies have found that younger age is linked to a greater likelihood of fatigue at 2 months [65] and at 1 year [51] post-stroke. Completing this equivocal picture are studies that failed to identify a significant association between age and fatigue [1, 12, 50]. It is difficult to account for the difference between these studies and draw firm conclusions about the relationship between age and post-stroke fatigue. Some may assume that the likelihood of experiencing fatigue will increase as people get older, but this is not borne out in the data.

Studies in the general population have indicated that fatigue prevalence is higher in women than men [66, 67]. Interestingly, one stroke study found this sex difference in their control participants, but did not identify any relationship between sex and fatigue in stroke survivors [50]. There are other studies that report no sex differences in fatigue after stroke [1, 11], but these are outweighed by the number of studies that have identified higher levels of fatigue in women than men after stroke [2, 3, 5, 36, 39, 62]. Women are also more likely to be depressed than men, but the gender imbalance in fatigue was present in several of these studies even after accounting for depression. The imbalance is not necessarily one of biology and physiology: another possibility is that female stroke survivors receive less support in completing household tasks than male stroke survivors and are thus more prone to fatigue.

Pre-Stroke Fatigue and Vascular Burden

Information on pre-stroke fatigue is typically acquired retrospectively, so reliability of the data might be called into question. With that caveat, there is evidence that pre-stroke fatigue is the most important factor in explaining post-stroke fatigue,

beyond even depression and functional independence [1]. Another study reported that pre-stroke fatigue was independently related to fatigue in the acute stage of stroke [39]. Given the vascular compromise (e.g., small-vessel disease, subclinical stroke) and co-morbidities (e.g., diabetes, heart failure) that exist prior to stroke, it is possible that pre-stroke fatigue may be a marker for these conditions. The findings that leukoaraiosis is independently associated with post-stroke fatigue [26], and that patients with pre-stroke fatigue have more co-morbidities than those without pre-stroke fatigue [1], are consistent with this argument.

Stroke-Specific "Organic" Factors

Organic factors stemming from the brain lesion itself may play an important role: fatigue is more prevalent after minor stroke (56 %) than after transient ischemic attack (29 %) [7]. These rates of fatigue were barely altered when stroke patients with baseline NIHSS of 0 were compared to TIA patients (57 % versus 29 %). The argument follows that fatigue is not simply a consequence of a stressful acute cerebral event, comorbidity, medication, or level of disability, as these factors were all comparable between the groups. If this is true, we should be able to identify some properties of stroke-related damage that are associated with the development of fatigue.

Lesion Location

It has been suggested that damage to the brainstem and reticular formation is likely to predispose to fatigue [14]. This was supported by the finding that infratentorial infarctions were related to an increased risk of fatigue (odds ratio 4.69, 95 % CI 1.03–21.47) [65]. We have known for 100 years that lesions in the brainstem can cause specific alterations to wake-sleep regulation [68]. Given the anatomy of the ascending reticular activating system, it is unsurprising that these brainstem lesions can block ascending pathways and produce a profound impairment of arousal that could be experienced as fatigue. It is clear, though, that the genesis of post-stroke fatigue cannot be reduced to brainstem damage alone. One study that included only patients with supratentorial stroke identified a high fatigue prevalence of 70 % at 1 year post-stroke [3]. Another study found that basal ganglia infarcts are more likely to produce fatigue than brainstem infarcts [5]. Yet many studies have failed to identify an association between lesion location and fatigue [63]. The best way to approach this question is to synthesise all the current evidence. In 2012, a systematic review was published on the link between lesion location and fatigue [69]. There was no conclusive evidence of a relationship; meta-analysis was not conducted due to the methodological differences between studies. Four ($n=675$) of 13 studies ($n=1613$) reported associations between fatigue and infratentorial lesion location (particularly brainstem) or basal ganglia stroke. It should be remembered that the absence of evidence does not mean evidence of absence. Simple structural

metrics such as location and size of the lesion may not reflect the most important aspects of damage; we also need to consider interruptions to large-scale neural networks, perfusion abnormalities, changes to functional connectivity, and other alterations that may be related to fatigue.

Stroke Type

Surprisingly little attention has been paid to whether stroke subtype has a differential effect on fatigue. Haemorrhagic stroke tends to be more severe than ischaemic stroke and is associated with increased mortality risk in the acute stage [70]. It might be argued that the haemorrhagic nature of the lesion could predispose to fatigue. When ischaemic and haemorrhagic stroke patients have been compared, however, no difference in occurrence of fatigue has been identified [3]. A study that had a more detailed breakdown of subtype yielded the same finding: there were no differences in fatigue between patients with intracerebral haemorrhage, large vessel infarct, lacunar infarct, or embolic infarct [71].

Neural Activity and Metabolism

In addition to structural alterations, brain imaging techniques have been used to investigate functional, metabolic, and perfusion changes in fatigue, although generally not in the context of stroke. Abnormal cortical activation on EEG has been associated with fatigue in both MS [72] and postpoliomyelitis [73] patients. Functional MRI has been used to show reduced functional interaction between cortical and subcortical areas in fatigued MS patients [74]. FDG-PET scanning has been employed in fatigued MS patients, revealing areas of hypometabolism in prefrontal cortex and adjacent white matter, premotor, and supplementary motor areas and putamen [75]. These authors hypothesised that fatigue in MS is associated with frontal cortex and basal ganglia dysfunction that might result from white matter demyelination. Whether similar changes in brain activity occur in post-stroke fatigue is yet to be documented.

Inflammatory Markers

There is a strong rationale to predict that pro-inflammatory cytokines are related to higher levels of fatigue after stroke. Patients with chronic fatigue syndrome often have elevated C-reactive protein and other inflammatory markers [76]. Inflammation has a prominent role in the ischaemic cascade that is triggered by stroke and might help to explain the onset of fatigue. This is another area, however, where data are scarce. One study quantified cytokines and other blood components in acute stroke and investigated their relationship to fatigue in the longer term [77]. Higher levels of glucose and IL-1β were associated with greater fatigue at 6 months, and higher

levels of glucose and lower levels of IL-1ra and IL-9 were associated with greater fatigue at 12 months. The authors argued that cytokine-induced sickness behaviour, especially in relation to IL-1β, could explain symptoms of fatigue, with disturbed glutamate signalling the most plausible mechanism. The data require replication, however, especially in light of the numerous comparisons made and the fact that none of the measured biomarkers were associated with fatigue at 18 months. One other study has investigated C-reactive protein, but this was only a small pilot in 28 patients [78]. There was some indication of higher levels of C-reactive protein in the fatigued group, but this could only be detected after excluding those with pre-stroke fatigue or symptoms of mood disorder.

One argument that has been proposed is that fatigue is associated with an underactive hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis forms a major part of the neuroendocrine system, controlling hormone release through complex feedback mechanisms in reaction to stress, and to regulate many other bodily functions. There is evidence that the HPA axis is underactive in patients with chronic fatigue syndrome, fibromyalgia, and post-poliomyelitis fatigue [20]. Pre-existing low cortisol levels might sensitise the HPA axis to the development of central fatigue after an acute stressor (such as stroke). Cortisol secreted by the adrenal gland acts via a negative feedback mechanism to reduce hormone release from the hypothalamus and anterior pituitary. If cortisol levels fail to normalise in the chronic phase of stroke, continued down-regulation of the HPA axis may result in persistent fatigue.

Comorbidities

Stroke patients often have numerous comorbidities, and these comorbidities may be important factors in the development of fatigue. The common stroke-related comorbidities of diabetes mellitus and myocardial infarction were both independently related to fatigue in a sample of 377 stroke patients [26]. These same two comorbidities were found to be significantly associated with fatigue in a young cohort of stroke survivors, though the correlations were not strong ($r = 0.13$ and 0.16) [43]. We know that the presence of diabetes and myocardial infarction are linked to mortality, and as such are possible mediators of the fatigue-mortality association. In a multivariate analysis of stroke patients and controls together, greater fatigue severity was independently associated with diabetes mellitus, alongside cerebral infarction, depression, and migraine [12]. This is interesting as it suggests that the effects of diabetes, depression, and migraine on fatigue are at least partially separable from the effects of stroke. The contribution of diabetes and ischaemic heart disease is not completely consistent: large studies exist that did not find higher levels of fatigue in the context of these comorbidities [1, 71]. These studies also reported similar rates of hypertension in those with and without post-stroke fatigue. The impact of blood pressure is complex, with the relationship to fatigue likely to be U-shaped rather than linear; that is, both hypertension and hypotension may lead to greater fatigue. We know that hypotension is related to fatigue in the general population [79]. In a detailed study of ambulatory blood pressure monitoring in stroke patients, fatigue

was more common in those with either hypertension or hypotension [80]. An added complication in stroke populations is the question of attribution: fatigue may result from the direct effects of low blood pressure, but it may also be explained by the use of antihypertensive medications, many of which are known to have symptoms of fatigue as side effects [80].

Medications

It is not only antihypertensives that have fatiguing effects. Antidepressants, anxiolytics, and benzodiazepines can all have sedative effects, producing drowsiness and lethargy that may manifest as fatigue. This is particularly relevant given the high prevalence of mood disorders and sleeping problems after stroke, increasing the likelihood that these medications will be prescribed. There is also evidence that another class of medication often used after stroke—statins—can sometimes produce rhabdomyolysis, and this muscle breakdown can be experienced as malaise and fatigue [81].

Pain

Stroke survivors who experience pain are particularly vulnerable to physical inactivity, poor sleep, and mood disorder, all factors that can contribute to fatigue. Naess and colleagues found that pain was significantly associated with post-stroke fatigue, independent of depression, and sleep disturbance [26]. Another study investigated the associates of both pain and fatigue after stroke, but did not assess the relationship between these two factors [71].

Co-existing and Bi-directional Factors

Physical Disability

Studies have identified strong and independent relationships between post-stroke fatigue and higher levels of disability [1, 12], but it is difficult to draw firm conclusions about the direction of causality. Profound one-sided weakness is a common acute stroke symptom, and poorer physical function in the first 2 weeks after stroke has been related to fatigue [39]. In a study that included both stroke patients and controls, the factor that explained most of the variance in fatigue in the stroke group was impairment in locomotion, whereas depression was the predominant factor in accounting for fatigue in controls [11]. Not only does hemiparesis contribute to physical inactivity, which can exacerbate fatigue, the compensatory strategies and motor re-learning that is required may also increase fatigue. The inefficiency of hemiparetic gait necessitates higher-than-usual energy expenditure; there is evidence that the energy cost of walking following stroke is double that of controls

[82]. The relationship is potentially bi-directional because the experience of fatigue can limit participation in rehabilitation and reduce task practice with the affected limbs, thus feeding into continued physical disability. Of course, post-stroke physical disability is a broader concept than hemiparesis. One stroke study identified dysarthria, a motor disorder of speech production, in 30 % of those with fatigue but only 14 % of those without fatigue [1]. Another study considered the items from the baseline NIHSS separately and found that facial palsy and arm paresis were significantly associated with 12-month fatigue; in this analysis dysarthria was not related to fatigue [71].

Depression

Of all the factors that have been associated with post-stroke fatigue, depression is the one that stands out as the most prominent. The finding of a significant independent association between depression and fatigue after stroke is well documented [3, 12, 44, 65]. In a meta-analysis of 19 stroke studies ($n = 6{,}712$), depression and fatigue were significantly associated (OR = 4.14, 95 % CI 2.73–6.27) (Fig. 14.2) [83]. The relationship has been identified in the first 2 weeks after stroke [39] and also at several years following stroke [4]. It is not only severe strokes that are linked to mood disorder and fatigue. In a group of people who were under age 70 and had experienced small, non-disabling first strokes, depression was associated with fatigue across the 12 months of follow-up [9]. Interestingly, there is some evidence

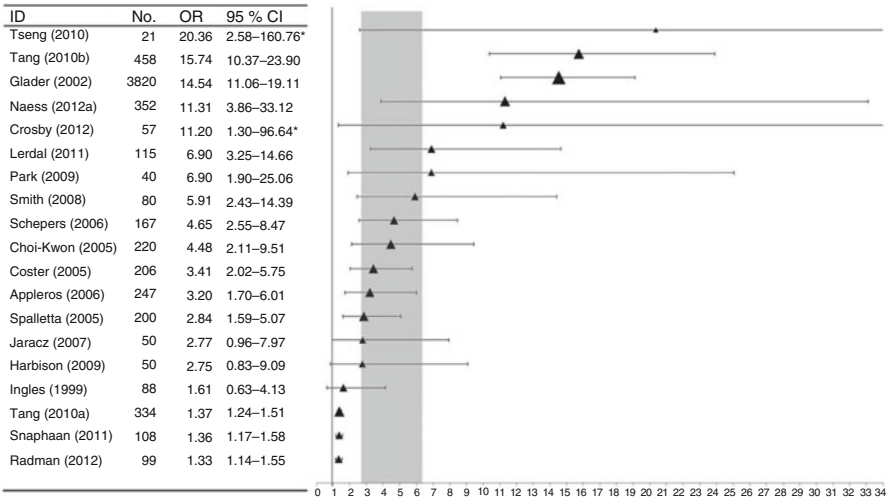

Fig. 14.2 Random-effects meta-analysis for the association between fatigue and depression after stroke. Horizontal axis is the odds ratio comparing occurrence of depressive symptoms in those with and without fatigue. *Error bars* represent 95 % CIs for the odds ratio from individual studies; *vertical grey bar* represents 95 % CI of the summary odds ratio (From Wu et al. [83]. Reprinted with permission from Wolters Kluwer Health)

to indicate that, controlling for other factors, a stroke patient is more likely to experience fatigue if they were depressed prior to their stroke [26].

It is clear that the relationship between depression and fatigue is a two-way association. Indeed, the association is so close that some have questioned whether it is meaningful to separate the two concepts. Many scales employed to assess depression include items on fatigue. Smith and colleagues addressed this issue by pooling items from the fatigue assessment scale and Beck depression inventory together [13]. Factor analysis of the combined item set yielded two distinct factors that represented the constructs of fatigue and depression. Consistent with this observation are the findings that many patients with post-stroke fatigue are not depressed [1, 11, 12, 36, 50]. It is possible that the relationship between depression and fatigue may be weaker in stroke than in the general population. Controlling for walking ability, depression scores only accounted for 11 % of variance in stroke fatigue scores, compared to 56 % of the variance in controls' fatigue [11].

Anxiety

Anxiety is not seen as so interlinked with fatigue; assessment scales for anxiety do not include fatigue as a symptom. There are studies, though, that have identified a significant association between anxiety and fatigue after stroke [9, 17]. A meta-analysis of four stroke studies ($n = 3{,}884$) found a trend towards an association (OR = 2.34, 95 % CI 0.98–5.58), but the relationship was weaker in studies that controlled for the influence of depression [83].

Locus of Control

In the many years since Albert Bandura published his groundbreaking paper [84], the concept of self-efficacy has become central to our conception of health, recovery, and personal agency. Self-efficacy describes a person's confidence in their ability to succeed in a particular situation. We can imagine two stroke patients with similar physical and cognitive impairments, one of whom has high and the other low self-efficacy. The first patient is likely to view their symptoms as challenges to be overcome, commit strongly to rehabilitation goals, and recover quickly from setbacks. The second is more likely to avoid challenging tasks, focus on negative outcomes, and lose confidence rapidly. From these outlines, we would expect level of self-efficacy to be associated with fatigue after stroke. While there is a very little research on this subject, there has been a study on the related concept of locus of control. People with a strong internal locus of control see themselves as having power over their own circumstances, whereas people with a more external locus of control see themselves more as passive agents. Schepers and colleagues demonstrated that stroke patients with a locus of control more directed to powerful others (e.g., doctors, care-givers) had higher levels of fatigue [3].

Cognitive Impairment

Cognitive impairment after stroke is common and can have major impacts on functional recovery and quality of life [85]. If the effort required to concentrate, problem solve, and remember is increased, then fatigue is likely to follow and also to feed back into these cognitive difficulties. In a study that included detailed neuropsychological examination, sustained attention and executive function were independently associated with fatigue at 12 months post-stroke [9]. There is evidence that even a single lacunar infarct can have subtle effects on cognitive performance, with reduced concentration and decreased capacity for mental effort [86]. Interestingly, mental speed and working memory have been correlated not only with cognitive fatigue but also with motor fatigue [52]. A strong target in the development of fatigue, particularly mental fatigue, is attentional dysfunction arising from damage to the reticular formation and related subcortical structures [14]. The link between post-stroke cognitive deficits and fatigue has not been easy to substantiate. When cognition has been assessed using a brief global screening tool (the MMSE), no relationship to fatigue has emerged [3, 12, 71]. Obtaining a self-report measure of fatigue in cognitively impaired stroke survivors can be difficult, and the problem is exacerbated in patients who also have pronounced fatigue or reduced level of consciousness. Another factor complicating measurement is the variation in cognition and fatigue across the day. A diurnal decline in cognitive performance was observed in stroke patients (but not controls), corresponding to the patients' subjective reports of increasing cognitive fatigue during the day [87]. There is also the impact of communication difficulties and fatigue, with cortical stroke patients often conscious of mental fatigue while speaking. The energy required to overcome aphasia can be seen as analogous to the compensation and effortful retraining of motor skills following stroke. Word-finding difficulties have also been linked to mental fatigue in post-poliomyelitis [88] and chronic fatigue syndrome [89].

Modifiable Behavioural and Environmental Factors

Sleep and Alertness

Fluctuations in daytime alertness and nighttime sleep quality may be linked to fatigue. Sleep-related breathing disturbances are present in the majority of stroke patients, and sleep-wake disturbances (including insomnia, excessive day-time sleepiness and fatigue) are also common [90]. Acute stroke patients often report poor sleep and drowsiness. In the chronic stage, there is evidence that stroke survivors have poorer sleep and greater daytime sleepiness than a normative healthy population [91]. In one cohort of chronic stroke patients, fatigue was significantly correlated with sleep disturbance [4]. Sleep disturbances have been associated with fatigue at 1 year post-stroke, though this relationship did not persist in a multivariate model [71]. Insomnia was reported by significantly more stroke survivors with

fatigue (22 %) than those without fatigue (11 %) [1]. Direct evidence of a link between sleep quality and fatigue after stroke is lacking, however, with all the studies cited here relying on self-report data for sleep disturbance.

Physical Activity

We know that patients are inactive in the acute stage of stroke [92], and this inactivity may trigger or worsen fatigue. One study in acute stroke demonstrated that early mobilisation (within 24 h of stroke) produces an increase in level of consciousness [93]. This is consistent with the observation that physical activity increases levels of brain neurotransmitters such as dopamine and norepinephrine, which increase arousal and facilitate information processing [94]. Yet the link between physical activity, fitness, and post-stroke fatigue has not been established. A systematic review on the topic identified only three studies, and no associations between fatigue and any measures of physical activity or fitness were found [95]. While leg strength of stroke survivors has been associated with fatigue [96], a study probing walking activity and fitness levels after stroke failed to identify significant correlations with fatigue [41]. A small study of nine stroke survivors considered the relationship between fitness, motor control, and fatigue as measured immediately following a 6-min-walk test [97]. Lower levels of fitness and poorer motor control were both strongly related to fatigue, with motor control emerging as an independent predictor in multivariate regression. This measure of fatigue "in the moment", however, is more reminiscent of exertion fatigue [18] than pathological chronic fatigue. Finally, it has been suggested that fatigue may have an indirect influence on physical inactivity by lowering self-efficacy expectations [98].

Nutrition

Surprisingly little research has investigated the link between this prominent modifiable environmental factor and fatigue after stroke. Malnutrition, often linked to dysphagia, is a frequent problem following stroke [99], and we know that dietary intake can influence fatigue. In cancer, for example, anaemia is a common cause of fatigue, and optimisation of nutrition has been proposed as a non-pharmacological therapy [100]. Yet the literature on the relationship between nutrition and fatigue is heavily weighted towards studies in elite athletes, with few studies in stroke or other chronic disease.

Models of Fatigue

Fatigue, like pain and hunger, can be thought of as a homeostatic emotion: it is an attention-demanding feeling that is evoked by an internal body state that motivates behaviour (such as inactivity or withdrawal) directed at maintaining the body's ideal

state. Homeostatic emotions have also been labelled primordial emotions [101]. This is because the motivations to act are driven by lower brain regions like the medulla and hypothalamus that are ancient in evolutionary terms. In contrast, "classic" emotions like anger and fear are mediated by higher, more recently evolved brain regions. It is likely that humans have been "using" fatigue as an adaptive response for a very long time. In terms of survival, fatigue warns us to slow down and conserve energy in the same way that thirst tells us to hydrate. Bud Craig used the concept of "interoception" to describe the internal feedback mechanisms that provide a sense of the physiological condition of the body [102, 103]. He argues that the primary interoceptive representation in the dorsal posterior insula engenders feelings from the body that include pain, temperature, itch, hunger, thirst, muscular sensations, and vasomotor activity. In humans, there is also meta-representation in the right anterior insula that appears to provide the basis for self-awareness of these homeostatic emotions. Thus, we might expect stroke-related damage to the hypothalamus or insula to be related to an imbalance in homeostatic emotions such as fatigue. The relevance of this to a theoretical model of post-stroke fatigue lies in the implication that fatigue is not necessarily maladaptive; as a response to the acute stress of stroke, it may serve an important purpose.

In their account of fatigue in neurological disorders, Chaudhuri and Behan focus on the distinction between central and peripheral fatigue and present a detailed biological model of chronic fatigue that is based on neuroendocrine functions [20, 22]. Central fatigue may occur due to a failure in the integration of limbic input and motor functions within the basal ganglia, affecting the striatal-thalamic-frontal cortical system [20]. In the stroke context, we might expect disruptions to the network comprising the basal ganglia and its interconnected regions, including the thalamus and dorsolateral prefrontal cortex, to result in fatigue. The finding cited earlier that basal ganglia infarcts are more likely to produce fatigue than brainstem infarcts [5] is consistent with this model.

A more recent attempt to explicate fatigue in neurological illness was made by Kluger and colleagues [104]. Their model included several of the important dimensions already discussed: perception of fatigue as distinct from performance fatigability, peripheral factors against central factors, and homeostatic regulation of activity.

A Proposed Model for Post-Stroke Fatigue

One thing missing from these more general fatigue models that needs to be incorporated into a post-stroke model of fatigue is a temporal dimension. Factors that are present prior to stroke can have an influence on post-stroke fatigue. Immediate impacts of stroke build on these existing vulnerabilities. In the physical realm, adjusting to and compensating for newly acquired weakness leads to muscular inefficiency, increased energy cost, and higher fatigue levels. In the cognitive realm, slowed processing speed, inability to sustain attention, and more diffuse neural activation reflect cognitive inefficiency that manifests as mental fatigue. At this early

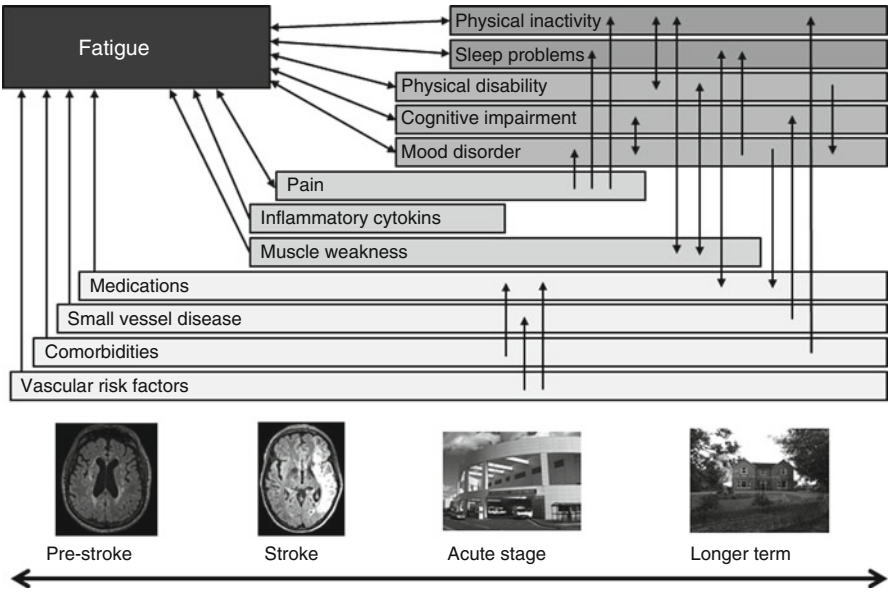

Fig. 14.3 Proposed explanatory model of post-stroke fatigue (Photo attributions: Lisa Jarvis and Richard Humphrey, Geograph project)

stage, many of these changes are part of the adaptive, restorative response to the acute stress of the stroke event. Fatigue, as a homeostatic emotion, is signalling the body to slow down, withdraw, and conserve resources. This is not to say, however, that fatigue in the acute stage should be ignored and potential treatment withheld. Fatigue early after stroke is one of the best predictors of long-term fatigue [2, 40, 65], and this persistent fatigue cannot be seen as an adaptive response. Factors that seem to perpetuate fatigue include mood disorder, sleep-wake disturbances, and inactivity. It may be that our understanding of post-stroke fatigue will be most enhanced not by isolating the initial triggers of fatigue, but by discovering why the body fails to return to a more normal homeostasis between the acute and chronic stages. In Fig. 14.3, we propose a model for post-stroke fatigue. It is important to emphasise that this constitutes a theoretical framework; it is not an exhaustive list of all contributing factors, and the strength of empirical support for each of the arrows is highly variable.

Interventions for Reducing Post-stroke Fatigue

Models of fatigue that are based on quantitative research can be merged with the subjective experience of stroke patients to inform intervention targets. Reports from patients indicate that fatigue often begins at the time of stroke and can be improved

by exercise, good sleep, rehabilitation, and mental stimulation [105]. In a typical case, fatigue might be triggered by factors related to stroke onset (e.g., the stroke lesion itself, functional impairments) and then exacerbated by physical inactivity, poor sleep, and boredom in the acute hospital. Barbour and Mead recently suggested that it is factors like these that should be considered when developing complex interventions to improve post-stroke fatigue [105]. Effective interventions have been elusive to date. A 2009 Cochrane review identified only three treatment trials (two drug, one self-management), none of which were effective in reducing post-stroke fatigue [106].

The behavioural and environmental factors outlined above are obvious targets for intervention. One avenue of research should be to adapt interventions that have been used successfully in other patient groups and test their efficacy in stroke. Graded exercise has been shown to be effective for chronic fatigue syndrome [107] and appears well suited to the management of post-stroke fatigue. Others have demonstrated the benefits of an extended outpatient rehabilitation programme for reducing fatigue in people with progressive MS [108]. Zedlitz and colleagues randomised chronic stroke survivors to a 12-week programme of either cognitive therapy alone or cognitive therapy combined with physical activity training [53]. Both groups exhibited significant reductions in fatigue, with the best results occurring in the combined treatment group. While this finding is very promising, it requires replication in a study with a standard care control group. Improving sleep quality is another prime target for treatment, given the potential influence on fatigue and the high prevalence of sleep-related breathing disturbances in stroke survivors. The most common disturbance is obstructive sleep apnoea, where breathing is interrupted by a physical block to airflow in the throat. Continuous positive airway pressure (CPAP) can be a very effective treatment for obstructive sleep apnoea, but demonstrating its efficacy in stroke has been complicated by poor levels of adherence [109]. Implementing a self-management programme has potential to reduce fatigue, with educational sessions on health promotion, stress management, and coping skills useful in reducing fatigue in people with cancer [110] and MS [111]. A subgroup of stroke patients in a large trial of chronic disease self-management, however, showed no improvement in fatigue [112].

Several drugs have been trialled for their effects on post-stroke fatigue. Given its success in ameliorating fatigue in MS [113], modafinil is a leading candidate. One study compared the effects of modafinil on fatigue in 14 brainstem-diencephalic stroke patients, 9 cortical stroke patients, and 17 MS patients [114]. Impact on fatigue was significantly greater in the brainstem stroke and MS groups than the cortical stroke group, leading to the suggestion that modafinil's effects were based on boosting alertness in the context of a dysfunctional reticular activating system. Again, replication is needed in bigger, placebo-controlled trials. In a larger and better-controlled trial, fluoxetine was found to be ineffective in reducing post-stroke fatigue, despite having positive effects on depression [38]. This failure of a selective serotonin reuptake inhibitor to reduce fatigue was replicated more recently with the agents citalopram and sertraline [115], implying that post-stroke fatigue is not closely associated with serotonergic dysfunction. In a study of subarachnoid

haemorrhage patients, treatment with tirilazad mesylate was associated with better sustained attention and lower levels of debilitating fatigue [116]. These findings, however, were based on only nine treated and nine control patients, so cannot be seen as definitive.

When considering the implementation of interventions, timing is critical. The brain's capacity for plastic change after stroke is not linear across time, and evidence suggests there is an early time window for interventions to have maximum benefit. Animal models indicate an increased capacity for plastic change immediately after cerebral infarction, as evidenced by cortical hyperexcitability, that subsides over subsequent months [117]. In human stroke, there is evidence of early hyperexcitability that appears to diminish by 3 months [118]. Because fatigue in the first weeks and months after stroke predicts fatigue in the longer term [2, 40, 65], early intervention holds great promise. Given the relationship between fatigue and active participation in rehabilitation [61], early intervention has the potential to spark a positive feedback loop between increased activity, heightened alertness, and reduced fatigue.

Clinical Management of Post-stroke Fatigue

The lack of efficacious interventions for post-stroke fatigue makes it difficult to recommend clinical management strategies with any confidence. The 2012 clinical guidelines from the UK Royal College of Physicians include only two recommendations: fatigue should be assessed, and those with fatigue should be given information and reassurance that their symptoms are likely to improve with time [119]. The second recommendation may appear overly hopeful in light of data showing continued high prevalence rates in the longer term. A systematic review of longitudinal studies, though, noted that fatigue was more likely to improve across time than to worsen [6], and it is important to give the patient some hope that fatigue symptoms will not persist indefinitely.

In practice, the first line of management is usually identification of reversible medical problems (e.g., pain, muscle spasticity), consideration of medications being taken and assessment for depression or anxiety, as these can all be related to fatigue and are potentially modifiable. The second line of management is advice regarding lifestyle factors. Alcohol increases fatigue and should be avoided. It is important to have a good sleep routine. Level of physical activity is a central issue and is often the focus of questions from patients with post-stroke fatigue. We know that people tend to be sedentary after stroke, leading to physical deconditioning, reduced endurance, and avoidance of exertion. This negative cycle is more pronounced in the context of fatigue. Regular physical activity should be encouraged, and the activity should be modest, spread throughout the day, and focus on regularity rather than level of performance [20]. These management strategies—medications, exercise, behavioural therapy, and sleep hygiene—are very similar to those that have been employed in fatigue related to MS [120] and cancer [121].

Future Directions

The first step towards a greater understanding of post-stroke fatigue is to operationalise its definition and measurement. Typically, the subjective-perception dimension of fatigue and the performance-fatigability dimension are kept separate. Future studies should investigate the relationship between these dimensions, potentially leading to a more unified musculo-psycho-physiological account of fatigue. Identification of causal and mechanistic factors underlying fatigue will be important. This will involve more sophisticated brain imaging approaches to identify the structural, functional, and metabolic effects of stroke. It will also involve the development of animal models of post-stroke fatigue, analogous to those that have been reported for post-operative fatigue [122]. Future studies will need to determine optimal levels of physical activity, sleep, and other behavioural factors in fatigue prevention and management. With our understanding of the contributors to fatigue enhanced by this foundation research literature, we will be able to design targeted intervention studies to test efficacy. Effective interventions can then be implemented in clinical practice, thus contributing to the central goal of reducing the burden of post-stroke fatigue.

Conclusion

Of all the complications that are experienced following stroke, fatigue is one of the most common and one of the least understood. Post-stroke fatigue has debilitating effects on independence and quality of life. While we have some knowledge of the many factors that are associated with fatigue after stroke, we are yet to identify causal relationships, and only a handful of interventions have been trialled. In our attempts to reduce post-stroke fatigue, we need to determine the factors that promote fatigue early after stroke, and also those that perpetuate fatigue in the longer term. Fatigue is multidimensional and complex, and we require more sophisticated models if we are to identify solutions. The fact that so many of the contributing factors to fatigue are potentially modifiable, either behaviourally or pharmacologically, should give us strong reason to believe that these solutions are within reach.

Patient Questions

Q. How long are these feelings of fatigue going to last?

A. Feelings of fatigue are often strongest in the weeks immediately following stroke. As time goes on, it is likely that your fatigue symptoms will improve, allowing fuller participation in everyday activities.

Q. Is rest or physical activity better for fatigue?

A. In moderation, rest and physical activity are both good for fatigue. Aim to include some physical activity in your daily routine, ideally at several different times throughout the day. The activity does not need to be exhausting—regularity is more important than intensity.

Q. What can I do to feel less fatigued?

A. In addition to staying physically active, there are several things you can do to reduce the chance of feeling fatigued and to manage fatigue symptoms when they do come on. Avoid drinking alcohol, as this can worsen fatigue. Make sure you have a good sleep routine: avoid caffeine in the evening, try to go to sleep at the same time each day. Plan your day so that tiring tasks are done when you feel best and break these tasks up with rest periods if you need to.

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Chapter 15
Mental Consequences of Stroke

Luis Ayerbe

Abstract Depression, anxiety, and emotionalism affect over half of stroke patients at some point after stroke. These problems are associated with higher mortality and disability rates (depression), lower quality of life (anxiety), and impaired personal relationships (emotionalism). Patients with severe strokes and previous history of depression have the highest risk of depression after stroke. The main predictor of anxiety seems to be depression itself. Clinicians involved in the care of stroke patients should be able to diagnose depression, anxiety, and emotionalism and provide information to patients and their carers. Antidepressants should be considered for the management of depression, anxiety, or emotionalism after stroke. Further research is required for the development and delivery of pharmacological and non-pharmacological interventions for depression, anxiety, and emotionalism after stroke in both primary and secondary care.

Keywords Stroke • Depression • Depressive disorder • Anxiety • Emotionalism

Key Messages

- Over half of stroke patients suffer from depression, anxiety, or emotionalism at some point after stroke with symptoms starting shortly after the acute event.
- Depression and anxiety may become chronic and recurrent problems affecting stroke survivors in the long term.
- Depression after stroke can lead to higher mortality and disability rates, lower quality of life, poor life satisfaction, less efficient use of rehabilitation services, and need for institutional care after stroke.
- Anxiety after stroke can lead to depression and lower quality of life.
- All clinicians from primary and secondary care regularly involved in care of stroke patients should be able to diagnose depression, anxiety, and emotionalism on clinical grounds.
- Antidepressants should be considered for the management of depression, anxiety, or emotionalism after stroke.

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Introduction

Psychiatric disorders after stroke are common. They can be distressing to patients and their relatives and may exacerbate physical impairment [1–5]. They can also complicate patients' care and have a negative impact on mortality, disability, and quality of life after stroke [3, 6–10]. However, psychiatric disorders are often underappreciated by clinicians, and a majority of long-term stroke survivors have reported that their emotional needs had not been met adequately [11]. This chapter will focus on common psychiatric problems that the clinicians involved in the care of stroke patients should be able to approach.

Depression

Depression is defined by the presence of at least five of the following symptoms that cause clinically significant impairment in daily life for a period of 2 weeks or more, with one of the symptoms being depressed mood and/or loss of interest or pleasure in life activities [12]:

1. Depressed mood most of the day
2. Diminished interest or pleasure in all or most activities
3. Significant unintentional weight loss or gain
4. Insomnia or hypersomnia
5. Agitation or psychomotor retardation noticed by others
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death or suicide

Aetiology of Depression After Stroke

The aetiology of depression after stroke is probably multifactorial. Depression may occur in any patient secondary (directly or indirectly) to the biopsychosocial stress of medical illness [13, 14]. It has been postulated that the greater the medical burden and the pre-existing vulnerability, the higher the risk of depression [9, 14, 15]. Several specific mechanisms for depression associated with physical illness, applicable to stroke patients, have been proposed [10, 13, 14]. These mechanisms include factors linked to the medical condition, any significant medical complication, and long-term dependence for activities of daily living [8]. Indeed, stroke and depression have risk factors in common, such as diabetes mellitus, and the onset of stroke and the uncertain or poor prognosis can have a negative impact on a patient's mood [14, 16]. The involvement of psychological mechanisms for depression among

patients with medical conditions such as stroke has also been reported [13, 14, 17–19]. These include the personal meaning of the illness for the individual, changes in sense of identity, alterations in body image, damaged self-esteem, dysfunctional attitudes (such as self-judgement on unrealistic standards) [10, 20], cognitive distortions [14], maladaptive coping strategies, and some types of personality [13, 14]. Biological mechanisms may also play a role in the association between stroke and depression [18, 19, 21]. These would include the damage on neurochemical pathways mediating mood [10, 13–15, 18, 21]. Finally, a number of sociological factors related to the physical disease may have an effect on patients' mood as well [13]. These would include concerns about relatives, such as difficulties in the education of children depending on the patient, stigmatisation, isolation, financial worries, the loss of social roles, employment or professional status, relocation, or institutionalisation [22, 23]. There are also social factors for depression not directly linked to stroke but prevalent among stroke survivors, for example, the loss of a spouse [10, 13, 14].

The Natural History of Depression After Stroke

Depression is more frequent among stroke survivors than in the general population [24–28]. It has a prevalence of around 30 % [2, 3], but at some point in the long term about 50 % of stroke survivors suffer from depression [29, 30]. Most patients develop their first symptoms shortly after the acute event and recover in the following months but have a high risk of recurrent depression in the long term [30]. Depression is not only a distressing condition for patients and families; it is also associated with higher rates of mortality, disability, anxiety, lower quality of life, poor life satisfaction, less efficient use of rehabilitation services, and need for institutional care [3, 6, 8].

Detection of Depression After Stroke

The guidelines of the Royal College of Physicians (RCP), European Stroke Organisation, and American Heart Association recommend multidisciplinary assessments for depression in all stroke patients [31–33]. Nurses, who have 24/7 contact with patients, particularly in inpatient settings, may be expected to be the ones who first notice when a patient is developing symptoms of depression, perform the initial assessment, and request a consultation [31]. Patients identified as having symptoms of mood disorder should have a more detailed assessment, seeking information on past history, potential causes, impact, and treatment preferences. Patients who do not become depressed shortly after stroke seem to be at lower risk for depression [30]. Except in those patients, given its chronic and recurrent nature, depression requires periodic clinical screening in the long term. To ensure that stroke patients at risk of depression receive continued care in the long term, good

coordination between secondary care specialists and primary care clinicians is essential. Patients with history of depression pre-stroke, affected by severe strokes, and with a high degree of disability or cognitive impairment after stroke have the highest risk of depression [3, 8]. Therefore, clinicians should pay particular attention to patients in these categories, who are especially vulnerable.

The diagnosis of depression is made on clinical grounds, using the criteria presented above. All doctors who see stroke patients regularly should be adequately trained to assess patients for depression using clinical criteria. For the assessment of depression in busy and resource-poor clinical settings, screening scales validated in stroke patients may also be useful [5, 34] (i.e. the Nine-Item Patient Health Questionnaire [35], the Hamilton Depression Rating Scale [36], the Center of Epidemiological Studies-Depression Scale [37], the Hospital Anxiety and Depression Scale [38], and the Beck Depression Inventory [36]). However, clinicians should know that according to a recent systematic review, the performance of scales is modest for case-finding (rule-in diagnosis) since all of them report a significant number of false positives. Conversely, the ability of scales to exclude (rule out) depression and confirm non-depressed status is high [34]. It should also be noted that, when they are used alone, screening depression scales have little or no impact on the detection and management of depression [34, 39]. In any case, if a scale is used, a thorough clinical assessment and management plan should always be arranged for patients showing positive screening results [34, 39].

The assessment of patients at high risk of depression (severe strokes, cognitive impairment, and/or history of depression) at a moment of high risk (within 6 weeks of stroke) may improve the positive predictive value of the screening tools. This would reduce the number of patients who receive unnecessary assessment after the first approach. The methods of assessment should be adapted for patients with communication problems, who are at high risk of depression, and may not be able to report their symptoms. In individuals with severe aphasia, an assessment tool designed specifically for this purpose, such as the Stroke Aphasic Depression Questionnaire (SAD-Q) or Depression Intensity Scale Circles (DISCs), may be used [33]. Many patients present with symptoms, such as psychomotor retardation or fatigue, that can be caused by depression or by the stroke itself, and this complicates their clinical assessment and management. Nevertheless, given the relevance of depression, all doctors who see stroke patients regularly should be familiar with these symptoms and should be able to assess patients for depression adequately.

Management of Depression After Stroke

There appears to be a benefit from adopting a holistic framework for the management of psychological problems after stroke. Interventions that address specific mood disorder tend to miss part of the complexity of life after stroke. Comprehensive-holistic rehabilitation programmes should integrate evaluations of cognition,

behaviour, and mood to approach the individual's difficulties [33]. Since depression and anxiety are often associated [6, 7], patients considered to have one of them should be assessed for other mood disorders [33]. Furthermore, specialist mental health teams should be involved in the management of patients with severe or persistent mood disorders.

Patients with mild or moderate problems should be provided with information, support, and advice about the mood disorder and the stroke [33]. The information may be provided with leaflets, workbooks, or verbal communication, including lectures or teaching sessions. Information is necessary to identify and act upon symptoms, manage exacerbations, facilitate access to effective treatments, and improve clinical outcomes [40]. A lack of information has a negative impact in compliance with stroke secondary prevention and psycho-social outcomes for both stroke patients and carers [41]. A Cochrane review reported that the provision of information to stroke patients and caregivers had no effect in depression rates, when depression was approached as a binary variable (depressed/not depressed), but it had a significant positive effect on depression scores [42]. The information provided in the trials included in the review contained at least one of the following components: the causes and nature of stroke, management and recovery from stroke, prevention or reduction of risk of recurrent strokes, and information on resources or services. Other interventions that may be considered for stroke survivors with mild or moderate depression are increased social interaction, increased exercise, goal setting, or other psychosocial interventions [33]. All stroke teams should have clinicians adequately trained to provide this care, although at this level the voluntary sector may be also involved.

If patients do not respond to information, support, and advice, then psychological or pharmacological treatments or a combination of both may be considered with the involvement of a clinician with expertise in managing mood disorder after stroke [33]. Whilst initial meta-analyses of randomised controlled trials (RCTs) found no evidence to support the routine use of pharmacotherapeutic or psychotherapeutic treatment for depression after stroke, subsequent RCTs and meta-analyses showed a small but significant effect of pharmacotherapy (but not psychotherapy) on treating depression but with an increase in gastrointestinal and neurological side effects [5, 43]. The National Institute for Health and Care Excellence (NICE) guidelines for depression in adults with chronic physical health problems recommend selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacological treatment, and a Cochrane review has shown SSRIs to improve not only depression but also dependence, disability, neurological impairment, and anxiety after stroke [44, 45]. However, there was heterogeneity between trials and methodological limitations in a substantial proportion of them. While this Cochrane review could find no evidence of an association between SSRIs and relevant side effects, some observational studies have reported an association between antidepressants and an increased risk of adverse outcomes including falls, fractures, upper gastrointestinal bleeding, self-harm, stroke, and all-cause mortality [46, 47]. The results of large, well-designed trials are needed to determine whether antidepressants should be given routinely to improve disability in stroke patients.

Patients prescribed antidepressants should be monitored for adverse effects, and treatment should be continued for at least 4 months beyond initial recovery. If the patient's mood has not improved within a month of initiating treatment, compliance with medication should be checked, and a higher dose of the same drug, or another antidepressant, should be considered. Patients on antidepressants should have regular medication reviews to assess the need to continue with the treatment. In patients with aphasia or other impairments that complicate assessment, careful observations over time (including response to a trial of antidepressant medication) may be used [33].

The management of depression after stroke requires long-term follow-up to assess adherence and efficacy of therapy and to change doses or stop treatment where necessary [48]. Adequately coordinated clinical attention provided by stroke physicians, general practitioners, and sometimes psychiatrists would prevent the fragmentation of the long-term care of stroke patients with or at risk of depression. It has been suggested that health services may not have the resources to screen and treat all patients with post-stroke depression [48]. Nonetheless, depression is associated with negative health outcomes that would be costly for the health service in the long term. While further research into the benefit of psychological care after stroke is needed, there is already some evidence suggesting that effective management of depression after stroke may be a cost-effective policy [49].

A Cochrane review of pharmacological and psychological interventions to prevent depression after stroke reported that psychological interventions led to a small but significant improvement in depression, but no evidence of an effect of antidepressants was observed. There was no evidence of psychotherapy or antidepressants improving cognitive function, activities of daily living, or disability [50]. The trials that have been published since then showed some evidence of benefit for antidepressant drugs, although their addition to the Cochrane analyses is unlikely to change substantially the overall estimate of effect [5, 51–53]. In accordance with this evidence, RCP guidelines recommend that antidepressants should not be used routinely to prevent the onset of depression [33].

Future Approach to Depression After Stroke

Most studies for prevention and treatment of depression after stroke address patients shortly after the acute event [43, 50]. However, depression has been observed to be a frequent problem up to 15 years after stroke [30]. Therefore, the development of screening, preventive, and therapeutic interventions for depression in the long term after stroke, involving primary care clinicians, is required. Primary care settings have an advantage over hospitals, when considering long-term interventions, as follow-up examination may be routine, brief, and easy to arrange and they are the place where the medical management of different problems is integrated. Ensuring a good coordination between primary and secondary care will be essential in the development of effective interventions for depression after stroke.

As well as the diagnosis, the management of depression after stroke should be approached holistically. It has been reported that patients with multi-morbidity often receive care from different teams in an uncoordinated way [54]. The results of studies of depression in the context of other diseases [55–59] suggest that depression may be relevant to patients affected by most long-term conditions [13]. An integrated approach to depression for all the chronically ill, including stroke survivors and also patients with less frequent and therefore less investigated problems, might be developed in the future.

Probably the biggest obstacle to routine use of psychological strategies is access to trained therapists, due to scarcity of services, long waiting lists for non-crisis cases, and financial cost. However, psychotherapeutic assistance may be provided not only through a formal process of psychotherapy but also in the context of the ongoing doctor-patient relationship. For many people with medical conditions, the relationship with a clinician who is prepared to listen to their experience is the most important component of their treatment [14]. Although the therapeutic relationship may be one of the most powerful tools to preserve and protect emotional well-being, this factor is often underestimated by practising clinicians. Appropriate training to make the relationship with the patient psychotherapeutic in itself could be suggested. Some medical patients who might benefit from psychotherapy may be reluctant to accept a treatment that implies that they are 'damaged' in yet another way. These patients may prefer brief and periodic interventions that emphasise psychoeducation provided by their usual doctor.

Most predictors of depression after stroke are not purely biological but psychological and sociological as well. The multidisciplinary care that patients with depression after stroke need may also have to be delivered in cooperation with professionals working outside the health service. There is already a systematic review reporting positive effects of tele-counselling (mental health services by telephone) on depression in patients with disabling medical conditions, including stroke [60]. The tele-counselling was provided in an average of eight sessions of 30–90 min each, over a 3-month period. The programmes involved individual sessions held once a week to once a month. Significant improvements, not only in depression but also in coping skills and strategies, and community integration were observed.

Another systematic review reported that there is limited to moderate evidence supporting community-based rehabilitation interventions delivered by allied health professionals and/or nursing staff to have a positive effect on different outcomes such as quality of life, participation, and depression after stroke [61]. There is a need for trials looking at a broader range of treatment and prevention strategies, including talking interventions delivered by trained and supervised lay workers, the provision of combined and collaborative care interventions, and trials of guided self-help [48].

A large proportion of stroke patients do not develop depression, and this introduces the concept of resilience [2, 3, 14, 62]. The study of resilience has become more relevant as there has been a shift from a problem-oriented approach to one that stresses prevention and the nurturing of strengths. There are trials that have reported successful interventions enhancing resilience in patients with other medical

conditions [63]. However, even though resilience is an interesting concept that opens a new way of looking at mental health problems in the medically ill, its routine application in clinical practice requires further research. A good conceptualisation of resilience and its potential role in stroke patients may help in the development of interventions to prevent and/or treat post-stroke depression.

Clinicians', patients', and carers' beliefs about depression after stroke also influence the effectiveness of its management. Further qualitative research studies investigating what doctors, patients, and carers think about depression after stroke, and its possible clinical approach, may also help in the development of effective interventions. Finally, future studies describing the natural history, predictors, and outcomes of depression after stroke, and the effect of interventions in low- and middle-income countries, are also required [48].

Anxiety

Anxiety has received comparatively less attention than other psychological problems that affect stroke patients [1]. Anxiety has been defined as a future-oriented mood state associated with preparation for possible upcoming negative events [64]. The diagnosis of generalised anxiety disorder (GAD) requires excessive and difficult-to-control anxiety and worry, occurring most days for at least 6 months and associated with at least three of the following symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance. These symptoms should cause clinically significant impairment in social, occupational, or other important areas of daily life. The disturbance is not due to the direct physiological effects of a substance (i.e. drug of abuse) or a general medical condition (i.e. hyperthyroidism) and does not occur exclusively during a mood disorder, psychotic disorder, or pervasive developmental disorder [12]. Certain physical symptoms such as palpitations, dizziness, or trembling may also be observed in patients with anxiety [1]. Genetic, neurological, and environmental factors play a role in the development of GAD [64, 65].

Natural History of Anxiety After Stroke

A systematic review reported that the pooled prevalence of anxiety after stroke was 18 % when it was assessed by clinical interview and 25 % when a rating scale was used [1]. However, anxiety affects more than half of stroke patients at some point in the long term. A large cohort study observed that up to 57 % of stroke patients presented symptoms of anxiety at some point within 10 years of stroke, with 58 % of them developing their first symptoms in the first 3 months [7]. The observed annual incidence of anxiety was up to 24 % and prevalence 32–38 % within 10 years of the acute event [7]. The dynamic natural history of anxiety after stroke has also been observed in other studies that reported that up to 40 % of patients with anxiety in the

first few months after stroke remained anxious 4–8 months later and up to 11 % of patients not anxious at 2 months became so 2–4 months later [66, 67]. Anxiety has also been reported to be associated with depression and poor quality of life in the long term after stroke [1, 7].

Detection of Anxiety After Stroke

In view of the frequency of anxiety among stroke survivors, its onset shortly after the acute event, and its strong association with depression, an assessment for anxiety within 6 weeks of stroke may be beneficial. Conducting an assessment for depression and anxiety in the same clinical interview may also help to approach patient mood holistically and plan appropriate clinical management.

A thorough clinical assessment is the foundation of diagnosing anxiety. An anxious patient can appear restless, irritable, or fatigued. Patients with anxiety may also have unexplained physical symptoms, such as chest pain and tachycardia. No laboratory testing is necessary to diagnose anxiety [68]. The diagnosis requires training, as anxiety and depression may not be easy to differentiate, and in many cases both disorders present simultaneously. Furthermore, a focus on somatic symptoms may distract patients and doctors from the psychological symptoms [65]. To improve detection and treatment of anxiety, the International Consensus Group on Depression produced two screening questions: 'During the past 4 weeks, have you been bothered by feeling worried, tense, or anxious most of the time?' and 'Are you frequently tense, irritable, and having trouble sleeping?' [69] However, it is not known how sensitive or specific these questions are [65]. A systematic review identified eight screening tools tested to detect anxiety after stroke; however, the actual clinical utility of all of them was uncertain [70].

Different predictors of anxiety after stroke have been investigated. It has already been mentioned that anxiety seems to be strongly associated with depression [1, 7]. The association between disability and anxiety reported in the literature is less consistent [1]. Therefore, when assessing patients, clinicians should pay particular attention to those showing symptoms of depression, and also to those with severe disability, who may be at highest risk of anxiety disorders. For the same reason, all patients diagnosed with anxiety should be assessed for depression and its adverse health outcomes [33]. While in the general population anxiety is associated with age 45–59 and female gender [65], most studies observing stroke patients reported no association between anxiety and age or gender [1]. Stroke location is also not associated with anxiety [1].

Management of Anxiety After Stroke

The NICE guidelines for GAD in the general population recommend providing information to patients about the diagnosis as early as possible to help them understand the disorder and start effective treatment promptly. When symptoms are not

improved after education and active monitoring, individual self-help or psychoeducational groups may be arranged [71]. For people with GAD and marked functional impairment or those who don't respond to these interventions, individual psychological intervention or drug treatment should be considered. There is no evidence that either mode of treatment is better [65]. It is also unclear whether the combination of drugs and psychotherapy is better than using one strategy alone [65]. If a patient chooses a psychological intervention, either cognitive behavioural therapy (CBT) or applied relaxation should be offered. CBT combines cognitive therapy – which focuses on monitoring thoughts and understanding self-perpetuated cognitive distortions, habitual thought patterns, and subsequent behaviours – with behavioural therapy, which aims to expose the patient to feared experiences (originally, phobias). CBT is usually provided by a specially trained psychotherapist on an individual basis, with 6–12 sessions of 1 h duration as standard. Some studies suggest that CBT can be delivered over the Internet, but how it compares to office-based CBT is unclear. Several other psychotherapeutic approaches can be combined with CBT [65], such as relaxation response training, acceptance-based behavioural therapy, emotion regulation therapy, and psychodynamic psychotherapy. Education on sleep hygiene, physical exercise, or self-help books or manuals may also be useful [65].

If a person prefers to be treated with drugs, sertraline is recommended by NICE as the initial treatment for GAD in the general population [71]. If sertraline is ineffective, an alternative SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) should be offered. Venlafaxine and duloxetine are SNRIs that are both licensed in the United Kingdom for GAD [65]. A recent Cochrane review on interventions for anxiety after stroke suggested that both paroxetine and buspirone are effective for treating anxiety after stroke [72]. Combining paroxetine and psychotherapy did not confer any significant additional benefit for stroke patients. Both paroxetine and buspirone have reported side effects including nausea or dizziness. However, the true level of effectiveness is uncertain due to the small number of trials available and their methodological limitations. The authors of the review concluded that there is insufficient evidence to guide practice in treating anxiety after stroke.

RCP stroke guidelines recommend that patients who are provided with antidepressants for anxiety after stroke should be monitored for adverse effects and treatment continued for at least 4 months beyond initial recovery. If the patient's mood has not improved 2–4 weeks after initiating treatment, and compliance with medication is appropriate, the dose may be increased or an alternative antidepressant may be employed [33]. NICE guidance on GAD suggests that pregabalin can be offered as an initial option for patients who cannot tolerate SSRIs or SNRIs. Benzodiazepines have confirmed efficacy primarily for the short-term treatment of GAD. NICE guidance recommends that they are offered for the treatment of GAD only as a short-term measure in crises. Antipsychotics are not recommended for GAD in primary care [71].

Referral to a mental health specialist should be considered when a patient has severe symptoms with marked functional impairment and risk of self-harm, significant co-morbidity, personality disorder, self-neglect, or an inadequate response to

previous interventions. The therapeutic approach should be guided by the person's preference [71]. However, it should be borne in mind that many recommendations do not account for the specific clinical situation of stroke patients [71]. Furthermore, most stroke teams may not have the resources to provide these services, especially psychotherapy. More research is required for the development and delivery of pharmacological and non-pharmacological interventions for anxiety after stroke, both in primary and secondary care.

Emotionalism

Emotionalism has been defined as unstable emotional experiences and frequent mood changes, with emotions that are easily aroused, intense, or out of proportion to events and circumstances [12]. Emotionalism is also called emotional lability, emotional incontinence, pathological laughing or crying, involuntary emotional expression disorder, emotional dysregulation, and pseudobulbar affect. Patients report that episodes of emotionalism are at best only partially subject to voluntary control, and unless they are cognitively impaired, they judge their emotional display as inappropriate and out of character [73]. Emotionalism is therefore a distressing and embarrassing problem that may lead to social avoidance and impaired quality of contact with friends and family. The prevalence of emotionalism after stroke varies across studies between 11 % and 52 % [4, 74–79]. Symptoms of emotionalism appear to start shortly after the acute event, and studies have shown prevalence to change with time after stroke, with one study reporting emotionalism in 13 of 89 patients (15 %) at 1 month, 25 of 119 patients (21 %) at 6 months, and 12 of 112 patients (11 %) at 12 months [4, 77].

Pathological crying seems to be more common than pathological laughter [4, 74, 79]. It can be triggered by discussion of sad realities, including the prognosis of the disease, sentimental stimuli such as visits of relatives, or the discussion of emotionalism itself [4]. Emotionalism has been observed to be associated with female gender, severe motor dysfunction [80], past medical history of depression [74], and cognitive impairment [4, 75]. A number of biological and anatomical predictors of emotionalism have also been reported, including ischaemic strokes, anterior cortical events [80], single lesions located in anterior regions of the cerebral hemispheres [81], lesions in the left frontal and temporal regions [4], and thalamic microbleeds [75]. However, while this evidence is valuable, the reduced number of studies and the small number of patients assessed in most of them make the predictors of emotionalism after stroke a matter of further research.

Patients and their relatives may be unaware of the existence of emotionalism in the context of stroke. However, given its frequency, numerous patients might benefit from its adequate identification and management. If clinicians do not ask specifically about symptoms of impaired emotional regulation, these symptoms may be unrecognised or misinterpreted as a symptom of a mood disorder [73]. RCP guidelines recommend that stroke survivors who persistently cry or laugh in unexpected

situations, or who are upset by their fluctuating emotional state, should be assessed by a specialist or member of the stroke team trained in the assessment of emotionalism [33]. Assessment scales developed specifically for emotionalism may be useful in clinical trials and to screen patients. However, the diagnosis of emotionalism should be based on clinical assessment [73]. A single screening question regarding the presence of frequent laughing or crying spells may be sufficient to identify patients with emotionalism. Once the patient's answer is confirmatory, a full clinical assessment should follow to investigate whether the patient's uncontrollable episodes of laughing or crying are actually emotionalism or an underlying mood disorder. Patients with emotionalism exhibit the emotional display in the absence of depressed mood or symptoms of mania. It should also be noted that although emotionalism and mood disorders appear to be different clinical entities, they may coexist in the same patient [73].

When the diagnosis of emotionalism is made, patients should be appropriately distracted from the provoking stimuli [33]. A Cochrane review of pharmacological interventions to treat emotionalism after stroke reported that antidepressant treatment reduced the frequency and severity of symptoms, but several methodological deficiencies in the studies were observed [82]. Most trials were small, had short duration, and inadequate concealment of the randomisation sequence. It is not possible to estimate accurately the benefits and risks of antidepressants on patients with emotionalism after stroke. Use of antidepressant treatments for persistent emotionalism is recommended by RCP guidelines [33]. However, evidence is lacking on the type of antidepressants, dose, and duration of treatment. The frequency of crying, effectiveness of the treatment, and possible side effects should be monitored. If the emotionalism has not improved 2–4 weeks after initiating treatment, and compliance with medication is adequate, an increase in dose or change to another antidepressant should be considered [33].

A thorough understanding of the aetiology and pathophysiology of emotionalism after stroke needs further research, looking at the biopsychosocial basis of human emotion. Meanwhile, the recognition, diagnosis, and treatment of this clinical entity is important to help patients and their carers improve their quality of life and relationships. No systematic reviews on the natural history predictors and outcomes of emotionalism after stroke have been published. It would be useful to have information on longer-term frequency and relapse rates in future studies. Further trials of high quality, investigating the effect of antidepressants in people with emotionalism after stroke, are also required.

Conclusion

Mental health disorders such as depression, anxiety, and emotionalism are common among stroke patients. These are distressing problems on their own, and they are also associated with other adverse outcomes. The detection and clinical management of mental health disorders is part of the routine care of stroke patients.

Therefore, clinicians who see stroke patients regularly should have the required skills to manage depression, anxiety, and emotionalism appropriately. A good coordination of the multidisciplinary teams across primary and secondary care is also essential to provide healthcare of good quality to stroke patients with psychiatric conditions. A number of interventions, including the provision of adequate information, psychotherapy, and antidepressants, should be considered for the management of depression, anxiety, or emotionalism after stroke. The development of more effective interventions to prevent and treat these problems is required. Such interventions are likely to improve the overall prognosis of stroke.

Patient Questions

Q. What are the possibilities of having depression, anxiety, or emotionalism after stroke?

A. Over 50 % of patients have depression, anxiety, or emotionalism at some point after stroke. In most cases, symptoms start shortly after stroke.

Q. What is the prognosis of these problems?

A. Depression and anxiety may be chronic and recurrent problems in the long term after stroke. Depression after stroke can lead to higher mortality and disability rates, lower quality of life, poor life satisfaction, and need for institutional care. Anxiety can lead to depression and lower quality of life. The prognosis of emotionalism is not known.

Q. Can my doctor help me with depression, anxiety, or emotionalism?

A. Your doctor should be able to diagnose these problems, in most cases without the need for any further tests. Treatments for depression, anxiety, and emotionalism, involving medication or psychotherapy, are available. You should discuss with your doctor what is the best option for you and what are the effects that can be expected from the treatment.

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Chapter 16
Future Developments

Lalit Kalra

Abstract The past decade has witnessed major advances in stroke care, but stroke continues to remain a major cause of death and the most common cause of adult physical disability. This chapter presents an overview of selected future developments which will have an impact on reducing stroke-related complications. Foremost amongst these is the prevention of post-stroke pneumonia, and the chapter discusses the difficulties in diagnosing post-stroke pneumonia and various interventions to reduce its incidence. Brain injury is a major consequence of stroke; imaging methods that may provide insight into repair mechanisms and their modulation using physical therapy, pharmacological interventions, and stem cells are discussed. Motor impairment is a major complication after stroke, and a commentary on the role of bi-hemispheric interactions and interventions for modulating this interaction to reduce impairments is given. Monitoring of stroke-related complications and their consequences is also important for reducing their incidence and quality assurance, and this chapter highlights ongoing initiatives and the use of health information technology to meet some of the challenges in improving stroke care.

Keywords Post-stroke pneumonia • Brain injury • MR imaging • Regeneration • Stem cells • Non-invasive brain stimulation • Monitoring and quality assurance • Health information technology

Introduction

The past decade has witnessed major advances in stroke care, notable amongst these being the advent of reperfusion treatments to reduce ischaemic damage to the brain, the widespread introduction of stroke units to prevent stroke-related complications and improve outcomes, and neurosurgical interventions to reduce mortality in patients with malignant infarcts or severe haemorrhagic strokes. Advances in vascular risk and carotid disease management, anti-thrombotic treatments, and anticoagulation in atrial fibrillation (to name a few) have also significantly decreased stroke incidence.

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Developments in imaging, especially the wider availability of multimodal CT and MR scanning, have allowed targeted delivery of interventions for prevention and treatment of acute ischaemic stroke and reducing the risk of haemorrhagic stroke due to vascular pathology or the use of anti-thrombotic agents. Despite these advances, stroke continues to be a major cause of death and the most common cause of adult physical disability. Residual brain damage (even after successful reperfusion) remains a major cause of impairments, and debate and controversy continues to exist over the best interventions to manage these impairments. The ability to monitor quality of care in preventing post-stroke complications and improving outcomes also remains a major concern for policymakers and healthcare providers.

This chapter presents an expert view of selected areas of development which will have a major impact on mitigating the consequences of stroke in the future and will concentrate on

- The definition and diagnosis of post-stroke pneumonias and their prevention
- Imaging as a tool for understanding processes involved in recovering from brain injury
- Current concepts in reducing the motor deficits after stroke that may have implications for other impairments
- The use of health information technology to monitor complications and drive up the quality of stroke care

Post-Stroke Pneumonia

Diagnosis of Post-Stroke Pneumonia

Pneumonia frequently complicates stroke and has a major impact on outcome. However, diagnosis of pneumonia in stroke is difficult because presentation may be non-specific, blood results may reflect concomitant pathology, and routine radiological examination or microbiological sampling may not be possible or performed. It is not surprising that the incidence of post-stroke pneumonia ranges from 2 % to 57 % in different studies, with a median incidence rate of 10 % (IQR 6.4–16.2 %) [1]. Patients who develop post-stroke pneumonia have higher mortality, longer length of hospital stay, worse rehabilitation outcomes, and higher care needs after discharge [1, 2]. Whilst most of the information in meta-analyses comes from studies during the first weeks after stroke, mainly during inpatient stays, longer-term studies in stroke patients have shown even higher incidence in stroke survivors of up to 20 % in the first 6 months [3]. The wide variations in the incidence rates for post-stroke pneumonia reflect not only the diversity of settings and patient populations in which these studies were undertaken but also the diversity in the criteria used to diagnose post-stroke pneumonia. A recent systematic review of studies on the diagnosis of stroke-associated pneumonia undertaken by the international Pneumonia In Stroke ConsEnsuS (PISCES) group concluded that the diagnostic approaches to pneumonia in stroke vary considerably, with less than a third of the studies having

used objective standardised criteria based on previously published criteria or guidelines and more than 60 % using ad hoc criteria, clinician-reported diagnosis, or initiation of antibiotics as evidence of infection [4]. Furthermore, biomarkers such as white cell counts and C-reactive protein have little more to add to the diagnostic conundrum, as stroke itself or other co-morbidities may be responsible for elevated levels. Hence, one of the first challenges for the future being addressed by the PISCES group is to agree to common terminology, diagnostic criteria, investigative approach, and guidelines to antibiotic initiation for this commonly encountered spectrum of lower respiratory tract infections complicating management of stroke patients.

Prevention of Post-Stroke Pneumonia

The most frequently reported risk factors for post-stroke pneumonia are older age, male sex, increasing stroke severity, reduced level of consciousness, the presence of swallowing difficulty, and the absence of cough [2]. The relation between dysphagia and cough in the incidence of post-stroke pneumonia is of particular interest. Dysphagia is associated with a 2- to 3-fold increase in risk of pneumonia after stroke, which increases further to 5- to 11-fold with the presence of aspiration [5]. Cough is protective; the lack of reflex cough after swallowing has been associated with an eightfold increase in the risk of post-stroke pneumonia [6]. It is not surprising that the most widely used strategy for the prevention of post-stroke pneumonia is the routine screening of stroke patients for swallowing difficulty, coupled with the implementation of dysphagia management strategies. There is some evidence to suggest that these measures can halve the risk of developing post-stroke pneumonia in dysphagic stroke patients [7, 8]. On the other hand, there is very little research on the role of cough in preventing post-stroke pneumonia or its consequences.

In addition to screening for dysphagia, other measures may further reduce the incidence of post-stroke pneumonia based on different patho-physiological and clinical justifications. Pharmacological approaches include the preventive administration of antibiotics to reduce fever and infection [9], the use of angiotensin-converting enzyme (ACE) inhibitors to improve reflex cough sensitivity [10], selective decontamination of the digestive tract to minimise exposure to pathogens [11], and pharmacological agents targeting stroke-induced immuno-suppression [12]. Non-pharmacological strategies include elevated positioning to prevent aspiration, intensive oral hygiene and dental treatment to reduce oro-pharyngeal colonisation with pathogens [13], passive mobilisation and re-positioning regimens to improve lung ventilation and airway clearance [14], and respiratory muscle training to improve respiratory muscle strength and peak cough flows aimed at facilitating rapid expulsion of aspirate from the bronchi [15].

Preventive use of antibiotics to reduce post-stroke pneumonia has merited considerable attention. A recently published meta-analysis included 5 randomised controlled trials that included 506 patients, 248 of whom were randomised to preventive

antibiotic therapy and 258 to control groups. Pooled analysis showed a non-significant reduction in mortality (13 % versus 15 %, RR 0.85, 95 % C.I. 0.47–1.51) and dependence (47 % versus 61 %, RR 0.67, 95 % C.I. 0.32–1.43) with preventive antibiotics [9]. The incidence of infections was, however, reduced significantly (22 % versus 36 %, RR 0.58, 95 % C.I. 0.43–0.79). The analysis was limited by small sample sizes and heterogeneity in study population, design, type of antibiotics used, and definitions of infection. Only 29–41 % of included patients in these studies were dysphagic, and it is not clear whether positioning and feeding strategies to prevent aspiration were being implemented in addition to antibiotic interventions. More importantly, critical adverse events such as toxin-positive Clostridium difficile (C diff) or methicillin-resistant staphylococcus aureus (MRSA) incidence related to antibiotic use were not evaluated in these studies.

The effectiveness of preventive use of antibiotics is being investigated in two large multi-centre trials (the Preventive Antibiotics in Stroke Study [16] and the Antibiotics to Reduce the Incidence and Consequences of Post Stroke Pneumonia Study [17]), which will be reporting their findings imminently. Other strategies have not been researched in any great depth but merit further investigation in future studies. Further research is also needed on strategies to prevent pneumonia in patients with long-standing swallowing problems or those with nasogastric tubes in whom the physiology may be different and on safety issues associated with prolonged antibiotic use.

Post-Stroke Brain Injury

Understanding Recovery After Injury

Recent years have seen significant advances in reperfusion techniques and acute care on specialist units aimed at reducing brain damage. Despite these advances, injury to the brain and consequent disability remain the most salient complications after stroke. It is estimated that 50 % of survivors have residual deficits and up to 30 % have permanent disability [18]. Recent studies show that the adult brain has capacity to reorganise after injury, and processes such as neovascularisation and neuronal plasticity in the unaffected areas around the injury contribute to limitation of impairments and recovery [19, 20]. Angiogenesis triggered by hypoxia in unaffected ipsilesional areas is an early event in plasticity, which promotes neurogenesis and neural cell migration [21]. In post-mortem studies, increased capillary density in peri-infarct areas has been associated with longer survival [22], and in vivo arterial spin labelling (ASL) studies have shown that increased perilesional perfusion correlates with tissue recovery in stroke survivors [23].

Developments in MRI have provided a non-invasive technique for monitoring changes in the recovering brain; most studies have focused on functional imaging or changes in lesion microstructure and its connections [24]. These studies have shown that motor recovery in stroke patients is associated with activation in the peri-infarct cortex and supplementary areas of the affected side and also in additional regions

including the ipsilesional sensorimotor and premotor cortex [25]. The cerebellum, thalamus, and prefrontal areas are also known to play an important part in restoration of function. The process of reorganisation is dynamic, and an evolution of changes with time and several different patterns have been described. These include activation of bilateral cerebellar and prefrontal areas, an initial increase followed by a decrease in activation of motor areas, and progression from early contralesion activity to late ipsilesional activity. Recent studies in acute recovery have also shown that the integrity of the corticospinal tract system is critical for motor recovery within the first 4 weeks of stroke, irrespective of involvement of the somatosensory system [26].

The complementary method of Proton Magnetic Resonance Spectroscopy (1H-MRS) provides the opportunity to study changes in metabolites as a window into neural repair, which may be more sensitive and provide greater information on repair processes [27]. N-acetylaspartate (NAA) is synthesised in neuronal mitochondria and is considered a good marker for neuronal integrity. A 1H-MRS signal at 1.28 parts per million (ppm) has been suggested as an exclusive biomarker of adult neural progenitor cells but needs confirmation [28].

Longitudinal studies suggest that evolution of injury may continue beyond the acute insult. A progressive decrease in NAA concentrations over 12 weeks, indicative of progressive neuronal loss, has been seen in infarcted areas in acute stroke patients [29]. Progressive neuronal loss may be present in areas remote from the infarct and from the time of injury; diffusion tensor imaging has shown progressive increase in diffusivity in the unaffected ipsilesional thalamus between 1 and 6 months after stroke [30]. Stroke patients have been shown to have lower NAA and higher myo-inositol concentrations in spared ipsilesional areas compared with healthy controls 6 months post stroke, which correlated with the extent of residual motor impairment [31].

Hence, stroke recovery is a complex interplay of evolving injury and regenerative processes consisting of vascular, neuronal, and microglial events occurring not only within areas directly involved in injury but also in spared regions. A limitation of existing studies is that most have either concentrated on evolution of injury or on regeneration but not on both simultaneously, or used single modalities in isolation. Although the majority of physiological processes involved with recovery may occur in the intact perilesional areas, most human studies have concentrated on structural characteristics of the lesion and its direct connections. New research that combines different modalities to follow in vivo the complex events associated with recovery, not only in infarcted but in other areas of the brain, will provide insight into endogenous repair mechanisms, which can be used to predict recovery after stroke or identify potential therapeutic targets.

Enhancing Post-Stroke Regeneration

Regenerative treatment approaches provide a novel intervention strategy that potentially has the capacity not only to modify disease pathology but also to repair and reverse damage. Given the emerging data on the longer-lasting effects of acute

ischaemia [29, 30], early reperfusion with thrombolytic agents or endovascular procedures remains the only available intervention to limit progressive post-ischaemic neuronal loss and reduce complications due to impairments after stroke. Preclinical studies show that cell-based and pharmacological therapies can both enhance brain repair processes substantially and improve functional recovery [20]. Cell-based therapies under investigation include use of bone marrow mesenchymal cells, cord blood cells, foetal cells, and embryonic cells. Pharmacological treatments of interest include already available growth factors such as erythropoietin and granulocyte colony-stimulating factor, drugs such as sildenafil, statins, nicotinic acid, minocycline, cholinesterase inhibitors, or fluoxetine, and novel agents such as cannabinoid CB2 receptor agonists or retinoids. These agents are known to result in a threefold or greater increase in neurogenesis in rodent models, but their potential in humans is not known. Nevertheless, these are extremely attractive candidate 'regenerative' therapies for stroke which, if proven in animal models, can be rapidly progressed to clinical trials and translated into clinical practice.

Translating cellular or pharmacological regenerative treatments proven to be successful in animal models for human use presents several challenges [20]. Although the success of stem cell implantation in experimental studies offers exciting opportunities for stroke repair, safety issues, including tumour formation and immune rejection, as well as ethical and technical challenges, have hampered progress of such treatments into clinical practice. Pharmacological treatments to modulate endogenous neurogenesis have their own ethical and technical challenges, but many are known to be safe as they are already in human use for other indications with known safety/tolerability profiles. At present, there are at least two ongoing stem cell therapy studies and a few studies of pharmaceutical modulators of neural repair in Phase II of development in the United Kingdom.

Post-Stroke Loss of Motor Function

Loss of motor function and the ability to walk or participate in daily living activities is a major complication of stroke, seen in about 50 % of survivors. Imaging research has shown that brain reorganisation responsible for motor recovery is a dynamic process involving not only the affected motor areas but also primary and supplementary motor areas on the contralesional side. It is now known that all muscles receive cortical outputs from both the right and the left hemispheres, but contralateral cortical outputs strongly dominate in health, and there is interaction between the two sides of the brain with transcallosal inhibition of the weak ipsilateral outputs by the contralateral hemisphere during normal activity. In stroke, interhemispheric transcallosal inhibition of the contralesional hemisphere from the ipsilesional hemisphere is decreased because of injury, resulting in the unveiling and/or recruitment of the functionally silent ipsilateral motor pathways from the contralesional unaffected hemisphere to the affected side of the body, and unopposed inhibition of mechanisms for recruitment of surviving contralateral motor pathways in the

affected hemisphere [32]. However, the recruitment of ipsilateral motor pathways from the unaffected hemisphere and inhibition of the dominant contralateral motor pathways that would normally be responsible for motor function is not always a harbinger for good recovery. Ipsilateral motor pathways to the same side of the body as the hemisphere have additional synapses, low fibre density, and little output to upper limb muscles. A poor motor outcome is more often seen in stroke patients who recover by ipsilateral pathways from the contralesional hemisphere compared with those recovering through perilesional motor reorganisation and activation of the contralateral pathways [33]. Stroke patients with the most successful recovery of motor function are those whose patterns of brain activity are comparable with healthy volunteers in stroke studies [34]. Hence, there is a strong case to support research on interventions that inhibit contralesional motor cortex and facilitate ipsilesional motor cortex activity for reducing the consequences of damage to the primary motor regions following a stroke and improving recovery in hemiparetic stroke patients.

The imbalance between hemispheres caused by unilateral damage following stroke may be addressed by several different techniques, using either the time-honoured physical therapy treatments or the newer, emerging non-invasive brain stimulation (NIBS) techniques. Of the physical therapy interventions, constraint-induced movement therapy (CIMT) has been most extensively investigated. It is based on the assumption that immobilisation of the unaffected side will prevent learned 'non-use' and promote use of the affected limb resulting in faster (and more complete) recovery. In the seminal Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial [35], CIMT was associated with statistically significant and clinically relevant improvements in arm motor function that persisted for at least 1 year. In fact, recovery in some domains was comparable with non-stroke controls. Another technique, bilateral movement training, which is aimed at balancing cortico-motor outputs between the affected and the unaffected hemispheres, has also shown to be effective in improving functional and mobility outcomes in stroke patients [36].

Despite both these and other similar techniques finding favour in clinical practice, there are several questions that remain unanswered and merit further investigation. The practicality and the cost-effectiveness of CIMT in clinical practice remains unproven [37], and a meta-analysis has suggested that recovery with CIMT is proportional to the amount of exercise given to the affected limb; it may be possible to achieve comparable benefits by less hazardous and less frustrating conventional therapy methods [38]. Similarly, several bilateral motor techniques do not appear to have significant benefits over conventional therapy in many domains, and their overall effectiveness remains unproven [39]. In addition, there continue to be controversies regarding patient selection, type and intensity of therapy, and clinical meaningfulness of improvements observed on impairment scores that still need resolution.

An alternative approach is to supplement conventional therapies aimed at restoring inter-hemispheric balance with NIBS. NIBS is a generic name for a range of stimulation techniques including excitatory stimulation of the ipsilesional

hemisphere, inhibitory stimulation of the contralesional hemisphere, or both, using either repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) [40]. A review of the use of rTMS in post-stroke motor deficits showed that both low-frequency rTMS to restore inhibition, applied over the unaffected hemisphere, or high-frequency rTMS to reactivate hypoactive regions of the affected hemisphere were associated with functional recovery [41]. There was great variation regarding the number of rTMS sessions required for a sustained effect and the timing of rTMS application after stroke. On the other hand, rTMS used as an adjuvant to constraint-induced therapy for upper limb hemiparesis had little effect on motor learning in a group of stroke survivors over and above constraint-induced therapy [42].

Small clinical studies have demonstrated that anodal tDCS stimulation results in modest motor improvements in stroke patients that outlast the period of stimulation. Similarly, downregulating excitability in the contralesional motor cortex in chronic stroke patients has also been associated with improvements in motor function [43]. Simultaneous stimulation of the ipsilesional cortex, with inhibition of the contralesional motor area, has shown mixed results; one study showed significant motor gains [44], whilst another showed a greater effect with anodal and cathodal stimulation compared with bilateral stimulation [45]. There is also evidence that the gains in motor recovery with different NIBS techniques vary between individuals with subcortical versus cortical strokes [40].

Despite these early proof-of-principle studies, there is no agreement on the extent or universality of these beneficial effects, and well-controlled multicentre randomised clinical trials are required to assess this issue. Further research is also needed to determine the most effective paradigms for NIBS and the most appropriate patient population for these interventions. The use of NIBS in conjunction with other methods like neuroimaging or genetic analyses may also prove particularly useful, not only to study what NIBS does to distributed brain activity but also to identify predictors of response to NIBS interventions.

Information Technology in Patient Care and Research

A challenge in preventing complications related to stroke and adverse events of specific treatments is access to information on their incidence and consequences for patients. This information can also help to drive the quality of treatments and services being provided, thus reducing their incidence or limiting the damage caused when complications occur. The Sentinel Stroke National Audit Programme (SSNAP) and preceding National Stroke Audits have shown how access to patient-level and systems-level health information can help to meet these challenges of providing affordable, high-quality, and effective stroke care that meets the needs of individuals and populations [46]. The SSNAP has the advantages of collecting clinical information at the patient level, with emphasis on processes of care across healthcare providers nationally in real time, which can be used for patient care,

assessment of practice variation, and clinical risk, pharmacovigilance, quality assurance, and assessments of comparative efficacy of different interventions to prevent complications. Such databases can contribute to shaping health policy, planning towards reducing stroke-related complications, and providing cost-effective stroke care, as has been demonstrated in the Stroke Improvement Programmes [47].

The first requirement of any stroke database that captures personal clinical and health information is that it should contribute towards reducing complications and promoting favourable outcomes by the optimisation of effective, efficient, safe, and timely delivery of direct healthcare to individuals. As shown in stroke audits, these data management systems have helped to improve investigations, optimised clinical care, aided communication processes between professionals, and prevented complications and poor outcome in stroke patients. The second requirement of a national database is that it should be available for secondary use to encompass activities such as quality and safety measurement, accreditation of units to deliver quality care with minimum complications, and research into improving outcomes. Secondary use of stroke care data can also enhance healthcare experiences for individuals, expand knowledge about complications and appropriate treatments, strengthen understanding about effective and efficient prevention and management of complications, and support the public health goal of reducing stroke mortality and morbidity. An area of much debate is the amount and types of data that are needed to be meaningful for delivering real-time safe healthcare and also be suitable for secondary use as defined above. Every single stroke episode for an individual generates thousands of data items and is open to capture of inaccurate information by the user and omissions or inaccuracies that are likely to multiply exponentially with the volume of data collected [46]. The cost of collecting and analysing data is significant and can often become a limitation in capturing good information. Hence, potential solutions are needed to develop methods that capture the most relevant data consistently, accurately, and cost-effectively to improve stroke care in the coming years.

Large databases such as the SSNAP can also contribute to health services changes aimed at preventing complications and improving outcomes. Much of the current evidence base for stroke care depends on the results of randomised trials, but these carefully controlled studies with very specific inclusion criteria and protocol-driven treatments do not adequately account for the variability seen in actual care [48]. Pragmatic information is needed to compare the effectiveness and safety of treatments in 'real-life' settings that incorporate variations in patient populations and management to make sound healthcare decisions. Databases such as the SSNAP can contribute to this process, but, as above, their contribution is dependent upon the quality and comprehensiveness of the clinical data collected. Studies have shown that such systems suffer from systematic biases of accuracy and quality inherent to data collected primarily for clinical care [49] and the challenge is to set up adequate training, effective governance structures, regulatory policies, and properly aligned organisational incentives for supporting these systems. It is also important how data collected routinely during patient care are analysed. The process of clinical care introduces treatment bias, in which the statistical association between therapy and outcome is confounded by measured and unmeasured factors that influence both the

choice of treatment and the likelihood of the outcome [50]. Nevertheless, the application of health information technologies will have a lot to contribute to enhancing physician performance, reducing complications, and improving patient outcomes in the future.

Conclusion

No single chapter can address all the developmental issues or the ongoing research and clinical initiatives that will have a major impact on reducing the future burden of stroke. However, this chapter covered selected major developments and initiatives that are likely to have an impact on making stroke care safer and more effective over the next few years. The topics covered are by no means exhaustive; there are many other areas where there will be important developments. There are several ongoing studies assessing the haemorrhagic risk in ageing brains that will have an important impact on safe thromboprophylaxis. There is no hard evidence to date to guide anticoagulant practices after an acute stroke; for example, the safest and the most effective time to start anticoagulation in patients with atrial fibrillation and stroke is still not known. There is need for further research and good evidence on reperfusion interventions in patients with stroke who do not have a known time of onset and on the benefits of endovascular interventions during and beyond the accepted time window for intervention.

What is known is that stroke research and clinical care have come a long way in the past decade, and there is no doubt that there will be major game-changing innovations over the next 10 years.

Patient Questions

Q. Why is the correct diagnosis of pneumonia important in stroke, and why can antibiotics not be given to all stroke patients without procrastination?

A. Stroke patients have greater susceptibility to pneumonias because of poor mobility, weakness of chest muscles, and swallowing problems. Pneumonias in stroke patients can be life threatening and are responsible for poorer recovery and longer time in hospitals. Yet, pneumonia in stroke patients can be difficult to diagnose because many patients may not have typical features of pneumonia, and many blood tests can be abnormal because of stroke per se rather than pneumonia. Although giving antibiotics to everyone may seem a simple solution, the use of antibiotics themselves is not without problems. In addition to the side effects that all drugs, including antibiotics, may have in some people, there is a real risk that with indiscriminate use, some patients will develop diarrhoea due to organisms such as Clostridium difficile that have high morbidity and mortality or succumb to infections that are resistant to antibiotics. This potential of harm can only be reduced by judicious use, and we need research to tell us who to treat and when to treat.

Q. What can we do to increase brain repair after stroke? Will administration of stem cells after stroke significantly reverse the damage to the brain?

A. The most effective and proven method to improve brain repair after stroke is rehabilitation given by a specialist multidisciplinary team working towards specific goals identified by patients. Stimulating an injured brain to do what it is supposed to be doing encourages neurogenesis to overcome the damage. It very much is a question of 'use it or lose it', and the amount of recovery depends upon the intensity of the activity being performed. However, as the brain is learning, it needs to be taught the right way of doing things for which specialist therapy input is needed. There are several other methods to complement this treatment, including the use of special devices and techniques and, now, stem cells. Although there is nearly a decade of experience of stem cell research in animals, human applications are only now being tested, and it will be some time before their full potential in stroke patients will be clear.

Q. How can we monitor complications after stroke and ensure that all patients receive the best possible care?

A. The best way to monitor complications after a stroke is to manage all stroke patients on specialist units dedicated to stroke care, where all the staff are trained in the prevention, detection, and treatment of stroke complications. Management of stroke is a multidisciplinary activity with involvement of doctors, nurses, therapists, psychologists, dieticians, and many other professionals, working together and with a common aim. Robust research has shown that such units significantly reduce complications, mortality, duration of hospitalisation, and institutionalisation. On the positive side, patients managed on such units have better functional abilities, psychological health, and quality of life after stroke compared to those managed in other settings.

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