Chapter 16
Future Developments

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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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A. Bhalla, J. Birns (eds.), *Management of Post-Stroke Complications*,
DOI 10.1007/978-3-319-17855-4_16

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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