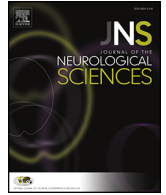




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## Review article

## Gastrointestinal complications after ischemic stroke

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## ABSTRACT

Ischemic stroke is an important cause of morbidity and mortality, and currently the leading cause of adult disability in developed countries. Stroke is associated with various non-neurological medical complications, including infections and thrombosis. Gastrointestinal complications after stroke are also common, with over half of all stroke patients presenting with dysphagia, constipation, fecal incontinence or gastrointestinal bleeding. These complications are associated with increased hospital length of stay, the development of further complications and even increased mortality. In this article we review the epidemiology, pathophysiology, diagnosis, management and prevention of the most common gastrointestinal complications associated with ischemic stroke.

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## 1. Introduction

Each year close to 17 million new strokes occur worldwide, representing an important public health burden, with the majority of

events causing permanent disability or death [1,2]. Although stroke mortality appears to be decreasing slightly in both high and low income countries, incidence is increasing. In 2010, there were 33 million stroke survivors and 5.9 million stroke-related deaths [1].

In the United States alone there are over 750,000 strokes each year (with approximately 610,000 of these being first attacks), and it is estimated that on average, every 40 s, someone in the United States has a

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stroke and one dies approximately every 4 min. In the United States, estimated health-care costs associated with stroke are close to \$70 billion, and it is currently the fourth cause of death and the first cause of long term disability [3,4].

Medical complications such as pneumonia and deep vein thrombosis are common after stroke, and can lead to increased morbidity and mortality. Gastrointestinal (GI) complications have received much less attention, but as many as 50% of stroke patients can present either dysphagia, constipation or GI bleeding [5,6] (Table 1). Recent studies suggest that GI complications can also contribute to increased length of stay, dependence, poor neurological outcome and even death (Table 2). These events present a major challenge to patient care, public health systems and rehabilitation providers. The purpose of this article is to review the problem of GI complications associated with ischemic stroke and discuss evidence-based management strategies for prevention and intervention.

## 2. Dysphagia

Dysphagia is one of the most common and widely studied GI complications of ischemic stroke. Around 30% to 70% (incidence depends on population factors as well as screening techniques) of patients with ischemic stroke present some kind of neurogenic dysphagia [7–9]. Dysphagia has emerged as an important cause of post-stroke malnutrition and pneumonia, and a major cause of post-stroke mortality [9]. Studies have shown that ischemic stroke mortality and disability are independently associated with the development of dysphagia [10,11] (Table 3). Oral and pharyngeal transit times are both affected in patients with post-stroke dysphagia. In a study of 40 post-stroke patients with dysphagia and swallowing difficulties, pharyngeal transit time was increased six-fold compared with controls [12]. Prolonged pharyngeal transit times seem to be selectively associated with risk for aspiration, especially for boluses with high viscosity [13].

Cerebral ischemia may lead to an interruption of the brain–gut axis, and to alterations in the neural circuits controlling various GI functions [5,6]. Advanced functional imaging studies have shed light on the cortico-medullar control of the GI tract, suggesting a multifocal bilateral neural circuit with no apparent hemispheric dominance [5,6]. In general, ischemic stroke involving the middle cerebral artery or bilateral hemispheric ischemic stroke is associated with a higher incidence and severity of dysphagia and related symptoms [10], and aspiration is more common in patients with brainstem [14–16], insular cortex and internal capsule lesions [17].

### 2.1. Treatment of post-stroke dysphagia

The options available for treatment of post-stroke dysphagia are limited, but the utility of transcranial magnetic stimulation (TMS) has been evaluated in small studies. In a study of 26 patients with monohemispheric ischemic stroke with post-stroke dysphagia randomized to receive either repetitive TMS to the affected motor cortex or

**Table 1**  
Incidence of gastrointestinal complications of ischemic stroke (selected studies).

Reference	n	Dysphagia	Constipation	Incontinence	Bleeding
Paciaroni [10]	406	34.7%			
Flowers [16]	250	44%			
Su [50]	154		55.2%		
Ingeman [51]	2969		7%		
Brittain [62]	1483			5%	
Nakayama [64]	935			40%	
Harari [60]	1069			30% <sup>a</sup>	
O'Donnell [70]	6853				1.5%
Hsu [71]	920				7.8%

<sup>a</sup> At 30 days post-stroke.

**Table 2**  
Effects of gastrointestinal complications over the clinical course of patients with ischemic stroke.

Complication	Effect	Reference
Dysphagia	Increased mortality and disability at 90 days	Paciaroni [10]
Constipation	Poor neurological outcome at 90 days	Su [50]
	Increased medical complications	Lin [52]
Incontinence	Increased dependence and 1 year mortality	Harari [60]
Bleeding	Increased mortality and dependence at 6 months	O'Donnell [70]

sham treatment, TMS led to significant improvements in dysphagia maintained over 2 months of follow-up [18]. In another similar study, 14 patients with subacute unilateral hemispheric infarction and dysphagia were randomized to anodal transcranial direct current stimulation (tDCS) versus sham stimulation to the sensorimotor cortical representation of swallowing in the unaffected hemisphere. Patients in the tDCS group showed a two-fold improvement in the Dysphagia Outcome and Severity Scale scores (DOSS) compared to patients in the sham stimulation groups [19]. Similar studies have found improvements in the DOSS after tDCS stimulation of pharyngeal motor cortex in patients with post-stroke dysphagia [20,21]. Functional magnetic stimulation of the suprahyoid muscles in 20 post-stroke patients with dysphagia was also able to improve pharyngeal transit time [22]. However, benefits on dysphagia reduction or actual swallowing function were lacking. On the other hand, recent meta-analyses of interventions for dysphagia, including electrical stimulation, drugs, acupuncture, physical therapy or nutritional support for post-stroke patients found no overall benefits in functional outcome or mortality [23,24]. Unfortunately, heterogeneity of the treatments evaluated and the outcomes assessed made pooled analyses difficult to interpret in some cases, such as in behavioral interventions, non-oral enteral feeding and modified diets [23].

Post-stroke pneumonia has been used to describe a pneumonia that occurs early after stroke, and it was traditionally thought to be secondary to aspiration of oral content (possibly during sleep) in patients with altered consciousness, difficulty swallowing and those unable to take food by mouth [9]. Depending on the medical setting, post-stroke pneumonia has an incidence ranging from 4% to 50% [25]. Although new theoretical advances suggest that immunological alterations such as stroke-induced immunodepression contribute to the pathophysiology of post-stroke pneumonia, dysphagia is still considered an important risk factor. Other risk factors reported include greater disability scores, mechanical ventilation, male sex, atrial fibrillation, dysarthria, diabetes, a history of smoking and low albumin, among others [25]. Post-stroke pneumonia is thought to worsen clinical outcomes in stroke by causing fever, electrolyte imbalance and hypoxia. Considering the few treatment options available, aggressive screening for post-stroke dysphagia, in order to ensure adequate initiation of feeding and preventing compli-

**Table 3**  
Selected independent risk factors for gastrointestinal complications following ischemic stroke.

Risk Factor	Complication	Reference	OR (95% CI)
Aspiration on clinical swallowing evaluation	Dysphagia	Kumar [26]	21.83 (8.16–58.42)
Bihemispheric infarcts			3.72 (1.33–10.43)
NIHSS score >12			2.51 (1.19–5.23)
Bedpan use			2.08 (1.053 to 4.121)
Anticholinergic drug use	Incontinence	Harari [60]	3.1 (1.1 to 10.2)
Needing help with toilet use			3.5 (1.4 to 17.3)
Age	Bleeding	Hsu [71]	1.25 (1.07 to 1.50)
MCA territory infarcts			9.47 (1.62 to 55.5)

Notes: OR: odds ratio; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; and MCA: middle cerebral artery.

cations such as aspiration pneumonia, would seem warranted.

## 2.2. Dysphagia screening

Clinical swallowing evaluation, videofluoroscopic evaluation, an NIHSS score >12 and stroke localization (bihemispheric) have all been shown to be effective in predicting post-stroke dysphagia [26,27]. The development of formal dysphagia screening protocols led to reduced incidence of pneumonia (from 5.4 to 2.4%) in a study in 15 acute care centers involving 2329 patients, even after adjusting for stroke severity [28]. However, in some sites included, data was obtained retrospectively and was based on routine documentation rather than actual practice; also age and ethnic characteristics were different among some sites. Similar results were replicated in a recent non-randomized single-center study including over 2000 patients [29], but comparisons were made between a pre-intervention and a post-intervention phase. Although no randomized controlled trials exist evaluating the effects of dysphagia screening over mortality or functional outcome, this relatively simple measure appears effective in reducing post-stroke complications and has been incorporated into practice guidelines (see below). Speech and language therapists are now an essential part of the multidisciplinary team in stroke units across the world, where swallowing disorders are routinely screened and managed using standardized protocols [30,31].

Specific recommendations have been established in most guidelines (Japanese and European ischemic stroke guidelines) [32]. Following the elimination of dysphagia screening recommendations in stroke by the Joint Commission, the American Heart Association (AHA) has published a scientific statement endorsing dysphagia screening and further clinical trials aimed at resolving these controversies [33]. To date, the most recent AHA guidelines on stroke management recommend dysphagia screening using a water-swallowing test at the bedside in order to determine optimal route of feeding [4]. A wet voice after swallow is a predictor of high risk for aspiration. Although the Japanese stroke guidelines suggest that it is preferable to use videofluoroscopic evaluations, they acknowledge the utility of a simple water-swallowing test. European guidelines do not recommend a specific approach. Since no instrumental examination can be considered as ideal in the evaluation of swallowing, and there are no large randomized trials comparing different screening strategies, the precise role for fluoroscopic and endoscopic procedures is yet to be determined.

The results of screening can lead to specific recommendations regarding the acute management of stroke. When a patient with post-stroke dysphagia is unable to swallow, and he is deemed unsafe or unable to meet his nutrition and hydration needs orally, a nasogastric or nasoduodenal tube may be inserted to provide feedings and facilitate drug administration [4]. Nasogastric tube placement can be performed within the first 24 h after assessment, and evaluation by a nutrition team is advisable. In a multicenter randomized control trial involving 859 stroke patients, early (within 7 days) tube feeding was associated with a reduced risk of death and an improved functional outcome [34]. However, a nasogastric tube does not eliminate the risk for aspiration pneumonia.

## 3. Alterations in GI motility

Besides dysphagia and alterations in voluntary control of oropharyngeal motility, recent studies suggest that impairments in GI motility are widespread after ischemic stroke. The esophageal sphincter is also affected in ischemic stroke patients. In a manometric study of 35 ischemic stroke patients, lower esophageal sphincter function was below normal in 24 patients while upper esophageal sphincter function was low in 30 patients [35]. These alterations can lead to aspiration, vomiting and predict feeding tube failure. Alterations in gastric emptying could also lead to decreased drug absorption. In a study of 12 acute ischemic stroke patients, the administration of oral paracetamol

showed a prolonged time to achieve peak concentrations as well as lower peak concentrations after a first dose in the paracetamol–time curve, compared with controls [36]. Cases of profound GI motility impairment have been reported after ischemic stroke affecting specific territories, such as bilateral posterior inferior cerebellar artery territory infarcts [37]. The physiopathological basis of widespread GI motility alterations remains poorly understood. Injury to various cortical areas and medullar nuclei involved in sphincter function and modulation of the autonomic nervous system are likely causes [5]. However, using a rat model of cerebral ischemia, investigators have shown that widespread mucosal damage in the small intestine is accompanied by decreased GI motility and increased levels of serum ghrelin [38]. Therefore, neurohormonal disturbances could partially account for these alterations. The clinical significance of these findings remains unclear.

Hiccups, now considered a diaphragmatic and intercostal muscular myoclonus followed by laryngeal closure, leading to air rushing into the lungs inducing vocal cord closure and a characteristic sound, are also associated with ischemic stroke [39]. Phrenic, vagus and sympathetic nerve reflexes modulated by midbrain centers are thought to underlie its anatomical substrate, but the precise mechanisms remain poorly understood. Both pontine and supratentorial ischemic strokes have been associated with persistent or intractable hiccups (defined as hiccups for 48 h and after 2 months, respectively) [39–41]. The incidence of post-stroke hiccups is unknown. In a single retrospective study, only 3 out of 270 patients in a tertiary teaching hospital had persistent hiccups after stroke [41]. These patients suffered from significant complications including aspiration pneumonia, respiratory arrest, and nutritional depletion. Chlorpromazine, the only Federal Drug Administration approved medical treatment for hiccups, has unfavorable side effects (such as sedation) for stroke patients [39,41]. A small non-randomized study showed that short term gabapentin was effective in stroke patients with intractable hiccups [42]. Other options are baclofen, haloperidol and carbamazepine. Single case reports of vagus nerve stimulation for intractable hiccups in stroke patients suggest that this intervention could also be effective [43,44]. In a controlled study of 80 patients with post-stroke hiccups, acupuncture and cupping appeared effective [45]. However, the control group received a non-standard drug (methylphenidate), and both patient selection and evaluation of effectiveness were heterogeneous. No reliable results from large clinical trials are available for making concrete recommendations.

## 4. Constipation and fecal incontinence

### 4.1. Constipation

Constipation and fecal incontinence are common symptoms among patients with central nervous system diseases, including ischemic stroke, and they negatively affect social functioning and quality of life [46,47]. Small studies that screened for GI complications after stroke revealed that the dominant GI symptom was constipation, independent of physical activity or hemisphere affected [48,49]. Incidences vary but have been reported to be as high as 55% in the first 4 weeks after ischemic stroke to up to 30% after 3 months [50]. Larger, population-based studies have found an incidence of 7% among 11,757 Danish patients admitted to stroke units [51]. Among post-stroke patients in rehabilitation facilities, the incidence of constipation is even higher (close to 80%), with near universal use of laxatives [52].

Often difficult to characterize due to inherently subjective components of symptomatology, constipation can be revealed by a history of laxative use or formal criteria such as the Rome II criteria for functional constipation. Possible causes of constipation are immobilization, insufficient water intake, reduced consciousness, abnormal colonic contractility or side effects from medication. Indeed, studies of colon motility in post-stroke patients using radio-opaque markers have shown that total colonic transit time is significantly prolonged in patients with constipation [53]. The development of post-stroke constipation has

been linked to poor neurological outcome, dependence and increased hospital length of stay [50,54].

Treatment modalities for post-stroke constipation are varied. Published guidelines only make general recommendations of bowel management aimed at preventing constipation [4]. Dietary adjustments, laxatives, prokinetic agents and enemas are used frequently, but evidence supporting their use is scarce. Avoidance of offending drugs is essential. Small randomized studies support the use of clinical/educational multidisciplinary interventions, including nurse and geriatrician based interventions, with benefits (subjective and objective improvement in bowel movements) lasting close to 6 months [55,56], and should constitute first line care. Other suggested interventions include enteral glucose feeding or carbonated water as opposed to tap water [57]. However, evidence for these interventions is of moderate quality. Sacral nerve stimulation is an experimental intervention so far not tested in post-stroke patients [58]. Although definitive, colostomy should probably be reserved for only the most severe and disabling cases.

#### 4.2. Incontinence

Fecal incontinence is also common after ischemic stroke, with incidences between 10 and 40%, but this complication has received much less attention than urinary incontinence in post-stroke patients [59]. Although many cases are transient, fecal incontinence can persist in ischemic stroke survivors many years after the event. In one of the largest epidemiological studies to date, prevalence of post-stroke fecal incontinence was 30% (7 to 10 days after stroke), 11% (3 months), 11% (1 year), and 15% (3 years after stroke) [60]. Among patients hospitalized in post-stroke rehabilitation centers fecal incontinence on admission has a prevalence of 40% [61], and most often affects the elderly. In a population wide survey including 1483 ambulatory stroke survivors in the United Kingdom, severe fecal incontinence occurred in 5%, a four-fold increase compared with non-stroke patients [62].

In an early cohort study of 135 stroke patients, it was noted that 14% had become fecally incontinent. However, they did so many months after stroke onset, leading to speculation that immobility and dependence were the main factors responsible for its development, instead of the acute vascular event itself [63]. Immediate factors associated with the development of fecal incontinence after stroke include advanced age, stroke severity, diabetes and comorbidity of other disabling diseases [60]. Factors associated with the delayed onset of fecal incontinence include anticholinergic drug use and need for assistance in toilet use [60] (Table 3). Urinary incontinence, another common complication after ischemic stroke, is closely associated with fecal incontinence, and its presence is a strong predictor for the development of fecal incontinence. The presence of fecal incontinence has been associated with increased risk for long-term facility placement and death within 1 year after the acute event [64]. However, a causal relationship is difficult to ascertain, since new-onset fecal incontinence after stroke could be a consequence of poor outcome and dependence, instead of a cause [65].

Screening for fecal incontinence can be straightforward, either with clinical examination or via established tools such as the Barthel Index bowel subscale. Management should include avoidance of offending drugs (mainly anticholinergic) and interventions aimed at optimizing toilet-use assistance, along with usual conservative management. However, there are no approaches supported by evidence-based medicine [66].

#### 5. GI bleeding

Gastroduodenal ulcers and GI bleeding are common complications encountered in the acute and chronic stages of ischemic stroke, and these have been associated with poor outcome. The reasons why GI bleeding occurs after stroke are unknown and have intuitively been attributed to stress ulcers, but gastroesophageal erosions and

hemorrhagic gastritis are also commonly found on endoscopy [67]. Gastroduodenal ulcers can also appear as a side effect of low-dose aspirin therapy in post-stroke patients. In prospective studies, close to 30% of patients evaluated prospectively with upper GI endoscopy had mucosal injuries [68,69]. In a retrospective study of 6853 patients with acute ischemic stroke in Canada, 1.5% experienced GI bleeding during hospitalization, of which 0.5% required blood transfusion [70]. Other large studies have found incidences closer to 8% [71]. GI ulcers occur in close to 44% of all patients admitted to neurological intensive care units with stroke diagnosis [72], and autopsy studies on stroke patients reveal that close to 20% have massive hemorrhage into the GI tract [73].

Besides stress and antiplatelet use, systemic inflammation and oxidative stress have also been proposed as pathophysiological mechanisms involved in post-stroke GI mucosal injury. In experimental ischemic stroke models, gastric mucosa edema, splinter hemorrhages and erosions are evident 48 h after middle cerebral occlusion in rats, along with mucosal endothelial cell necrosis and inflammatory cell infiltration [74]. Antioxidants and inhibitors of the nitric-oxide pathway are also able to modulate post-stroke ulcerogenesis [75]. Reductions of gastric mucosal blood flow during ischemic stroke could also contribute to ulcerogenesis [76]. Other experimental studies have shown that activation of noradrenergic neurons acting through alpha1-adrenoceptors leads to decreases in gastric mucosal blood flow and mucosal injury after ischemic stroke [77].

Risk factors for GI bleeding in post-stroke patients have been identified (Table 3). Previous history of peptic ulcer disease, *Helicobacter pylori* infection, cancer, stroke severity, middle cerebral artery infarcts, renal or hepatic dysfunction and age are all independent predictors of GI bleeding, and GI bleeding has been independently associated with in-hospital mortality, death at 6 months or severe dependence at discharge [78,70,71]. In a Chinese registry of over 14,000 stroke patients, development of pneumonia was also found to be significantly associated with GI bleeding [79].

#### 5.1. Treatment

Treatment of gastro-duodenal ulcers and GI bleeding in ischemic stroke patients should follow usual guidelines, which are beyond the scope of this review. There could be a role for careful selection of antiplatelet agents as secondary stroke prevention with the aim of reducing post-stroke GI bleeding. Two available meta-analyses have shown that clostazol is associated with fewer GI bleeding events compared to aspirin, although with a higher incidence of other GI adverse effects [80,81]. On the other hand, both aspirin-dipyridamole and aspirin-clopidogrel combinations seem to be associated with higher rates of GI bleeding compared to monotherapy [82]. In the context of primary prevention of ischemic stroke in patients with non-valvular atrial fibrillation, the introduction of novel oral anticoagulants into clinical practice could also lead to changes in the incidence of GI bleeding. While apixaban (ARISTOTLE trial) is associated with lower overall bleeding events, both rivaroxaban (ROCKET AF trial) and dabigatran (RE-LY trial) at the most effective dose (150 mg) were associated with slightly higher rates of GI bleeding, when compared to warfarin therapy [83–85]. In all trials, bleeding events were defined by different criteria and pooled for analysis, with emphasis on intracranial bleeding, making direct conclusions over GI safety difficult. As evidence on this matter continues to evolve, novel therapeutic strategies will prove to be important in reducing post-stroke GI bleeding incidence. The use of routine gastroprotective drugs as prophylaxis in ischemic stroke patients is controversial, but some international guidelines (Japanese stroke guidelines) recommend the use of intravenous antiulcer medications with a moderate quality of evidence [86].

## 6. Mucosal barrier function and bacterial translocation: a link to infections?

Infections after ischemic stroke are common regardless of optimal medical management, and there is enough evidence to suggest that infections increase mortality and lead to neurological deterioration in hospitalized ischemic stroke patients [87,88]. Pneumonia and urinary tract infections are some of the most common complications associated with ischemic stroke. A cytokine-mediated anti-inflammatory response associated with ischemic stroke has been proposed as a pathogenic factor in the development of post-stroke infections (post-stroke immunodepression) [89]. Experimental studies have shown that ischemic stroke induces an extensive apoptotic loss of lymphocytes and a shift from T helper cell (Th)1 to Th2 cytokine production, changes that lead to pneumonia and septicemia [90].

A recent hypothesis contends that post-stroke immunodepression affects the intestinal mucosa, possibly affecting its barrier function, changes that could lead to increased bacterial translocation, septicemia and systemic infections. In a mouse model of cerebral ischemia, intestinal Peyer's patches revealed a significant reduction of T and B cell counts, without changes in lamina propria or in macrophage counts [91]. Using a rat model of middle cerebral artery occlusion, investigators were able to show that ischemic stroke led to intestinal mucosa injury and bacterial translocation into blood, mesenteric lymph nodes, liver, spleen and lung, in up to 55% of animals at 24 h [92]. Similar findings were obtained in a rat model of cerebral ischemia, showing colonic inflammation as well as increased bacterial translocation [93].

The breakdown of the intestinal mucosal barrier in ischemic stroke could partially account for increased rates of infections. The use of prophylactic antibiotics is not the standard of care in the treatment of ischemic stroke, but there are large trials underway to test whether their use could be of clinical value [94,95]. Prompt recognition and treatment of infectious complications is currently recommended by AHA stroke guidelines [4].

## 7. Visceral thromboembolism

When the etiology of ischemic stroke is systemic embolism, a cardioembolic source is most likely. There are cases where the source of the emboli remains difficult to establish, but findings of abdominal visceral infarction could point towards a common (presumably cardioembolic) source. In a case-control study of 260 consecutive autopsies of patients with ischemic stroke, infarction of visceral organs was present in 21%, and of these, 76% had a definite cardiac source [96]. Most of the infarctions were renal, and only a small percentage were mesenteric. The same group followed up these findings with diffusion-weighted magnetic resonance abdominal imaging in 27 consecutive patients with acute ischemic stroke or transient ischemic attack. Six of these patients had a visceral infarction, including renal and splenic infarctions [97]. The clinical relevance and true incidence of synchronous intestinal microinfarctions in patients with ischemic stroke remain unknown, and are an interesting avenue for future research. An interesting question would be whether findings of visceral infarctions in patients with ischemic stroke of unknown etiology would benefit from anticoagulation.

## 8. Conclusions

While infectious and thrombotic complications have received comparatively much more attention, GI complications are very common after acute ischemic stroke, and they contribute to adverse outcomes including disability, poor neurological function and even death. Recent evidence has identified adequate and effective screening strategies, risk factors and treatment options for these debilitating complications. However, further research aimed at evidence-based preventive strategies, as well as randomized clinical treatment trials, will be invaluable in the integral management of post-stroke GI complications.

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