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Review

Beyond the Brain: The Systemic Pathophysiological Response to Acute Ischemic Stroke

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Stroke research has traditionally focused on the cerebral processes following ischemic brain injury, where oxygen and glucose deprivation incite prolonged activation of excitatory neurotransmitter receptors, intracellular calcium accumulation, inflammation, reactive oxygen species proliferation, and ultimately neuronal death. A recent growing body of evidence, however, points to far-reaching pathophysiological consequences of acute ischemic stroke. Shortly after stroke onset, peripheral immunodepression in conjunction with hyperstimulation of autonomic and neuroendocrine pathways and motor pathway impairment result in dysfunction of the respiratory, urinary, cardiovascular, gastrointestinal, musculoskeletal, and endocrine systems. These end organ abnormalities play a major role in the morbidity and mortality of acute ischemic stroke. Using a pathophysiology-based approach, this current review discusses the pathophysiological mechanisms following ischemic brain insult that result in end organ dysfunction. By characterizing stroke as a systemic disease, future research must consider bidirectional interactions between the brain and peripheral organs to inform treatment paradigms and develop effective, comprehensive therapeutics for acute ischemic stroke.

Keywords Stroke; Disease progression; Pathologic processes; Physiopathology; Translational medical research

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Introduction

Acute ischemic stroke (AIS) is a major cause of mortality and long-term disability world-wide that lacks curative therapies.[1,2] Recent key advancements in pharmacological thrombolysis and mechanical endovascular thrombectomy remain limited by a narrow therapeutic window and restrictive eligibility.[3,4] Additionally, the spectrum of rehabilitation paradigms implores evidence base,[5] while efforts targeting neuroprotection largely fail to translate to human therapies.[6] AIS research has historically focused on these central nervous system (CNS) interventions to reduce infarct volume and address neuronal viability. More recently, however, detrimental effects of AIS on the heart[7] and immune system[8] have gained popularity. Indeed, medical complications following AIS such as pneumonia are strong predictors of mortality and functional outcome.[9,10] To that end, we queried the National Center for Biotechnology Information and National Library of Medicine database through PubMed using a combination of keywords including "ischemic stroke" and the system of interest to identify relevant literature addressing systemic effects of AIS. We found a small but growing body of evidence pointing to far-reaching pathophysiological consequences in peripheral tissues including immune, respiratory, urinary, cardiovascular, gastrointestinal, musculoskeletal, and endocrine

systems (Supplementary Figure 1). Following AIS, the majority of these organ systems suffer disturbances ranging in severity from subclinical laboratory abnormalities to life-threatening arrhythmias or infections (Figure 1). In this current review, we discuss the mechanisms by which AIS induces these systemic pathophysiological responses and summarize their subsequent clinical manifestations.

The crosstalk between the stroke-affected brain and end organ systems

It is now widely accepted that AIS has dramatic consequences on the fine balance between the brain and the rest of the human body (Table 1, Supplementary Table 1).[9,11] Following AIS, many systems demonstrate time-dependent progression of acute stroke-induced alterations preceding chronic deficits

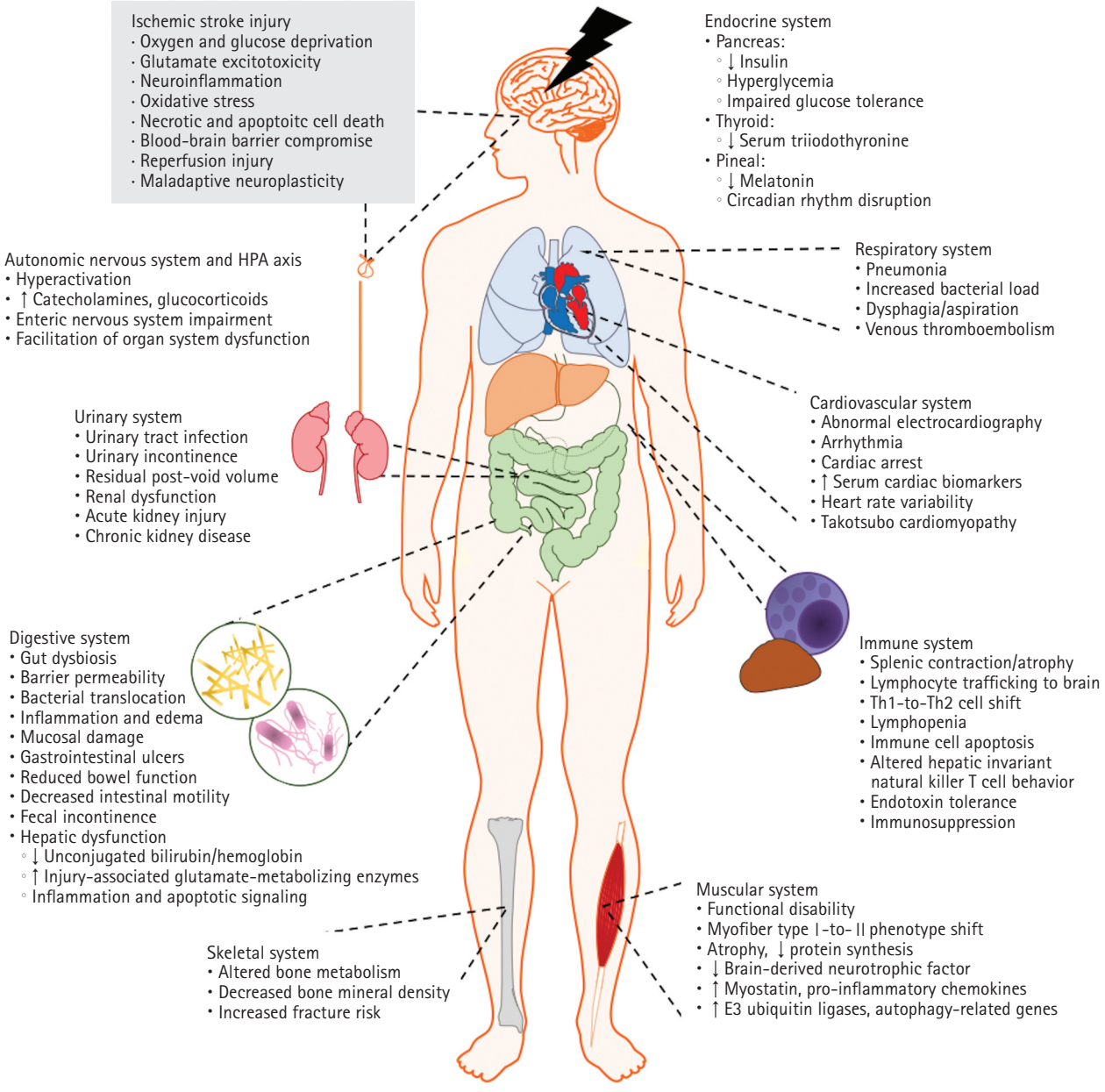

Figure 1. The multi-systems effect of ischemic stroke. Ischemic stroke deprives the brain of sufficient blood flow, prompting a cascade of neurotoxic events that result in inflammation, neurotoxicity, and cell death (gray box). In addition to the resultant cerebrovascular injury, the pathophysiological consequences of ischemic stroke reach outside of the central nervous system and orchestrate organism-wide dysfunction. In this figure, the complexity of stroke pathophysiology is viewed through the lens of human body systems. The unconstrained influence of detrimental consequences reaches cardiac, endocrine, gastrointestinal, lymphoid, and musculoskeletal tissues, highlighting the bidirectional crosstalk between the brain and each affected organ system, and supporting the labeling of stroke as a systemic disease.

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(Figure 2).[12-14] These alterations are believed to be mediated by three overlapping mechanisms involving immune, autonomic, and motor pathways (Figure 3).

Shortly after AIS, a severe state of immunodepression is seen resulting in the high incidence of post-stroke infections.[9,11] This post-stroke immunodepression is mediated by the autonomic and hypothalamic pituitary adrenal axis (HPA) activation and the interaction of the stroke-affected brain with the immune system through complement activation and release of damage-associated molecular patterns (DAMPs).[15,16] Additionally, HPA activation is thought to be a critical channel through which multiple other systems are dysregulated, resulting in cardiac, renal, and gastrointestinal imbalances. Furthermore, motor pathway impairment secondary to AIS contributes to muscle wasting while the associated immobility increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) (Table 1). These factors overlap resulting in the worsening morbidity and mortality of AIS (Figure 3). In the following sections, these overlapping mechanisms and their subsequent clinical implications are discussed in further detail.

Stroke-induced immunodepression

Within hours of AIS, autonomic activation and release of DAMPs affect the various immune cells in the body. Immune cells from lymphoid populations in the spleen, gut-associated lymphoid tissue (GALT), and bone marrow reach brain vasculature and parenchyma.[17,18] Together with resident microglia, the arriving neutrophils, monocyte/macrophages, and innate lymphocytes (e.g., natural killer [NK] cells) respond by producing proinflammatory mediators, after which T- and B-cell activation delivers its adaptive response.[17-19] The roles of T-cell subsets have been thoroughly investigated, where pro-inflammatory T-helper (Th1), Th17, γδ T-cells, and cluster of differentiation 8+ (CD8+) T-cells promote initial tissue damage, enhance blood brain barrier breakdown, and contribute to neuronal apoptosis.[19] Following this acute activation phase, an abrupt anti-inflammatory shift supervenes. This process is thought to be mediated by autonomic and neuroendocrine dysfunction, monocyte deactivation, and NK cell impairment that suppress immune activity. In addition, peripheral mobilization and apoptosis decrease blood lymphocyte counts by half.[20] The shift toward anti-inflammatory Th2 cells and expansion of protective forkhead box protein P3+ (FoxP3+) regulatory T-cells (Tregs)

Table 1. Systemic complications of ischemic stroke

Complication	Characterized by	Underlying pathophysiologies	Reference
Infection	Commonly stroke-associated pneumonia, urinary tract infection	Immunodepression, gut dysbiosis, autonomic activation, immobility	P. [15,20,27,35-37] C. [8,24,34,43,44,47-49,52,56]
Pulmonary embolism	Heightened VTE risk, resulting in DVT development and transfer to pulmonary circulation	Autonomic dysfunction, immobility, coagulant activation post-infection	C. [100-102,111]
Renal dysfunction	Low eGFR, incontinence, development of AKI/CKD/ESRD	Sympathetic output, inflammation	P. [112] C. [76-79,113,114]
Cardiac dysfunction	Cardiac arrhythmias, systolic dysfunction, ECG abnormalities, silent myocardial ischemia, cardiac arrest, Takotsubo cardiomyopathy	Sympathetic signaling, vagal modulation	P. [7,62] C. [10,57-61,63,64]
Gastrointestinal concerns	Intestinal muscosa damage, decreased gut motility, GI bleeds, bowel dysfunction	Autonomic dysfunction, gut dysbiosis	P. [66] C. [65,67]
Hepatic dysfunction	Hepatic inflammatory/apoptotic activation, hepatic ketogenesis, compromised hepatic insulin signaling, increased ER stress, altered bilirubin/liver enzyme levels	Catecholamine surge, noradrenergic-mediated innervation	P. [71-74] C. [68]
Endocrine imbalance	Decreased insulin release, hyperglycemia; decreased T3, thyroid imbalance, reduced T3-related neuroprotection; decreased melatonin, circadian shift and sleep disturbance, reduced melatonin-related neuroprotection	Sympathetic signaling; inflammatory mediators, glucocorticoids; autonomic disruption	P. [84,85] C. [80-83,86]
Musculoskeletal decline	Bone loss, remodeling disorder, increased fracture risk, low BMD/BMC; repressed skeletal muscle repair, increased catabolic activity, atrophy, altered inflammatory signaling, myofiber phenotype shift, functional disability	Sympathetic activation, immobility	P. [13,104,105,107] C. [103,109,115]

P., preclinical studies; C., clinical studies; VTE, venous thromboembolism; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; ECG, electrocardiography; GI, gastrointestinal; ER, endoplasmic reticulum; T3, triiodothyronine; BMD, bone mineral density; BMC, bone mineral content.

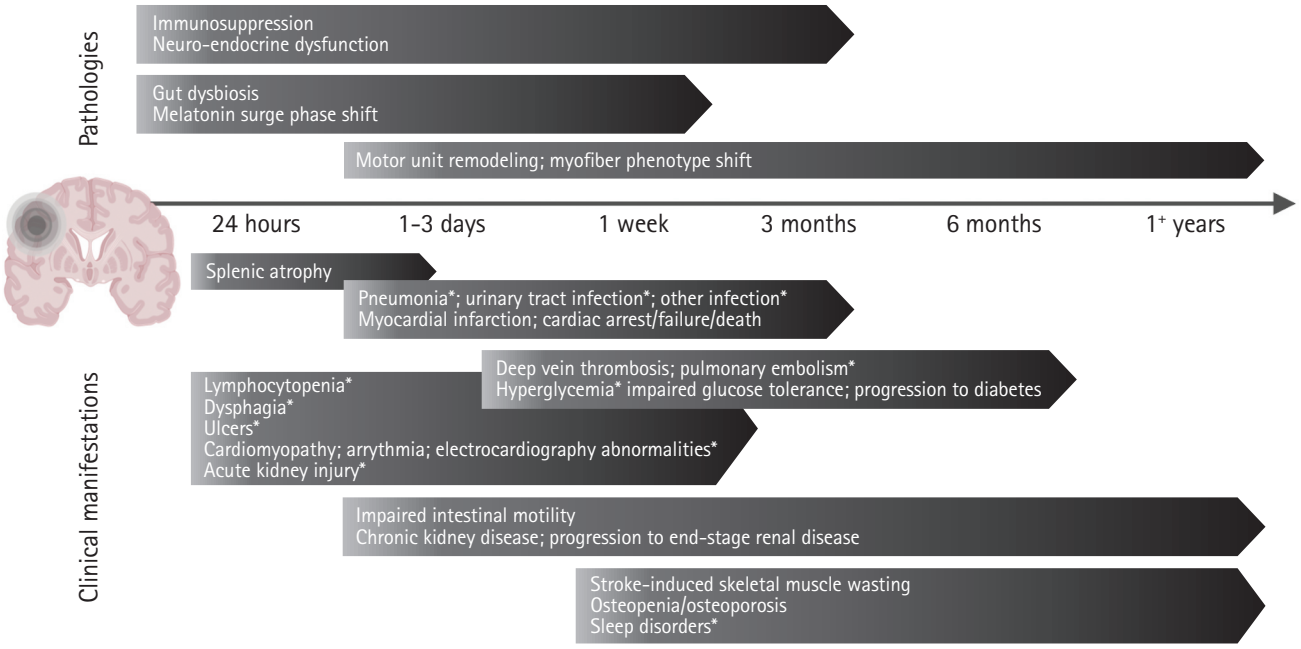

Figure 2. Timeline of systemic complications following stroke. Systemic responses to ischemic stroke present clinically within hours and continue developing well beyond hospital discharge. Though some are transient in nature, many complications progress chronically into the months and years that follow. This timeline summarizes the onset and evolution windows of clinical manifestations (e.g., pneumonia) and associated pathologies (e.g., immunosuppression). Brain graphic created with BioRender. *Denotes predictors of poor outcome.

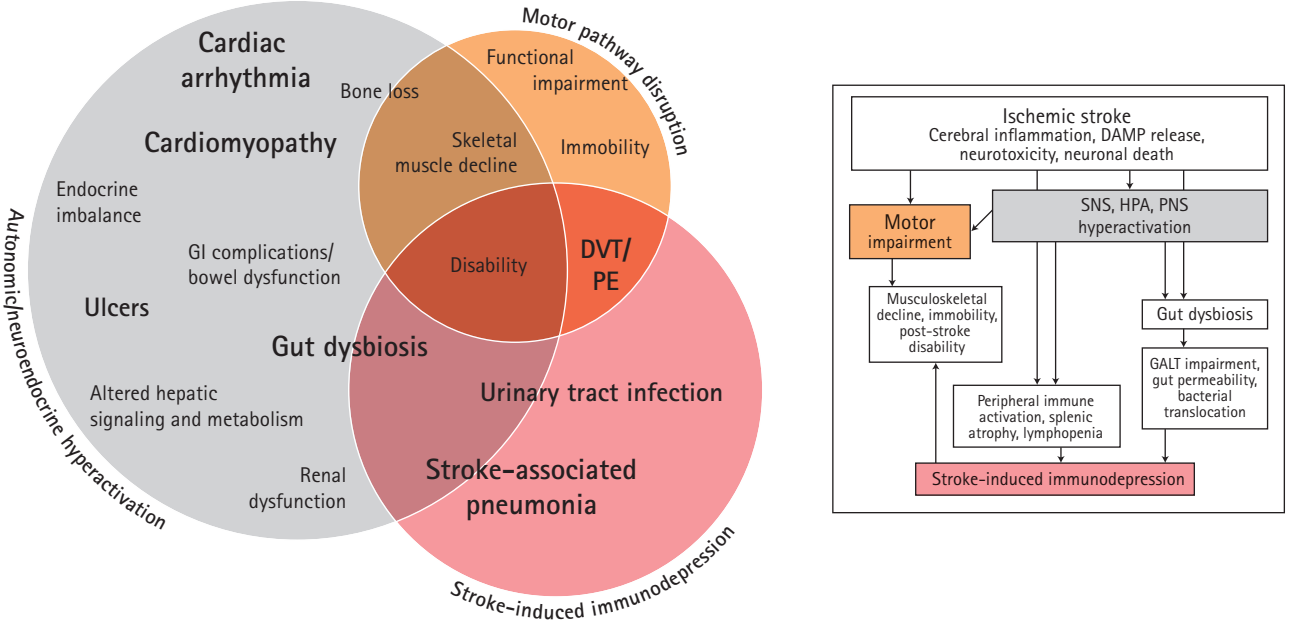

Figure 3. The pathophysiological sequelae of ischemic stroke. The impact of ischemic stroke reaches systemic proportions through evolution of three main pathophysiologies: stroke-induced immunodepression, autonomic and neuroendocrine dysfunction, and motor pathway disruption (flow chart). Each pathophysiology then facilitates development of the detrimental clinical complications observed beyond the stroke-affected brain (Venn diagram). Though much overlap exists between influential pathophysiologies and the ensuing complications, this figure presents a simplified overview of how the pathophysiological sequelae of ischemic stroke culminates in a vast array of clinical complications. GI, gastrointestinal; DVT, deep vein thrombosis; PE, pulmonary embolism; DAMP, damage-associated molecular pattern; SNS, sympathetic nervous system; HPA, hypothalamic pituitary adrenal axis; PNS, parasympathetic nervous system; GALT, gut-associated lymphoid tissue.

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protect against further neuroinflammation.[21] While limiting excessive immunological brain injury, the diminished immune capacity prevents sufficient inflammatory response to infection.[15] Though exact mechanisms of prompt immune activation and opposing immunodepression are not fully understood, known participants in brain-immune communication after stroke are described below.

DAMPs and endotoxin tolerance

DAMPs are intracellular biomolecules that initiate an immune response upon release from necrotic cells. Upon detection by pattern recognition receptors on immune cells (e.g., receptor for advanced glycation end products [RAGE], toll-like receptors [TLRs]), DAMPs acutely amplify pro-inflammatory cytokine production.[15] This disproportionately large immune reaction incites immature monocyte migration from bone marrow, proliferation of bone marrow-derived suppressor cells in the spleen, lymphopenia, and immune cell apoptosis.[22,23] DAMP-induced exhaustion of monocyte function yields a state of endotoxin tolerance, a phenomenon that protects the stroke-affected brain from further damage but leaves immune cells unable to elicit adequate pro-inflammatory reaction to insult.[8]

Monocytes from AIS patients exhibit decreased surface expression of major histocompatibility complex (MHC) class II molecule human leukocyte antigen D related (HLA-DR) and consequently exist in a state of diminished antigen presentation.[24] Neuronal chromatin-associated nuclear protein high-mobility group box 1 protein (HMGB1), a pivotal DAMP in stroke pathology, is elevated in serum within hours.[15] Both markers of immunodepression, low MHC II and HLA-DR at post-stroke day one predicted infection up to 2 weeks later,[24] while preclinical blocking of the HMGB1-RAGE pathway attenuated immunodepression and lymphocyte inactivation.[22] Mitochondrial DAMPs are also markedly increased in plasma after stroke. Circulating mitochondrial DNA strongly correlated with the impaired response of refractory-state monocytes and infection.[8] Furthermore, healthy monocytes cultured in stroke patient serum containing mitochondrial DNA exhibited the same refractory state.[8]

Invariant natural killer T (iNKT) cells are a unique group of innate immune cells that survey the blood for circulating immunogens. Recent data suggest iNKT cells in liver sinusoids detect and respond to brain injury.[25] Following middle cerebral artery occlusion (MCAO), iNKT cells demonstrated decreased crawling activity specific to cerebral ischemia, as hindlimb ischemia-reperfusion had no effect on iNKT mobility.[25] Post-stroke changes to iNKT behavior also contribute to immunodepression and increased infection risk. While iNKT numbers were not altered by stroke-induced lymphopenia, activation marker CD69 increased in peripheral blood and liver iNKT populations after MCAO prior to the anti-inflammatory cytokine shift. Neutrophil infiltration, edema, and bacterial load also increased in the lungs within 24 hours, consistent with clinical outcomes.[25]

Splenic volume and cell cycling

The spleen is a lymphoid organ functioning in blood filtration and immune response. Preclinical stroke studies describe immediate decreases in splenic volume and T-cell antigen response.[20,23] Similarly, stroke survivors experience splenic atrophy with re-expansion beginning after 48 hours.[12] Prompted by sympathetic hyperactivation, contributors to splenic contraction include immune cell release followed by apoptosis of lymphocyte subsets: B-, T-, and NK cells.[16,20,26] Confirming the impact of apoptosis in immunodepression, experimental treatment with systemic caspase inhibitor quinolyl-valyl-O-methyl-aspartyl-[-2,6-difluorophenoxy]-methyl ketone (Q-VD-OPH) minimized stroke brain injury, improved splenocyte survival, and reduced bacteremia.[27]

To delineate the spleen's role in stroke injury, independent preclinical studies showed splenectomy either 2 weeks before MCAO[28] or in the immediate hours afterward[29] decreased infarct volume and neurological deficits. Interestingly, splenectomy immediately before stroke induction did not improve infarct volume or neuroimmune response,[17,30] though variance in stroke model, post-operative recovery, and immune compensation warrant further investigation.[10,30]

Gut dysbiosis

The microbial population in the intestinal tract interacts with specialized GALT to regulate T-cell homeostasis and establish the maturing immune system. Disruption of the intestinal microbiome, or gut dysbiosis, is observed following AIS.[14] Because microbial metabolites influence immune polarization, gut dysbiosis affects intestinal lymphocyte populations.[31] Due to its role in immune response and systemic inflammation, gut dysbiosis is addressed in the context of neuroimmune dysregulation.

In response to inflammatory stress and altered vagal communication with the intestinal tract, gut dysbiosis after stroke is characterized by a reduction in species diversity, imbalance in phyla predominance, and altered metabolite production.[14,32] Preclinically, dysbiosis directly primed inflammatory γδ T-cells in the gut, which then trafficked to the brain and exacerbated stroke evolution.[31] Recolonizing germ-free mice with dysbiotic bacteria from stroke-affected mice yielded larger lesions and deficits after MCAO, while healthy fecal transplantation normalized microbiota, reduced infarct size, and attenuated pro-

inflammatory T-cell polarization.[14] Following the post-stroke immunosuppressive shift, mesenteric lymph node dendritic cells prompt migration of protective Tregs to the gut to decrease γδ T-cell movement to the brain.[19] Compared to mice with less severe dysbiosis, mice with excessive dysbiosis had significantly more γδ T-cells, fewer Tregs, larger infarcts, and greater neurological deficits.[33]

Clinically, AIS patients presented with altered fecal bacterial counts and organic acid levels, as well as disrupted biomarkers of metabolism and inflammation.[32] Gut microflora are further disturbed by antibiotic administration for infection control.[34] Intestinal edema and inflammation after experimental stroke compromised mucosal barrier function and may enable bacterial translocation to various organs.[35] Indeed, bacteremia occurred acutely following rodent stroke[34] and was observed in AIS patients at admission.[14] Microbes detected in the lungs originated in the host's small intestine, with translocation to the spleen, liver, and mesenteric lymph nodes as early as 24 hours.[34,35] These findings indicate gut dysbiosis is both a consequence of and subsequent contributor to stroke pathophysiology, though a clinical link between dysbiosis and stroke outcomes remains to be established.

The systemic consequences of stroke-induced immunodepression

The critical suppression of the immune system manifests clinically as infection, including stroke-associated pneumonia (SAP) and urinary tract infection (UTI), the most frequently encountered complications in stroke patients.[36]

Stroke-associated pneumonia

Murine studies report increased bacterial load in lungs and peripheral blood by 24 hours post-MCAO.[20] Obstructing sympathetic activity with a β-blocker, however, prevented bacterial infection and reduced mortality highlighting the role of sympathetic system activation.[20,37] Immunodepression was further demonstrated using *Streptococcus pneumoniae* exposure: while 200,000 colony-forming units (CFUs) were required to cause pneumonia in sham animals, only 200 CFUs were necessary in stroke mice, again preventable with sympathetic blockade.[37] Marked lymphopenia was prevented through glucocorticoid receptor blockage, while both HPA and sympathetic inhibition protected against lymphocyte apoptosis.[18]

Stroke-induced parasympathetic stimulation is widely accepted as another contributor to infection through initiation of anti-inflammatory pathways.[14,38,39] Vagal signaling and cholinergic activation target α7-nicotinic acetylcholine receptors (α7-nAChR) across cell types, including lung epithelial cells and resident immune alveolar macrophages.[40] Mice after MCAO presented with significant parasympathetic response and pneumonia, while vagotomy or α7-nAChR-deficiency maintained pulmonary immune defense and prevented SAP.[40]

Clinically, SAP is a major complication of AIS affecting one-third of patients.[41] In contrast to preclinical data, human studies utilizing β-blockers to address infection report mixed outcomes, from protective[42] to unfavorable.[43] Aspiration is another important mechanism of SAP,[9] though prevention measures alone do not eliminate infection. Indeed, a multi-center study established dysphagia and immunodepression as independent predictors of SAP.[24] Dysphagia correlated with SAP only in patients with low monocytic HLA-DR, suggesting screening for both dysphagia and immunosuppression could identify SAP risk.[24] Though SAP is linked to functional decline and mortality,[36] prophylactic administration of antibiotics failed to improve either outcome in clinical trials.[44,45] This emphasizes the knowledge gap regarding complex pathophysiological mechanisms of post-stroke immunodepression and the fragile lung-brain axis.

Urinary tract infection

AIS severity is an independent predictor of UTI[41] which is in turn associated with worse outcomes, longer hospital stays, and poor discharge outcome.[41] Despite lowering UTI frequency, prophylactic antibiotics did not benefit functional outcome or reduce mortality in clinical trials similar to SAP.[46] Risk factors include catheter use, incontinence, and post-void residual urine volume,[47] though high rates of UTI have been reported in patient cohorts both with (50%) and without (24%) indwelling catheters.[48] Programs that prompted routine assessment, stop orders, or early removal reduced catheter duration and incidence of UTI,[49] as did measuring post-void urine volume with portable bladder ultrasound.[47] Antimicrobial or antibiotic-impregnated catheters have been shown to delay or prevent bacteriuria, but evidence of UTI reduction is scarce[50] and highlights immune system complexity after stroke.

Autonomic and neuroendocrine dysregulation

Dysregulation of autonomic and HPA systems has widespread effects on all body organs (Figure 3). The mechanisms by which the autonomic system communicates with the peripheral immune system have been most thoroughly investigated and will be discussed in depth first.

Sympathetic hyperactivation

The pro-inflammatory cytokine surge after AIS activates the

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sympathetic nervous system (SNS), triggering catecholamine production at the adrenal medulla and sympathetic nerve terminals.[20] This initiates immune cells mobilization, stimulates their apoptosis, and inhibits further cytokine production.[20] Murine studies identified sympathetic activation as the direct cause of spontaneous bacterial infection after stroke,[20] while pharmacological inhibition of splenic adrenergic receptors reduced infarct volume, preserved splenic weight, and protected against high bacterial load.[51] Though splenectomy was protective, denervation alone did not alter splenic weight or infarct volume[51] suggesting a regulatory role for circulating catecholamines over direct sympathetic innervation. Indeed, patients with post-stroke infection presented first with increased catecholamine levels.[52]

On the other hand, noradrenergic-mediated innervation, rather than humoral input, is responsible for post-stroke iNKT behavior. Direct injection of norepinephrine into livers of sham-operated mice mimicked the immunosuppressive iNKT response to stroke and increased infection risk, whereas β-adrenergic receptor inhibition or reduction of hepatic noradrenergic nerve terminals attenuated the MCAO-induced immunosuppressive shift in mice,[25] similar to results in the spleen.[51]

HPA axis dysregulation

HPA axis overactivation releases glucocorticoids from the adrenal cortex, promoting the immunosuppressive shift to anti-inflammatory cytokine production.[20] Glucocorticoids have been shown to impede pro-inflammatory cytokine production as well, and stunt immune cell proliferation to promote apoptosis.[53] Clinically, AIS prompts an abrupt increase in cortisol, which is linked to post-stroke infection, mortality, and functional dependence.[54] Experimental blocking of glucocorticoid receptors prevented the immunosuppressive stroke-associated lymphopenia.[18,20] Many studies report diurnal pattern disruption of cortisol after stroke, though full implications of the shift remain unknown.[54]

Parasympathetic vagal activation

The parasympathetic nervous system is involved with neuroimmune regulation following stroke through inflammatory stimulation of the vagus nerve.[40] The subsequent release of acetylcholine activates α7-nAChR, triggering the vagal cholinergic anti-inflammatory pathway[55] which inhibits pro-inflammatory macrophage activity. Studies employing vagal stimulation[38] and α7-nAChR agonists[39] confirm vagal/α7-nAChR involvement in reducing cerebral inflammation. The other consequence of the parasympathetic vagal activation is its effect on the brain and peripheral NK cell regional population in mice and patients.[26] A decrease-then-recovery of NK counts occurred in the periphery, but the opposite—initial increase, then subsequent contraction—was observed in the brain. In addition, cholinergic exposure suppressed NK function in the brain but not in the periphery.[26] This suggests compartment-specific mechanisms may be ideal targets for preventing immunodepression in the periphery while leaving the protective shift in the brain undisturbed.

The systemic consequences of autonomic/neuroendocrine dysregulation

Overstimulation of sympathetic, HPA, and parasympathetic pathways mediates the systemic disease progression, prompting a clinical cascade of cardiac, gastrointestinal, hepatic, renal, and endocrine complications.

Cardiovascular dysfunction

Stroke severity, disability, and mortality are higher in patients with lower cardiac function.[56,57] Conversely, AIS induces cardiac dysfunction without prior risk factors or pre-existing heart disease.[57,58] This manifests with electrocardiographic abnormalities, elevated serum cardiac troponin T in the absence of myocardial infarction, depressed cardiac function in the acute phase, or severe complications such as arrhythmias or cardiac arrest.[56-58] Incidentally, 19% of AIS patients had a serious or fatal cardiac event in the first 3 months.[10]

Takotsubo cardiomyopathy (TTC) is a stress-induced transient weakening and ballooning of the left ventricle that is seen in a subset of AIS patients. Commonly asymptomatic, TTC may mimic myocardial infarction in injury biomarkers and electrocardiography and is associated with insular infarcts and poor outcomes.[59,60] Heart function typically returns to normal over several weeks, but severe cases increase risk for cardiac embolism, respiratory failure, and death.[59]

Cardiac dysfunction following AIS has been attributed to sympathetic and parasympathetic imbalance. One study confirmed overstimulation of cardiac sympathetic innervation using the catecholamine synthesis rate-limiting enzyme tyrosine hydrolase.[7] Sympathetic hyperstimulation also blunts vagal influence, as confirmed in stroke patients via heart rate variability testing.[61] HPA activation and hypothalamic paraventricular nucleus output also prompted cardiac arrhythmias and impaired cardiac output in rat models.[62] Brain regions of cardiovascular interest are the brainstem (e.g., rostral ventrolateral medulla) and insular cortex. The laterality hypothesis maintains left and right insular cortices control cardiac parasympathetic and sympathetic activity respectively, and while patient studies indicate heightened severity of cardiac dysfunction with insular strokes,

presentation and degree of laterality remain controversial.[63,64]

Gastrointestinal and metabolic impairments

Autonomic dysfunction impairs enteric communication and, consequently, gastrointestinal function. Additional contributors include inactivity, diet, and various medications.[65] Preclinical and clinical studies alike report bowel dysfunction and gastrointestinal impairment after stroke.[14] Reduced intestinal motility results in constipation and new-onset fecal incontinence in up to half of AIS patients.[65] Rodent studies identified histological damage, gastric edema, hyperemia, altered cellular composition, and hemorrhagic erosion of the gastric mucosa after stroke,[66] which present clinically as ulcers.[67] Acid-suppressive therapy may reduce gastrointestinal bleeding,[67] but the underlying intestinal inflammation, gut dysbiosis, and autonomic contributors remain.

Metabolic homeostasis in the liver is impaired after AIS and correlates with infarct volume.[68] Stroke is associated with reduced unconjugated bilirubin and hemoglobin levels at admission[68] while increasing glutamate-metabolizing enzymes associated with liver injury (e.g., glutamate oxaloacetate transaminase [GOT]), a possible prompt for peripheral glutamate metabolism in response to glutamate release from the ischemic brain.[68] Plasma and neuronal sources of GOT support scavenging[69] and excitotoxic glutamate metabolism[70] after AIS respectively, though post-stroke implications of hepatic GOT are yet to be revealed. Additionally, experimental stroke promoted inflammation, DNA fragmentation, and apoptotic signaling in the liver through kinase activation (i.e., c-JUN N-terminal kinases [JNKs], extracellular signal-regulated kinases [ERKs]).[71] Compromised hepatic insulin signaling, increased expression of gluconeogenic genes, and increased endoplasmic reticulum stress have been reported in the liver and are attributed to the post-stroke catecholamine surge.[72]

Hepatic ketogenesis is another hepatic disturbance seen in animal models. Stroke-affected mice develop ketogenesis when fed fat-rich diet, even when the diet was not sufficient to trigger ketosis pre-stroke.[73] This phenomenon may have a potential role in angiogenesis and neuroprotection following AIS.[74]

Kidney dysfunction

Stroke-induced autonomic hyperactivation brings an increase in sympathetic activity and systemic inflammation, disrupting renal homeostasis.[75] Up to one-third of stroke patients experience renal impairment during hospital stay.[76] AIS patients can develop acute kidney injury, defined as decreased urine output or increased absolute serum creatinine within 48 hours.[77] Influential factors beyond sympathetic activity include hydration status, contrast nephrotoxicity, and vascular intervention.[77] Stroke survivors can also suffer progression of chronic kidney disease that can evolve to end stage renal disease.[78] Post-stroke renal dysfunction upon hospitalization is a prognostic indicator of mortality at 10 years[76] and thus supports the case for identification and management.

Other disturbances include urinary incontinence, with or without urgency, in half of AIS patients. Given the complex neurological control over micturition, lesion size may be of greater concern than specific localization to certain brain areas.[79]

Endocrine imbalance

Stroke-induced sympathetic signaling to the pancreas blocks insulin release, making hyperglycemia common after stroke even in non-diabetic patients.[80] Hyperglycemia commonly extends beyond the acute period to involve impaired glucose tolerance at discharge or progression to diabetes.[80] While hyperglycemia is associated with larger infarcts and worse functional outcome, clinical trials found no therapeutic benefit to intensive blood glucose control, noting induced hypoglycemia is of equal concern.[81]

Low levels of thyroid hormone triiodothyronine (T3) have been observed immediately following stroke in more than half of patients, independent of pre-existing thyroid conditions.[82] Low serum T3 and positive thyroid autoantibodies were associated with worse outcomes following AIS.[82,83] Experimental T3 administration after MCAO reduced cerebral edema by inhibiting aquaporin-4 (AQP4) expression,[84] but clinical T3 supplementation has not been tested. Possible explanations of thyroid hormone disruption after AIS include pro-inflammatory mediators and glucocorticoid influence.[82]

Stroke disrupts the circadian rhythms and melatonin production, even when lesions do not affect pineal gland control.[85] A preclinical study observed a phase shift in melatonin release after stroke,[85] and clinical AIS studies reported decreased melatonin at day 1.[86] Melatonin treatment was neuroprotective after rodent stroke, where proposed mechanisms are mitochondrial apoptosis pathway inhibition and promotion of neuronal survival pathways,[87] suggesting the melatonin decrease following stroke may be from swift metabolism to combat stroke-induced damage.

Motor pathway disruption

Focal weakness as a result of motor pathway disruption is commonly seen post-AIS.[1,2,5] In addition to the motor system lesion, the pathophysiology of motor impairment stems also from the neuroplastic response, which alters upstream/down-

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stream non-lesioned networks.[88] Neuroimaging advancements (e.g., functional magnetic resonance imaging) foster detailed study of motor mapping after stroke.[89] Stroke patient testing found functional coupling between cortical activity and muscle output is markedly reduced in the acute phase and remains as such even when motor performance improves.[90] Interestingly, patients without apparent improvement still exhibited complex changes over time due to motor network connectivity.[91] Investigated mechanisms of motor functional recovery include axonal sprouting,[92,93] white matter repair,[94] neurogenesis,[95] and ipsilesional/contralesional network reorganization.[96] Just as consequences of stroke disability maladaptively alter cortical mapping and hinder recovery,[97] interventions targeting beneficial neuroplastic reorganization can strengthen tracts and improve recovery.[98,99]

Systemic consequences of motor pathway disruption and immobility

Motor pathway disruption and secondary immobility result in increased risk of venous thromboembolism (VTE) formation and widespread impacts to the musculoskeletal system.

Deep vein thrombosis and pulmonary embolism

Post-stroke VTE risk ranges from 8% to 30% and is independently associated with AIS severity.[1,100,101] Especially in the acute phase when hemodynamics, inflammation, and immobility compound, DVT may develop and travel to the lungs, yielding life-threatening PE.[100] Atherosclerotic predisposition was explored as a potential link between AIS and VTE, but causation was determined unlikely.[101] Infection, however, is associated with both coagulation system activation and immobilization.[101] As such, stroke-associated infection, prothrombotic activity, inflammation, dehydration, and immobility all serve roles in VTE development after stroke.[101] Prophylactic chemical DVT dosages and intermittent pneumatic compression reduce DVTs in AIS patients.[4,102]

Bone loss and remodeling disorder

Chronic stroke patients experience bone loss as mineral density declines significantly within one year and fracture risk increases up to 7-fold.[103] The pathophysiology of bone loss extends beyond immobility and asymmetric weight-bearing to disruption of central brain centers controlling skeletal homeostasis.[104] Inner ear vestibular lesioning in rats decreased bone formation without affecting resorption or locomotor activity;[104] these alterations in bone metabolism were attributed to SNS outflow and prevented with β2-adrenergic receptor blockade.[104] Likewise, serum bone formation marker N-terminal propeptide of type 1 procollagen (PINP) decreased independent of activity level in MCAO rats, with no change in resorption marker C-terminal telopeptide of type I collagen (CTX).[105] Further investigation is needed to define exact pathways involved with brain control of bone metabolism and stroke-induced remodeling disorders.

Skeletal muscle decline

Stroke prompts severe alterations to skeletal muscle tissue. Myofiber analysis identified a shift in myosin heavy chain predominance toward fast-twitch isoforms with initial denervation that declined as motor recovery and spasticity progressed.[106] Reduced gait speed is also associated with the post-stroke atrophy response.[106] Catabolic activity in mouse stroke-affected muscle was measured as increased expression of apoptotic and proteasome proteolytic markers and significantly correlated with infarct size.[107] Proposed contributors to skeletal muscle decline after stroke include reduced feeding and inactivity, sympathetic activation, and infection. Weight loss and muscle wasting, however, were not altered by high-caloric diet, sympathetic blockade, or antibiotic treatment,[107] suggesting mechanisms unique to stroke are responsible for the observed pathophysiology.

Exact molecular mechanisms of AIS-induced muscular decline are unclear. Myostatin is upregulated in post-stroke paretic muscle.[13,108] Myostatin inhibits the anabolic Akt/mammalian target of rapamycin (mTOR) pathway while increasing ubiquitin-proteasome activity and autophagy-lysosome proteolysis.[108] Inhibiting myostatin with PINTA745 promoted recovery of muscle mass and function in rodents.[108] Providing similar results, progressive resistance training decreased patient myostatin mRNA and stimulated muscle hypertrophy.[109] Separately, stroke upregulated pro-inflammatory interferon-γ-induced protein 10 (IP-10/CXCL10) in rat paretic muscle while prompting significant loss of brain-derived neurotrophic factor (BDNF), an important mediator for muscular repair.[13]

Data propose the systemic inflammatory response following AIS reaches skeletal muscle and influences its reparative capacity. Clinical data regarding muscle pathophysiology and associated mechanisms are limited and identifies a need for evidence-based models of rehabilitation that address stroke-induced skeletal muscle decline.

Conclusions and future directions

A growing body of evidence recognizes acute and chronic repercussions in peripheral tissues that worsen stroke evolution and alter prognosis (Figures 1 and 4). The aforementioned ramifications of ischemic stroke on autonomic, neuroendocrine,

Key points:

- The stroke-affected brain elicits wide-spread end organ dysfunction.
- Associated clinical manifestations arise via three overlapping major pathophysiological mechanisms:
  - › autonomic and neuroendocrine hyperactivation
  - › stroke-induced immunodepression
  - › disruption of central motor pathways
- Repercussions of stroke in the periphery worsen infarct evolution and functional outcome.
- An integrative progression in the future of stroke research will:
  - › address the complexity of systemic stroke pathophysiologies
  - › resist reductionist approaches to target organ systems in isolation
  - › consolidate knowledge across clinical and translational specialties to inform comprehensive therapeutics

Figure 4. Ischemic stroke: a systemic disease overview. An overview of the key points, as detailed in this review, is presented in a summary box.

immune, and motor systems are a conduit for injury response to move beyond the CNS. As presented herein, the individual clinical manifestations of AIS cannot simply be attributed to a single pathophysiological mechanism. Rather, each complication stems from a myriad of influencers and, likewise, prompts new deficits while magnifying the existing disease state.

The disappointing translational failure of AIS therapeutics and neuroprotective agents from bench to bedside is markedly pronounced in comparison to clinical trial successes across various other medical conditions.[110] This is partly related to the widespread complex pathophysiology of AIS in the body. Central to this issue is a call for integrative progression in stroke research, where experts consolidate therapeutic knowledge to address the complexity of stroke pathophysiology.

The concept of AIS as a systemic disease is clear when considering how pathophysiological mechanisms reach nearly every organ system in the human body. Hence, reductionist approaches that fail to consider bidirectional crosstalk between the CNS and periphery limit our ability to conceptualize new paradigms of patient care. A comprehensive understanding of post-stroke systems biology offers new direction to mechanistic discovery, defining multi-system targets to include the SNS, gut microbiome, neuroimmune interactions, and musculoskeletal metabolism. As such, collaborative research efforts across clinical specialties are necessary to inform methods and achieve the future of integrative stroke therapeutics.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2019.02978.

Disclosure

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Supplementary Table 1. Literature summary: systemic pathophysiology of ischemic stroke

Study	Summary
Immune system: immunosuppression	
Pre-clinical	
Offner et al. (2006a)[1]	Ischemic stroke activates the peripheral immune system with acute alterations in the spleen.
Offner et al. (2006b)[2]	Immunosuppression yields splenic atrophy, lower T-cell response, increased CD4+FoxP3+Treg cells.
Gu et al. (2012)[3]	Stroke affects T-cell populations and prompts an inflammatory shift from Th1 to Th2 response.
Gu et al. (2013)[4]	T-cell dysfunction after stroke is a main contributor to immune cell reduction in blood and spleen.
Braun et al. (2007)[5]	Q-VD-OPH prevented brain damage, splenic/thymic apoptosis, infection; improved survival.
Wong et al. (2011)[6]*	Hepatic iNKT cell behavior is altered via noradrenergic signaling; contributes to immunosuppression.
Kim et al. (2018)[7]	HMBG1 release causes inflammation in the brain and periphery and is associated with infection.
Walker et al. (2010)[8]	Other CNS injuries such as TBI reduce splenic volume and present some benefit to splenectomy.
Ajmo et al. (2008)[9]	Splenectomy 2 weeks pre-stroke decreased activated microglia/peripheral immune cells and infarct volume.
Dotson et al. (2015)[10]	Splenectomy 2 weeks pre-stroke decreased infarct size and inflammation in male mice but not females.
Kim et al. (2014)[11]	Pre-stroke splenectomy reduced monocyte/macrophage infiltration, not infarct growth/edema.
Zierath et al. (2017)[12]	Pre-stroke splenectomy had no effect on infarct volume, immune response to brain antigen, outcomes.
Belinga et al. (2016)[13]	Post-stroke splenectomy was neuroprotective via reduced TLR4/NF-κB expression, inflammation.
Kharrazian (2015)[14]	The gut microbiome is disrupted after other neurological injuries such as TBI.
Kigerl et al. (2018)[15]	Other CNS injuries such as SCI cause dysbiosis, intestinal permeability, bacterial translocation.
Singh et al. (2016)[16]*	Dysbiosis is associated with immune dysfunction/poor outcomes.
Stanley et al. (2018)[17]	Stroke alters gut microbiome within 24 hours.
Winek et al. (2016)[18]	Microbiota-depletion with antibiotics until 3 days pre-stroke caused colitis/decreased survival.
Tascilar et al. (2010)[19]	pMCAO caused intestinal mucosal damage/bacterial translocation at PSD1-3.
Benakis et al. (2016)[20]	Gut dysbiosis directly affects intestinal T-cells and exacerbates stroke evolution.
Crapser et al. (2016)[21]	Gut permeability/bacterial translocation contribute to infection after stroke induction.
Oyama et al. (2018)[22]	Gut permeability/bacterial translocation were not seen 24 to 72 hours post-tMCAO.
Clinical	
Chamorro et al. (2012)[23]*,†	Brain-immune interaction aids immunosuppression; increases infection/morbidity/mortality.
Liu et al. (2017)[24]†	Immunosuppression in the brain and periphery is controlled by separate and distinct mechanisms.
Johnston et al. (1998)[25]*	Pneumonia, UTI, congestive heart failure, and others contribute to mortality/negative outcomes.
Chiu et al. (2016)[26]	Splenic atrophy correlates with increased blood lymphocytes/decreased blood neutrophils.
Vogelgesang et al. (2008)[27]*	Slow CD4+ T cell count recovery may identify patients at risk of infection.
Mocco et al. (2006)[28]	Stroke activates the complement system, as demonstrated in peripheral blood levels of complement factor 3a (acute increase), 5a (delayed increase), and sC5b-9 (acute decrease).
Planas et al. (2012)[29]	Lymph node CD68+MHCII+macrophages near activated T-cells react to neuronal antigens.
Yang et al. (2011)[30]†	Brain-derived HMGB1 prompts inflammatory response, ischemia-reperfusion injury via TLR4.
Liesz et al. (2015)[31]*,†	DAMPs/HMBG1-RAGE contribute to monocyte exhaustion, lymphopenia, immune suppression.
Harms et al. (2008)[32]	PSD1 monocytic HLA-DR level is an independent predictor of infection.
Hug et al. (2009)[33]*	Infarct volume predicted SAP; associated with decreased HLA-DR, lymphocytopenia, monocyte dysfunction.
Hernandez-Jimenez et al. (2017)[34]	Impaired monocyte function/low HLA-DR correlate with circulating mtDNA; identifies infection risk.
Hoffmann et al. (2017)[35]*	Immunodepression (reduced monocytic HLA-DR) and dysphagia are independent, screenable predictors of SAP.
van de Beek et al. (2009)[36]*	Meta-analysis of post-stroke infection confirmed no benefit of prophylactic antibiotics over standard treatment.

Supplementary Table 1. Continued

Study	Summary
Badve et al. (2018)[37]*	Evidence is insufficient to recommend routine administration of post-stroke antibiotics for infection control.
Yin et al. (2015)[38]	Stroke causes gut dysbiosis and low blood TMAO levels.
Stanley et al. (2016)[39†]	Gut permeability promotes bacterial translocation and infection.
Yamashiro et al. (2017)[40,41]	Gut dysbiosis is associated with changes to host metabolism, inflammation.
Autonomic/neuroendocrine systems: sympathetic, parasympathetic, and HPA axis dysfunction	
Pre-clinical	
Prass et al. (2003)[42]	Catecholamines mediate immunodepression, infection, splenic atrophy, lymphocyte apoptosis.
Ajmo et al. (2009)[43]	Splenic response is regulated by catecholamines, α- and β-adrenergic receptors.
Yan et al. (2014)[44]	Sympathetic overactivation after stroke suppresses the immune system and reduces splenic volume; reversible with sympathetic block.
Mracsko et al. (2014)[45]	Immune compromise is mediated by SNS and HPA axis dysfunction.
Ay et al. (2011)[46]	Vagal stimulation confirmed role of α7-nAChR in reducing cerebral ischemia after stroke.
Han et al. (2014)[47]	α7-nAChR activation decreases cerebral inflammation following experimental stroke.
Engel et al. (2015)[48]	The parasympathetic anti-inflammatory cholinergic pathway is activated after stroke and contributed to pneumonia development; prevented with vagotomy or α7-nAChR deficiency.
Clinical	
Chamorro et al. (2007)[49]	Stroke-induced circulating catecholamines were associated with infection and 3 months mortality.
McCulloch et al. (2017)[50†]	β2-Adrenergic receptors mediate marginal zone B-cell/plasma IgM loss, high bacterial load, infection.
Dziedzic et al. (2007)[51]	β-Blockers reduced mortality independent of other risk factors.
Sykora et al. (2015)[52*]	On-stroke β-blockers decreased pneumonia/mortality; no effect on function.
De Raedt et al. (2011)[53]	Pre-stroke β-blocker use did not impact stroke severity/3 months outcome.
Maier et al. (2018)[54]	β-Blocker therapy had no reduction effect on post-stroke infections and was indicated as a possible contributor to UTI development.
Westendorp et al. (2016)[55]	Pre-stroke use of β-blockers was associated with higher infection incidence and SAP.
Starr et al. (2017)[56]	Non-selective β-blockers were associated with infection; no effect on disability/mortality.
Harms et al. (2011)[57*]	Anterior MCA lesion/high urine NE associated with low monocyte HLA-DR, predicted infection.
Haeusler et al. (2008)[58]	Immunosuppression presents with decreased lymphocytes and monocyte/Th1 function. Plasma cortisol was elevated in patients who later developed infection.
Barugh et al. (2014)[59]	Stroke-increased cortisol is associated with dependency, mortality, lymphopenia, stroke severity.
Respiratory system: stroke-associated pneumonia	
Pre-clinical	
Prass et al. (2006)[60]	Immunodeficiency facilitates spontaneous bacteremia/pneumonia via sympathetic activity.
Suda et al. (2018)[61]	Infection during hospitalization predicts worse functional outcome/death at 3 months.
Clinical	
Walter et al. (2007)[62]	Dysphagia, infection on admission, and NIHSS score predict SAP in NICU.
Lakshminarayan et al. (2010)[63]	Dysphagia screening predicts pneumonia, but broader selection criteria are warranted.
Kalra et al. (2015)[64]	Clinical trial found prophylactic antibiotics for SAP failed to improve outcomes/mortality.
Xi et al. (2017)[65]	Antibiotic use for SAP had no impact on functional outcomes or mortality.
Respiratory system: venous thromboembolisms–DVT/PE	
Clinical	

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Supplementary Table 1. Continued

Study	Summary
Kelly et al. (2004)[66]	Ischemic stroke patients are at risk for VTE; half of DVT and PE cases identified via magnetic resonance direct thrombus imaging had been overlooked by the attending team.
Pilato et al. (2013)[67]	Case report stressed clinical risks/concerns of post-stroke, post-thrombolysis PE.
Pongmoragot et al. (2013)[68]	PE is associated with in-hospital complications, disability, poor outcome, fatality within 1 year.
Bembenek et al. (2012)[69]	DVT incidence is 9% within 1 week, predicted by high CRP/pre-stroke disability.
Douds et al. (2014)[70]	VTE incidence was 3% despite VTE prophylaxis.
Rinde et al. (2016)[71]	VTE risk after stroke increases 3-fold within 3 months.
Sandercock et al. (2015)[72]	Routine anti-coagulants are not recommended for DVT/PE prevention due to hemorrhage risk.
CLOTS Trials Collaboration (2013)[73]	IPC devices are effective at reducing DVT risk.
Dennis et al. (2015)[74]	Anticoagulants decrease VTEs, increase bleed risk. IPCs reduced DVTs in immobile patients.
Morelli et al. (2019)[75]	Post-stroke infection may contribute to VTE development through coagulation system activation and resulting immobilization.
Urinary system: urinary tract infection	
Clinical	
Ersoz et al. (2007)[76]	Post-stroke UTI affects patients both with (50%) and without (24%) indwelling catheters.
Indredavik et al. (2008)[77]*	UTI is a common complication at 1 week and 3 months.
Stott et al. (2009)[78]	UTIs are associated with catheter use, disability, death.
Ifejika-Jones et al. (2013)[79]	In-hospital UTI predicts discharge setting dependency.
Huang et al. (2004)[80]	Prompting removal of urinary catheters decreased incidence of UTI in ICU patients.
Topal et al. (2005)[81]	Assessment prompts and bladder scans reduced catheter use and incidence of post-stroke UTI.
Titsworth et al. (2012)[82]	Programs emphasizing sterility, less catheter use, and early removal decreased use and UTI rates.
Chen et al. (2018)[83]	Portable bladder ultrasound (residual post-void volume) reduced UTIs even with catheterization.
Muramatsu et al. (2018)[84]	Antimicrobial catheter use did not reduce catheter-associated UTIs.
Urinary system: renal dysfunction	
Pre-clinical	
Hachinski et al. (1992)[85]	Renal nerve sympathetic activity/plasma NE present differently in left vs. right MCAO.
Clinical	
Dziedzic et al. (2004)[86]	Urine albumin and serum IL-6 are elevated after stroke.
Thomas et al. (2019)[87]	Urinary incontinence affects half of stroke patients with 15% still incontinent at 1 year; evidence to direct continence interventions is insufficient.
Pettersen et al. (2006)[88]	Urinary incontinence with impaired awareness after stroke predicted mortality and 3 months outcome.
Lee et al. (2016)[89]	Albuminuria after stroke is associated with additional adverse events and mortality.
Tsagalis et al. (2009)[90]	Low eGFR predicts cardiovascular complications/mortality within 10 years.
Shrestha et al. (2017)[91]	Stroke reduces eGFR, causes renal impairment.
Khatri et al. (2014)[92]	AKI is common and is associated with in-hospital mortality.
Nadkarni et al. (2015)[93]	AKI with dialysis is linked to higher discharge dependency/death.
Zorrilla-Vaca et al. (2018)[94]	AKI is associated with mortality; kidney function should be tested acutely.
Arnold et al. (2018)[95]	Inflammation and sympathetic output contribute to AKI within 48 hours of stroke.
Wu et al. (2016)[96]	Stroke increases risk of renal dysfunction, CKD, ESRD.
Cardiovascular system: cardiac dysfunction	
Pre-clinical	

Supplementary Table 1. Continued

Study	Summary
Jia et al. (2015)[97]	MCAO causes cardiac arrhythmias via glutamate-mediated PVN activation.
Bieber et al. (2017)[98]	Sympathetic signaling causes systolic dysfunction.
Clinical	
Daniele et al. (2002)[99]	Stroke causes new-onset ECG abnormalities, commonly arrhythmias.
Di Pasquale et al. (1988)[100]	Exercise testing revealed silent myocardial ischemia in stroke patients without symptoms of ischemic heart disease.
Adams et al. (2003)[101]	Some stroke patients may have asymptomatic coronary artery disease.
Ay et al. (2006)[102]	Cardiac troponin T is elevated without apparent injury.
Touze et al. (2005)[103]	Risk of MI and vascular death is high after ischemic stroke; screening efforts need improved.
Joundi et al. (2016)[104]	Cardiac arrest correlates with severe comorbidities/disability/30-day mortality.
Prosser et al. (2007)[105]	Serious adverse events are common during week 2 and predictable.
Yoshimura et al. (2008)[106]	TTC is common in women with insular/vertebrobasilar infarcts.
Jung et al. (2016)[107]	Post-stroke TTC is associated with insular infarcts, poor outcomes, inflammation, and mortality.
Milionis et al. (2013)[108]	Low left ventricular EF is associated with disability/comorbidity/death within 1 year.
Colivicchi et al. (2004)[109]	Right insular lesions are associated with cardiac dysfunction/arrhythmias.
Laowattana et al. (2006)[110]	Left insular lesions predicted MI/cardiac death; right had no association.
Korpelainen et al. (1996)[111]	Medulla lesions cause abnormal HRV.
Francica et al. (2015)[112]	Submaximal exercise improved HRV and cardiac vagal modulation.
Tahsili-Fahadan et al. (2017)[113]	Stroke induces abnormal ECG, arrhythmias, elevated enzymes.
Digestive system: gastrointestinal complications	
Pre-clinical	
Xu et al. (2012)[114]	MCAO increased intestinal mucosal damage/ghrelin, decreased motility.
Feng et al. (2010)[115]	CGRP at reperfusion attenuates gastric mucosal damage.
Clinical	
Hsu et al. (2009)[116]	GI hemorrhage increased proportionate to number of risk factors.
Chen et al. (2011)[117]	Risks for upper GI bleeds include impaired consciousness, longer stay, anticoagulant use.
Ogata et al. (2014)[118]	GI bleeds are rare and linked to mortality/poor outcome.
Li et al. (2017)[119]	Nearly half of patients suffer from bowel complications.
Harari et al. (2003)[120]	New-onset fecal incontinence affects 30% of patients, lasting up to 3 years.
Schaller et al. (2006)[121]	GI complications contribute to poor nutrition status linked with worse outcomes.
Yi et al. (2011)[122]	Constipation presented with impaired swallowing/colon motility.
Digestive system: hepatic dysfunction	
Pre-clinical	
Ottani et al. (2009)[123]	Stroke activates inflammatory/apoptotic pathways in the liver.
Puchowicz et al. (2008)[124]	Diet-induced ketosis proved neuroprotective in rat brain after MCAO.
Koch et al. (2017)[125]	Stroke induced hepatic ketogenesis and production of neuroprotective hepatic βOHB, mediated through noradrenergic innervation.
Wang et al. (2014)[126]	Catecholamine levels compromise hepatic insulin signaling, increase expression of gluconeogenic genes, and increase endoplasmic reticulum stress in the liver after stroke.
Clinical	

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Supplementary Table 1. Continued

Study	Summary
Pineda et al. (2008)[127]	Serum direct bilirubin is increased after stroke and associated with higher stroke severity.
Luo et al. (2013)[128]	Stroke elevated serum direct bilirubin and total bilirubin, correlating with stroke severity.
Muscari et al. (2014)[129]	Stroke alters unconjugated bilirubin/liver enzyme levels.
Endocrine system: insulin and hyperglycemia	
Pre-clinical	
Zhu et al. (2004)[130]	Optimal blood glucose must be maintained to avoid both hyper- and hypoglycemia.
Clinical	
Szczudlik et al. (2001)[131]	Post-stroke transient hyperglycemia is common and increases 30-day mortality.
Baird et al. (2003)[132]	Persistent hyperglycemia was associated with poor function and infarct expansion.
Vancheri et al. (2005)[133]	Post-load hyperglycemia at discharge predicts new-onset diabetes after 3 months.
Ntaios et al. (2010)[134]	Both hyper- and hypoglycemia are dangerous and affect outcome.
Gray et al. (2004)[135]	GKI infusion corrected hyperglycemia with low risk of hypoglycemia.
Bruno et al. (2008)[136]	Aggressive hyperglycemia correction was well-tolerated and superior to routine care.
Bruno et al. (2014)[137]	More evidence is needed to argue continuous insulin infusion vs. standard subcutaneous insulin.
Johnston et al. (2019)[138]	The SHINE clinical trial found no therapeutic benefit of aggressive treatment of hyperglycemia.
Endocrine system: low T3 and positive thyroid autoantibodies	
Pre-clinical	
Sadana et al. (2015)[139]	Neuroprotective T3 decreases edema via AQP4 suppression.
Clinical	
Zhang et al. (2010)[140]	Low T3 is associated with high severity scores and worse outcome.
Cho et al. (2014)[141]	Positive thyroid autoantibodies correlated with unfavorable outcomes.
Endocrine system: melatonin and circadian dysfunction	
Pre-clinical	
Meng et al. (2008)[142]	Stroke shifts timing of melatonin secretion.
Bhattacharya et al. (2014)[143]	Neuroprotective melatonin reduced infarct size, deficits, edema, and apoptosis.
Kilic et al. (2004)[144]	Melatonin protects against neuronal injury through inhibition of caspase-3.
Kilic et al. (2005)[145]	Acute neuroprotection from melatonin involves phosphatidyl inositol-3 kinase/Akt signaling.
Manev et al. (1996)[146]	Melatonin-deficient rats exhibit greater neurodegeneration.
Clinical	
Ritzenthaler et al. (2009)[147]	Stroke decreases nocturnal urinary melatonin excretion.
Vinogradov et al. (2015)[148]	Melatonin assisted recovery from sleep initiation disturbance insomnia.
Musculoskeletal system: bone loss and remodeling disorder	
Pre-clinical	
Borschmann et al. (2017)[149]	Serum PINP was significantly reduced at PSD28.
Vignaux et al. (2015)[150]	Bone metabolism/skeletal homeostasis disruption is attributed to sympathetic hyperactivation.
Clinical	
Kanis et al. (2001)[151]	Fracture risk increases 7-fold within first year of hospitalization.

Supplementary Table 1. Continued

Study	Summary
Pang et al. (2005)[152]	The paretic arm presents with lower BMD/BMC/lean mass and higher fat mass.
Pang et al. (2007)[153]	Upper extremity impairment measures are determinants of bone demineralization.
Kapral et al. (2017)[154]	Low-trauma fracture risk increases after stroke, supporting need for BMD screening.
Borschmann et al. (2018)[155]	Motor control, standing/walking recovery at 6 months inversely correlated with bone loss.
Musculoskeletal system: skeletal muscle pathophysiology	
Pre-clinical	
Desgeorges et al. (2015)[156]	Akt/mTOR repression and increased ubiquitin-proteasome activity contribute to atrophy.
Springer et al. (2014)[157]	Catabolic/proteasome activity were not prevented by autonomic/immune intervention.
Sen et al. (2017)[158]	Stroke disrupts inflammatory and regenerative signaling in muscle.
Desgeorges et al. (2017)[159]	Anti-myostatin treatment reduced muscle loss and improved function.
Clinical	
Jorgensen et al. (2001)[160]	Loss of lean muscle mass and BMC are common during the first year.
Benecke et al. (1983)[161]	Upper limb denervation occurs at 2 to 3 weeks, after which denervation decreases.
De Deyne et al. (2004)[162]	Myofiber phenotype changes contribute to functional disability.
Ryan et al. (2011)[163]	Resistance training repressed myostatin and induced hypertrophy.
Scherbakov et al. (2013)[164]	Muscle pathologies present but are not addressed in rehabilitation guidelines.
Referenced guidelines and statistic reports	
Benjamin et al. (2019)[165]*	Heart disease and stroke statistics—2019 update: a report from the American Heart Association
Collaborators GBDN (2019)[166]*	Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the global burden of disease study 2016
Collaborators GBDS (2019)[167]*	Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the global burden of disease study 2016
Powers et al. (2018)[168]*	2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association
Pierot et al. (2018)[169]	Standards of practice in acute ischemic stroke intervention: international recommendations
Sacks et al. (2018)[170]	Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke: from the American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of Neurointerventional Surgery (SNIS), and World Stroke Organization (WSO)
Johnson et al. (2016)[171]	Stroke: a global response is needed. World Health Organization Bulletin
Winstein et al. (2016)[172]*	Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association
Platz (2019)[173]*	Evidence-based guidelines and clinical pathways in stroke rehabilitation-an international perspective

CD4, cluster of differentiation 4; FoxP3, forkhead box protein P3; Treg, regulatory T-cell; Th, T-helper; Q-VD-OPH, quinolyl-valyl-O-methylaspartyl-[-2,6-difluorophenoxy]-methyl ketone; iNKT, invariant natural killer T (cell); HMBG1, high-mobility group box 1; CNS, central nervous system; TBI, traumatic brain injury; TLR, toll-like receptor; NF-κB, Nuclear factor κB; SCI, spinal cord injury; PSD, post-stroke day; pMCAO, permanent MCA occlusion; tMCAO, transient MCAO; UTI, urinary tract infection; MHC, major histocompatibility complex; DAMP, danger-associated molecular pattern; RAGE, receptor for advanced glycation end product; HLA-DR, human leukocyte antigen D related; SAP, stroke-associated pneumonia; mtDNA, mitochondrial DNA; TMAO, trimethylamine N-oxide; HPA, hypothalamic-pituitary adrenal; SNS, sympathetic nervous system; nAChR, nicotinic acetylcholine receptor; IgM, immunoglobulin M; MCA, middle cerebral artery; NE, norepinephrine; NIHSS, National Institutes of Health Stroke Scale; NICU, neurological intensive care unit; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; CRP, C-reactive protein; IPC, intermittent pneumatic compression; ICU, intensive care unit; IL-6, interleukin 6; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; PVN, paraventricular nucleus; ECG, electrocardiography; MI, myocardial infarction; TTC, Takotsubo cardiomyopathy; EF, ejection fraction; HRV, heart rate variability; CGRP, calcitonin gene-related peptide; GI, gastrointestinal; βOHB, β-hydroxybutyrate; GKI, glucose/potassium/insulin; SHINE, Stroke Hyperglycemia Insulin Network Effort; T3, triiodothyronine; AQP4, aquaporin-4; PINP, N-terminal propeptide of type 1 procollagen; BMD, bone mineral density; BMC, bone mineral content; mTOR, mammalian target of rapamycin.
*Publication addresses multiple organ systems; †Publication also contains pre-clinical data.

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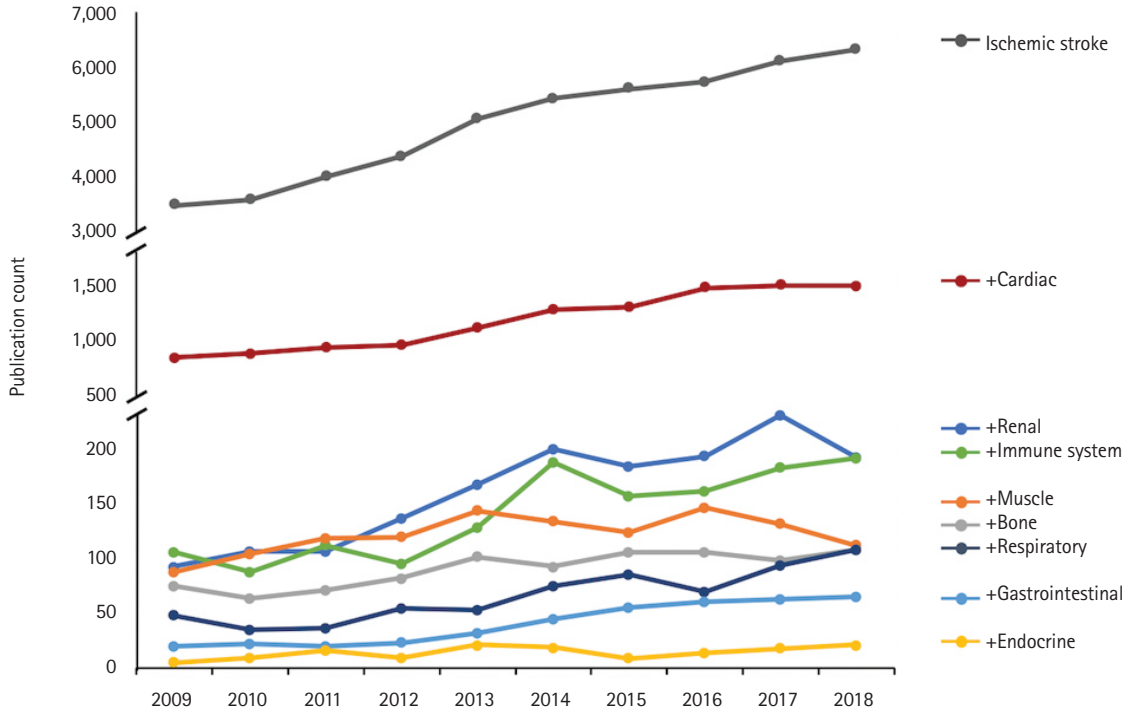

Supplementary Figure 1. A decade of ischemic stroke literature. Ischemic stroke drives development of systemic pathologies. Queries of stroke literature by year (National Center for Biotechnology Information and National Library of Medicine database; PubMed) show annual ischemic stroke publications have steadily increased in number since 2009. However, searches of ischemic stroke literature associated with various system-specific terminology (e.g., [(ischemic stroke) AND cardiac]) revealed little attention has been given to peripheral consequences of stroke over the past decade. Indeed, in 2018 when ischemic stroke publications numbered more than 6,000, seven of the eight peripheral systems examined had less than 200 publications, five of which had 100 or less. The eighth system reflected cardiac outcomes in ischemic stroke at around 1,400 publications—more in comparison given the clinical link in cardio- and cerebrovascular research—though still a mere fraction overall. Data are reported as publication count (y-axis; split twice to denote full spread across systems) by publication year (x-axis).

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