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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