

# **Stroke in Childhood**

## **Clinical guideline for diagnosis, management and rehabilitation**

**May 2017**

### **Appendix 4**

Contains:

- Search Strategy
- Data extraction form
- Evidence tables
- List of included studies

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The Royal College of Paediatrics and Child Health (RCPCH) is a registered charity in England and Wales (1057744) and in Scotland (SC038299).

# Appendix 4a: Search strategy

## Inclusion/exclusion criteria

### Inclusion

#### Population

- Children and young people (aged 29 days to 18 years at time of presentation) with arterial ischaemic stroke (AIS) and haemorrhagic stroke (HS) up until their transition to adult care
- Consideration will also be given to the management of unruptured, at risk vascular malformations in children and young people (arteriovenous malformations, cavernous malformations, cerebral aneurysms and arteriovenous fistulae)

#### Study design

- Observational studies (cohort, case-control, retrospective or prospective):
  - AIS questions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22
  - HS questions: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24
  - Parent/family impact, information and support needs: 25
  - Rehabilitation: 23, 24, 26, 27, 28, 29
- Cross-sectional studies:
  - AIS questions: 3, 4, 6, 7, 15
  - HS questions: 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15
  - Parent/family impact, information and support needs: 25
- Randomised controlled trials:
  - AIS questions: 3, 4, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22
  - HS questions: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24
  - Parent/family impact, information and support needs: 25
  - Rehabilitation: 23, 24, 26, 27, 28, 29
- Systematic reviews:
  - AIS questions: 3, 5, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22
  - HS questions: 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24
  - Parent/family impact, information and support needs: 25
  - Rehabilitation: 23, 24, 26, 27, 28, 29

### Exclusion

#### Population

- Neonates (0 to 28 days)
- Children and young people with other types of stroke syndromes
- Eighteen years or more at the time of presentation

#### Study design

- Case reports: excluded for all questions where fewer than five children are reported on
- Literature reviews: excluded for all questions
- Editorials: excluded for all questions
- Letters: excluded for all questions
- Unpublished research: excluded for all questions

#### Limits

- AIS searches were carried out on literature published from January 1995 to December 2015.
- HS searches were carried out on literature published from January 1995 to February 2016
- English language only, no grey literature, no hand searching of journals

# Search strategies

## Arterial ischaemic stroke (AIS)

### Screening, diagnosis and further investigations (search 2)

Database(s): Embase

(Dates searched: January 1995 – November 2015)

#	Searches
1	exp cerebrovascular accident/
2	exp brain hypoxia/or brain infarction/
3	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
5	brain ischemia/
6	arterial ischemic stroke.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	child/
9	adolescent/
10	infant/
11	(child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric or preschool).ti,ab.
12	8 or 9 or 10 or 11
13	7 and 12
14	diagnosis/
15	diagnostic procedure/or checklist/or clinical assessment tool/or clinical observation/
16	diagnostic imaging/or multimodal imaging/
17	*early diagnosis/
18	emergency health service/
19	emergency care/
20	"sensitivity and specificity"/
21	risk factor/
22	(prehospital\$ or pre-hospital\$ or pre hospital\$ or ambulance\$ or paramedic\$ or EMS).tw.
23	(stroke\$ adj5 (scale\$ or screen\$ or checklist\$ or assess\$ or identif\$ or recogni\$ or evaluat\$ or diagnos\$ or detect\$)).tw.
24	(predictive adj5 value\$).tw.
25	(sensitivity or specificity).tw.
26	(likelihood adj3 ratio\$).tw.
27	(sign*1 or symptom* or present*5 or dignos*3 or assessment or feature*1).ti,ab.

28	sickle cell anemia/
29	congenital heart disease/
30	"inborn error of metabolism"/co [Complication]
31	genetic disorder/co [Complication]
32	moyamoya disease/
33	infection/co [Complication]
34	computer assisted tomography/
35	echography/
36	nuclear magnetic resonance imaging/or diffusion weighted imaging/
37	neurologic examination/
38	(imag*3 or MRI or diffusion weighted mri or tomograph* or computed tomography or x-ray or sonograph*).ti,ab.
39	(echocardiogra* or "duplex or doppler adj uss or ultrasonogra*" or angiogra*).ti,ab.
40	(blood adj (test* or coagul* or clotting or thrombophilia)).ti,ab.
41	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	13 and 41
43	comment/or editorial/or letter/or historical article/
44	case report/
45	letter.pt.
46	editorial.pt.
47	note.pt.
48	exp animal/not human/
49	nonhuman/
50	exp animal studies/
51	animals, laboratory/
52	exp animal experiment/
53	exp experimental animal/
54	exp animal model/
55	exp rodentia/
56	conference abstract.pt.
57	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58	42 not 57
59	limit 58 to (english language and yr="1995 - 2015")

## Database(s): MEDLINE

(Dates searched: January 1995 – November 2015)

#	Searches
1	diagnosis/or diagnosis, differential/or "diagnostic techniques and procedures"/or diagnostic imaging/or early diagnosis/
2	Emergency Medical Services/or prehospital diagnosis.mp.
3	(prehospital\$ or pre-hospital\$ or pre hospital\$ or ambulance\$ or paramedic\$ or EMS).tw.
4	(stroke\$ adj5 (scale\$ or screen\$ or checklist\$ or assess\$ or identif\$ or recogni\$ or evaluat\$ or diagnos\$ or detect\$)).tw.
5	"Sensitivity and Specificity"/
6	(predictive adj5 value\$).tw.
7	(sensitiv\$ or specificity).tw.
8	(likelihood adj3 ratio\$).tw.
9	(sign*1 or symptom* or present*5 or dignos*3 or assessment or feature*1).ti,ab.
10	risk factors/
11	(risk* adj3 (factor* or indicator* or predictor*)).ti,ab.
12	Anemia, Sickle Cell/
13	Heart Defects, Congenital/
14	Genetic Diseases, Inborn/
15	Metabolic Diseases/
16	Heart Diseases/
17	Arterial Occlusive Diseases/or Moyamoya Disease/
18	Infection/co [Complications]
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
20	"diagnostic techniques and procedures"/or diagnostic imaging/or tomography/or ultrasonography/or diagnostic techniques, neurological/
21	Tomography, X-Ray Computed/or Magnetic Resonance Imaging/
22	Diffusion Magnetic Resonance Imaging/
23	(imag*3 or MRI or diffusion weighted mri or tomograph* or computed tomography or x-ray or sonograph*).ti,ab.
24	(echocardiogra* or "duplex or doppler adj uss or ultrasonogra*" or angiogra*).ti,ab.
25	(blood adj (test* or coagul* or clotting or thrombophilia)).ti,ab.
26	20 or 21 or 22 or 23 or 24 or 25
27	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
28	19 or 26 or 27
29	Stroke/
30	Brain Ischemia/

31	Cerebrovascular Disorders/
32	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
33	"arterial ischemic stroke*".ti,ab.
34	Carotid Artery Thrombosis/
35	brain infarction/
36	"arterial ischemic stroke*".ti,ab.
37	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
38	(carotid adj3 disease).ti,ab.
39	(carotid adj3 thrombosis).ti,ab.
40	"brain attack*".ti,ab.
41	((intracranial or cerebral or intra-cranial) adj3 (thrombosis or disease* or embol*)).ti,ab.
42	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	Pediatrics/
44	adolescent/or child/or infant/
45	(kid*1or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
46	43 or 44 or 45
47	42 and 46
48	comment/or editorial/or letter/or historical article/
49	case reports/
50	exp animals/not humans/
51	Animals, Laboratory/
52	exp Animal Experimentation/
53	exp models, animal/
54	exp Rodentia/
55	48 or 49 or 50 or 51 or 52 or 53 or 54
56	28 and 47
57	56 not 55
58	limit 57 to (english language and yr="1995 -2015")

### Management, rehab and long term care (search 3)

Database(s): Embase

(Dates searched: January 2000 – November 2015)

#	Searches
1	pediatrics/
2	child/

3	adolescent/
4	(child* or teenage* or pediatric* or paediatric* or adolescent* or baby or babies or kid*1).ti,ab.
5	1 or 2 or 3 or 4
6	psychosocial rehabilitation/or cognitive rehabilitation/or pediatric rehabilitation/or rehabilitation/
7	occupational therapy/
8	physiotherapy/
9	psychotherapy/
10	treatment outcome/or outcome assessment/
11	disability/
12	daily life activity/
13	speech disorder/
14	cognitive defect/
15	learning disorder/
16	psychosocial disorder/
17	communication disorder/or language disability/
18	speech rehabilitation/or speech therapy/
19	motor dysfunction/
20	psychomotor disorder/
21	(standard* or "goal setting" or framework or elements or assessment or management or disabilit*).ti,ab.
22	((standard* or sensory or motor or function* or cogniti*2 or disabilit* or visual or hearing or speech or language or learning or social or psychological or neurological or intellectual or psychomotor or communication or framework) adj3 (assessment* or management or impairment or rehabilitation)).ti,ab.
23	(goal setting or early intervention or strategy or developmental care or early ambulation or long term care or long term management).ti,ab.
24	(care plan or individual* care or tailored care or discharge plan* or community care or hospital care).ti,ab.
25	(hydration or nutrition* or swallowing or dysphagia or mobili* or strength or pain or enviroment* or spasticity or therapy).ti,ab.
26	(bimanual or mirror therapy or treadmill training or robotics or TMS or stimulation or FES or botulinum toxin or visual reality or orthotic*).ti,ab.
27	human relation/
28	electrostimulation therapy/
29	kinesiotherapy/
30	motor activity/
31	neuromuscular electrical stimulation/
32	cerebrovascular accident/
33	brain ischemia/

34	brain injury/or acquired brain injury/
35	(cerebrovascular accident* or cerebral ischemia or stroke or brain injury).ti,ab.
36	brain infarction/
37	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
38	32 or 33 or 34 or 35 or 36
39	5 and 37 and 38
40	limit 39 to (human and english language and yr="2000 -Current")
41	limit 40 to (book or conference abstract or conference proceeding or editorial or erratum or letter or note or report or trade journal)
42	40 not 41
43	from 42 keep 10000-10314

## Database(s): MEDLINE

(Dates searched: January 2000 – November 2015)

#	Searches
1	Pediatrics/
2	exp adolescent/or exp child/or exp child, preschool/
3	(child* or teenage* or pediatric* or paediatric* or adolescent* or baby or babies or kid*1).ti,ab.
4	1 or 2 or 3
5	Rehabilitation/
6	Developmental Disabilities/or Psychomotor Disorders/or Cognition Disorders/or Psychomotor Performance/or Motor Skills/
7	Treatment Outcome/or "Outcome Assessment (Health Care)"/
8	"Activities of Daily Living"/
9	Disability Evaluation/
10	communication disorders/or language disorders/or learning disorders/
11	Speech Disorders/
12	Interpersonal Relations/
13	early ambulation/or exercise therapy/or occupational therapy/or "rehabilitation of speech and language disorders"/or language therapy/or therapy, computer-assisted/
14	Motor Activity/
15	(standard* or "goal setting" or framework or elements or assessment or management or disabilit*).ti,ab.
16	"Early Intervention (Education)"/
17	((standard* or sensory or motor or function* or cogniti*2 or disabilit* or visual or hearing or speech or language or learning or social or psychological or neurological or intellectual or psychomotor or communication or framework) adj3 (assessment* or management or impairment or rehabilitation)).ti,ab.

18	(goal setting or early intervention or strategy or developmental care or early ambulation or long term care or long term management).ti,ab.
19	(care plan or individual* care or tailored care or discharge plan* or community care or hospital care).ti,ab.
20	(hydration or nutrition* or swallowing or dysphagia or mobili* or strength or pain or enviroment* or spasticity or therapy).ti,ab.
21	physical therapy modalities/or electric stimulation therapy/or exercise movement techniques/or exercise therapy/
22	(bimanual or mirror therapy or treadmill training or robotics or TMS or stimulation or FES or botulinum toxin or visual reality or orthotic*).ti,ab.
23	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	Brain Injuries/
25	cerebrovascular disorders/or brain ischemia/or brain infarction/or stroke/
26	(cerebrovascular accident* or cerebral ischemia or stroke or brain injury).ti,ab.
27	24 or 25 or 26
28	4 and 23 and 27
29	limit 28 to (english language and humans and yr="2000 -2015")
30	limit 29 to (case reports or comment or editorial)
31	29 not 30

## Database(s): PsycInfo

(Dates searched: January 2000 – November 2015)

#	Searches
1	cerebrovascular accidents/
2	cerebral ischemia/
3	brain damage/or traumatic brain injury/
4	arterial ischemic stroke.ti,ab.
5	(cerebrovascular accident* or cerebral ischemia or stroke* or brain injury).ti,ab.
6	1 or 2 or 3 or 4 or 5
7	pediatrics/
8	(child* or teenage* or pediatric* or paediatric* or adolescent* or baby or babies or kid*1).ti,ab.
9	7 or 8
10	6 and 9
11	exp rehabilitation/or "activities of daily living"/
12	exp psychosocial rehabilitation/
13	exp neuropsychological rehabilitation/or cognitive rehabilitation/or neuropsychological assessment/or neurorehabilitation/
14	rehabilitation.ti,ab.

15	educational psychology/
16	motor performance/
17	exp physical therapy/
18	exp Perception/or exp Perceptual Motor Processes/
19	exp Motor Skills/
20	speech therapy/or communication disorders/or language therapy/
21	cognitive therapy/
22	(training or re-training or therap* or rehab* or treatment*).ti,ab.
23	goal setting/
24	interdisciplinary treatment approach/
25	(bimanual or mirror therapy or treadmill training or robotics or TMS or stimulation or FES or botulinum toxin or visual reality or orthotic*).ti,ab.
26	computer games/or computer simulation/
27	problem solving/
28	exp school transition/or schools/
29	(school* or educat* or learn* or teach*).ti,ab.
30	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31	10 and 30
32	limit 31 to (human and english language and (100 childhood or 140 infancy <2 to 23 mo> or 160 preschool age or 180 school age or 200 adolescence ) and yr="2000 -2015")

## Medical, surgical and endovascular interventions (search 4)

Database(s): Embase

(Dates searched: January 1995 – November 2015)

#	Searches
1	exp cerebrovascular accident/
2	exp brain hypoxia/or brain infarction/
3	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
5	brain ischemia/
6	arterial ischemic stroke.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	child/
9	adolescent/
10	infant/
11	(child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric or preschool).ti,ab.

12	8 or 9 or 10 or 11
13	7 and 12
14	comment/or editorial/or letter/or historical article/
15	case report/
16	letter.pt.
17	editorial.pt.
18	note.pt.
19	exp animal/not human/
20	nonhuman/
21	exp animal studies/
22	animals, laboratory/
23	exp animal experiment/
24	exp experimental animal/
25	exp animal model/
26	exp rodentia/
27	conference abstract.pt.
28	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	13 not 28
30	limit 29 to (english language and yr="1995 -Current")
31	interventional radiology/
32	angioplasty/or laser angioplasty/or angioplasty catheter/
33	laser angioplasty/or percutaneous transluminal angioplasty/
34	percutaneous transluminal angioplasty/or percutaneous transluminal angioplasty balloon/
35	thrombectomy/or thrombectomy catheter/
36	embolectomy/
37	(interventional adj3 (radiolog\$ or radiograph\$ or neuroradiolog\$)).tw.
38	(thrombectomy or embolectomy or atherect\$).tw.
39	(thromboaspiration or arterial recanalization).tw.
40	cerebral revascularization/
41	reperfusion/
42	dilatation/
43	((clot or thrombus or thrombi or embol\$) adj5 (aspirat\$ or remov\$ or retriev\$ or fragment\$ or retract\$ or extract\$ or obliterated\$ or dispers\$)).tw.
44	(ultrasound\$ or ultrasonic\$ or ultrasonogra\$ or sonograph\$ or insonation).tw.
45	((transcranial adj5 doppler) or TCD or TCCD).tw.

46	(sonothrombolysis or sonothromboly\$ or sonolys\$ or sonothrombotripsy or thrombotripsy).tw.
47	fibrinolytic therapy/
48	fibrinolysis/or fibrinolytic agent/or plasmin/or plasminogen/or plasminogen activator/
49	tissue plasminogen activator/or urokinase/
50	(thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
51	(tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
52	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase).tw.
53	secondary prevention/
54	decompression surgery/or decompressive craniectomy/
55	neurosurgery/
56	craniotomy/
57	skull surgery/
58	(decompress\$ or craniectom\$ or craniotom\$ or hemi?craniect\$ or trepa\$ or treph\$).tw.
59	antithrombocytic agent/or anticoagulant agent/
60	blood transfusion/or exchange blood transfusion/
61	sickle cell anemia/
62	moyamoya disease/
63	congenital heart disease/co, dm, pc, rt, su, th [Complication, Disease Management, Prevention, Radiotherapy, Surgery, Therapy]
64	(refer*3 or prevent* or treat* or management or surgical or medical or intervention* or therap*).ti,ab.
65	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66	29 and 65
67	exp cerebrovascular accident/
68	exp brain hypoxia/or brain infarction/
69	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
70	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
71	brain ischemia/
72	arterial ischemic stroke.mp.
73	67 or 68 or 69 or 70 or 71 or 72
74	child/
75	adolescent/
76	infant/
77	(child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric or preschool).ti,ab.
78	74 or 75 or 76 or 77

79	73 and 78
80	diagnosis/
81	diagnostic procedure/or checklist/or clinical assessment tool/or clinical observation/
82	diagnostic imaging/or multimodal imaging/
83	*early diagnosis/
84	emergency health service/
85	emergency care/
86	"sensitivity and specificity"/
87	risk factor/
88	(prehospital\$ or pre-hospital\$ or pre hospital\$ or ambulance\$ or paramedic\$ or EMS).tw.
89	(stroke\$ adj5 (scale\$ or screen\$ or checklist\$ or assess\$ or identif\$ or recogni\$ or evaluat\$ or diagnos\$ or detect\$)).tw.
90	(predictive adj5 value\$).tw.
91	(sensitivity or specificity).tw.
92	(likelihood adj3 ratio\$).tw.
93	(sign*1 or symptom* or present*5 or dignos*3 or assessment or feature*1).ti,ab.
94	sickle cell anemia/
95	congenital heart disease/
96	"inborn error of metabolism"/co [Complication]
97	genetic disorder/co [Complication]
98	moyamoya disease/
99	infection/co [Complication]
100	computer assisted tomography/
101	echography/
102	nuclear magnetic resonance imaging/or diffusion weighted imaging/
103	neurologic examination/
104	(imag*3 or MRI or diffusion weighted mri or tomograph* or computed tomography or x-ray or sonograph*).ti,ab.
105	(echocardiogra* or "duplex or doppler adj uss or ultrasonogra*" or angiogra*).ti,ab.
106	(blood adj (test* or coagul* or clotting or thrombophilia)).ti,ab.
107	80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106
108	79 and 107
109	comment/or editorial/or letter/or historical article/
110	case report/
111	letter.pt.

112	editorial.pt.
113	note.pt.
114	exp animal/not human/
115	nonhuman/
116	exp animal studies/
117	animals, laboratory/
118	exp animal experiment/
119	exp experimental animal/
120	exp animal model/
121	exp rodentia/
122	conference abstract.pt.
123	109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122
124	108 not 123
125	limit 124 to (english language and yr="1995 -Current")
126	66 and 125
127	66 not 126
128	limit 127 to (english language and yr="1995 -2015")

## Database(s): MEDLINE

(Dates searched: January 1995 – November 2015)

#	Searches
1	Stroke/
2	Brain Ischemia/
3	Cerebrovascular Disorders/
4	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
5	"arterial ischemic stroke*".ti,ab.
6	Carotid Artery Thrombosis/
7	brain infarction/
8	"arterial ischemic stroke*".ti,ab.
9	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
10	(carotid adj3 disease).ti,ab.
11	(carotid adj3 thrombosis).ti,ab.
12	"brain attack*".ti,ab.
13	((intracranial or cerebral or intra-cranial) adj3 (thrombosis or disease* or embol*)).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15	Pediatrics/
16	adolescent/or child/or infant/
17	(kid*1or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
18	15 or 16 or 17
19	14 and 18
20	comment/or editorial/or letter/or historical article/
21	case reports/
22	exp animals/not humans/
23	Animals, Laboratory/
24	exp Animal Experimentation/
25	exp models, animal/
26	exp Rodentia/
27	20 or 21 or 22 or 23 or 24 or 25 or 26
28	19 not 27
29	limit 28 to (english language and yr="1995 -Current")
30	limit 28 to english language
31	radiography, interventional/or radiology, interventional/
32	catheterization/or angioplasty/or angioplasty, balloon/or angioplasty, balloon, laser-assisted/or angioplasty, laser/or atherectomy/or balloon dilatation/or catheter ablation/
33	thrombectomy/or embolectomy/
34	((interventional adj3 (radiolog\$ or radiograph\$ or neuroradiolog\$)).tw.
35	Cerebral Revascularization/or reperfusion/or dilatation/
36	((thrombectomy or embolectomy or atherect\$).tw.
37	((thromboaspiration or arterial recanalization).tw.
38	((clot or thrombus or thrombi or embol\$) adj5 (aspirat\$ or remov\$ or retriev\$ or fragment\$ or retract\$ or extract\$ or obliterated\$ or dispers\$)).tw.
39	((ultrasound\$ or ultrasonic\$ or ultrasonogra\$ or sonograph\$ or insonation).tw.
40	((transcranial adj5 doppler) or TCD or TCCD).tw.
41	((sonothrombolysis or sonothromboly\$ or sonolys\$ or sonothrombotripsy or thrombotripsy).tw.
42	thrombolytic therapy/
43	fibrinolytic agents/or plasmin/or plasminogen/or tissue plasminogen activator/or exp plasminogen activators/or urokinase-type plasminogen activator/
44	fibrinolysis/
45	((thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
46	((tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.

47	(anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase).tw.
48	Secondary Prevention/
49	decompression, surgical/or neurosurgical procedures/or craniotomy/or trephining/
50	(decompress\$ or craniectom\$ or craniotom\$ or hemi?craniect\$ or trepa\$ or treph\$).tw.
51	Platelet Aggregation Inhibitors/
52	Anticoagulants/
53	Blood Transfusion/
54	Anemia, Sickle Cell/
55	Moyamoya Disease/
56	Cardiovascular Abnormalities/co, pc, rt, su, th [Complications, Prevention & Control, Radiotherapy, Surgery, Therapy]
57	(refer*3 or prevent* or treat* or management or surgical or medical or intervention*).ti,ab.
58	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59	30 and 58
60	limit 59 to (english language and yr="1995 -2015")
121	120 not 119 (this is minus search 2 to avoid the duplication*)

## Database(s): MEDLINE (including sickle cell)

(Dates searched: January 1995 – November 2015)

#	Searches
1	stroke/
2	cerebrovascular disorders/
3	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4	(carotid adj3 disease).ti,ab.
5	"brain attack*".ti,ab.
6	brain infarction/
7	brain ischemia/
8	"arterial ischemic stroke*".ti,ab.
9	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
10	((intracranial or cerebral or intra-cranial) adj3 (thrombosis or disease* or embol*)).ti,ab.
11	carotid artery thrombosis/
12	(carotid adj3 thrombosis).ti,ab.
13	intracranial hemorrhage/
14	brain hemorrhage/

15	"hemorrhagic stroke".ti,ab.
16	"haemorrhagic stroke".ti,ab.
17	(brain adj3 (bleed or haemorrhage or hemorrhage)).ti,ab.
18	pediatrics/
19	adolescent/or child/or infant/
20	(kid*1 or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
21	"sickle cell anemia".ti,ab.
22	Anemia, sickle cell/
23	"sickle cell disease".ti,ab.
24	"sickle cell disorders".ti,ab.
25	"bone marrow transplant*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
26	"stem cell transplant*".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
27	cord blood stem cell transplantation/
28	hematopoietic stem cell transplantation/
29	mesenchymal stem cell transplantation/
30	peripheral blood stem cell transplantation/
31	bone marrow transplantation/
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
33	18 or 19 or 20
34	21 or 22 or 23 or 24
35	25 or 26 or 27 or 28 or 29 or 30 or 31
36	32 and 33 and 34 and 35

## Database(s): Cochrane (including sickle cell)

(Dates searched: January 1995 – November 2015)

#	Searches
1	MeSH descriptor: [Stroke] explode all trees
2	MeSH descriptor: [Cerebrovascular Disorders] explode all trees
3	stroke*
4	CVA
5	poststroke*
6	apoplexy
7	"cerebrovascular accident"
8	carotid near/3 disease
9	"brain attack"
10	MeSH descriptor: [Brain Infarction] explode all trees
11	MeSH descriptor: [Brain Ischemia] explode all trees
12	arterial ischemic stroke
13	((cerebro* or brain or cerebral or intra-cranial) near/3 (infarct* or accident or ischemia))
14	((intracranial or cerebral or intra-cranial) near/3 (thrombosis or disease* or embol*))

15	MeSH descriptor: [Carotid Artery Thrombosis] explode all trees
16	carotid near/3 thrombosis
17	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
18	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
19	"hemorrhagic stroke"
20	"haemorrhagic stroke"
21	((brain) near/3 (bleed or haemorrhage or hemorrhage))
22	MeSH descriptor: [Pediatrics] explode all trees
23	MeSH descriptor: [Adolescent] explode all trees
24	MeSH descriptor: [Child] explode all trees
25	MeSH descriptor: [Infant] explode all trees
26	kid* or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric
27	"sickle cell anemia"
28	MeSH descriptor: [Anemia, Sickle Cell] explode all trees
29	"sickle cell disease"
30	"sickle cell disorders"
31	"bone marrow transplant"
32	"stem cell transplant"
33	MeSH descriptor: [Cord Blood Stem Cell Transplantation] explode all trees
34	MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees
35	MeSH descriptor: [Mesenchymal Stem Cell Transplantation] explode all trees
36	MeSH descriptor: [Bone Marrow Transplantation] explode all trees
37	MeSH descriptor: [Peripheral Blood Stem Cell Transplantation] explode all trees
38	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 21
39	22 or 23 or 24 or 25 or 26
40	27 or 28 or 29 or 30
41	31 or 32 or 33 or 34 or 35 or 36 or 37
42	38 and 39 and 40 and 41

# Haemorrhagic stroke (HS)

## Screening, diagnosis and further investigations (search 2)

Database(s): Embase

(Dates searched: January 1995 – January 2016)

#	Searches
1	child
2	adolescent
3	infant
4	(kid*1 or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
5	1 or 2 or 3 or 4
6	cerebrovascular accident
7	brain hypoxia
8	brain hemorrhage
9	subarachnoid hemorrhage
10	cerebrovascular disease
11	(cerebrovascular adj3 (accident or disorder* or hemorrhage or haemorrhage or bleed)).ti,ab.
12	(brain adj3 (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)).ti,ab.
13	stroke.ti,ab.
14	(CVA or poststroke or apoplexy).ti,ab.
15	((hemorrhagic or haemorrhagic) adj3 stroke).ti,ab.
16	(brainstem adj3 (accident or haemorrhage or hemorrhage or bleed)).ti,ab.
17	(cerebral adj3 (accident or disease or haemorrhage or hemorrhage or bleed)).ti,ab.
18	(carotid adj3 (disease or haemorrhage or hemorrhage)).ti,ab.
19	(intracranial adj3 (hemorrhage or haemorrhage or bleed)).ti,ab.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	blood clotting disorder
22	congenital blood vessel malformation/or cerebrovascular malformation/or arteriovenous malformation
23	"inborn error of metabolism"
24	moyamoya disease
25	infection
26	intracranial aneurysm
27	aneurysm
28	cavernous hemangioma
29	arteriovenous fistula

30	genetic disorder
31	heart disease
32	von Willebrand disease
33	fibrinogen
34	blood clotting factor 10/or blood clotting factor 9/or recombinant blood clotting factor 8/or blood clotting factor 10 deficiency/or blood clotting factor 5 deficiency/or blood clotting factor 11 deficiency/or blood clotting factor 8/or blood clotting factor 7/or blood clotting factor 7 deficiency/or blood clotting factor 13 deficiency/or blood clotting factor/or recombinant blood clotting factor 7a
35	coagulopathy.tw.
36	congenital vascular malformation.tw.
37	congenital vascular lesion.tw.
38	congenital vascular anomal*.tw.
39	acquired vascular anomal*.tw.
40	acquired vascular lesion.tw.
41	inborn error of metabolism.tw.
42	genetic disorder.tw.
43	moyamoya.tw.
44	infection.tw.
45	(arteriovenous adj (malformation or fistula)).tw.
46	AVM.tw.
47	((intracranial or arterial) adj aneurysm).tw.
48	vascular abnormality.tw.
49	(cavernous malformation or cavernoma).tw.
50	((warfarin or phenytoin or dilantin or barbiturate) adj4 pregnancy).tw.
51	(risk adj (factor or indicator or predictor)).tw.
52	genetic disease.tw.
53	(heart adj (disease or defect)).tw.
54	arterial occlusive disease.tw.
55	vitamin k deficiency.tw.
56	von willebrand disease.tw.
57	fibrogen.tw.
58	(F1 or FII or FV or FVII or FVIII or FX or FXI or FIX or FXIII).tw.
59	(factor adj (I or II or V or VII or VIII or IX or XI or XIII)).tw.
60	(inherited coagulation adj (disorder or deficiency)).tw.
61	(inherited platelet adj (disorder or deficiency)).tw.

62	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61
63	diagnosis
64	clinical assessment tool
65	clinical observation
66	checklist
67	multimodal imaging
68	early diagnosis
69	emergency health service
70	emergency care
71	risk factor
72	ambulance
73	screening
74	recognition
75	predictive value
76	"sensitivity and specificity"
77	symptom
78	clinical feature
79	diagnosis.tw.
80	(diagnostic adj (procedure or technique or imaging)).tw.
81	(clinical adj (assessment tool or observation or feature)).tw.
82	(checklist or screening or assessment or identification or recognition or evaluation or detection).tw.
83	multimodal imaging.tw.
84	early diagnosis.tw.
85	(emergency adj (health service or care or medical services)).tw.
86	risk factor.tw.
87	(prehospital or ambulance or paramedic or EMS).tw.
88	scale.tw.
89	(predictive value or sensitivity or specificity or likelihood ratio).tw.
90	(sign or symptom or present or feature).tw.
91	63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90
92	computer assisted tomography
93	diffusion weighted imaging
94	neurologic examination

95	imaging
96	X ray
97	echography
98	nuclear magnetic resonance imaging
99	echocardiography
100	angiography
101	blood clotting
102	hemophilia
103	physical examination
104	eye examination
105	stiff neck
106	magnetic resonance angiography
107	computed tomographic angiography
108	digital subtraction angiography
109	((computer assisted or computed) adj tomography).tw.
110	tomograph*.tw.
111	((diffusion weighted or nuclear magnetic resonance) adj imaging).tw.
112	neurologic examination.tw.
113	(imaging or x-ray or MRI or diffusion weighted MRI or echography or nuclear magnetic resonance imaging or sonography or echocardiogram or duplex doppler USS or ultrasonography or angiogram).tw.
114	(blood adj (test or coagulation or clotting)).tw.
115	(hemophilia or haemophilia).tw.
116	magnetic resonance venography.tw.
117	MRV.tw.
118	((physical or eye) adj examination).tw.
119	(neck adj stiff*).tw.
120	magnetic resonance angiogram.tw.
121	computed tomography angiogram.tw.
122	(digital subtraction angiography or DSA).tw.
123	92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122
124	5 and 20
125	62 or 91 or 123
126	124 and 125
127	limit 126 to (human and english language and journal and (child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))

## Database(s): MEDLINE

(Dates searched: January 1995 – January 2016)

#	Searches
1	child
2	adolescent
3	infant
4	(kid*1 or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
5	1 or 2 or 3 or 4
6	cerebrovascular accident
7	brain hypoxia
8	brain hemorrhage
9	subarachnoid hemorrhage
10	cerebrovascular disease
11	(cerebrovascular adj3 (accident or disorder* or hemorrhage or haemorrhage or bleed)).ti,ab.
12	(brain adj3 (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)).ti,ab.
13	stroke.ti,ab.
14	(CVA or poststroke or apoplexy).ti,ab.
15	((hemorrhagic or haemorrhagic) adj3 stroke).ti,ab.
16	(brainstem adj3 (accident or haemorrhage or hemorrhage or bleed)).ti,ab.
17	(cerebral adj3 (accident or disease or haemorrhage or hemorrhage or bleed)).ti,ab.
18	(carotid adj3 (disease or haemorrhage or hemorrhage)).ti,ab.
19	(intracranial adj3 (hemorrhage or haemorrhage or bleed)).ti,ab.
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	blood clotting disorder
22	congenital blood vessel malformation/or cerebrovascular malformation/or arteriovenous malformation
23	"inborn error of metabolism"
24	moyamoya disease
25	infection
26	intracranial aneurysm
27	aneurysm
28	cavernous hemangioma
29	arteriovenous fistula
30	genetic disorder
31	heart disease

32	von Willebrand disease
33	fibrinogen
34	blood clotting factor 10/or blood clotting factor 9/or recombinant blood clotting factor 8/or blood clotting factor 10 deficiency/or blood clotting factor 5 deficiency/or blood clotting factor 11 deficiency/or blood clotting factor 8/or blood clotting factor 7/or blood clotting factor 7 deficiency/or blood clotting factor 13 deficiency/or blood clotting factor/or recombinant blood clotting factor 7a
35	coagulopathy.tw.
36	congenital vascular malformation.tw.
37	congenital vascular lesion.tw.
38	congenital vascular anomal*.tw.
39	acquired vascular anomal*.tw.
40	acquired vascular lesion.tw.
41	inborn error of metabolism.tw.
42	genetic disorder.tw.
43	moyamoya.tw.
44	infection.tw.
45	(arteriovenous adj (malformation or fistula)).tw.
46	AVM.tw.
47	((intracranial or arterial) adj aneurysm).tw.
48	vascular abnormality.tw.
49	(cavernous malformation or cavernoma).tw.
50	((warfarin or phenytoin or dilantin or barbiturate) adj4 pregnancy).tw.
51	(risk adj (factor or indicator or predictor)).tw.
52	genetic disease.tw.
53	(heart adj (disease or defect)).tw.
54	arterial occlusive disease.tw.
55	vitamin k deficiency.tw.
56	von willebrand disease.tw.
57	fibrogen.tw.
58	(F1 or FII or FV or FVII or FVIII or FX or FXI or FIX or FXIII).tw.
59	(factor adj (I or II or V or VII or VIII or IX or XI or XIII)).tw.
60	(inherited coagulation adj (disorder or deficiency)).tw.
61	(inherited platelet adj (disorder or deficiency)).tw.
62	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61

63	diagnosis
64	clinical assessment tool
65	clinical observation
66	checklist
67	multimodal imaging
68	early diagnosis
69	emergency health service
70	emergency care
71	risk factor
72	ambulance
73	screening
74	recognition
75	predictive value
76	"sensitivity and specificity"
77	symptom
78	clinical feature
79	diagnosis.tw.
80	(diagnostic adj (procedure or technique or imaging)).tw.
81	(clinical adj (assessment tool or observation or feature)).tw.
82	(checklist or screening or assessment or identification or recognition or evaluation or detection).tw.
83	multimodal imaging.tw.
84	early diagnosis.tw.
85	(emergency adj (health service or care or medical services)).tw.
86	risk factor.tw.
87	(prehospital or ambulance or paramedic or EMS).tw.
88	scale.tw.
89	(predictive value or sensitivity or specificity or likelihood ratio).tw.
90	(sign or symptom or present or feature).tw.
91	63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90
92	computer assisted tomography
93	diffusion weighted imaging
94	neurologic examination
95	imaging
96	X ray

97	echography
98	nuclear magnetic resonance imaging
99	echocardiography
100	angiography
101	blood clotting
102	hemophilia
103	physical examination
104	eye examination
105	stiff neck
106	magnetic resonance angiography
107	computed tomographic angiography
108	digital subtraction angiography
109	((computer assisted or computed) adj tomography).tw.
110	tomograph*.tw.
111	((diffusion weighted or nuclear magnetic resonance) adj imaging).tw.
112	neurologic examination.tw.
113	(imaging or x-ray or MRI or diffusion weighted MRI or echography or nuclear magnetic resonance imaging or sonography or echocardiogram or duplex doppler USS or ultrasonography or angiogram).tw.
114	(blood adj (test or coagulation or clotting)).tw.
115	(hemophilia or haemophilia).tw.
116	magnetic resonance venography.tw.
117	MRV.tw.
118	((physical or eye) adj examination).tw.
119	(neck adj stiff*).tw.
120	magnetic resonance angiogram.tw.
121	computed tomography angiogram.tw.
122	(digital subtraction angiography or DSA).tw.
123	92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122
124	5 and 20
125	62 or 91 or 123
126	124 and 125
127	limit 126 to (english language and humans and ("all infant (birth to 23 months)" or "all child (0 to 18 years)") and humans and (clinical study or clinical trial, all or controlled clinical trial or evaluation studies or journal article or meta analysis or observational study or randomized controlled trial or "review" or systematic reviews))

## Database(s): Cochrane

(Dates searched: January 1995 – January 2016)

#	Searches
1	MeSH descriptor: [Child] explode all trees
2	child* or adolescen* or infant? or teenage* or baby or babies or pediatric or paediatric or school* or kid?
3	cerebrovascular next (accident or disorder or haemorrhage or hemorrhage or bleed)
4	brain next (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)
5	stroke or CVA or poststroke or apoplexy
6	(hemorrhagic or haemorrhagic) next stroke
7	brainstem next (accident or hemorrhage or haemorrhage or bleed)
8	cerebral next (accident or disease or hemorrhage or haemorrhage or bleed)
9	carotid next (disease or hemorrhage or haemorrhage)
10	intracranial next (haemorrhage or hemorrhage or bleed)
11	MeSH descriptor: [Stroke] explode all trees
12	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
13	coagulopathy
14	congenital vascular next (malformation or anomal* or lesion)
15	acquired vascular next (anomal* or lesion)
16	inborn error of metabolism
17	genetic next (disorder or disease)
18	moyamoya disease
19	arteriovenous next (malformation or fistula)
20	AVM
21	(intracranial or arterial) next aneurysm
22	cavernous malformation
23	cavernoma
24	(warfarin or phenytoin or dilantin or barbiturate) near pregnancy
25	risk next (factor or indicator or predictor)
26	heart next (disease or defect)
27	arterial occlusive disease
28	vitamin k deficiency
29	von willebrand disease
30	fibrinogen
31	F next (I or II or V or VII or VIII or X or IX or XI or XIII)
32	inherited coagulation next (disorder or deficiency)
33	inherited platelet next (disorder or deficiency)
34	MeSH descriptor: [Disseminated Intravascular Coagulation] explode all trees
35	MeSH descriptor: [Central Nervous System Vascular Malformations] explode all trees
36	MeSH descriptor: [Metabolism, Inborn Errors] explode all trees
37	MeSH descriptor: [Genetic Diseases, Inborn] explode all trees
38	MeSH descriptor: [Moyamoya Disease] explode all trees
39	MeSH descriptor: [Arteriovenous Malformations] explode all trees
40	MeSH descriptor: [Intracranial Aneurysm] explode all trees
41	MeSH descriptor: [Central Nervous System Vascular Malformations] explode all trees
42	MeSH descriptor: [Hemangioma, Cavernous] explode all trees
43	MeSH descriptor: [Arteriovenous Fistula] explode all trees
44	MeSH descriptor: [Heart Defects, Congenital] explode all trees
45	MeSH descriptor: [Arterial Occlusive Diseases] explode all trees
46	MeSH descriptor: [Vitamin K Deficiency] explode all trees
47	MeSH descriptor: [von Willebrand Diseases] explode all trees
48	MeSH descriptor: [Fibrinogen] explode all trees
49	MeSH descriptor: [Blood Coagulation Disorders] explode all trees
50	MeSH descriptor: [Blood Platelet Disorders] explode all trees
51	diagnosis
52	diagnostic next (procedure or technique or imaging)

53	clinical next (assessment tool or observation or feature)
54	checklist or scale or screening or assessment or identification or recognition or evaluation or detection
55	multimodal imaging
56	early diagnosis
57	emergency next (health service or care or medical services)
58	risk factor
59	prehospital or ambulance or paramedic or EMS
60	predictive value or sensitivity or specificity or likelihood ratio
61	sign or symptom or present
62	MeSH descriptor: [Diagnosis] explode all trees
63	MeSH descriptor: [Checklist] explode all trees
64	MeSH descriptor: [Multimodal Imaging] explode all trees
65	MeSH descriptor: [Emergency Medical Services] explode all trees
66	MeSH descriptor: [Risk Factors] explode all trees
67	MeSH descriptor: [Mass Screening] explode all trees
68	MeSH descriptor: [Symptom Assessment] explode all trees
69	MeSH descriptor: [Sensitivity and Specificity] explode all trees
70	MeSH descriptor: [Signs and Symptoms] explode all trees
71	(computer assisted or computed) next tomography
72	tomography
73	diffusion weighted imaging
74	magnetic resonance imaging
75	nuclear magnetic resonance imaging
76	(neurologic* or physical or eye) next exam*
77	imaging
78	x-ray
79	diffusion weighted MRI
80	echography or sonography or echocardiogram or angiogram
81	duplex doppler USS
82	ultrasonograph*
83	duplex doppler ultrasonograph*
84	blood next (test or coagulation or clotting)
85	hemophilia or haemophilia
86	magnetic resonance venography
87	MRV
88	neck stiff*
89	magnetic resonance angiogra*
90	computed tomography angiogra*
91	digital subtraction angiogra* or DSA
92	MeSH descriptor: [Tomography] explode all trees
93	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
94	MeSH descriptor: [Neurologic Examination] explode all trees
95	MeSH descriptor: [Neuroimaging] explode all trees
96	MeSH descriptor: [X-Rays] explode all trees
97	MeSH descriptor: [Echocardiography] explode all trees
98	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
99	MeSH descriptor: [Ultrasonography] explode all trees
100	MeSH descriptor: [Hematologic Tests] explode all trees
101	MeSH descriptor: [Phlebography] explode all trees
102	MeSH descriptor: [Hemophilia A] explode all trees
103	MeSH descriptor: [Physical Examination] explode all trees
104	MeSH descriptor: [Cerebral Angiography] explode all trees
105	#1 or #2 104
106	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

107	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
108	#51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70
109	#71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104
110	#105 and #106
111	#107 or #108 or #109
112	#110 and #111

## Database(s): CINAHL

(Dates searched: January 1995 – January 2016)

#	Searches
S1	(MH "Child+")
S2	(MH "Adolescence+")
S3	AB child* OR adolescen* OR infant* OR teenage* OR baby OR babies OR pediatric OR paediatric OR school* OR kid*
S4	AB cerebrovascular N3 (accident OR disorder OR hemorrhage OR haemorrhage Or bleed)
S5	AB brain N3 (hypoxia OR haemorrhage OR hemorrhage OR accident OR bleed OR attack)
S6	AB stroke OR CVA OR poststroke OR apoplexy
S7	AB (hemorrhagic OR haemorrhagic) N1 stroke
S8	AB brainstem N3 (accident OR hemorrhage or haemorrhage OR bleed)
S9	AB cerebral N3 (accident OR disease OR haemorrhage OR hemorrhage OR bleed)
S10	AB carotid N3 (disease OR haemorrhage OR hemorrhage)
S11	AB intracranial N3 (haemorrhage OR hemorrhage OR bleed)
S12	(MH "Stroke+")
S13	(MH "Intracranial Hemorrhage+") OR (MH "Cerebral Hemorrhage+")
S14	AB coagulopathy
S15	TX congenital vascular N1 (malformation OR anomal* OR lesion)
S16	TX acquired vascular N1 (anomal* OR lesion)
S17	TX inborn error of metabolism
S18	TX genetic N1 (disease OR disorder)
S19	TX moyamoya disease
S20	TX infection
S21	TX arteriovenous malformation OR AVM OR vascular abnormality
S22	TX (intracranial OR arterial) N1 aneurysm
S23	TX cavernous malformation OR cavernoma
S24	TX arteriovenous fistula
S25	TX (warfarin OR phenytoin OR dilantin OR barbiturate) N3 pregnancy
S26	TX risk N1 (factor OR indicator OR predictor)
S27	TX heart N1 (disease or defect)
S28	TX arterial occlusive disease
S29	TX vitamin K deficiency
S30	TX von willebrand disease
S31	TX fibrinogen
S32	TX F N1 (II OR II OR V OR VII OR VIII OR X OR IX OR XI OR XIII)
S33	TX inherited coagulation N1 (disorder OR deficiency)
S34	TX inherited platelet N1 (disorder OR deficiency)
S35	(MH "Blood Coagulation Disorders, Inherited+") OR (MH "Blood Coagulation Factors+") OR (MH "Blood Coagulation Disorders+")
S36	(MH "Vascular Malformations+")
S37	(MH "Metabolism, Inborn Errors+")

S38	(MH "Moyamoya Disease")
S39	(MH "Arteriovenous Malformations+")
S40	(MH "Cerebral Aneurysm")
S41	(MH "Hemangioma, Cavernous")
S42	(MH "Arteriovenous Fistula")
S43	(MH "Heart Diseases+") OR (MH "Heart Defects, Congenital+")
S44	(MH "Arterial Occlusive Diseases+")
S45	(MH "Vitamin K Deficiency+")
S46	(MH "Von Willebrand Disease")
S47	(MH "Fibrinogen+")
S48	(MH "Blood Coagulation Factors+")
S49	(MH "Blood Platelet Disorders+")
S50	TX diagnosis
S51	TX diagnostic N1 (procedure OR technique OR imaging)
S52	TX clinical N1 (assessment tool OR observation OR feature)
S53	TX checklist OR scale OR screening OR assessment OR identification OR recognition Or evaluation OR detection
S54	TX multimodal imaging
S55	TX early diagnosis
S56	TX emergency N1 (health service OR care OR medical service)
S57	TX risk factor
S58	TX prehospital OR ambulance OR paramedic OR EMS
S59	TX predictive value OR sensitivity OR specificity OR likelihood ratio
S60	TX sign OR symptom OR present
S61	(MH "Diagnosis+")
S62	(MH "Diagnostic Imaging+")
S63	(MH "Clinical Assessment Tools+")
S64	(MH "Checklists")
S65	(MH "Diagnostic Imaging+")
S66	(MH "Emergency Medical Services+") OR (MH "Emergency Service+")
S67	(MH "Sensitivity and Specificity")
S68	TX (computer assisted OR computed) N1 tomography
S69	TX tomography
S70	TX diffusion weighted imaging
S71	TX (neurologic* OR physical OR eye) N1 exam*
S72	TX imaging
S73	TX x-ray
S74	TX diffusion weighted MRI OR MRI
S75	TX echography OR echocardiogram OR sonogra* OR angiogram
S76	TX duplex doppler USS OR ultrasonography
S77	TX duplex doppler ultrasonography
S78	TX blood N1 (test OR coagulation OR clotting)
S79	TX hemophilia OR haemophilia
S80	TX magnetic resonance venography OR MRV
S81	TX neck N1 stiff*
S82	TX magnetic resonance angiogram
S83	TX computer tomography angiogram
S84	TX digital subtraction angiography
S85	(MH "Tomography+")
S86	(MH "Magnetic Resonance Imaging+")
S87	(MH "Neurologic Examination+")
S88	(MH "X-Rays")
S89	(MH "Echocardiography+")
S90	(MH "Ultrasonography, Doppler, Transcranial")
S91	(MH "Ultrasonography, Doppler, Duplex+")
S92	(MH "Angiography, Digital Subtraction")
S93	(MH "Hemophilia") OR (MH "Von Willebrand Disease")

S94	(MH "Physical Examination+")
S95	S1 OR S2 OR S3
S96	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S97	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49
S98	S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67
S99	S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94
S100	S95 AND S96
S101	S97 OR S98 OR S99
S102	S100 AND S101

## Medical, surgical and endovascular interventions (search 4)

### Database(s): Embase

(Dates searched: January 1995 – January 2016)

#	Searches
1	child/
2	adolescent/
3	infant/
4	(kid*1 or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
5	pediatrics/
6	(preschool or school).ti,ab.
7	cerebrovascular accident/
8	brain hypoxia/
9	brain hemorrhage/
10	subarachnoid hemorrhage/
11	cerebrovascular disease/
12	(cerebrovascular adj3 (accident or disorder* or hemorrhage or haemorrhage or bleed)).ti,ab.
13	(brain adj3 (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)).ti,ab.
14	stroke.ti,ab.
15	(CVA or poststroke or apoplexy).ti,ab.
16	((hemorrhagic or haemorrhagic) adj3 stroke).ti,ab.
17	(brainstem adj3 (accident or haemorrhage or hemorrhage or bleed)).ti,ab.
18	(cerebral adj3 (accident or disease or haemorrhage or hemorrhage or bleed)).ti,ab.
19	(carotid adj3 (disease or haemorrhage or hemorrhage)).ti,ab.
20	(intracranial adj3 (hemorrhage or haemorrhage or bleed)).ti,ab.
21	plasma factor/or fresh frozen plasma/or plasma transfusion/
22	blood clotting factor 11/or blood clotting factor 11a/or blood clotting factor 7/or blood clotting factor/or von Willebrand factor/or blood clotting factor 10/or blood clotting factor 8/or blood clotting factor 9/or blood clotting factor 10a/or blood clotting factor 5/or blood clotting factor 6/
23	prothrombin/or prothrombin complex/
24	fibrinogen/
25	cryoprecipitate/
26	((coagulation or clotting or plasma) adj factor).tw.
27	(factor adj (I or II or V or VII or VIII or IX or XI or XIII)).tw.
28	(prothrombin complex concentrate or PCC).tw.
29	(fibrinogen or fresh frozen plasma or cryoprecipitate).tw.
30	(FI or FII or FV or FVII or FVIII or FX or FXI or FIX or FXIII).tw.
31	decompression/or decompression surgery/
32	neurosurgery/
33	craniotomy/
34	craniectomy/

35	plasma transfusion/or blood transfusion/
36	coil embolization/
37	moyamoya disease/
38	endovascular aneurysm repair/or endovascular surgery/
39	clip/
40	stent/
41	decompress*3.tw.
42	neurosurg*.tw.
43	(craniotomy or hemicraniectomy or craniectomy).tw.
44	(trepanning or trephining or trephination or trepanation).tw.
45	((blood or plasma) adj transfusion).tw.
46	platinum coil.tw.
47	moyamoya.tw.
48	(refer or prevent* or treat* or manage*).tw.
49	((surg* or medical or endovascular) adj3 intervention).tw.
50	(clip* or coil* or stent*).tw.
51	embolisation.tw.
52	1 or 2 or 3 or 4 or 5 or 6
53	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
54	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
55	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
56	52 and 53
57	54 or 55
58	56 and 57
60	limit 58 to (human and english language and journal and (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))

## Database(s): MEDLINE

(Dates searched: January 1995 – January 2016)

#	Searches
1	child/
2	adolescent/
3	infant/
4	(kid*1 or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
5	pediatrics/
6	(preschool or school).ti,ab.
7	cerebrovascular accident/
8	brain hypoxia/
9	brain hemorrhage/
10	subarachnoid hemorrhage/
11	cerebrovascular disease/
12	(cerebrovascular adj3 (accident or disorder* or hemorrhage or haemorrhage or bleed)).ti,ab.
13	(brain adj3 (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)).ti,ab.
14	stroke.ti,ab.
15	(CVA or poststroke or apoplexy).ti,ab.
16	((hemorrhagic or haemorrhagic) adj3 stroke).ti,ab.
17	(brainstem adj3 (accident or haemorrhage or hemorrhage or bleed)).ti,ab.
18	(cerebral adj3 (accident or disease or haemorrhage or hemorrhage or bleed)).ti,ab.
19	(carotid adj3 (disease or haemorrhage or hemorrhage)).ti,ab.
20	(intracranial adj3 (hemorrhage or haemorrhage or bleed)).ti,ab.
21	plasma factor/or fresh frozen plasma/or plasma transfusion/

22	blood clotting factor 11/or blood clotting factor 11a/or blood clotting factor 7/or blood clotting factor/or von Willebrand factor/or blood clotting factor 10/or blood clotting factor 8/or blood clotting factor 9/or blood clotting factor 10a/or blood clotting factor 5/or blood clotting factor 6/
23	prothrombin/or prothrombin complex/
24	fibrinogen/
25	cryoprecipitate/
26	((coagulation or clotting or plasma) adj factor).tw.
27	(factor adj (I or II or V or VII or VIII or IX or XI or XIII)).tw.
28	(prothrombin complex concentrate or PCC).tw.
29	(fibrinogen or fresh frozen plasma or cryoprecipitate).tw.
30	(FI or FII or FV or FVII or FVIII or FX or FXI or FIX or FXIII).tw.
31	decompression/or decompression surgery/
32	neurosurgery/
33	craniotomy/
34	craniectomy/
35	plasma transfusion/or blood transfusion/
36	coil embolization/
37	moyamoya disease/
38	endovascular aneurysm repair/or endovascular surgery/
39	clip/
40	stent/
41	decompress*3.tw.
42	neurosurg*.tw.
43	(craniotomy or hemicraniectomy or craniectomy).tw.
44	(trepanning or trephining or trephination or trepanation).tw.
45	((blood or plasma) adj transfusion).tw.
46	platinum coil.tw.
47	moyamoya.tw.
48	(refer or prevent* or treat* or manage*).tw.
49	((surg* or medical or endovascular) adj3 intervention).tw.
50	(clip* or coil* or stent*).tw.
51	embolisation.tw.
52	1 or 2 or 3 or 4 or 5 or 6
53	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
54	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
55	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
56	52 and 53
57	54 or 55
58	56 and 57
59	limit 58 to (human and english language and journal and (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)) [Limit not valid in Ovid MEDLINE(R); records were retained]

## Database(s): Cochrane

(Dates searched: January 1995 – January 2016)

#	Searches
1	MeSH descriptor: [Child] explode all trees
2	child* or adolescen* or infant? or teenage* or baby or babies or pediatric or paediatric or *school or kid?
3	cerebrovascular next (accident or disorder or hemorrhage or haemorrhage or bleed)
4	brain next (hypoxia or haemorrhage or hemorrhage or accident or bleed or attack)
5	stroke or CVA or poststroke or apoplexy
6	(hemorrhagic or haemorrhagic) next stroke
7	brainstem next (accident or hemorrhage or haemorrhage or bleed)
8	cerebral next (accident or disease or haemorrhage or hemorrhage or bleed)
9	carotid next (disease or haemorrhage or hemorrhage)

10	intracranial next (haemorrhage or hemorrhage or bleed)
11	MeSH descriptor: [Stroke] explode all trees
12	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
13	(coagulation or clotting or plasma) near factor
14	factor next (I or II or V or VII or VIII or IX or X or XI or XIII)
15	prothrombin complex concentrates or PCC or fibrinogen or fresh frozen plasma or cryoprecipitate
16	F next (I or II or V or VII or VIII or IX or X or XI or XIII)
17	MeSH descriptor: [Blood Coagulation Factors] explode all trees
18	MeSH descriptor: [Blood Coagulation] explode all trees
19	MeSH descriptor: [Plasma] explode all trees
20	MeSH descriptor: [Prothrombin] explode all trees
21	MeSH descriptor: [Fibrinogen] explode all trees
22	decompress*
23	neurosurgical procedure*
24	craniotomy or craniectomy or hemicraniectomy or trepanning or trephining or trephination or trepanation
25	(blood or plasma) next transfusion
26	platinum coil or clip* or coil* or stent* or embolisation
27	moyamoya disease
28	refer or prevention or treatment or management or surg* or medical or intervention
29	MeSH descriptor: [Decompression] explode all trees
30	MeSH descriptor: [Neurosurgical Procedures] explode all trees
31	MeSH descriptor: [Craniotomy] explode all trees
32	MeSH descriptor: [Decompressive Craniectomy] explode all trees
33	MeSH descriptor: [Trephining] explode all trees
34	MeSH descriptor: [Blood Transfusion] explode all trees
35	MeSH descriptor: [Platelet Transfusion] explode all trees
36	MeSH descriptor: [Moyamoya Disease] explode all trees
37	MeSH descriptor: [Endovascular Procedures] explode all trees
38	MeSH descriptor: [Surgical Instruments] explode all trees
39	MeSH descriptor: [Stents] explode all trees
40	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
41	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
42	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #38 or #39
43	#1 or #2
44	#40 and #43
45	#41 or #42
46	#44 and #45

## Database(s): CINAHL

(Dates searched: January 1995 – January 2016)

#	Searches
S1	(MH "Child+")
S2	AB child* OR adolescen* OR infant* OR teenage* OR baby OR babies OR pediatric OR paediatric OR school OR kid*
S3	(MH "Adolescence+")
S4	S1 OR S2 OR S3
S5	AB cerebrovascular N3 (accident OR disorder OR hemorrhage OR haemorrhage OR bleed
S6	AB brain N3 (hypoxia OR haemorrhage OR hemorrhage OR accident OR bleed OR attack)
S7	AB stroke OR CVA OR poststroke OR apoplexy
S8	AB (hemorrhagic OR haemorrhagic) N1 stroke
S9	AB brainstem N3 (accident OR hemorrhage OR haemorrhage OR bleed)

S10	AB cerebral N3 (accident OR disease OR haemorrhage OR hemorrhage OR bleed)
S11	AB carotid N3 (disease OR haemorrhage OR hemorrhage)
S12	AB intracranial N3 (haemorrhage OR hemorrhage OR bleed)
S13	(MH "Stroke+")
S14	(MH "Intracranial Hemorrhage+")
S15	(MH "Cerebral Hemorrhage+")
S16	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17	TX (coagulation OR clotting OR plasma) N1 factor
S18	TX factor N1 (I OR II OR V OR VII OR VIII OR IX OR X OR XI OR XIII)
S19	TX prothrombin complex concentrates OR PCC OR fibrinogen OR fresh frozen plasma OR cryoprecipitate
S20	TX F N1 (I OR II OR V OR VII OR VIII OR IX OR X OR XI OR XIII)
S21	(MH "Blood Coagulation Factors+") OR (MH "Blood Coagulation+")
S22	(MH "Plasma+")
S23	(MH "Fibrinogen+")
S24	S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S25	TX decompress* OR neurosurgical procedure OR craniotomy OR craniectomy OR hemicraniectomy OR trepanning OR trephining OR trephination OR trepanation
S26	TX (blood OR plasma) N1 transfusion
S27	TX platinum coil OR clip* OR coil* OR stent* OR embolisation OR embolization
S28	TX moyamoya disease
S29	TX refer OR prevent* OR treat* OR manage* OR surg* OR medical OR intervention
S30	(MH "Decompression, Surgical+")
S31	(MH "Neurosurgery+")
S32	(MH "Craniotomy+")
S33	(MH "Decompressive Craniectomy")
S34	(MH "Platelet Transfusion") OR (MH "Blood Transfusion+")
S35	(MH "Moyamoya Disease")
S36	(MH "Stents+")
S37	S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36
S38	S4 AND S16
S39	S24 OR S37
S40	S38 AND S39

## Parent family impact, information & support needs (search 5)

Database(s): MEDLINE

(Dates searched: January 1995 – November 2015)

#	Searches
1	Stroke/
2	Brain Ischemia/
3	Cerebrovascular Disorders/
4	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
5	"arterial ischemic stroke".ti,ab.
6	Carotid Artery Thrombosis/
7	brain infarction/
8	"arterial ischemic stroke".ti,ab.
9	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
10	(carotid adj3 disease).ti,ab.
11	(carotid adj3 thrombosis).ti,ab.
12	"brain attack".ti,ab.
13	((intracranial or cerebral or intra-cranial) adj3 (thrombosis or disease* or embol*)).ti,ab.
14	Brain Injuries/
15	"brain injur".ti,ab.
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	Pediatrics/
18	adolescent/or child/or infant/
19	(kid*1or child* or teenage* or baby or babies or adolescent or infant or pediatric or paediatric).ti,ab.
20	17 or 18 or 19
21	comment/or editorial/or letter/or historical article/
22	case reports/
23	exp animals/not humans/
24	Animals, Laboratory/
25	exp Animal Experimentation/
26	exp models, animal/
27	exp Rodentia/
28	21 or 22 or 23 or 24 or 25 or 26 or 27
29	16 and 20
30	29 not 28
31	limit 30 to english language
32	exp Needs Assessment/
33	Patient Education as Topic/
34	Patient-Centered Care/
35	patient satisfaction/or exp patient preference/
36	((famil* or parent* or patient* of sibling* or teacher* or child*) adj3 (support* or impact* or signpost* or preference* or satisfaction or information or needs or coordinat*)).ti,ab.
37	Health Personnel/or care worker.mp.
38	Access to Information/
39	Information Services/
40	Knowledge/
41	Social Support/
42	*Counseling/
43	Parents/ed [Education]
44	*Communication/
45	Information Seeking Behavior/
46	communication barriers/
47	Health Knowledge, Attitudes, Practice/
48	Life Change Events/

49	((doctor or parent or nurse or child* or adolescent* or professional or person* or carer* or famil*) adj3 (communic* or interaction* or information or education* or support*)).ti,ab.
50	((stroke or brain injury) adj2 (information or education* or support*) adj2 (intervention* or program* or resource* or material* or pack* or leaflet* or need* or requirement* or access* or pathway*)).ti,ab.
51	Caregivers/ed [Education]
52	community health services/or child health services/or "early intervention (education)"/
53	((patient or inpatient or carer* or care?giver* or consumer* or child or you*2 or parent* or famil*) adj2 (helpline* or advice line* or newsletter* or knowledge or inform* or educa* or advoc* or literature or infopack* or knowledge or leaflet* or booklet* or handout* or decision aid* or pamphlet* or training or factsheet* or counsel* or internet or website* or support*)).ti,ab.
54	Voluntary Health Agencies/
55	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56	31 and 55
57	cerebral hemorrhage/or intracranial hemorrhage, hypertensive/
58	16 or 57
59	20 and 58
60	59 not 28
61	55 and 60
62	limit 61 to english language

## Database(s): PsycInfo

(Dates searched: January 1995 – November 2015)

#	Searches
1	cerebrovascular accidents/
2	cerebral ischemia/
3	brain damage/or traumatic brain injury/
4	arterial ischemic stroke.ti,ab.
5	(cerebrovascular accident* or cerebral ischemia or stroke* or brain injury).ti,ab.
6	exp cerebral hemorrhage/
7	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident* or ischemia)).ti,ab.
8	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
9	brain damage/
10	exp sickle cell disease/
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	pediatrics/
13	(child* or teenage* or pediatric* or paediatric* or adolescent* or baby or babies or kid*1).ti,ab.
14	adolescent.mp.
15	12 or 13 or 14
16	exp parent training/
17	health knowledge/
18	exp health literacy/or client education/or health knowledge/or health service needs/
19	exp Client Participation/
20	communication/or interpersonal communication/or persuasive communication/or verbal communication/or communications media/or information/or exp information dissemination/
21	information seeking/or computer searching/or information/or information literacy/or information services/
22	exp social support/or reference groups/or social networks/or support groups/
23	organizations/or nonprofit organizations/
24	exp Social Support/
25	counseling/or community counseling/or educational counseling/or genetic counseling/
26	exp Client Satisfaction/
27	client attitudes/or client centered therapy/
28	((famil* or parent* or patient* of sibling* or teacher* or child*) adj3 (support* or impact* or signpost* or preference* or satisfaction or information or needs or coordinat*)).ti,ab.

29	((doctor or parent or nurse or child* or adolescent* or professional or person* or carer* or famil*) adj3 (communic* or interaction* or information or education* or support*)).ti,ab.
30	((patient or inpatient or carer* or care?giver* or consumer* or child or you*2 or parent* or famil*) adj2 (helpline* or advice line* or newsletter* or knowledge or inform* or educa* or advoc* or literature or infopack* or knowledge or leaflet* or booklet* or handout* or decision aid* or pamphlet* or training or factsheet* or counsel* or internet or website* or support*)).ti,ab.
31	exp Caregivers/or exp Social Support/or exp Family Intervention/or exp Family Relations/
32	((stroke or brain injury) adj2 (information or education* or support* or counsel*)).ti,ab.
33	((famil* or parent* or patient* of sibling* or teacher* or child*) adj3 (intervention* or program* or resource* or material* or pack* or leaflet* or need* or requirement* or access* or pathway*)).ti,ab.
34	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	11 and 15 and 34
36	limit 35 to english language
37	limit 36 to ("0100 journal" or "0110 peer-reviewed journal" or "0120 non-peer-reviewed journal" or "0130 peer-reviewed status unknown")

## Appendix 4b: Data extraction form

<b>Reviewer's Name:</b>	<b>Date:</b> <a href="#">Click here to enter a date.</a>	
<b>Study first author &amp; year of publication:</b>		
<b>Journal:</b>		

  

<b>Based on your reading of the paper, please tick the appropriate box.</b>	<b>Include</b> paper <input type="checkbox"/> <b>Exclude</b> paper <input type="checkbox"/> I cannot confidently include this paper, but feel it has some merit and adds value to the question(s) posed <input type="checkbox"/>
<b>Comments</b>	
<i>Relating particularly to the benefits and limitations of the study.</i>	
<b>Study characteristics</b>	
Was the aim of the study stated clearly in the abstract, introduction, or methods section?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Aim of the study (as stated by the author)	
What is the study design? (e.g. case report, case series, cohort, cross-sectional study)	
What is the study timeframe? (i.e. when did the recruitment of participants or/and the follow up take place?)	
Country of origin (where was the study carried out?)	
Funding source:	
<b>Study population</b>	
Please describe the study population:	<b>Number:</b> <b>Age (report statistics including variance):</b> <b>Gender (M/F):</b> <b>Ethnicity:</b> <b>Inclusion criteria of participants:</b> <b>Exclusion criteria of participants:</b> <b>Comorbidities:</b> <b>Any other characteristics:</b>
Please describe the control population (if applicable):	<b>Number:</b> <b>Age (report statistics including variance):</b> <b>Gender (M/F):</b> <b>Ethnicity:</b> <b>Inclusion criteria of participants:</b> <b>Exclusion criteria of participants:</b> <b>Comorbidities:</b> <b>Any other characteristics:</b>
Were the cases collected in more than one centre?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Did participants enter the study at a similar point in the condition?	Yes <input type="checkbox"/> No <input type="checkbox"/>
<b>Risk factor, Intervention, Exposure or Clinical Feature (e.g. risk factor)</b>	
Please give details of the intervention/exposure used/described in the study	
Was the intervention clearly described in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/>

	N/A <input type="checkbox"/>
Were additional interventions/exposures (co-interventions) clearly reported in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Please add details:
<b>Outcome measures</b>	
What outcome measures were used in the study?  <i>Please list all outcomes used to assess effectiveness of the interventions or impact of risk factors, e.g. outcomes related to:</i> <ul style="list-style-type: none"> <li>• prevalence of risk factors</li> <li>• clinical symptoms/signs, setting of diagnosis</li> <li>• accuracy, timing, sensitivity or frequency of imaging modalities</li> <li>• types and use of investigations</li> <li>• measures of stroke outcome, complication development or recurrence</li> <li>• measures of efficacy of an intervention</li> </ul>	
<b>Results and conclusions</b>	
What are the main findings?	
<i>Include the numerical and statistical results if relevant</i>	
Are patient being followed-up in the study?	Yes <input type="checkbox"/> No <input type="checkbox"/>
How long are patients followed-up in the study?  <i>Note specified end points used to decide end of follow-up (e.g. death, complete cure). Note if follow-up period is shorter than originally planned.</i>  <b><i>Please tick box if follow up is not reported</i></b>	Not reported <input type="checkbox"/>
Was the loss to follow-up reported?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are adverse events reported?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Are the conclusions supported by the results?	Yes <input type="checkbox"/> No <input type="checkbox"/>
<b>Overall assessment</b>	
Does this study help to answer a key question?	Yes <input type="checkbox"/> No <input type="checkbox"/>
<i>Summarise the main conclusions of the study and indicate how it relates to a key question. Include any comments on choice of study design, likely validity of the conclusions etc.</i>	Please indicate the key question this paper helps to answer (refer to the list of clinical questions):

#### Study quality assessment checklist:

<b>For case-control studies</b>	
1. The study addresses an appropriate and clearly focused question?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
2. The cases and controls are from comparable populations?	Yes <input type="checkbox"/>

	No <input type="checkbox"/>
	N/A <input type="checkbox"/>
3. The same exclusion criteria used for both cases and controls?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
4. Was the participation rate for each group reported?  Please indicate the number of cases and controls:	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>  vs.
5. Participants and non-participants are compared to establish their similarities or differences?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
6. Cases are clearly defined and differentiated from controls?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
7. It is clearly established that controls are not cases?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
8. Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
9. Exposure status is measured in a standard, valid, and reliable way?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
10. The main potential confounders are identified and taken into account in the design and analysis?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
11. Have confidence intervals been provided?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
<b>For cross-sectional survey, case series, comparative cross-sectional survey, cohort study, prospective/retrospective case series</b>	
12. Was the sample representative of the target population?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
13. Were study participants recruited in an appropriate way?	Yes <input type="checkbox"/>

	No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
14. Was the sample size adequate?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
15. Were the study subjects and the setting described in detail?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
16. Was the data analysis conducted with sufficient coverage of the identified sample?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
17. Were objective, standard criteria used for the measurement of the condition?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
18. Was the condition measured reliably?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
19. Was there appropriate statistical analysis?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
20. Are all important confounding factors/subgroups/differences identified and accounted for?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
21. Were subpopulations identified using objective criteria?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
22. Overall risk of bias?	Low <input type="checkbox"/> Mod <input type="checkbox"/>

	High <input type="checkbox"/> Comment:
<b>For randomised, non-randomised trials</b>	
23. Was an appropriate randomisation method used?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
24. Was there adequate concealment of allocation?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
25. Were groups comparable at baseline?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
26. Did the comparison groups receive the same care apart from the intervention of interest?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
27. Were participants receiving care kept blind to their treatment allocation?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
28. Were individuals administering care kept blind to treatment allocation?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
29. Were all groups followed for equal amount of time?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
30. Were groups comparable for treatment completion?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
31. Were groups comparable with respect to availability of outcome data?	Yes <input type="checkbox"/> No <input type="checkbox"/>

	N/A <input type="checkbox"/> Comment:
32. Did the study have an appropriate length of follow-up?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
33. Did the study use a precise definition of outcome?	Low <input type="checkbox"/> Mod <input type="checkbox"/> High <input type="checkbox"/> Comment:
34. Did the study use a valid and reliable method to determine outcome?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
35. Were investigators kept blind to participant's exposure to intervention?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
36. Were investigators kept blind to other confounding and prognostic factors?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
<b>For systematic reviews (CASP)</b>	
37. Did the review address a clearly focused question?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
38. Did the authors look for the right type of papers?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
39. Do you think all the important, relevant studies were included?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
40. If the results of the included papers were combined in the review was it reasonable to do so?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

	Comment:
41. How precise are the results?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
42. Can the results be applied to our target population?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
43. Were all important outcomes considered?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/> Comment:
44. Are any benefits worth the harms and costs?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>

## Appendix 4c: Evidence tables

### Chapter 3: Acute diagnosis of stroke in childhood

Clinical presentation and diagnosis (imaging) of acute diagnosis of stroke in AIS								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
<b>Presentation</b>								
Abend (2011)	USA	To define the incidence of seizures as a presenting symptom of acute AIS in children and to identify risk factors for seizures at stroke onset.	Cohort	60 children with AIS. Age: 5.7 years median. Gender: 40 male, 20 female. Ethnicity: 43 white, 14 black, and 3 other.	NA	-	Seizures were found at initial presentation in 13 children. Clinical signs at presentation included hemiparesis (13), mental status change (5), visual deficit (3), dysarthria or aphasia (2), and ataxia (1). Risk factors for seizures include young age: (median age, 1.1 years [IQR, 0.7 to 2.8 years] vs 10 years [IQR, 2.3 to 13.8 years]). In the whole sample $\leq 3$ years (n=25) 11 (44%) presented with seizure. There was no statistically significant difference in sex, race, stroke risk factors, or infarct location between those with and without seizures.	Moderate
Abram (1996)	USA	To assess the natural history, prognostic factors, and lipid and apolipoprotein abnormalities of idiopathic ischemic childhood stroke.	Retrospective case series	42 children with AIS. Age: 6.8 years (mean age at the time of stroke). Gender: 60% male, 40% female. Ethnicity: 86% Caucasian, and 14% African-American.	NA	Good outcome group: mean follow-up interval of 6.8 years (SD, 4.8 years). Poor outcome group: mean follow-up interval	All patients presented with a hemiparesis (62% on right, 38% on left). 24% experienced a self-limited transient episode of hemiparesis within a month before hospitalization. In 10%, a more indolent course was noted over the preceding week and month. In the remaining two thirds of cases, the onset of hemiparesis was acute. 19% of children presented with concurrent seizure, 12% had fever, and 9.5% had coma. Good outcome children n=24, had average age of	Low

						of 8.4 years (SD, 6.0 years).	5.9 (SD 4.8) at presentation and bad outcome n=18, had mean age of 8 (SD 4.7). While presenting features are also presented by outcome, there was no statistical analysis to show any difference and small numbers.	
Alhaboob (2014)	Pakistan	To study a cohort of children with (cPACNS) and evaluate efficacy and safety of their management.	Cohort	68 children admitted with AIS. Age: $8.5 \pm 3.5$ years (mean age) (42 patients were <5 years and 26 >5 years). Gender: 42 male, 26 female. Ethnicity: not stated	NA	2 years	Neuroimaging studies revealed AIS in 50 patients (73.5%), HS in 10 (14.7%) and ischemic-haemorrhagic lesions in 8 (11.8%). Presenting symptoms and signs included fever (20%), headache (64%), disturbed consciousness (30%), seizures (55%), hemiparesis (60%), and motor deficit (70%).	Low
Al-Sulaiman (1999)	Saudi Arabia	To report the clinical features and neuroimaging correlates of stroke in Saudi children seen over a 5-year period at the King Fahd Hospital of the University, Al-Khobar, Saudi Arabia.	Case series	31 cases of stroke of 20,895 children seen. Age: 3 months to 11 years (mean age, 26.2 months). Gender: 18 male, 13 female. Ethnicity: Saudi	NA	-	Ischemic stroke (28 cases) accounted for most of the cases (90%); ICH (2 cases) and subarachnoid haemorrhage (1 case). 28/31 cases presented with weakness, 8/31 with seizures, 2 with coma, 6 with language difficulty, 2 with vomiting and 1 headache. Pure motor hemiparesis was the most frequent presentation of lacunar infarcts (12/13 cases), and no patient had pure sensory stroke or ataxic hemiparesis. Headache and vomiting were uncommon. 12/28 IS cases had presented with hemiparesis.	Low
Al-Tawari (2000)	Australia	To provide an assessment strategy for vertebrobasilar strokes in children.	Retrospective Case series	9 children with vertebrobasilar stroke.	NA	-	Frequent presenting features included headache, hemiparesis, ataxia and cranial nerve palsies. Aphasia occurred in 2 and afebrile seizures in 1 patient. Five patients	Low

				Age: 18 months to 15 years. Gender: 6 male, 3 female. Ethnicity: not stated			had depressed consciousness extending to coma in 3. Etiological factors included trauma to the head or neck in 5, rheumatic endocarditis with artificial valve embolism in 1, brain stem encephalitis in 1 and undetermined aetiology in 2. Diagnostic neuroimaging studies including MRI showed infarction in the territories of the occluded arteries. MRA showed occlusion of the vertebral artery and/or its branches in 5 patients, while the other 4 patients had involvement of the basilar artery and/or its branches. No abnormalities of blood coagulation were detected.	
Braun (2007)	Canada	To investigate the association between temporal features of the onset of neurological symptoms and stroke aetiology in children with AIS.	Consecutive cohort	56 children (from 98) with a confirmed diagnosis of AIS. Age: 6/12 to 18 years (mean age 6.1 years for arteriopathic stroke group, 8.5 for non-arteriopathic group). Gender: 33 male, 23 female. Ethnicity: not stated.	NA	Follow-up vascular imaging, performed 6 months after	Headache and seizures accompanied the onset of stroke in 45% and 16%, respectively. There were no significant differences for age, gender, location of infarction, seizures, and headache between the arteriopathic and non-arteriopathic group. The mode of onset is non-abrupt in the majority (68%) of children with arteriopathic stroke, whereas most children (72%) with stroke attributable to a non-arteriopathic cause have an abrupt start of symptoms. With non-abrupt onset, the odds of having an arteriopathic aetiology was 6.1 (95% CI, 1.6 to 22.8; P= 0.007) adjusted for age and localization of AIS.	Low
Chabrier (2000)	France	To investigate the underlying mechanism and risk factors of AIS.	Retrospective case series	59 children with cerebral arterial infarction. Age: 3 months to 16 years (median	NA	30 months (mean)	Patients presented with an acute focal motor deficit; 57 children had hemiplegia and 2 had a bilateral motor deficit. Altered consciousness was present in 19 (32%) children. Headache (16 children) or neck	Low

				age 6 years, 11 months). Gender: 33 male, 26 female. Ethnicity: not stated.			pain (2 children) accompanied or preceded the manifestations of cerebral ischemia in 18 (31%) patients, with intervals from 5 minutes to 5 days. 14 (24%) patients presented with focal (8 patients) or generalized (6 patients) seizures. The pathophysiologic process could be established for 78% of the children. Arteriopathic stroke (31 patients, or 53%) was the most common. The arteriopathies were either progressive (moyamoya in 4 patients, or 7%) or non-progressive (27 patients, or 46%).	
Chabrier (2003)	France	To add 12 new children observed consecutively at a single centre. Special emphasis is placed on the significant presenting symptoms in relation to the location of the dissected artery and on the outcome.	Case series	12 AIS cases. Age: 2 to 12 years (cervical dissection), 5 to 16 years (intracranial dissection). Gender: 8 male, 4 female. Ethnicity: not stated.	NA	-	Five children had cervical dissection and 7 intracranial dissection. Clinical presenting features include motor deficit, headache or cervicgia in 4/5 & 5/7. Decrease of consciousness level in 3/5 & 5/7. Seizures 2/5 & 1/7, Decrease of consciousness level in 3/5 & 5/7. Cervical arterial dissection: Trauma or physical exertion preceding in 4 and 6 patients (mean 6.5 days before). Headache/cervicgia proceeded or at time of stroke in 4. 2/5 treated with anticoagulation, 3/5 with aspirin. No haemorrhage, 1 recurrence on anticoagulation. Intra-cranial dissection occurred during physical exercise in 5. Four had intense headache at time of stroke, No recurrences.	Low
Chadehumbe (2009)	USA	To determine the incidence of seizures within the first 24 hours of stroke,	Cohort	31 children identified with stroke (17	NA	-	Seizures occurred within 24 hours of the stroke in 58% (18/31) of children. No significant differences were found in the	Moderate

		including ischemic strokes and intracranial haemorrhage.		ischemic strokes, 12 intracerebral haemorrhages, and 2 subarachnoid haemorrhages). Age: less than or equal to 18. Gender (M/F): unclear. Ethnicity: not stated			rate of seizure by stroke subtype. The relative risk for seizure in the acute stroke setting in children vs. adults is 18. Seizure more common in stroke in children vs adults (58% vs 3.1%). There was no reported difference in type of stroke, gender or age. The youngest children trended towards having higher rates of early seizure in the stroke setting: of the 13 strokes between 0 and 5 years, 9(69%) had early seizures, compared to 9/18 (50%) in those 6 years and older.	
Christerson (2010)	Sweden	To evaluate the incidence, presenting symptoms, diagnostic delay, risk factors and short-term outcome of childhood stroke in a population-based cohort of Swedish children.	Retrospective case notes review	51 children with first stroke 926 with AIS). Age: >28 days, but <18 years (median age 13, AIS median age of 9 years). Gender 23 male 11 AIS), 28 female (15 AIS). Ethnicity: 49 Caucasian, 2 Asian	NA	-	Presenting features frequently in AIS: Hemiparesis was seen in 17 cases, with 50% having had facial palsy. Eight children had dysphasia, 7 visual defects, 6 loss of consciousness, 5 headache, 5 nausea/vertigo, 4 generalised seizures, 3 irritability, 3 focal seizure, 3 sensory disturbances, and 1 eye deviation. HS cases (n = 21). Presenting features frequently in HS: 13 children had nausea/vertigo, 12 headache, 12 loss of consciousness, 5 disorientation, 4 eye deviation, 4 hemiparesis, 3 generalised seizure, 2 facial palsy, 2 visual defects, 2 stiff neck, 1 Irritability.	Low
Delsing (2001)	Netherlands	To identify early prognostic factors in children with ischemic arterial stroke.	Case series	31 AIS cases. Age: 1 month to 16 years (mean 4.3 years). Gender 19 male, 12 female. Ethnicity: unclear	NA	1.6 - 5.9 years (mean 3.5 years).	The most common presenting symptoms, alone or in combination, included hemiparesis (23 children (74%)) and aphasia (8 children (25%)). Other presenting symptoms were seizures (6 children (19%)), altered level of consciousness (5 children (16%)), ataxia (2	Low

							children (7%)), blindness (1 child (3%)), and sensory disturbances (1 child (3%)). Recurrent stroke presented with hemiparesis (8 children (80%)) and sensory disturbances (2 children (20%)). Forty-one stroke episodes were observed, with 7 children (22%) having 1-2 recurrences.	
Emam (2009)	Saudi Arabia	To examine risk factors, clinical presentation, imaging findings and outcomes of paediatric stroke in Saudi Arabia.	Case series	25 mixed AIS & HS children. Age: 4.5 +/- 3.8 years (up to 16 years). Gender: 11 male, 14 female. Ethnicity: not stated.	NA	-	Clinical presentation highlighted that seizure was the commonest clinical presentation (54%) followed by hemiplegia (31%) and decreased level of consciousness (30%). Risk factors included SCD 36%, cardiac disorders 16%, vascular abnormality 12%, and haematological 12%.	Low
Ganesan (2002)	UK	To ascertain whether posterior circulation stroke in children has distinctive clinical or radiologic features.	Case series	22 children with posterior circulation stroke. Age: 8 months to 16 years. Gender: 17 male, 5 female. Ethnicity: not stated.	NA	-	Headache was an initial symptom in 10 patients and neck pain in 1. Four patients had a reduced conscious level at presentation. One patient, with occipital lobe infarction, presented with focal seizures. Two patients presented with serial TIA. The remaining patients presented with clinical stroke and a mixture of brainstem and cerebellar signs.	Low
Giroud (1997)	France	To re-evaluate the clinical features of stroke in children, their outcome and the place of the different mechanisms, in the light of CT-scan and magnetic resonance imaging.	Case series	54 children (31 with AIS, 23 HS). Age: 10.4 years (mean). Gender: 17 male, 24 female. Ethnicity: Caucasian, except 1 child from Korea	NA	Mean follow-up of 4.5 years (1 year to 10 years)	Unilateral sensory-motor deficit was present in 15 cases (48%) with basal ganglia infarct in 6 cases, hemianopia in 2 cases (6%), isolated pure motor hemiplegia in 13 cases (42%) with internal capsular infarct in 7 cases, and aphasia in 14 cases (45%) of a Wernicke type in 12 cases, of a Broca type in 2 cases. In 2 cases there was a cerebellar syndrome by infarction of a cerebellar lobe. Motor seizures were	Low

							observed in the first 15 days in 11 cases (35%) on the same side as the hemiplegia. Early coma was present in 1 case (3%) and cephalalgia in 12 cases (38%). No recurrent strokes were observed.	
Glauser (1995)	USA	To determine the accuracy of neurologic examination and neurologic history in detecting evidence of a cerebral infarction diagnosed by magnetic resonance imaging (MRI) in children with sickle cell haemoglobinopathy.	Cross sectional	30 children with sickle cell haemoglobinopathy. Age: $9.8 \pm 3.3$ years. Gender: unclear Ethnicity: not stated.	NA	-	17 children (57%) had MRI evidence of cerebral infarction based on demonstration of parenchymal abnormalities in a vascular distribution. Among these, 12 (71%) had an abnormal neurologic examination, and 11 (65%) had a history of a prior neurologic event. Among the 13 children with normal MRIs, 12 (92%) had normal neurologic examinations, and no child had a previous history of a neurologic event. The most common presenting neurologic complaint was hemiparesis followed by seizures (six events) and aphasia (four events). In two cases seizures were the only presenting symptom. Focal status epilepticus was seen in two children.	Moderate
Goeggel Simonetti (2013)	Switzerland	To calculate the incidence of Basilar Artery Stroke (BAS) in children and to analyse the clinical presentation, risk factors, radiological findings, therapeutic approaches, and outcome of BAS in childhood.	Prospective population based study	7 basilar artery stroke (BAS) cases. Age: 9 years (median). Gender: 6 male, 1 female (for the study population) Ethnicity: Caucasian (for the study population)	NA	Median follow-up lasted 6 months (IQR=3–24mo)	Presenting signs and symptoms comprised impaired consciousness (64), quadri- or hemiparesis (58), bulbar dysfunction (46), vomiting, nausea (43), and headache (41). Prodromes occurred in 43% of cases. Aetiology was largely vasculopathic (38), but often unknown (40).	Low
Gokben, (2007)	Turkey	To evaluate risk factors and outcome	Retrospective case series	31 children with AIS.	NA	1 - 148 months	19 children (61.3%) presented with hemiparesis, with 6 (19.3%) presenting	Low

		in children with arterial ischemic stroke in the metropolitan area of Izmir, Turkey.		Age: 3 months to 15 years (mean 4.48 years). Gender: 18 male, 13 female. Ethnicity: Turkish			with aphasia. Seizures along with focal neurologic deficits were seen in 6 (19.3%). The others displayed headache, nausea/vomiting, or visual field defects.	
Hartman (2009)	USA	To explore associations between age, clinical presentation, or predisposing conditions and delayed diagnosis of arterial ischemic stroke.	Retrospective chart review	125 cases reviewed. Age 6.7 years (mean). Gender: 71 male, 54 female. Ethnicity: Caucasian (28%), African American (14%), Hispanic (30%), Asian (9%), Other (18%)	NA	-	57% were classed as ischaemic stroke and 25% as haemorrhagic with the remainder being mixed. Presentation included altered mental status being 27%, headache 16%, hemiparesis 22% fever 5%, and seizure 18%. Only 89% of patients presented within 6 hours of symptom onset.	Moderate
Hines (2011)	USA	To determine the frequency of acute care visits and risk factors for central nervous system (CNS) events in children with homozygous sickle cell disease (SCD-SS) with an acute headache.	Retrospective cohort	102 headache presentations (73 children with SCD-SS) Age: 5 to 21 years Gender: 62 female. Ethnicity: not stated	NA	-	Headache was the main complaint in 102 of 2,685 acute care visits (3.8%) by children with SCD-SS. Acute CNS events were detected in 6.9% of these visits. Neuroimaging was performed in 42.2% of visits, and acute CNS events were identified in 16.3% of studies. Factors associated with acute CNS events included older age, history of stroke, transient ischemic attack, or seizure, neurologic symptoms, focal neurologic exam findings, and elevated platelets. Acute headache is common in paediatric SCD-SS and more frequently associated with acute CNS events than in the general paediatric population.	Low

Incecik (2010)	Turkey	To investigate the risk factors and treatment outcomes for ischemic stroke in children	Retrospective chart review	93 children with AIS. Age: mean age at presentation ranged from 1 month to 14 years (mean: 56.60 ± 46.90 months). Gender: 50 male, 43 female. Ethnicity: not stated	NA	The mean duration of follow-up was 32.86 ± 24.38 months (4–96 months).	Focal neurological signs were the most common presentation, with hemiparesis/hemiplegia being the most common focal sign (92.4%). 37% had focal or generalized convulsions and 33.3% (n = 31) had loss of consciousness during stroke onset. Isolated or combined cranial nerve palsies were present in 23.6% of children.	Low
Kalita (2013)	India	To evaluate the aetiology, type and predictors of outcome of paediatric stroke from Northern India.	Cohort	62 children with AIS (79 in total). Age: 0.6-18 years. Gender: 53 male, 26 female. Ethnicity: not stated.	NA	-	Presenting symptom include motor deficit (46), visual deficit (1), ataxia (2), altered sensorium (12), headache (1), seizures (17).	Low
Kirton (2013)	Canada	To compare pathologically proven vs clinically suspected FMD stroke cases in determining diagnostic features.	Retrospective case series	81 cases of childhood stroke. Age: 0 to 16 years. Gender: pathologically proven FMD 59% male, clinically suspected FMD 48% male Ethnicity: not stated.	NA	Mean duration of follow-up was 42.8 months (3.6 years), with a range of 1 to 228 months	Clinical presentation signs include acute motor deficits or hemiplegia (65%), seizures (33%). Pathologically proven FMD more likely to present in first year of life.	Low

Ladner (2015)	USA	To characterize the final diagnoses of children with brain attacks in the emergency department where the paediatric acute stroke protocol was activated and to describe the time to neurological evaluation and neuroimaging.	Retrospective case series	124 stroke alerts in children (30 confirmed and 2 children had a transient ischemic attack; 21 (70%) AIS, 9 (30%) ICH. Age: 11.2 $\pm$ 5.2 years. Gender: 63 male, 61 female. Ethnicity: not stated.	NA	-	Most common presenting signs include hemiparesis/weakness (65%), altered mental status (44%) and headache (37%).	Low
Lagunju (2013)	Nigeria	To investigate prevention with hydroxyurea of secondary stroke in children with SCD.	Cohort	32 children with SCD. Age: 7 years, 7 months (mean). Gender: 22 male, 10 female. Ethnicity: African.	NA	-	Presenting symptoms include hemiparesis (93.8%), speech abnormalities (53.1%), seizures (40.6%), coma (25%).	Low
Lee (2008)	Taiwan	To investigate the clinical spectrum, risk factors, outcomes, and prognostic risk factors of childhood ischemic stroke in a tertiary medical center in Taiwan.	Retrospective study	94 children (88 AIS, 6 SVT). Age: 40 days and 18 years (mean: 7.8 $\pm$ 5.9 years). Gender: 58 male, 36 female. Ethnicity: not stated.	NA	The mean interval of follow-up was 3 years (range: 0.2–10 years).	Focal neurological signs (76%) were the most common presentation and hemiplegia was the most common focal sign. Twenty-eight percent of the children had seizures and 26% had diffuse neurological signs. Fever was found in 11% of the children.	Low
Lee (2012)	Korea	To assess ischemic stroke aetiologies, including metabolic causes in Korean children, and compare these with stroke aetiologies in Western	Retrospective review/Cohort	62 children with AIS. Age: 1 month to 17 years (mean 61.2 months $\pm$ 54.7 months).	NA	Variable	Children > 1 year were more likely to present with hemiplegia 35.7% vs 79.1%, while children $\leq$ 1 year were more likely to present with seizure 71.4% vs 20.8% and fever 42.9% vs 6.3%. There was no significant difference in the age group of	Moderate

		children. To also evaluate the relationship between stroke aetiology and clinical outcomes in childhood ischemic stroke.		Gender: 33 male, 29 female. Ethnicity: Korean Asian.			children presenting with mental change, headache, cranial nerve palsy, vomiting or dysarthria. Hemiplegia 69.3% and seizures 32.3% were the most common presenting sign and symptom, and seizures were significantly more common in <12m vs older children (71.4% vs 21.8%).	
Mackay (2011)	International	To describe the prevalence and spectrum of risk factors in childhood AIS, whether risk factors vary by age and region, association between RFs and type of presentation and RFs and AIS characteristics.	Prospective study	676 children with AIS. Age: 5.7 years (median), range 29 days to 18 years. Gender: 399 male, 277 female. Ethnicity: (carried out in) Australia, Canada, Chile, China, Georgia, Germany, Malaysia, Thailand, UK, USA.	NA	-	Signs at presentation: focal signs 82% n=557 of which hemiparesis n=480, speech disturbance n=248, visual disturbance n=72, other n=113. Diffuse signs 64% n=431 of which reduced consciousness n=287, headache n=185, papilledema n=13, other n=116 Seizures 31% n=198 Focal signs were independently associated with arteriopathy OR 2.08 (95% CI 1.22-3.56) and hemiparesis OR 2.21 (95% CI 1.38-3.53). Diffuse signs were independently associated acute systemic conditions OR 1.96 (95% CI 1.24-3.09). Diffuse signs were independently associated with chronic head and neck disorders OR 1.93 (95% CI 1.00-3.73). Diffuse signs were independently associated with acute head and neck disorders OR 1.88 (95% CI 1.22-2.90).	Moderate
Mackay (2014)	Australia	To describe the presenting features and prevalence of conditions causing stroke.	Prospective observational study	287 children with AIS. Age: 9.8 years (median), IQR 5.0-13.8.	NA	-	A history of disorders relevant to stroke was identified in 39% with a history of headaches or migraine (8.3%) and malignancy (6%) being the most common conditions. Presenting symptoms: Headache (56%, 95% CI 50-62),	Moderate

				Gender: 130 male, 157 female. Ethnicity: not stated		<p>vomiting (36%, 95% CI 31-42), focal weakness (35%, 95% CI 29-40), focal numbness (24%, 95% CI 20-30), visual disturbance (23%, 95% CI 18-28), febrile or afebrile seizures (21%, 95% CI 16-26), altered mental status (21%, 95% CI 16-25), dizziness (20%, 9% CI 16-25), speech disturbance (17%, 95% CI 13-22), ataxia (14%, 95% CI 10-19), loss of consciousness (11%, 95% CI 8-16), faint (11% 95% CI 8-15), vertigo (3% 95% CI 16-61), other (20% 95%CI 16-25).</p> <p>Presenting signs: focal weakness (31% 95% CI 26-36), focal sensory disturbance (13% 95% CI 10-18), speech disturbance (8% 95% CI 5-12), leg weakness (15% 95%CI 11-20), facial weakness (15% 95% CI 11-19), arm weakness (14% 95%CI 11-19), hand weakness (12% 95%CI 8-16), ataxia (10% 95%CI 7-14), inability to walk (10% 95% CI 7-14), eye movement abnormality (9% 95% CI 6-13), arm sensory disturbance (9% 95%CI 6-13), leg sensory disturbance (7% 95% CI 4-10), visual defects (7% 95% CI 4-11), dysarthria (6% 95%CI 4-9), facial sensory disturbance (4% 95%CI 2-7), Glasgow Coma Scale abnormal &lt;15 (28% 95%CI 23-33), Glasgow Coma Scale &lt;9 (4% 95%2-7), pupillary abnormality (3% 95%CI 1-5), hand sensory disturbance (3% 95%CI 1-6), dysphasia (3% 95%CI 1-6), paralysis (0.7% 95%CI 0.8-7), sensory neglect (0.3% 95%CI 0.8-2), other neurologic signs (8% 95%CI 5-12), no neurologic signs (34 95%CI 29-40)</p>	
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Mallick (2014)	England	To examine the risk factors, presenting features and incidence of AIS	Population based cohort study	<p>96 children with AIS.</p> <p>Age: 6.2 years (mean), range 29 days to 16 years.</p> <p>Gender: 49 male, 47 female.</p> <p>Ethnicity: 66 White, 14 Asian, 9 Black, 7 Other.</p>	NA	-	<p>Presenting features were: focal features (85%); hemiparesis (72%), facial weakness (41%), speech disturbance (33%), visual disturbance (5%), other focal features (19%). Diffuse features (61%); decreased consciousness level (42%), headache (24%), vomiting (10%), papilloedema (1%), other diffuse features (8%). Any seizure (29%); focal seizures (20%), generalised seizures (11%), both focal and generalised seizures (2%).</p> <p>32 (33%) of children had both focal and diffuse presenting features, five (5%) had focal features and seizures, eight (8%) had diffuse features and seizures, and 14 (15%) had focal features, diffuse features and seizures.</p> <p>Presenting features by age group:</p> <p>Focal features: &lt;1 year = 12 (75%), 1-5 years = 42 (89%), 6-10 years = 7 (70%), 11-15 years = 21 (91%), p=0.18.</p> <p>Hemiparesis: &lt;1 year = 11 (69%), 1-5 years = 40 (85%), 6-10 years = 6 (60%), 11-15 years = 12 (52%), p=0.02.</p> <p>Facial weakness: &lt;1 year = 4 (25%), 1-5 years = 22 (47%), 6-10 years = 4 (40%), 11-15 years = 9 (39%), p=0.50.</p> <p>Speech disturbance: &lt;1 year = 2 (13%), 1-5 years = 15 (32%), 6-10 years = 4 (40%), 11-15 years = 11 (48%), p=0.12.</p> <p>Diffuse features: &lt;1 year = 10 (63%), 1-5 years = 22 (47%), 6-10 years = 10 (100%), 11-15 years = 17 (74%), p=0.004</p> <p>Decreased conscious level: &lt;1 year = 9 (60%), 1-5 years = 17 (36%), 6-10 years = 5</p>	High
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							(50%), 11-15 years = 9 (39%), $p=0.39$ . Headache: <1 year = 0 (0%), 1-5 years = 6 (13%), 6-10 years = 5 (50%), 11-15 years = 12 (52%), $p<0.0001$ . Seizures: <1 year = 12 (75%), 1-5 years = 12 (26%), 6-10 years = 2 (20%), 11-15 years = 2 (9%), $p<0.0001$ .	
Mallick (2015)	UK	To assess delays in the diagnosis of childhood stroke.	Cohort database review	96 children with AIS. Age: 3.8 years (median), IQR 1.6 to 9.8 years. Gender: 51% male, 49% female. Ethnicity: not stated.	NA	-	Presenting features: focal features 81 (85%), diffuse features 59 (62%), Glasgow coma scale <9 18 (20%), seizures 28 (29%)	High
Mancini (1997)	France	To study associated conditions and specific causes.	Case series	35 children with AIS. Age: 2 months to 17 years. Gender: 19 male, 16 female. Ethnicity: not stated.	NA	-	Clinical presentation: acute hemiplegia (18 cases, 45%), hemichorea (4 cases, 10%), epileptic seizures (8 cases, 20%), status epilepticus (3 cases, 8.5%), visual disorders (5 cases, 12.5%), eye sight disorders (2 cases, 5.7%), cephalalgia (5 cases, 12.5%), migraine (1 case 2.8%), initial coma (2 cases 5.7%).	Low
Matta (2006)	Brazil	To describe the aetiologies, neurological manifestations and neuro-imaging findings of children with cerebrovascular disorders.	Case series	23 children with AIS. Age: 8.78 (mean), range 1 to 15 years. Gender: 9 male, 14 female. Ethnicity: not stated.	NA	-	Symptoms: hemiparesis/hemiplegia (18), seizures (9), quadriplegia (3).	Moderate

McColl (1999)	Scotland	To investigate the role of thrombophilia in AIS - specifically the prevalence of Factor V Leiden, prothrombin 20210 G-A and MTHFR C6771 mutations.	Retrospective case series	50 children with AIS. Age: 51 months (median), range 10 to 168 months. Gender: 28 male, 22 female. Ethnicity: not stated.	219 random unselected cord blood controls	-	All neonatal strokes presented either with seizures alone or a combination of focal weakness and seizures. 33 of the non-neonatal cases presented with hemiparesis, sometimes accompanied with seizures. The remaining 6 cases presented with cerebellar signs (2), visual field defects (2), isolated cranial nerve palsy (1) or coma (1).	Moderate
Ndiaye (2013)	Senegal	To determine risk factors, clinical and radiological features and outcome of arterial ischemic stroke in a cohort of Senegalese infants.	Retrospective cohort	48 children with AIS. Age: 2 months to 18 years. Gender: 20 male, 28 female. Ethnicity: not stated.	NA	-	The onset of clinical signs was either sudden or rapidly progressive over few hours. The most common symptoms were hemiparesis in 45/48 (93.75%), motor partial seizures in 11/48 (24.44%), and Broca's aphasia 16/48 (33.3%).	Low
Per (2014)	Turkey	To summarise the aetiology, risk factors, initial complaints, clinical features, laboratory, radiological findings, and clinical follow-up data of the children with ischemic stroke.	Case series	130 children with AIS. Age: 1 month to 16 years. Gender: 68 male, 62 female. Ethnicity: not stated.	NA	-	Presenting signs: fever (16), seizure (76), altered consciousness (19), headache (8), nausea/vomiting (14), hemiparesis/hemiplegia (63), cranial nerve palsy (18), speech impairment (9), visual impairment (2), extremity weakness (14), gaze palsy (7). Focal neurological signs were the most common presentation (87%).	Moderate
Rafay (2006)	Canada	To determine the frequency; identify the associated risk factors; determine the clinical presentation, imaging features, and treatment strategies; and report the clinical and angiographic outcome of arterial	Case series	16 children with AIS. Age: 9.4 years (median), range 6 months to 16.4 years. Gender: 8 male, 8 female.	NA	-	Presenting symptoms: persistent focal neurologic deficits (87.5%), headache (44%), altered consciousness (25%), seizures (12.5%) Presenting signs: focal motor and sensory deficits (93%), speech deficits (50%), cranial nerve palsies (37.5%), visual field defect (25%), ataxia (12.5%).	Low

		dissection in the paediatric ischemic stroke population.		Ethnicity: not stated.				
Rollins (2013)	USA	To describe timely diagnosis, imaging and outcomes with anticoagulation treatment in childhood AIS.	Case series	15 children with AIS. Age: 7.8 years (mean), range 9 months to 17 years. Gender: 10 male, 5 female. Ethnicity: not stated.	NA	-	Vague symptoms contributed to delays in diagnosis. Symptoms: headaches (eight); visual problems (eight), seizure-like activity (seven), motor deficits (six), and decreased level of consciousness in four. Paediatric National Institutes of Health Stroke Scale was 1-34; <10 in eight; 3 in 1, 10-20 in two, and >20 in four.	Moderate
Shi (2008)	China	To review cases of paediatric arterial ischemic stroke among Chinese subjects and thereby evaluate risk factors, clinical and neuroimaging features, and treatment, to establish a reasonable guide- line for assessment and management of the disease.	Cohort series	157 children with AIS. Age: 32 months (median), range 4 to 192 months. Gender: 92 male, 65 female. Ethnicity: Chinese	NA	-	The male: female ratio was 1.4:1. The median age at presentation was 32 months (range, 4-192). The 84 children who were 36 months old (the youngest group, 53.5% of the total) had the highest stroke rate of any age group for ischemic stroke, and the 13 children aged 13-16 years (the oldest group, 8.3% of the total) had the lowest stroke rate. Clinical features: Hemiparesis 128 (81.5%) Right in 70, Left in 58, Alternate hemiplegia 2 (1.3%), Monoparesis 4 (2.6) Seizures 32 (20.4%), Dysphasia 25 (15.9%), Change in consciousness 9 (5.7) Other (include headache, dizziness, visual impairment, and ataxia) 23 (14.6%)	Moderate
Songsaeng (2010)	France	To analyse the clinical presentation, characteristics and outcomes of paediatric vertebral artery dissections.	Case series	29 children with AIS. Age: 8.2 years (mean), range 2 months to 15 years.	NA	-	VBD occurred predominantly in boys (3:1). 10 children presented with SAH (all had headache and nuchal rigidity, 2 had neuro deficits), 16 presented with ischemic symptoms (8 with headache, 5 with vertigo, and 10 had focal neuro symptoms)	Low

				Gender: 22 male, 7 female. Ethnicity: not stated.				
Steinlin (2005)	Switzerland	To report incidence, manifestation, risk factors, and short term neurological outcomes of stroke in children.	Cohort	40 children with AIS. Age: 5.6 years (mean). Gender: 54 male, 26 female (including children with SVT). Ethnicity: 67 Caucasian, other ethnicities not described.	NA	6 months	For AIS in children, presentation hemiparesis in 77%, cerebellar symptoms and seizures in 20%. Headaches were preceding symptom in 3 patients.	Low
Sun (2013)	China	To determine aetiology, clinical presentation and radiological features of neurological deficit for paediatric AIS.	Retrospective cohort	42 children with AIS. Age: 9 months to 13 years. Gender: 21 male, 21 female. Ethnicity: not stated.	NA	-	The most commonly reported signs and symptoms among all 42 PAIS cases involved limited physical activity. Specifically, 95.2% (n=40) of cases presented with paralysis, which manifested as hemiplegia (n=32), alternating hemiplegia (n=5), and monoplegia (n=3). The second most common sign overall was convulsion (26.2%, n=11). The majority of cases (n=11) experiencing convulsions were 3 years-old or younger (72.7%, n=8). Eight children experienced delirium, 75.0% (n=6) of whom were under 3 years-old. The less frequent symptoms reported were fever (n=12), headache (n=5), and ataxia (n=1). Hemiplegia was the most common sign in children over 3 years-old, while seizures	Moderate

							(partial or generalized) was the most common for children 3 years-old and younger.	
Tuckuviene (2011)	Denmark	To study the incidence rate, clinical characteristics, risk factors and sequelae of AIS in children.	Cohort	211 children with AIS. Age: 0 to 18 years. Gender: 118 male, 93 female. Ethnicity: not stated.	NA	12 months	Symptoms at presentation: in children <1 year - seizures (85.3%), hemiparesis (17.3%), N. facialis paresis (2.7%), altered mental status (5.3%), headache/syncope/abnormal muscle tonus/nausea/vomiting (6.7%). In children 1-14y - seizures (19.2%), hemiparesis (71.2%), N. facialis paresis (35.6%), altered mental status (17.3%), visual disturbance (9.6%), speech problems/aphasia (21.2%), headache/syncope/abnormal muscle tonus/nausea/vomiting (28.9%). Adolescents 15-18y - seizures (21.9%), hemiparesis (43.8%), N. facialis paresis (12.5%), altered mental status (34.4%), visual disturbances (15.6%), speech problems/aphasia (25.0%), headache/syncope/abnormal muscle tonus/nausea/vomiting (46.9%).	Low
Wang (1998)	Taiwan	To compare clinical manifestations, associated diseases, treatment and mortality rate.	Retrospective case series	65 children with AIS. Age: 0 to 18 years. Gender: 37 male, 28 female. Ethnicity: not stated.	NA	-	Presenting symptoms: motor deficits (65.8%), seizures (55.3%), consciousness disturbance (52.6%)	Moderate
Yock-Corrales (2011) (1)	Australia	To assess the applicability of adult stroke scales in childhood arterial ischemic stroke (AIS).	Retrospective case series	47 children with AIS. Age: 9 years (median) range 4	NA	-	34 had anterior, 12 had posterior and 1 child had anterior and posterior circulation infarcts. The most common presenting stroke symptoms were arm (63%), face	Low

				months to 16 years. Gender: 24 male, 23 female. Ethnicity: not stated.			(62%), leg weakness (57%), speech disturbance (46%) and headache (46%). The most common signs were arm (61%), face (70%) or leg weakness (57%) and dysarthria (34%). 36 (78%) of children had at least one positive variable on FAST and 38 (81%) had a positive score of $\geq 1$ on the ROSIER scale. Positive scores were less likely in children with posterior circulation stroke.	
Yock-Corrales (2011) (2)	Australia	To determine the clinical characteristics of radiologically confirmed paediatric stroke on presentation to the emergency department (ED) of a tertiary hospital; specifically, to describe the major arterial ischemic and haemorrhagic stroke subtypes in children.	Retrospective case series	50 children with AIS. Age: 7 years (mean) S.D. 5.1 years. Gender: 25 male, 25 female. Ethnicity: not stated.	NA	-	Acute ischemic stroke presented with symptoms of focal limb weakness (64%; 95% confidence interval [CI] 49% to 77%), facial weakness (60%; 95% CI 45% to 73%), and speech disturbance (46%; 95% CI 31% to 60%). Few patients with acute ischemic stroke presented with vomiting and altered mental status. Most patients with acute ischemic stroke had a Glasgow Coma Scale (GCS) score of 14 or greater (86%; 95% CI 73% to 94%) and presented with at least 1 focal neurologic sign (88%; 95% CI 73% to 98%). Haemorrhagic stroke presented with headache (73%; 95% CI 54% to 87%), vomiting (58%; 95% CI 40% to 75%), and altered mental status (48%; 95% CI 30% to 67%). GCS score in haemorrhagic stroke was less than 14 in 38% and less than 8 in 19% (95% CI 7% to 37%). Less than one third of patients had focal limb weakness, facial weakness, or slurred speech.	Moderate
Zimmer (2007)	USA	To determine whether there are more age related variations in the clinical presentation of AIS.	Case series	76 children with AIS. Age: 0.2 to 18.5 years.	NA	-	Children aged <1 year were significantly more likely than older children to present with epileptic seizures (45.5% vs 10.8%, $P=0.01$ ) and altered mental status (36.4% vs	Moderate

				Gender: 41 male, 35 female. Ethnicity: 83% White, 11% African American, 7% Hispanic.			7.7%, P0.02), and there was a trend for them to be less likely than older children to present with focal weakness (45.5% vs 76.9%, P 0.06). Children aged <1 year with cerebral arterial ischemic stroke were more likely to present with epileptic seizures and altered mental status than children aged >1 year, and may be less likely to present with focal weakness.	
<b>Imaging in AIS</b>								
Buerki (2010)	Switzerland	To describe neuroimaging patterns associated with AIS in childhood and to differentiate them according to stroke aetiology.	Retrospective cohort review	79 children with AIS. Age: 5 years 3 months (median), range 2 months to 15 years 8 months. Gender: 48 male, 31 female. Ethnicity: not stated.	NA	-	Stroke was confirmed in the acute period in 36 out of 41 children who underwent CT, in 53 of 57 who underwent T2-weighted magnetic resonance imaging (MRI) and in all 48 children who underwent diffusion-weighted MRI. AIS occurred in the anterior cerebral artery (ACA) in 63 participants and in all cases was associated with lesions of the middle cerebral artery (MCA). The lesion was cortical–subcortical in 30 out of 63 children, cortical in 25 out of 63, and subcortical in 8 of 63 children. Among participants with AIS in the posterior circulation territory, the stroke was cortical–subcortical in 8 out of 16, cortical in 5 of 16, and thalamic in 3 out of 16 children.	Low
Buompadre (2009)	Argentina	To describe the main neurological manifestations, neuroimaging findings, risk factors, and outcome in a series of children who were admitted because of basal	Prospective and retrospective case series	28 children with AIS. Age: 3.3 years (median) range 3 months to 10 years. Gender: 14 male, 14 female.	NA	24 months (median)	All patients evidenced hypodensities in the basal ganglia on the brain CT scan at the time of diagnosis. In 6 children, the first brain CT scan (within 8 hrs) was normal. 24 (86%) children had MRI which was more efficient in showing the anatomical extension of the AIS.	Moderate

		ganglia and internal capsule stroke.		Ethnicity: not stated.				
Husson 2002	France	To compare the results of MRA with those of CA for the study of cerebral arteries in children with arterial infarction in an arterial distribution.	Case series	24 children with AIS. Age: 7 years (mean), range 6 months to 14 years. Gender: 13 male, 11 female. Ethnicity: not stated.	NA	-	MRA was concordant with CA in detecting defects in large cerebral vessels. No false-positive results while investigating intracranial arterial lesions with MRA were observed. There was some discordance between MRA and CA, mainly overestimation of stenosis and under diagnosis of distal arterial lesions with MRA. MRA is sensitive enough to provide an adequate evaluation in the initial stage of arterial brain diseases in childhood. CA should be considered in situations in which MRA is normal, small-artery diseases are suspected, or uncertainties about the differential diagnosis of ICA lesions persist and for an accurate assessment of the effect of therapeutic trials on the arterial wall.	Low
Mallick (2015)	UK	To investigate the time to diagnosis in a cohort of children with stroke.	Cohort	96 children with AIS, 43 with HS. Age: 3.8 years (median), IQR 1.6 to 9.8 years. Gender: 51% male, 49% female. Ethnicity: not stated	NA	-	Imaging: first neuroimaging modality CT (68%), MRI (29%), cranial ultrasonography (2%). First imaging was diagnostic of stroke in 76% First imaging diagnostic of stroke by modality: CT 66%, MRI 100%, cranial ultrasonography 50%.	High
Mancini (1997)	France	To investigate a 10-year review of a neuropediatric department experience	Case series	35 children with AIS. Age: 2 months to 17 years.	NA	-	CT performed in all patients. CT was sufficient for diagnosis in 14 cases (40%). MRI was performed in 21 patients (52.5%).	Low

		with childhood ischemic cerebrovascular disease.		Gender: 19 male, 16 female. Ethnicity: not stated.			MRI demonstrated the signal changes in the ischaemic area as a low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. In 6 cases MRI was more contributory than CT scans in demonstrating watershed infarcts or ischaemia with basilar artery territory. Angiography was performed in 12 patients (30%) through percutaneous femoral artery catheterization. Angiography provided a firm diagnosis of moyamoya in 2 patients and displayed abnormalities in patients with sickle cell anaemia and homocystinuria.	
Martin (2011)	Switzerland	To investigate the delay from the onset of symptoms to AIS diagnosis in children and potential contributing factors.	Retrospective review	91 children with AIS. Age: 1 month to 16 years. Gender: 61 male, 30 female. Ethnicity: not stated.	NA	-	The time to diagnosis (by neuroimaging) was <6 hours in 32 (35%), 6–12 hours in 23 (25%), 12–24 hours in 15 (16%) and >24 hours in 21 (23%) children. Of 74 children not hospitalised when the stroke occurred, 42% had adequate outpatient management. Delays in diagnosis were attributed to: parents/caregivers (n=20), physicians of first referral (n = 5) and tertiary care hospitals (n = 8). A comorbidity hindered timely diagnosis in eight children. No other factors were associated with delay to diagnosis. A total of 17 children were inpatients at AIS onset. MRI was abnormal in 4 children with normal CT. MRI seems to be better at picking up AIS.	High
McGlennan (2008)	UK	To investigate the timing and course of investigation and diagnosis in children	Retrospective case review	50 children with AIS.	NA	-	First imaging modality was CT 37 (74), MRI 13 (26)	Low

		with acute arterial ischaemic stroke (AIS) and factors influencing this using a retrospective case-note review.		Age: 3 years 4 months (median), range 2 months to 16 years 10 months. Gender: 26 male, 24 female. Ethnicity: not stated.			Time to first imaging (CT or MRI) (n=46) <6h 13 (23.8), 6–12h 8 (17.4), 12–24h 7 (15.2), >24h 18 (39.1) Results of first imaging (n=49) AIS confirmed 32 (65.3), AIS not confirmed 17 (34.7) Results when first modality CT (n=36) AIS confirmed 19 (52.8), AIS not confirmed 17 (47.2) Second modality imaging confirmed (in most cases MRI) (n=37) AIS 37 (100), did not confirm AIS 0. Time to MRI (n=47) <6h 1 (2.1), 6–12h 1 (2.1), 12–24h 2 (4.3), >24h 43 (91.5) Result of MRA (n=37) Normal 8 (21.6), Abnormal 29 (78.4) The high false negative rate for CT in this study further reinforces the need for MRI for accurate diagnosis.	
Paonessa (2010)	Italy	To assess aetiology of paediatric stroke and diagnostic protocol.	Case series	41 children with AIS. Age: 12 years (mean) range 5 to 16 years. Gender: 22 male, 19 female. Ethnicity: not stated.	NA	-	23 patients underwent MRI, 3 cases were studied by CT without MRI, and 15 underwent both CT and MRI studies. In 9 cases, intra-arterial digital subtraction angiography (IADSA) was performed after non-invasive preliminary assessment. 17 (41%) children had HS and 24 (59%) had ischemic stroke. MRI provides the greatest amount of diagnostic information CT is useful when child cannot tolerate MRI Angiography performed 7/41. Unknown cause of stroke in 8/41 (20.5%).	Low
Rafay (2006)	Canada	To determine the frequency; identify the associated risk factors; determine the	Case series	16 children with AIS. Age: 9.4 years (median), range 6	NA	-	CT of the head was performed in 15 (94%), MRI in 14 (88%) and MR angiography in 11 (69%), conventional angiography was performed in all children.	Low

		clinical presentation, imaging features, and treatment strategies; and report the clinical and angiographic outcome of arterial dissection in the paediatric AIS population.		months to 16.4 years. Gender: 8 male, 8 female. Ethnicity: not stated.			Initial CT performed within 24 hours of first presentation, showed infarction in 13 children. Follow-up CT showed infarction in all children. Among 14 children who had MRI, ischaemic changes were seen in all patients. MR angiography performed in 11 children detected abnormality in all. Conventional angiogram was abnormal in all 16 children.	
Rollins (2000)	USA	To report of experience of MR, MR angiography and catheter angiography in children with acute idiopathic cerebral infarction.	Case series	18 children with AIS. Age: 7 years (mean), range 4 months to 16 years. Gender: 9 male, 9 female. Ethnicity: not stated.	NA	-	Comparison DSA:MRA MRA judged inferior to DSA in 7/17 patients [but see comments below] ICA occlusion often indistinguishable from stenosis on MRA Overall results: MRA in findings true positive in 17; false negative in 2; false positive in 0 and true negative in 15. PPV for MRA 100% and NPV 88%. $P < .0005$ between MRA and DSA for detection of carotid or MCA disease Group with basal ganglia infarcts: MRA true positive in 10/12; false positive in 0; true negative in 13 and false negative in 1. PPV for MRA compared with DSA for proximal MCA disease = 100% and NPV 93% ( $p = < .0005$ ). Overall conclusions: MRI and MRA should be obtained in all children with acute hemiplegia Basal ganglia infarct with normal MRA or proximal MCA disease does not require DSA DSA should be considered when basal	Low

							ganglia infarcts are associated with ICA disease on MRA or if hemispheric infarcts are present	
Srinivasan (2009)	Australia	To identify the delays involved in diagnosing AIS.	Retrospective cohort	107 children with AIS. Age: 36 months (median), range 6 to 118 months. Gender: male:female ratio 1.27:1 Ethnicity: not stated.	NA	-	The proportions of children who underwent brain MRI, brain CT imaging, or ultrasonography as initial imaging were 88.9%, 94.9%, and 30%, respectively. MRI and CT scanning were performed as initial imaging primarily in the older population, with more ultrasound studies in the neonatal population. Imaging: in initial imaging CT yielded negative results despite AIS for 62 of 74 children, ultrasonography yielded negative results for 3 of 6 children and MRI confirmed all strokes in 8 children.	Moderate

Clinical presentation and diagnosis (imaging) of acute diagnosis of stroke in HS								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
<b>Presentation</b>								
Visudhiphan (1996)	Thailand	To describe the aetiologies of stroke.	Case series	68 children with stroke, 30 with ICH. Age: 6m to 5y (n=8), 5 to 10y (n=10), 10 to 15y (n=12). Gender: 20 male, 10 female. Ethnicity: not stated.	NA	-	Presenting signs: Headache (23, 77%), vomiting (17, 57%), disturbances of consciousness (19, 63%), abnormal fundi (9, 30%), unilateral neurological signs (17, 57%).	Low

Wang (1998)	Taiwan	To describe the clinical manifestations, associated diseases, treatment and mortality rate of stroke in childhood.	Case series	65 children with stroke, 27 with ICH. Age: 7 years 5 months (mean). Gender: 37 male, 28 female. Ethnicity: not stated.	NA	-	Clinical signs: consciousness disturbance (15, 55.6%), seizure (14, 51.9%), motor deficit (14, 51.9%), headache (11, 40.7%), vomiting (12, 4.4%), pathologic respiration (2, 7.4%), anisocoria (2, 7.4%).	Low
Suh (2001)	UK and France	To describe the aetiologies of ICH in children under 2 years of age.	Case series	20 children with ICH. Age: < 2 years. Gender: 10 male, 10 female. Ethnicity: not stated.	NA	-	Symptoms at presentation: seizure (10, 55%), deficit (3, 17%), macrocephaly/hydrocephalus (2, 11%), coma (3, 17%).	Low
Stieltjes (2005)	France	To describe the risk factors, presentation and outcome in patients with haemophilia experiencing an ICH	Cohort	58 children with ICH. Age: 10 neonates, 48 children < 15 years. Gender: not stated. Ethnicity: not stated.	NA	-	In children <2y first documented symptom: apathy and/or unusual tears (20.7%), vomiting (17.2%), coma (13.8%). Overall symptoms: apathy/unusual tears (77.4%), motor dysfunction (53.1%), neurovegetative dysfunction (40.6%), increased head perimeter (34.5%), seizure (34.4%).	Moderate
de Ribaupierre (2008)	Switzerland	To analyse the signs and symptoms of HS in children and their treatment.	Case series	22 children with HS. Age: 10.8 years (mean), range 2 months to 18 years. Gender: 9 male, 13 female. Ethnicity: not stated.	NA	-	77% presented with headache, 41% had sudden onset headache 9% had progressive headache. 23% had no or subtle neurology at onset of headaches but 27% had moderate and 11% severe neurological symptoms. 41% had a normal GCS at presentation.	Moderate

Deng (2015)	China	To describe the number and risk factors for stroke.	Cohort	249 children with HS. Age: 10.2 years (mean), S.D. 5.2 years. Gender: 153 male, 78 female. Ethnicity: Chinese	NA	-	Presenting signs: 35.1% hemiplegia, 5.2% facial paralysis, 6.5% speech disturbance, 5.6% visual disturbance, 16.5% reduced conscious level, 74% headache, 14.3% seizures.	Low
Kumar (2009)	India	To determine the causes, course and outcome of HS.	Case series	50 children with HS. Age: 13.8 years (mean), range 2 months to 17 years. Gender: 31 male, 19 female. Ethnicity: Indian.	NA	3.12 years (mean)	Presenting signs: signs of raised intracranial pressure (headache, vomiting, nausea) 70%, deterioration in sensorium 50%, limb weakness 36%, seizures 28%.	Low
Elalfy (2010)	Egypt	To discuss ICH in children with immune thrombocytopenic purpura, incidence, risk factors, management and outcome.	Case series	10 children with ICH. Age: 7.5 years (median). Gender: 6 male, 4 female. Ethnicity: Egyptian.	NA	-	Presenting signs: petechiae and ecchymoses (10), other bleeding sites (7), headache, nausea, vomiting and drowsiness (6).	Low
Xia (2008)	China	To describe the characteristics of cerebrovascular disease in children	Retrospective case series	204 children with HS. Age: mean age 12.7 (boys), 13.1 (girls). Gender: 134 male, 70 female. Ethnicity: not stated.	NA	-	Headache = 144, 70.6%, vomiting = 102, 50%, impaired consciousness = 46, 22.5%, convulsions = 44, 21.6%, focal neurological deficits = 27, 13.2%, accidental discovery without symptoms = 10, 4.9%.	Moderate

Saraf (2012)	India	To report on patients with aneurysms treated using endovascular techniques	Case series	23 children with aneurysms, 61% ruptured. Age: 13 years (mean), range 2 months to 18 years. Gender: 17 male, 6 female. Ethnicity: not stated.	NA	-	Children with ruptured aneurysms presented with headache and focal neurological deficits.	Moderate
Ahn (2012)	South Korea	To investigate the clinical features and role of bypass surgery in children with moyamoya who presented with bleeding.	Case series	13 children with moyamoya who presented with bleeding. Age: 11 years (mean), range 4 to 18 years. Gender: 6 male, 7 female. Ethnicity: not stated.	NA	-	8 patients were symptomatic, of these 7 had a TIA and 5 subsequently had an ICH and presented with an intraventricular haemorrhage. The most common clinical manifestation at the time of first haemorrhage was altered mental state (7) and hemiparesis (8). One patient had seizures.	Low
Al-Jarallah (2000)	USA	To analyse the clinical features, risk factors, and outcomes of children with ICH	Retrospective case series	68 children with ICH. Age: 7.1 years (mean), range 3 months to 18 years. Gender: 43 male, 25 female. Ethnicity: not stated.	NA	-	Headache (31, 45.6%), vomiting (14, 20.6%), irritability (6, 8.8%), seizures (25, 36.8%) of which focal seizures (6) and generalised seizures (19), hemiparesis (11, 16.2%), aphasia (3, 4.4%), coma (2, 2.9%), lethargy (3, 4.4%), Macrocephaly (1, 1.5%), miscellaneous (7, 10.3%).	Moderate
Aydinli (1998)	Turkey	To describe the presenting clinical and laboratory features and outcome of	Retrospective case series	11 children with HS.	NA	-	Seizure (10, 90.9%), drowsiness (9, 81.2%), poor sucking (7, 63.6%), vomiting (5, 45.5%), fever (5, 45.5%), pallor (5, 45.5%),	Moderate

		late new-born haemorrhagic disease (vitamin K deficiency diagnosed with HS).		Age: 56 days (mean), range 30 to 119 days. Gender: 8 male, 3 female. Ethnicity: not stated.			acute diarrhoea (3, 27.3%), irritability/high pitched cry (2, 18.2%). Examination findings: bulging or tense fontanelle (8, 72.2%), bleeding from puncture sites (4, 36.6%), anisocoria (4, 36.6%), weak neonatal reflexes (2, 18.2%), cyanoses (2, 18.8%), 1 each of strabismus, opisthotonos, dehydration, asymmetric clonus, increased deep tendon reflexes, decreased deep tendon reflexes, bleeding from mouth.	
Liu (2016)	China	To present the clinical, angiographic and long term surgical outcomes of haemorrhagic and ischaemic moyamoya patients.	Retrospective case series	30 children with HS. Age: 12.6 years (mean), range 4 to 16 years. Gender: 10 male, 20 female. Ethnicity: not stated.	NA	6.4 years	6 (20%) had headaches or minor TIA before haemorrhage, 24 (80%) were asymptomatic.	Low
Lo (2008)	USA	To determine whether the risk factors for ICH have changed and estimate the residual deficits in survivors.	Retrospective case review	85 children with ICH. Age: 7 years (median), range 7 days to 17 years. Gender: 54 male, 31 female. Ethnicity: 67 White, 10 African American, 1 South East Asian, 1 Asian Indian, 1 Other, 5 Unknown.	NA	25 months (median)	In children <6y (34) presenting signs were: mental status changes (18, 53%), convulsions (11, 32%), vomiting (7, 21%), respiratory distress (4, 12%), decreased movement/weakness (4, 12%) In children ≥6y (51) presenting signs were: headache (37, 73%), mental status changes (29, 57%), focal neurological deficits (20, 39%), nausea or vomiting (17, 33%), convulsions (8, 16%), miscellaneous (12, 24%) In all children blood pressure was elevated above the 90th centile in 38 (45%)	Moderate

Giroud (1997)	France	To describe the clinical and etiological features of stroke.	Retrospective case series	54 children with stroke, 23 with HS. Age: 9.5 years (mean). Gender: 12 male, 11 female. Ethnicity: Caucasian. One girl was Korean but not stated whether she had AIS or HS.	NA	-	Early and transient coma (5, 21%), cephalalgia (15, 65%), sensorimotor hemiplegia (14, 60%), pure motor hemiplegia with ophthalmoplegia (1, 4%), aphasia (9, 39%), and early motor seizure (9, 39%).	Low
<b>Imaging in HS</b>								
de Ribaupierre (2008)	Switzerland	To analyse the signs and symptoms of HS in children and their treatment.	Case series	22 children with HS. Age: 10.8 years (mean), range 2 months to 18 years. Gender: 9 male 13 female. Ethnicity: not stated.	NA	-	Investigations: All had emergency cerebral CT scan with and without contrast When haemorrhage suggested aneurysm rupture multislice CT angiography was performed, intra-arterial angiography not necessary for aneurysm diagnosis When AVM was suspected intra-arterial cerebral angiography was necessary - most children required anaesthesia for this procedure When cavernous angioma was suspected or when aetiology remained unknown MRI was used.	Moderate
Fasulakis (2003)	South Africa	To compare conventional catheter angiography to magnetic resonance angiography in the detection of intracranial AVMs and aneurysms	Case series	19 children with AVM and aneurysms. Age: 8.7 years (mean), range 1 month to 16 years.	NA	-	Lesions were identified in 15 patients on MRA and 11 patients on CCA. MRA disclosed 1 probable aneurysm with vessel spasm, 9 AVMs, 3 haemorrhages and 2 indeterminate lesions. CCA showed 9 AVMs and 2 indeterminate lesions.	Low

				Gender: 10 male, 9 female. Ethnicity: not stated.			MRA demonstrated 3 cases of focal parenchymal haemorrhage Authors conclude that the high sensitivity of MRA in detecting AVM (compared with CCA) and the low incidence of aneurysms (in this population) should lead to the use of MRA as the initial imaging following intracerebral haemorrhage diagnosed by CT-especially out of hours.	
Xia (2008)	China	To describe the characteristics of cerebrovascular disease in children.	Retrospective case series	204 children with cerebrovascular disease. Age: mean age 12.7 years (boys), 13.1 (girls). Gender: 134 male, 70 female. Ethnicity: not stated.	NA	-	CT was performed to confirm haemorrhage in 195 children. Aetiology was chiefly based on DSA in 130 children or pathology in 78 children. To screen aetiologies MRI/MRA was performed on 66 children and CTA on 25 children. MRI was performed on 31 children suspected of cavernoma, of which 29 were treated surgically and in 28 (96.6%) the imaging diagnosis was consistent with the pathological diagnosis. MRI/MRA was 100% diagnostically consistent with DSA in 8 children with moyamoya CTA had a diagnostic coincidence of 78.9% (15/19) and was performed on children highly suspected of AVM or aneurysm who couldn't tolerate DSA.	Moderate
Al-Jarallah (2000)	USA	To analyse the clinical features, risk factors, and outcomes of children with ICH.	Retrospective case series	68 children with ICH. Age: 7.1 years (mean), range 3 months to 18 years.	NA	-	36 (52.9%) patients underwent standard cerebral angiography. The likelihood of establishing the cause of bleeding was greater when evaluation included standard cerebral angiography. A probable cause for the haemorrhage was identified in 35 (97.2%) of 36 patients who	Moderate

				Gender: 43 male, 25 female. Ethnicity: not stated.			had angiography versus 26 (81.3%) of 32 in the group without angiography. The timing of angiography after haemorrhage varied, but no major complications resulted from the angiography.	
Ladner (2015)	USA	To assess the speed with which paediatric stroke evaluation took place and characterise final diagnoses of children with brain attacks in the emergency department when the stroke protocol is activated.	Database review	124 stroke alerts, 32 confirmed strokes, 9 HS. Age: (all) 10 years (mean) S.D. 5 years. Gender: 20 male, 12 female. Ethnicity: White 66%, Hispanic 3%, Black 29%.	NA	-	All children under went neuroimaging except 1. MRI first study in 93 of 123 (76%). Median time from emergency department arrival to MRI was 94 min (IQR 49-151 min) and for CT 59 min (IQR 40-112 min). Overall time to any first scan was 79 min (IQR 45-422 min). Factors in cases with longer latencies were low suspicion for stroke (13, 57%), outside acute intervention window (10, 43%), need for anaesthesia (4, 17%), and medical instability (3, 13%). Anaesthesia was required for 9 of 93 (10%) children with MRI. The majority of MRI scans were within 120 minutes of ED arrival. The majority of CT scans were within 60 minutes of ED arrival.	Low
Koelfen (1995)	Germany	To explore the use of MRA in children	Prospective case series	140 children referred for MRA. Age: 3 weeks to 18 years. Gender: 71 male, 69 female. Ethnicity: not stated.	NA	-	MRA could visualised the following arteries at all ages: internal carotid (ICA, ACA, MCA, PCA, VA, and BA). Primary branches of posterior circulation (PICA, AICA, SCA) and the anterior and posterior communicating arteries were identified inconsistently but the number of arteries visualised increased up to the age of 6y	Moderate

							<p>Secondary branches of ACA, MCA and PCA could be seen up to the high cortical segments in some older children</p> <p>The lenticulostriatae, thalamostriatae, and choroid artery were never visualized.</p> <p>MRA revealed anatomic variations in 21 patients (15%).</p> <p>In 22 of 32 children with malformations of the brain abnormal intracranial vasculature was seen.</p> <p>18 children with known or suspected vascular malformations were studied by MRA and were positive for intracerebral haemorrhage in 9 (50%).</p> <p>Delineation of all vascular territories wasn't possible due to limited size of imaging volume used.</p> <p>Complete definition difficult in complex AVM with multiple feeding arteries arising from different vascular distributions</p> <p>After haemorrhages, time of flight MRA was unreliable in the first examination because the high signal from the acute hematoma could not always be differentiated precisely from the high signal of the moving blood.</p> <p>In 6 children neither DSA nor MRA was able to demonstrate the cause of intracerebral haemorrhage seen on conventional MRI.</p> <p>In 3 children with AVMs, MRA was used after the operation/embolization for controlling the results. No discrepancy was found between MRA and DSA findings.</p>	
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## Chapter 4: Referral pathways and further investigations

<b>Referral pathway AIS and HS</b> <b>Does the setting where children with AIS/HS receive acute care affect mortality, morbidity, and complications?</b> <b>What are the key elements and individuals involved in the acute care of children with AIS/HS?</b>								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Bernard (2014)	USA, Canada	To describe the development of primary paediatric stroke centres in preparation for participation in the Thrombolysis in Paediatric Stroke (TIPS) trial.	Cross-sectional study	17 Centres, 16 in USA, 1 in Canada	NA	-	There was a significant increase in the centres self-perception of site readiness to treat acute stroke when comparing readiness before and after preparation for the TIPS trial.	Moderate
Ichord (2011)	USA	To evaluate interrater reliability (IRR) of a paediatric adaptation of the National Institutes of Health Stroke Scale (PedNIHSS).	Multi-centre prospective cohort	113 children with AIS. Age: 2 to 19 years. Gender: 71 male, 42 female. Ethnicity: not stated	NA	-	PedNIHSS was judged as excellent. Interrater reliability was excellent as measured by concordance correlation coefficient of 0.97 (95% CI, 0.94 to 0.99); intraclass correlation coefficient of 0.99 (95% CI, 0.97 to 0.99); precision measured by Pearson p of 0.97; and accuracy measured by the bias correction factor of 1.0.	Moderate
Kalita (2013)	India	To evaluate the aetiology, type and predictors of outcome of paediatric stroke from Northern India	Cohort	79 children, 62 with AIS. Age: 144.8 months (mean), range 0.6 to 18 years. Gender: 53 male, 26 female. Ethnicity: not stated	NA	-	This study includes a diagram of the pathway used which briefly looks like: suspected stroke - neuroimaging - evaluation of risk factors and determination of aetiology (haemogram, fasting blood glucose/lipid profile, renal profile, liver profile, serum electrolytes, coagulation profile, ECG, chest x-ray, urine routine exam, HIV serology, HBsAG, anti HCV antibody) - vascular imaging (MRA or CTA) - cardiac evaluation (ECG, ECHO) - history of fever, headache, other features	Low

							of CNS infection, CSF study and work up for CNS infection - evaluation for prothrombotic conditions, haemoglobinopathies (SCA), metabolic work up, x-ray for cervical rib, atlantoaxial dislocation, vasculitis work up - if all the above are negative evaluate for patent foramen ovale including transesophageal ECHO - if still no aetiology established then label as cryptogenic.	
Ladner (2015)	USA	To assess the speed with which paediatric stroke alert evaluations took place and to characterize the final diagnoses of children with brain attacks in the emergency department (ED) when the paediatric acute stroke protocol was activated.	Case series	124 children with stroke. Age: 11.2 years (mean) S.D. 5.2 years. Gender: 63 male, 61 female. Ethnicity: White, non-Hispanic 65%, White Hispanic 4%, Black 29%, Asian 2%, Native American 1%.	NA	-	Median time from ED arrival to MRI was 94 (IQR 49–151) minutes and for computed tomography, 59 (IQR, 40–112) minutes. The overall time to first scan (any) was 79 (IQR, 45–422) minutes. 30 (24%) children had a stroke, 2 (2%) children had a TIA. 21/30 (70%) were IS and 9/30 (30%) HS. 17 (14%) had non-stroke neurological emergencies, and 75 (61%) had other stroke mimics.	Low
Gumer (2014)	Conducted in USA, international studies	To examine the aetiologies of stroke and develop an initial diagnostic evaluation for a paediatric patient presenting in an emergency department.	Systematic review	1457 children, 195 with HS. Age: 8.2 years (median). Gender: male:female ratio 1.3:1.0. Ethnicity: non-Hispanic White, Afro-Caribbean,	NA	-	Authors propose CT without sedation urgently to distinguish HS from AIS, then evaluation for bleeding dyscrasia, MRA for those without blood dyscrasia and contrast angiography if MRA abnormal. In emergency department: perform non-contrasted head CT, if HS suspected evaluate for bleeding dyscrasias, if eliminated do MRA, if MRA normal do contrast angiography.	Low

				Black, Hispanic and Asian.				
Srinivasan 2009	Australia	To identify the delays involved in diagnosing paediatric arterial ischemic stroke (AIS), a major cause of morbidity and death in children	Cohort	107 children with AIS. Age: 36 months (median), range 6 to 118 months. Gender: male:female ratio 1.27:1	NA	-	Median time from symptom onset to radiologic confirmation 24.8h (IQR 10.2-67.0h). For inpatients the median time was 21.3h (IQR 5.8-54.1), four outpatients median time was 27.4h (IQR 18.9-74.6h) p<0.001 Time from clinical onset to first evaluation by a physician was median 1h (IQR 0-4.5h). For inpatients the median time was 20min (IQR 0-180min), for outpatients the median time was 120 min (IQR 57-408 min) p=0.003. Time to initial imaging was 11.4h (IQR 4.6-25.5h) for inpatients and 9.6h (IQR 4.5-20.6h) for outpatients, p>0.05. 26% of children were suspected of having AIS by the first physician. 86% of children had a focal sign at first physician assessment. The presence of a focal sign was associated with increased suspicion of AIS (p=0.02) with 30% of children with focal signs (76) being suspected of AIS compared to none of the children without focal signs (12). But focal sign was not associated with a shorter time to stroke confirmation.	Moderate
Statler 2011	USA	To describe demographic and clinical characteristics of children with ischemic or haemorrhagic stroke, including identified predisposing conditions, (2) to compare acute care	Cohort	10,236 children from the KID database, 4,424 HS, 5,813 AIS. Age: less than 1 to 18 years.	NA	-	Median length of stay was greater for Children's than non-Children's Hospitals. Additional CT or MRI were more common at Children's Hospitals, but rates of other types of imaging were similar by hospital type. Pharmacological therapy was reported in only 73 (<1%) patients overall.	Moderate

		utilization patterns between non-Children's and Children's Hospitals, and (3) to identify factors associated with aggressive care (pharmacological therapy or invasive interventions) or in-hospital mortality.		Gender: 55% male, 45% female. Ethnicity: not stated.			Invasive therapies (surgical, catheter-directed, or exchange transfusion) were reported in only 14%. Rates of surgical intervention, were similar by hospital type; all other forms of invasive therapy were more common at Children's than non-Children's Hospitals. Intensive care was provided more commonly at Children's than non-Children's Hospitals. Regarding advanced monitoring, only ICP or intravascular monitoring rates were similar between hospital types; all others were greater at Children's Hospitals. Although more children were discharged routinely from Children's than non-children's Hospitals, in-hospital mortality did not differ by hospital type. Adjusted odds of receiving aggressive care increased slightly for each 1-year increase in age (OR:1.01, 95% CI: 1.00–1.03). the adjusted odds of receiving aggressive care increased 1.7-fold for children who suffered HS, 1.7-fold for those treated at Children's Hospitals, and 1.3-fold for those having a predisposing condition.	
Martin 2011	Switzerland	To investigate the delay from the onset of symptoms to AIS diagnosis in children and potential contributing factors.	Case series	91 children with AIS. Age: 5.3 years (median), range 1 month to 16 years. Gender: 61 male, 30 female. Ethnicity: not stated.	NA	-	The time to diagnosis (by neuroimaging) was <6 hours in 32 (35%), 6–12 hours in 23 (25%), 12–24 hours in 15 (16%) and >24 hours in 21 (23%) children. 49 of the 54 CT scans (91%) and all of the 72 MRI investigations confirmed AIS. Of 74 children not hospitalised when the stroke occurred, 42% had adequate outpatient management. Delays in diagnosis were attributed to: parents/caregivers (n =	High

							20), physicians of first referral (n = 5) and tertiary care hospitals (n = 8). A comorbidity hindered timely diagnosis in eight children.	
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## Chapter 5: Acute management

In children with AIS what is the optimal way to assess neurological status and stroke severity?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Beslow 2012	USA	To establish relationship of modASPECTS [modified Alberta Stroke Programme Early CT Score] to infarct volume in perinatal and childhood AIS and to establish the inter-rater reliability of the score.	Cross-sectional	Children: 40 children ( and 31 neonates) Age: median 3.7 years, inter-quartile range 0.3 to 12 years Gender: 42 males, 29 females (whole population) Ethnicity: 44 white, 20 black, 3 mixed race, 4 unknown/other race (whole group)	NA	-	ModASPECTS correlated well with infarct volume/ Intraclass correlation coefficients for three raters = 0.94 [95% CI 0.91-0.97, p<0.001] for childhood group ModASPECTS score of 5 = differentiator for small v large volume stroke. In childhood group sensitivity and specificity of modASPECTS > /= 5 for predicting large infarct were 80% [95%CI 65.4-90.4%] and 87% [95%CI 76.7-93.9%] respectively. Assessment of stroke volume of 5% or greater important as predicts increased risk of haemorrhagic transformation and poorer outcome at follow up by Paediatric Stroke Outcome Measure.	Moderate
Beslow 2012 (2)	USA and Canada	To assess the concurrent validity and reliability of estimating the PedNIHSS score retrospectively from medical records.	Cross-sectional	Children: 75 Age: mean 7.5 years Gender: 40 males, 35 females Ethnicity: 56 white (8 Hispanic), 11 black 6 Asian, 1 mixed, 1 of unknown race.	NA	-	The mean and median total prospective and retrospective PedNIHSS scores were not different for the 75 subjects (P 0.49 Student t test; P 0.37 Wilcoxon rank sum). The mean prospective total PedNIHSS score for the 75 participating children was 8.2 (SD, 7) with a median of 6 (interquartile range, 3–12), and the mean total retrospective PedNIHSS score was 7.6 (SD, 7) with a median of 5 (interquartile range, 3–11). In regression analysis, R2 for the retrospective estimations of the total scores and the prospectively assigned total	Moderate

							scores was 0.76, slope 0.87 (95% CI, 0.77–0.97), intercept 1.62, and P .001. Interrater Reliability of Retrospective Scores for the total score, the ICC was 0.95 (95% exact CI, 0.94–0.99). PedNIHSS score can be assessed retrospectively from neurological examinations found in the medical record with excellent concurrent validity and interrater reliability.	
Brush 2013	Australia	To determine the prevalence of hypertension (HPT) in the acute phase after ischemic stroke (IS) and explore its relationship to outcome.	Retrospective review	Children: 90 Age: median 3.8 years, range 1 month to 18 years Gender: 49 males, 41 females Ethnicity: not stated	NA	-	81/90 (91%) children had AIS. 53/84 patients (63%) who had blood pressure readings available had at least 1 episode of hypertension (standard error: 0.053, 95% CI 51.9%–73.4%) (49/53 were AIS cases) and 19 (22%) had HPT on 3 consecutive days. HPT was more prevalent at both ends of the age spectrum and there was no statistically significant association between HPT and any of the risk factors or underlying conditions. The relative risk of 12-month mortality was 4.5 times higher (95% CI 0.6–34.5, p = 0.096) and relative risk of death in the hospital was 1.7 times higher (95% CI 1.4–2.0, p= 0.05) if the patient experienced HPT. Hypertensive was shown to correlate with 12-month mortality and more significantly with death during admission. There was no association between HPT and vascular territory, aetiology, recurrence or neurologic disability.	Moderate
Chen 2009	USA	To investigate utility of pulsed arterial spin labelling (ASL) perfusion MRI in characterising acute	Cohort	Children: 10 Age: 1 to 18 years Gender: 7 males, 3 females	NA	-	Acute and follow-up infarct volumes significantly larger in cases with hypoperfusion v. hyper or normal perfusion.	Moderate

		and subacute alteration in cerebral blood flow in children with AIS and to describe how haemodynamic alterations relate to cerebral anatomic and vascular abnormalities demonstrated by conventional MRI and MRA		Ethnicity: not stated			Interhemispheric perfusion deficit correlates with degree of stenosis on MRA, extent of lesion on DWI and follow-up T2 infarct volume. 9 patients had single lesion (7 in MCA and 2 in PCA territories) 1 patient had 2 lesions Results similar to those reported in adult literature regarding perfusion /diffusion mismatch and planning thrombolysis.	
Crossen 2010	Netherlands	To study functional outcome in children aged 1 month to 18 years after paediatric arterial ischaemic stroke (PAIS) and to identify risk factors influencing their quality of life.	Case series	Children: 76 Age: median 2 years 6 months, range 1 month to 17 years Gender: 35 males, 41 females Ethnicity: not stated	NA	≥1 year	Significant risk factors at presentation for a poor neurological outcome were Younger age at onset of PAIS was correlated with a higher mRS (modified Rankin Scale) at 12 months after onset (Spearman's $r=0.27$ , $p=0.02$ ) and had thus a poorer outcome, infarction in the right middle cerebral artery territory, and fever at presentation. Proportional odds regression analysis revealed that younger age at onset, fever, and stroke in the right MCA territory (including all four subcategories) were the strongest predictors of a poor neurological outcome at 12 months after onset of PAIS. 54% of children had severe neurological impairments at 12 months after PAIS, and at last follow-up more than half needed remedial teaching, special education, or institutionalization. Health-related quality of life (HRQOL) questionnaires showed a significantly lower HRQOL in all age groups.	High
Delsing 2001	Netherlands	To identify early prognostic factors in children with ischemic arterial stroke.	Case series	31 children with AIS. Age: 4.3 years (mean).	NA	7 years (median)	Presentation with an altered level of consciousness, seizures, or both ( $P=0.02$ ) and a completed or cortical completed stroke of the middle cerebral artery	Low

				Gender: 19 male, 12 female. Ethnicity: not stated.			(P=0.012) were found to be significant risk factors for poor outcome. No significant correlation was found between prognosis of childhood stroke and aetiology, age at presentation, or gender.	
Goldenberg 2009	International	To describe frequencies and predictors of acute treatments and early outcomes in the International Paediatric Stroke Study (IPSS), a large international series of childhood AIS.	Multi-centre observational cohort	661 children with AIS. Age: 28 days to 19 years. Gender: 391 male, 270 female. Ethnicity: not stated.	NA	-	In multivariate analysis, arteriopathy adjusted (OR 1.83, 95%CI 1.16–2.89, P=0.009), bilateral ischaemia (adjusted OR 1.83, 95% CI 1.03–3.25, p=0.04), and decreased consciousness at presentation (adjusted OR 1.95 (95% CI 1.25–3.02, P=0.003) were prognostic of adverse outcome.	High
Ichord 2011	USA	To evaluate interrater reliability (IRR) of a paediatric adaptation of the National Institutes of Health Stroke Scale (NIHSS).	Multi-centre prospective cohort	25 children with AIS that underwent simultaneous examinations from 2 investigators. Age: 9.7 (mean) S.D. 5.2 years. Gender: 15 male, 10 female. Ethnicity: not stated.	88 children with AIS. Age: 10.4 years (mean), S.D. 5.4 years. Gender: 56 male, 32 female. Ethnicity: not stated.	-	NIHSS was excellent as judged by the IRR group. IRR was excellent as measured by concordance correlation coefficient of 0.97 (95% CI, 0.94 to 0.99); intraclass correlation coefficient of 0.99 (95% CI, 0.97 to 0.99); precision measured by Pearson p of 0.97; and accuracy measured by the bias correction factor of 1.0.  The study also provided a description of stroke types in relation to imaging and NIHSS.	Moderate
Kalita 2013	India	To evaluate the aetiology, type and predictors of outcome of paediatric stroke from Northern India.	Cohort	79 children with stroke, 62 had AIS, 10 HS, 7 CVST. Age: 144.8 months (mean), range 0.6 to 18 years.	NA	-	Mortality significantly related to GCS≤9 at admission, brainstem lesion, and both supratentorial and infratentorial lesions. Focal deficit at presentation associated with low mortality. In multivariate analysis, mortality related only to GCS score.	Low

				Gender: 53 male, 26 female. Ethnicity: not stated.				
Lee 2008	Taiwan	To investigate the clinical spectrum, risk factors, outcomes, and prognostic risk factors of childhood ischemic stroke in a tertiary medical center in Taiwan.	Retrospective chart review	94 children with AIS. Age: 7.8 years (mean), range 40 days to 18 years. Gender: 58 male, 36 female. Ethnicity: not stated.	NA	-	A predictor of mortality was consciousness impairment at presentation (odds ratio:11.4; P = 0.004). Fever at presentation was a predictor of neurological deficits (odds ratio:8.15; P=0.02). Age, gender, and risk factors were not related to prognosis. Twelve (16%) children had recurrent ischemic stroke. Recurrence was highly correlated with moyamoya syndrome/disease (odds ratio:9.3; P = 0.007), ill-defined vasculopathy (odds ratio:15; P =0.02), and mitochondrial disease (odds ratio:15; P = 0.02)	Low
Sultan 2015	USA	To evaluate a method of scoring severity of stenooclusive arteriopathy in childhood AIS and its association with recurrence.	Cross sectional	18 children with AIS and recurrence. Age: 8.96 years (median), range 1.28 to 16.96. Gender: 13 male, 5 female. Ethnicity: not stated.	31 children with AIS without recurrence. Age: 6.42 years (median), range 0.37 to 17.85 years. Gender: 23 male, 8 female. Ethnicity: not stated.	2.2 years (median)	Age [hazard ratio (HR) 1.04, 95% CI 0.96–1.14, P = 0.33], chronic condition without moyamoya arteriopathy (0.29, 95% CI 0.07–1.22, P = 0.09), and thrombophilia (HR 1.14, 95% CI 0.44–2.96, P = 0.78) were not associated with recurrence rate. Higher CVSS was associated with higher rate of recurrence [HR per point 1.09, 95% CI 1.04–1.16, P = 0.001]. In those with moyamoya arteriopathy, the CVSS was associated with time to recurrence, with a HR per CVSS point of 1.11 (95% CI 1.03–1.19, P = 0.004). In those without moyamoya arteriopathy, the CVSS was not associated with time to recurrence, with a HR of 0.91 (95% CI 0.75–1.09, P = 0.32).	Moderate

							The rate of a recurrent event was more than three times higher for a score of $\geq 7$ compared with lower scores (HR 3.04, 95% CI 1.07–8.62, $P = 0.04$ ).	
Toure 2009	France	Whether the location of a stroke affects outcomes in children	Retrospective case series	46 children with AIS (32 anterior group, 14 posterior group). Age: Anterior group - 5.6 years (mean), range 3 months to 16 years, posterior group 7.5 years (mean), range 15 months to 15 years. Gender: anterior group 19 male, 13 female, posterior group 11 male, 3 female. Ethnicity: not stated.	NA	26 months (mean)	Mild to severe impairments persisted for 28 children (61 %), with no difference between the anterior and the posterior groups ( $p = 0.89$ ). After follow-up five children (11 %) had had a recurrence of stroke: four in the posterior group (29 %) and one in the anterior group (3 %; $p=0.025$ ). Large majority of children with posterior stroke were boys. Recurrence: 5 children (11%) had recurrence, 4 in the posterior group (29%) and 1 in the anterior group (3%) $p=0.025$ . Time between first accident and recurrence was 5 days to 1 year. All new events affected the same arterial territory as the initial stroke. 3 recurrences in patients with anti-platelet treatment and 1 treated with anti-coagulant.	Moderate

In children with HS what is the optimal way to assess neurological status and stroke severity?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Vaid 2008	India	Discuss the epidemiology, clinicoradiological profile, outcomes and management issues of children with aneurysms	Retrospective case series	27 children with HS. Age: 13.19 years (mean), S.D. 3.72 years.	NA	18.67 months (mean)	Pre-operatively 21 (78%) patients had a good Hunt and Hess grade (0-3) on admission and 6 (22%) had poor pre-operative status (grade 4-5). At final follow-up 21 patients (78%) had favourable outcome, 3 (11%) had unfavourable	Low

				Gender:14 male, 13 female. Ethnicity: not stated.			outcome, and 3 (11%) died (2 pre-operatively, 1 post). Of the 21 patients that had favourable post-operative outcome, 19 (90%) had good preoperative grades and out of the 6 with poor outcome, 4 (67%) had poor pre-operative grades.	
Sharma 2007	India	Review aetiology, clinical characteristics, aneurysm morphology and surgical outcome in children with intracranial aneurysms	Retrospective case series	55 children with aneurysms, 78% HS. Age: 13.3 years (mean), range 7 months to 18 years. Gender: 38 male, 17 female. Ethnicity: not stated	NA	9.5 months	In the 43 patients with SAH Hunt and Hess gradings were as follows: Grade I n=10 (23.2%), Grade II n=17 (39.5%), Grade III n=23.2), Grade IV n=5 (11.6%), Grade V n=1 (2.3%)	High
Griffiths 1998	Canada	Investigate early presentation and high mortality rates in children with AVM	Retrospective case series	18 children with AVM. Age: 10 years 8 months (median). Gender: 6 male, 12 female. Ethnicity: not stated	NA	Up to 5 years	Children with Botterell score I (mild) 4 had a normal outcome, score 2-3 (moderate) 2 had a normal outcome and 2 had a residual neurological deficit, score 4-5 (severe) 1 had normal outcome, 2 had residual neurological deficit and 6 died.	Low
Wojtacha 2001	Poland	Compare clinical and anatomical features of aneurysms in children with adults	Retrospective case series	17 children with aneurysms. Age: 15 years (mean), range 10 to 18 years. Gender: 13 male, 4 female. Ethnicity: Polish	NA	-	Hunt and Hess grade on admission: 8 (50%) grade 1, 3 (18.8%) grade 2, 1 (6.3%) grade 3, 4 (25%) grade 4. Glasgow outcome scale - good outcome (grade I and II) in 12 cases (70.6%), poor outcome (grades III and IV) in 3 cases (17.6%), 2 (11.8%) died.	Low

Li 2014 (2)	China	To evaluate surgical outcomes of cavernous malformations and identify risk factors associated with post-operative full recovery and rebleeding	Case series	52 children with cavernous malformations. Age: 12.2 years, range 1 to 17 years. Gender: 37 male, 15 female. Ethnicity: not stated.	NA	-	The mean modified Rankin Scale (mRS) score at admission was $2 \pm 1.1$ (range 1–4): 25 patients (48.1%) had an mRS score of 1; 11 patients (21.2%) had a score of 2; and the remaining 16 patients (30.8%) had a score of either 3 or 4. At surgery, the radiographic characteristics of all lesions were categorized into either Zabramski Type I (n =24 [46.2%]) or II (n=28 [53.8%]).	Moderate
Liang 2009	China	To describe the clinical and radiological features and the therapeutic outcome and clarify the choice of therapeutic strategies for paediatric intracranial aneurysms.	Case series	24 children with aneurysms. Age: 8.83 (mean), range 1 to 14 years. Gender: 14 male, 10 female. Ethnicity: not stated.	NA	-	Hunt–Hess classification, 21 patients were in a good preoperative state: 13 were in grade 0, six in grade 2, and two in grade 3. Three patients in grade 4 were in a poor preoperative state. According to the Fisher grading system, 13 patients were in grade 1 (no history of SAH), five were in grade 2, two were in grade 3, and four were in grade 4.	Low
Di Rocco 2000	Italy	To report the authors' experience with 37 parenchymal AVMs	Retrospective case series	37 children with AVM. Age: 8.15 years (mean), range 1 month to 15.2 years. Gender: 12 male, 16 female. Ethnicity: not stated.	NA	64.7 months (mean)	Presenting signs: 72.9% signs and symptoms of intracranial hypertension, 51.3% focal neurological deficits, 16.2% seizures, 70.3% haemorrhage, 54.1% no alteration of conscious level, 18.9% grade I-II coma, 27% grade III-IV coma Site of haemorrhage 28: supratentorial, 9 infratentorial Spetzler-Martin grade: II/III 72.9% I 8.2% IV 16.2% V 2.7%	Moderate

**What is the framework for early functional assessment in children with AIS**

Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Davis 2010	Australia	To determine the reliability of the AHA when used with children and youth who have unilateral motor impairment following ABI	Retrospective review of video recorded as part of clinical assessment	26 children with ABI. Age: 6.83 years (mean), range 22 months to 16.5 years. Gender: 14 male, 12 female. Ethnicity: not stated.	NA	-	Interrater reliability ICC 0.85-0.93 (domain scores) 0.97 (0.93-0.99 95%CI) (total scores) classified as 'excellent'. Most variation for 'chooses assisting hand' (0.55) in categories of somewhat effective or ineffective. And 'moves forearm' (0.59) in all categories (except does not do).	Low
Morgan 2004	Australia	To document the clinical characteristics of acute dysphagia in a group of paediatric patients after traumatic brain injury	Case series	14 children with TBI. Age: 7.11 years (mean), range 4.1 to 15 years. Gender: 7 male, 7 female. Ethnicity: not stated.	NA	-	Cognitive rating – 8/14 RLA score III (localised response), 3/14 IV (confused/agitated), 2/14 V (confused, non-agitated), 1/14 II (generalised response) 14/14 severe oral=motor impairment on VMPAC, (range 4/20-6/20) – including tonal deficits, altered respiratory support, immature reflex patterns, reduced oral-motor integrity 14/14 had deficits in all oromotor categories of the FDA – including reflex, jaw, lip and tongue function. 14/14 had oral-motor dysfunction for puree and semi-solid foods on SOMA. 1/14 severe dysphagia precluded assessment on more challenging food textures. 12/13 abnormal oral-motor dysfunction for solid food. 10/13 oral-motor dysfunction for cracker consistency. 3/13 oral=motor dysfunction for fluids. Feeding trial results: >50% had cognitive/behavioural deficits; oral	Low

							sensitivity affected in 1/3rd; abnormal reflexes noted in majority of patients. f) 9/14 had severe dysphagia on PHAD, 5/14 moderate dysphagia	
Gordon 2014	UK	To identify the literature describing the outcome of AIS in children beyond impairments of body structures and functions, and using the ICF framework to classify the domains of disability and functioning addressed and where gaps in the knowledge remain for further research.	Systematic review	28 studies of children with AIS. Sample sizes 11-145 children.	NA	-	The use of the ICF-CY classification has illustrated the limited number of studies addressing activity, participation, and environmental characteristics. Findings suggest clinical outcome is diverse, yet the relative influence of factors in addition to that of the brain injury itself remains unknown. Only one tool, the PSOM, has been validated for use with the child stroke population. A relatively small proportion of paediatric stroke literature is focused on outcome beyond body structures and functions as classified using the ICF-CY. Knowledge of health and well-being after stroke is, therefore, incomplete. The relationship between impairments in body structures and functions, limitations in activities and participation, and the impact of environmental factors remain to be studied.	Moderate
Massaro 2014	Italy	To compare the Non-Communicating Children's Pain Checklist Postoperative Version (NCCPC-PV), the Echelle Douleur Enfant San Salvador (DESS) and the Children's Hospital of	Cohort	40 children with cognitive impairment. Age: 9.1 years (mean), IQR 4.2 to 14.8 years. Gender: 21 males, 19 females.	NA	-	The correlation between the NCCPC-PV and the DESS was strong (Spearman correlation coefficient = 0.76) and better than between each scale and the CHEOPS. Although the DESS showed better inter-rater agreement, it was more dependent on familiarity with the child and was judged more difficult to use by all observers. The NCCPCPV was the easiest	Moderate

		Eastern Ontario Pain Scale (CHEOPS).		Ethnicity: not stated.			use and the most appropriate for rating the child's pain. The NCCPC-PV was the easiest to use for pain assessment in cognitively impaired children and should be adopted in clinical settings.	
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What are the likely complications during the acute and sub-acute phase of recovery from AIS and HS and what are the ways to detect, prevent and minimise them?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Beslow 2011	USA	To determine the proportion of children with haemorrhagic transformation in a prospectively identified cohort of children with AIS.	Cohort	63 children with AIS. Age: 5.7 years (median), range 1 month to 18 years. Gender: 44 male, 19 female. Ethnicity: 43 White, 15 Black, 3 Hispanic, 2 Mixed Race.	NA	-	Neurological outcome classified using PSOM. Haemorrhagic transformation (HT) occurred in 19 of 63 children (30% , 95%CI 19%-43%) only 2 (3%) of whom were symptomatic. Most of the haemorrhages were petechial in nature. HT was less common in children with vasculopathy (RR 0.27) than other mechanisms. It was not significantly associated with anticoagulation versus antiplatelet therapy but was associated with larger infarct volumes ( $p = 0.0084$ ).	Moderate
Singh 2012	USA	To describe the risk of seizures in children with acute stroke and identify factors predicting their later risk of epilepsy	Observational	77 children with stroke. Age: 8.4 years (mean). Gender: 55 male, 22 female. Ethnicity: not stated	NA	-	Risk factors: seizure - SCD 3 (13%), cardiac 2 (8%), none 5 (21%). No seizure - SCD 9 (17%), cardiac 10 (19%), none 11 (21%) Seizure was a initial sign of stroke in 16 (21%) and in 3 (4%) seizure occurred within 24h of presentation, 4 (5%) had early post stroke seizure, 1 (1%) had late post stroke seizure. 21% had clinical seizures. An additional 10% of patients had a clinical seizure during the acute hospitalization. Non-convulsive status epilepticus was captured only in patients with prolonged electroencephalograms and always within 24 hours of monitoring. Six months after their stroke, 24% of patients had epilepsy, Six patients (17%) had status epilepticus. Status epilepticus did not vary in stroke	Moderate

							subtypes, but was more common in infants (1-12 months old) and occurred only in patients with cortical involvement of their strokes.	
Yang 1995	US	To evaluate the risk of seizures and recurrent seizures after stroke	Retrospective case series	73 children with stroke, 56 AIS, 12 HS. Age: 86 months (mean), range 2 months to 17 years. Gender: 37 male, 36 female. Ethnicity: 52 Black, 21 White.	NA	14 years	Initial seizure occurred in 36/73 Recurrent seizure in 21/73 Majority of initial seizures occurred within (69.4%) within first 24 hours. Patients with late onset seizures had higher risk of recurrent seizures. Patients with cortical involvement had significantly greater risk of recurrent seizures. No difference between ischaemic and haemorrhagic stroke. More likely if cortical involvement	Moderate
Wang 1998	Taiwan	Describes clinical manifestations, associated diseases, treatment and mortality rate of children's stroke	Case series	65 children with stroke, 27 with HS. Age: 7 years 5 months (mean). Gender: 37 male, 28 female. Ethnicity: not stated.	NA	-	Outcomes: normal (7), loss to follow-up (2), death (13), motor deficit (3, 25%), visual impairment (1, 8.3%), ataxia (1, 8.3%), mental/psycho-motor retardation (2, 16.6%)	Low

## Chapter 6: Arterial Ischaemic Stroke

Risk factors for AIS and AIS recurrence								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Azab et al (2014)	Egypt	To investigate whether iron-deficiency anaemia is a risk factor for cerebrovascular events and childhood-onset ischemic stroke.	Case-control	21 children with stroke diagnosis. Age: 12 to 72 months (median 36 months). Gender: 15 male, 6 female. Ethnicity: not stated	100 healthy children. Age: mean 34 months (+/- 14 months). Gender: 67 male, 33 female.	-	Previously healthy children who developed stroke are 3.8 times more likely to have iron deficiency anaemia than healthy children, who do not develop stroke. There was significant interaction between iron deficiency anaemia and thrombocytosis among studied cases. Iron deficiency anaemia is a risk factor for childhood stroke.	Moderate
Ganesan et al (2003)	UK	To describe the risk factors associated with AIS in patients from a single tertiary center in the United Kingdom over a 22-year period.	Case series	212 AIS cases. Age: 5 years (median) range 21 days to 19.7 years. Gender: 115 male, 87 female. Ethnicity: 42 Afro-Caribbean, 17 Black Asian, 2 Far East, 151 White	NA	-	Cerebral arterial abnormalities, previous varicella zoster infection, trauma, recent infection, and anaemia were common in children presenting with first AIS and previously undetected structural cardiac abnormalities were rare.	Moderate
Amlie-Lefond et al (2009)	International sample	To use data from the IPSS, a large international series of childhood stroke cases, to determine the prevalence and predictors of cerebral arteriopathy and FCA among children with AIS.	Prospective cohort	525 children Age: 31 days to 19 years (median 5.7 years) Gender: 59% male, 41 % female. Ethnicity: (only available for 94 children) 64 White, 23 Black, 7 Other Ethnicity	NA	-	Arteriopathy is prevalent in children with AIS. Arteriopathy positive risk factors are SCD, age 5-9, recent upper respiratory tract infection. Arteriopathy negative risk factors are cardiac history, recent sepsis.	Moderate

Dowling et al (2013)	International sample	To evaluate the patient characteristics, clinical presentations, stroke characteristics from imaging studies, and early outcomes of children with AIS with reported cardiac disorders compared to those of children with other causes of stroke.	Prospective cohort	667 children with AIS. Age: 29 days to 19 years (median 5.7 years). Gender: 59% male, 41% female. Ethnicity: not stated.	NA	-	Cardiac disorders were found in nearly a third (30.6%) of children with AIS. 16% had suffered their stroke within 72 hours of cardiac surgery and 9% within 72 hours of cardiac catheterisation.	Moderate
Fox et al (2015)	USA	To develop a better understanding of stroke risk factors in children with CHD. To inform prevention strategies.	Case-control	412 children with stroke. Age: 7.4 (mean) +/- 7.5 years Gender: 73% male Ethnicity: 60% non-white	1236 age matched stroke free children. Age: 11.6 (mean) +/- 6.3 Ethnicity: 60% non-white	-	CHD was associated with AIS. Children who had undergone cardiac surgery were at an increased risk of stroke even outside of the perioperative period.	Moderate
Benedik et al (2011)	Slovenia	To compare the prevalence of right to left shunt in children with AIS.	Case-control	30 children with AIS. Age: 13 years (mean) +/- 3 years. Gender: 15 male, 15 female. Ethnicity: 29 White, 1 Black	26 age and sex matched children. No history or clinical evidence of stroke.	-	Right to left shunt was associated with AIS. Prevalence of right to left shunt was higher in children with AIS of undetermined aetiology than in children with determined aetiology and controls.	Low
Strater et al (1999)	Germany	To evaluate the relationship between AIS and thrombophilia risk factors in children with cardiac disease.	Case-control	38 children with AIS and cardiac disease. Age: 8 aged less than 12 months, 13 aged 1 to 10 years, 12 aged 10 to 18 years. Gender: 21 male	100 age matched children. Ethnicity: Caucasian	-	Positive risk factors for AIS in children with cardiac disease were Lipoprotein (a) >30 mg/dl, protein C deficiency, anticardiolipin antibodies and combined prothrombotic disorders. FV G1691A and prothrombin G20210 A mutations were not associated with AIS	Low

				Ethnicity: Caucasian				
Fullerton et al (2003)	USA	To investigate the demographics of childhood stroke	Retrospective cohort	2278 children with first admission for stroke. Age: 30 days to 20 years. Gender: 51% male. Ethnicity: Black 7%, Hispanic 39%, White 43%, Asian 10%	NA	-	Compared to White children: Black children were at higher risk of AIS even when cases of SCD were excluded, Hispanic children were at lower risk. Boys were at higher risk for AIS than girls even when cases precipitated by trauma were excluded.	Moderate
Mallick et al (2014)	UK	To examine the risk factors, presenting features and incidence of AIS.	Case series	96 children with AIS. Age: 29 days to 16 years (mean 6.2 years). Gender: 49 male, 47 female. Ethnicity: 66 White, 14 Asian, 9 Black, 7 Other.	NA	-	Compared to White children: Asian children had a higher relative risk, and Black children had a higher relative risk for AIS. Incidence of AIS was highest in children <1 year. Boys were not found to have a higher relative risk for AIS than girls.	High
Golomb et al (2009)	International sample	To examine the association between gender and AIS	Retrospective case series	1187 children with AIS or CSVT. Age: 0 to 19 years. Gender: 710 males, 477 females Ethnicity: not stated but children were enrolled from China, Malaysia, Thailand, Australia, Canada, Chile, Georgia, Germany, UK, and USA.	NA	-	Overall, there was a higher proportion of boys with AIS but this did not quite reach significance. In pre-adolescent children there was a higher proportion of boys with AIS and although this was true for adolescent children as well it was not significant.	Moderate

Lo et al (2009)	USA	To assess the prevalence of stroke and the associated risk factors.	Case series	1851 children with AIS. Age: 30 days to 20 years. Gender: 965 male, 883 female. Ethnicity: White 661, Black 315, Hispanic 264, Asian/Pacific Islander 38, Native American <10, Other 78, Missing 485.	NA	-	Boys were more likely to have AIS than girls, particularly in the 15-20 age group. 70% of AIS cases had no coexisting diagnosis.	Low
Askalan et al (2001)	Canada	To examine Varicella Zoster infection in the 12 months preceding stroke.	Cohort	22 children with AIS and Varicella infection. Age: 4 years (mean) S.D. 2.4 years. Gender: 15 male, 7 female Ethnicity: not stated.	48 children with AIS. Age: 5 years (mean) S.D. 3.1 years. Gender: 31 male, 17 female. Ethnicity: not stated	2.1 years (mean)	There was a three-fold increase in AIS in children who had preceding varicella infection and a 2 fold increase in recurrent AIS and TIA.	Moderate
Fullerton et al (2015)	International sample	To test the hypothesis that infection transiently increases the risk of AIS in children and	Case-control	355 children with AIS. Age: 7.6 years (median), IQR 2.8-14.3. Gender: 199 males, 156 female. Ethnicity: Non-Hispanic 81%, Hispanic 13%, Mixed or Other 5%	354 routine and trauma visit controls. Age: 9 years (median) IQ range 4.4-13.3. Gender: 199 males, 156 females. Ethnicity: non-Hispanic 78%,	-	In children who had had an infection in the week preceding the stroke there was a 6.3 fold increased risk of AIS. Children with some/few/no vaccinations were at a higher risk of AIS (OR 7.3 (p<0.001)). In multivariate analyses risk factors for AIS were infection, under-vaccination, black race and rural residence.	Low

					Hispanic 13%, Mixed or Other 9%			
Hills et al (2014)	USA	To investigate the timing and number of minor infections in the 2 year period prior to an event, to assess the increased risk of AIS.	Case-control	102 children with AIS without a preceding or concurrent major infection. Age: 11.6 years (median) IQR 3.4 to 17.2 years. Gender: 56 males, 46 females. Ethnicity: White 46.1%, Black 12.7%, Hispanic 17.6%, Asian 15.7%.	306 age and facility matched controls. Age: 11.6 years (median) IQR 3.2-17.2 years. Gender: 159 males, 147 females. Ethnicity: White 41.5%, Black 11.1%, Hispanic 14.4%, Asian 9.8%.	-	The period for the highest risk of stroke after a doctor visit for infection was 3 days. This dropped away to no increased risk after 1 week. A greater number of infections over the 2 year period did not result in higher risk of AIS.	High
Thomas et al (2014)	UK	To test the hypothesis that children who develop chickenpox are at an increased risk of AIS in the following 12 months.	Case series	60 children who had experienced chickenpox and a stroke or TIA during follow-up. Age: 3.9 years (median), IQR 1.9 to 6.4 years. Gender: Ethnicity: not stated	NA	1 year	There was a 4 fold increased risk of AIS in 0-6 months following chickenpox. There was no increased risk 7-12 months after chickenpox.	Low
Wang et al (2) (2009)	China	To investigate the association of the genetic variants in the CTLA-4 and CD28 genes of children who have an idiopathic AIS.	Case-control	51 children with idiopathic AIS. Age: 4 years (mean) range 1 to 11 years. Gender: not stated. Ethnicity: Chinese	74 healthy children. Age: not stated Gender: not stated	-	A single nucleotide polymorphism, CTLA-4+49A/G located in exon 1 of the CTLA gene was associated with AIS. Homozygous carriers of the G allele of this single nucleotide polymorphism were more common in cases than controls.	Moderate

					Ethnicity: Chinese		The CD281VS3+17TT genotype was more common in cases than controls.	
Bowers et al (2002)		To assess the incidence of stroke in children with CNS tumors and identify significant stroke risk factors.	Retrospective case series	807 children with CNS tumors. Age: 6 years (median at diagnosis) range 0-18 years. Gender: 54.9% male, 45.1% female. Ethnicity: not stated	NA	4.6 years (mean)	1.6% of children with CNS tumours were found to have had a non-perioperative AIS. Treatment with radiation therapy and the presence of an optic pathway glioma were the only significant risk factors identified.	Low
Campan et al (2012)	USA	Incidence of stroke in children with brain tumours and the relevance of irradiation as a risk factor.	Retrospective case series	431 children with brain tumour. Age: 8.9 years (mean) S.D. 4.7 years Gender: 57.5% male, 42.5% female. Ethnicity: White 73.8%, Black 14.1%, Hispanic 4.2%, Asian 2.3%, Other 3%, Unknown 2.3%.	NA	6.3 years (mean)	3.2% of children had an AIS or TIA during the follow-up period. Of the 14 children who had an event, 13 received radiation. Median time from first radiation to first event was 4.9 years. The incidence of AIS or TIA was 100 fold higher in this population than in the general population and cranial irradiation is an important risk factor.	Moderate
Belisario et al (2010)	Brazil	To investigate whether the presence of alpha thalassaemia trait mitigated the effect of HbSS/HbS $\beta$ 0 on stroke risk	Retrospective case series.	221 children with SCD. Age: 2.5 to 10.4 years. Gender: 102 males, 119 females. Ethnicity: Afro-Caribbean by inference.	NA	-	Children with HbSS and no deletion of $\alpha$ genes 26.4% had cerebrovascular disease (either stroke or high risk of one on basis of TCD). HbS and heterozygous for $\alpha$ thal CVD frequency was 7.3%, HbS and homozygosity for $\alpha$ thal CVD frequency 0%. Probability of children without $\alpha$ thal presenting with CVD was 3.9 times higher than those who were hetero- or homozygous (P= 0.007)	High

Bernaudin et al (2015)	France	To investigate the rate of silent infarcts in children with SCA – HbSS or HbS $\beta$ 0 with no overt stroke.	Case series	189 children with SCA. Age: 0 to 18 years. Gender: 88 males, 101 females. Ethnicity: Afro-Caribbean.	NA	9.9 years (mean) range 2.2-19.9 years	20.1% of patients developed a SCI. Cumulative risk for SCI increased as the child aged with no plateau. Baseline Hb<7 g/dL, acute anaemia, and eICA stenosis were significant and independent risk factors for SCI in children with SCA. Children on a transfusion programme or HU for high risk TCDs remained at high risk of silent infarct.	High
Cancio et al (2015)	USA	To analyse the clinical, neuroradiological, psychometric and academic outcomes in children with SCA.	Case series	37 children with SCA. Age: 16 months, range 7 months to 4 years. Gender: 18 male, 19 female. Ethnicity: African American.	NA	14 years, range 7 months to 19.5 years.	59% of children has a SCI over the course of follow-up.	Moderate
Silva et al (2011)	Brazil	To investigate the risk factors for AIS in children with SCD.	Case series	262 children with SCD. Age: 6.2 years (median), range 2 to 11.2 years. Gender: 115 male, 147 female Ethnicity: not stated	NA	-	Children with stroke or high risk TCD, when compared to low risk, were younger, had lower Hb, higher leukocytosis, and higher reticulocytosis. On multivariate analysis high reticulocyte count remained the only significant variable associated with cerebrovascular disease. High reticulocyte count raised the probability that the child would develop CVD before age 10.	Moderate
Tang et al (2001)	USA	To investigate the association between GT repeat polymorphism within angiotensin gene and risk of stroke in SCD.	Case-control	21 children with SCD and a history of stroke. Age: 2 to 22 years Gender: 14 male, 7 female.	42 children with SCD but no history of stroke.	-	GT-repeat alleles A3 and/or A4 of the AGT gene conferred a 4 fold increase in the risk of stroke. No significant association between BP and A3 /A4 alleles. There was no statistically significant association between SBP and A3/A4 distribution.	Low

				Ethnicity: African-American	Age: matched (no other detail given) Gender: 28 male, 14 female (paper says 2x sex matched controls for each child) Ethnicity: African-American.		Authors suggest association between A3 and A4 alleles and risk of stroke.	
Avcin et al (2008)		To investigate the association of anti-phospholipid antibodies with clinical disease including AIS in a paediatric population.	Case series	129 children with anti-phospholipid syndrome. Age: 10.7 years (mean), range 1-17.9 years. Gender: 46 male, 54 female. Ethnicity: not stated	NA	-	AIS occurred in 31/121 children and was more common in primary APS (23/60) than APS associated with autoimmune disease (7/60) p<0.001.	Low
Akar et al (2000)	Turkey	To evaluate to evaluate the role of FV 4070 A → G mutation in Turkish children with cerebral infarct.	Case control	48 children with cerebral infarct. Age: 10 months to 18 years. Gender: not stated. Ethnicity: Turkish	82 unrelated children with no personal or family history of thrombosis or stroke	-	10/48 cases were found to carry the FV 1299 His→Arg mutation (1 homozygous) vs 7/82 controls. The cerebral infarct risk for FV 1299 was OR 2.4 (CI 0.9-6.8). When excluding all underlying conditions other than thrombophilic factors, incidence of FV 1299 was 8/35 (22.8%) OR 2.7 (CI 1.4-4.8). When excluding FV1691 G→A & PT 20210 G→A, incidence of FV 4070 mutation was 7/21 (33.3%), OR 3.9 (CI 1.2-12.3).	Moderate
Akar et al (2001)	Turkey	Investigated the role of mutations in homocysteine	Case control	46 children with AIS.	68 healthy unrelated children with	-	No difference between patients and controls for the distribution of (MTHFR)	Low

		metabolism pathway in children with AIS.		Age: 10 months to 18 years. Gender: not stated. Ethnicity: Turkish.	no personal history of thrombosis, stroke, or Behcet's disease.		677 C-T, methylene tetrahydrofolate reductase MTHFR 1298 A±C, methylene tetrahydrofolate dehydrogenase (MTHFD) 1958 G±A and methionine synthase reductase (MTRR) 66 A±G alleles. There was no risk for double gene alterations (MTHFR 677 C-T vs. 1298 A-C) after individuals with FV 1691 A mutation is excluded. 12/46 patients were found to carry FV 1691 A mutation (26.0%), one being homozygote vs 3/68 of controls. The cerebral infarct risk for FV 1691 A was found to be 6.4 (CI 95% 1.7-23.0). 8/46 patients were found to carry PT 20210 A mutation (16.6%). Authors concluded that t FV 1691 A and PT 20210 A mutations are important and must be included to the routine analysis of paediatric stroke patients.	
Balcerzyk et al (2010)	Poland	To evaluate the possible association between APOE gene epsilon polymorphism and AIS in children.	Case control	72 children with AIS. Age: 8.8 years (mean), S.D. 5.6 years. Gender: 42 male, 30 female. Ethnicity: European continental.	71 gender and age matched children. Age: 8.2 years (mean) S.D. 5.4 years. Gender: 41 male, 30 female. Ethnicity: European continental.	-	No difference was found in genotype and allele distribution between cases and controls. Study findings did not confirm that e polymorphism of the apolipoprotein E gene is a risk factor for AIS in children.	Low
Barreirinho et al (2003)	Portugal	To identify thrombophilic conditions that might be	Case control	21 children with AIS.	115 gender and region of	-	In children with AIS, the odds ratios of having FV Leiden (G1691A) or FII variant	Low

		related to the development of stroke in children.		Age: 5.3 years (mean) range 2 months to 13 years. Gender: 33% male, 67% female. Ethnicity: not stated	origin matched children.		(G20210A) were 4.63 (95% CI: 0.95- 22.40) and 11.79 (95% CI: 1.02-136.52) compared to controls respectively.	
Bonduel et al (2003)	Argentina	To determine the association between Factor V Leiden and thromboembolism.	Case control	44 children with AIS. Age: 7.7 years (mean), range 0.2 to 15.2 years. Gender: 30 male, 14 female. Ethnicity: not stated	102 healthy children. Age: 7.1 years (mean), range 0.2-15.7. Gender: 62 male, 40 female. Ethnicity: not stated.	-	OR for FVL 1.16 (0.2-13.2), p=0.99. No cases of PT20210A found. No association was found between these associations and AIS.	Low
Burghaus et al (2006)	Germany	To evaluate the role of the elevated $\alpha$ 1-AT concentration in paediatric patients with AIS.	Case control	81 children with AIS. Age: 2.5 years (median) range 1 month to 18 years. Gender: not stated. Ethnicity: Caucasian.	229 child outpatients for minor surgery. Age: not stated. Gender: not stated. Ethnicity: Caucasian	-	Median values of $\alpha$ 1-AT were significantly higher in patients compared to controls. 17.3% of patients compared to 6.2% of controls had $\alpha$ 1-AT concentrations above the 90 <sup>th</sup> centile. There was a significantly increased odds of AIS in patients with $\alpha$ 1-AT above the 90 <sup>th</sup> centile. Total $\alpha$ 1-AT concentrations above the 90 <sup>th</sup> centile independently increase the risk of AIS 4 fold in Caucasian children.	Moderate
Cangoz et al (2004)	Turkey	To evaluate the role of FVIII levels in the occurrence of paediatric stroke.	Case control	20 children with AIS. Age: 8 months to 14 years. Gender: 11 male, 9 female. Ethnicity: not stated.	40 healthy age matched children without a family history of stroke or thrombosis.	-	A weak positive association between FV1691A and high FVIIIc levels was determined. Comparison of the prevalence of high FVIIIc levels in patients and healthy subjects with and without FVL/PT 20210 indicated that high FVIII levels are an independent risk factor. Prevalence of risk factors:	Low

							1:5 patients had FVL (background in Northern European population is 1:20 3:20 heterozygotes for prothrombin gene mutation (background 1:100) 1:5 independently raised FVIII taken on 2 occasions at least 4 months apart. Elevated FVIII level is a possible and independent risk factor for childhood AIS.	
Djordjevic et al (2012)	Serbia	To examine the role of common thrombophilic mutations in children with stroke.	Case control	80 children with AIS. Age: 6.7 (mean) S.D. 4.9 years. Gender: 46 male, 34 female. Ethnicity: Serbian	100 healthy children. Age: 9.5 years (mean) S.D. 0.5 years. Gender: 46 male, 54 female. Ethnicity: not stated.	-	No significant differences in the frequency of factor V (FV) Leiden, FII G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T variants between patients and controls. Carriers of 677CT genotype have 3.62 higher risk of developing AIS in children than in adults ( $P < .001$ ). Heterozygosity for MTHFR C677T variant represents a possibly important risk factor for paediatric stroke.	Low
Haywood et al (2005)	International sample		Systematic review of case control studies	18 case control studies including 3235 children with AIS. Age: 28 days to 18 years at time of AIS. Gender: not stated. Ethnicity: not stated	9019 age matched controls.	-	The pooled OR (and 95% CI) were: protein C deficiency, 6.49 (2.96 to 14.27); protein S deficiency, 1.14 (0.34 to 3.80); AT deficiency, 1.02 (0.28 to 3.67); APCr, 1.34 (0.16 to 11.52); FV1691 GA, 1.22 (0.80 to 1.87); PT20210GA, 1.10 (0.51 to 2.34); MTHFR C677T, 1.70 (1.23 to 2.34); and total plasma homocysteine .95th centile, 1.36 (0.53 to 3.51). Only protein C deficiency and MTHFR C677T were associated with raised odds of AIS.	Moderate
Kenet et al (2010)	International sample	Assessed the association between thrombophilia and first stroke.	Systematic review and meta-analysis	1764 children with AIS in 22 studies. Age: birth to 18 years. Gender: not stated.	2799 children with no history of stroke.	-	The following thrombophilic risk factors were associated with AIS: antiphospholipid antibodies/lupus anticoagulants, protein C deficiency, lipoprotein (a), Factor V	High

				Ethnicity: not stated.			G1691A, Factor II G20210A, MTHFR TT, $\geq 2$ genetic traits. The following were NOT associated with AIS: antithrombin deficiency, protein S deficiency.	
Kenet et al (2000)		To investigate the prevalence of thrombophilia risk factors in children with ischaemic stroke.	Case control	58 children with AIS. Age: 7.2 years (mean) S.D. 6.5. Gender: 30 male, 28 female. Ethnicity: Asia/Africa: 29.3%, Europe/America 46.6%, Mixed 13.8%, Arab 6.9%, Unknown 3.4%	145 children for elective surgery, trauma or elective admission. Age: 9.3 years (mean) S.D. 6.5 years. Gender: not stated. Ethnicity: not stated	-	31/58 paediatric stroke patients (53.4%) had at least 1 thrombophilia marker vs 25.5% of controls. None had protein S or anti- thrombin III deficiency 3. Protein C deficiency was higher in stroke group than controls but not statistically different Heterozygous FII G202104A and homozygous MTHFR 677T were not associated with increased risk of stroke APLA was associated with a >6-fold risk of stroke Heterozygosity for FVL increased the risk of stroke by almost 5-fold.	Low
McColl et al (1999)	UK	Investigated the role of thrombophilia in AIS – specifically the prevalence of Factor V Leiden, prothrombin 20210 G-A and MTHFR C6771 mutations.	Case series	39 children with AIS plus 11 neonates with AIS. Age: 51 months, range 10-168 months. Gender: 28 male, 22 female. Ethnicity: not stated.	219 cord blood controls.	-	In the children with AIS available for haematological analysis (37) none had deficiencies of antithrombin, protein C or protein S, one case had mildly elevated IgG anticardiolipin antibody. The odds ratios for stroke were not significantly increased in carriers of FVL, prothrombin 20210A allele or MTHFR C677T homozygosity. After adjusting for cases that had a precipitating factor for stroke, ORs were largely unchanged.	Moderate
Nowak-Gottl et al (1999)	Germany	Investigated the role of prothrombotic risk factors, elevated Lp (a) and homocysteinemia as risk factors of AIS in children	Case control	148 with AIS. Age: 4.5 years (median) range 6 months to 16 years.	296 age and sex matched children. Age: 5 years, range 6	-	The following frequencies (patients v controls), odds ratios (ORs), and confidence intervals (CIs) of single risk factors were found: Lp(a) G30 mg/dL (26.4% v 4.7%; OR/CI, 7.2/3.8 to 13.8;	Moderate

		who do not show additional clinical risk factors.		Gender: male to female ratio 1:1.1. Ethnicity: Caucasian.	months to 16 years. Gender: male to female ratio 1:1.1. Ethnicity: Caucasian.		P<.0001), FV G1691A (20.2% v 4%; OR/CI, 6/2.97 to 12.1; P<.0001), protein C deficiency (6% v 0.67%; OR/CI, 9.5/2 to 44.6; P =.001), PT G20210A (6% v 1.3%; OR/CI, 4.7/1.4 to 15.6; P= .01), and the MTHFR TT677 genotype (23.6% v 10.4%; OR/CI, 2.4/1.53 to 4.5; P<.0001). A combination of the heterozygous FV G1691A mutation with increased Lp(a) (n= 11) or the MTHFR TT677 genotype (n =5) was found in 10.8% of cases, but only 0.3% of controls (OR/CI, 35.75/4.7 to 272; P< .0001). Authors conclude that increased Lp (a) levels, the FV G1691A mutation, protein C deficiency, the prothrombin G20210A variant, and the MTHFR TT677 are important risk factors for spontaneous ischemic stroke in childhood.	
Sirachainan et al (2006)	Thailand	Identified whether hyperhomocysteinemia is a risk factor for AIS and whether MTHFR C677T, vitamin B12 and folate status influence homocysteine levels	Case control	28 children with AIS. Age: 9.3 years (mean) S.D. 4.5 years. Gender: 57.1% male, 42.9% female. Ethnicity: Thai.	100 children. Age: 9.7 (mean) S.D. 5.4. Gender: 52% male, 48% female. Ethnicity: Thai.	-	The mean total plasma homocysteine level in patients was 8.7±3.6 mmol/L, significantly higher than those of the control group 7.5±2.4 mmol/L (P=0.01). The patients with total plasma homocysteine greater than the 95th percentile of 11.5 mmol/L showed a significant increase in the risk of developing AIS [OR 8.2, 95% CI 1.4-47.2, P=0.02].	Moderate
Teber et al (2010)	Turkey	To investigate whether elevated lipoprotein (a) levels are associated with increased risk of AIS.	Case control	52 children with AIS. Age: 3.24 years (mean) S.D. 4.35 years.	78 age and gender matched children with no history of	-	The median value of lipoprotein (a) level was 11.85 (range: 1.90-140) in the AIS group and 6.02 (range:0.64-76.8) in the age-matched control group (P <.05). 14/52 (26.9%) patients had lipoprotein (a) level higher than the cut-off level of 30 mg/dL	Moderate

				Gender: 31 male, 21 female. Ethnicity: Turkish.	stroke or chronic illness.		compared to 10/78 (12.8%) in the control group.	
Van Beynum et al (1999)	Netherlands	To assess the association between moderate hyperhomocysteinemia and AIS	Case control	45 children with AIS. Age: 1.8 years (mean) range 0 to 15.7. Gender: 30 male, 15 female. Ethnicity: Dutch	234 healthy secondary school children and younger children recruited in hospital. Age: 8.6 years (mean) range 0-19.3 years. Ethnicity: Dutch	-	Hyperhomocysteinemia was present in 8 (18%) of the 45 patients with ischemic stroke vs 11 (5%) of the controls with odds ratio of 4.4 (95% CI, 1.7 to 11.6). There was a trend towards an increase in the risk of AIS associated with hyperhomocysteinemia in increasing age groups 0-1.2y OR 1.9 (95% CI 0.4-8.8), 1.2-4.8y OR 4.0 (95% CI 0.6-27.0), 4.8-19.3 OR 7.4 (95% CI 1.1-48.6), 4.8-19.3 OR 4.4 (95% CI 1.1-48.6).	Moderate
Zak et al (2009)	Poland	Analyze the relationship between the methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and stroke and to observe whether there is any significant transmission of MTHFR alleles from heterozygous parents to their affected off- spring.	Case control	64 children with AIS. Age: 8.7 years (mean) range 6 months – 18 years. Gender: 29 male, 29 female. Ethnicity: Caucasian.	59 healthy children. Age: 9 years (mean), S.D. 5.9 years. Gender: 38 male, 21 female. Ethnicity: Caucasian	-	The T allele was more frequent in the stroke group (38%) than in controls (25%, P = 0.029, odds ratio = 1.84, 95% CI 1.02-3.32) Carriers of the T allele were more frequent in patients with stroke (61%) than in controls (46%) (p=0.092, OR 1.85, 95% CI 1.85-4.04) Higher frequency of T allele in male patients compared to male controls (46% vs. 25%, P = 0.009, odds ratio = 2.53, 95% CI 1.19-5.42) The number of T allele carriers was again more prevalent in boys with stroke (71%) than in healthy boys (45%, P= 4.023, odds ratio 3.09, 95% CI 1.15-8.31). Frequency of TT homozygotes among boys with ischemic stroke was almost 4-fold higher than in healthy boys (20% vs. 5%, P = 0.015, odds ratio= 7.35, 95% confidence	Low

							<p>interval 1.07-63.44, Fisher exact: 1-tailed, P = 0.020, 2-tailed P= 0.023)</p> <p>The carrier state of T allele of 677C&gt;T polymorphism was the only risk factor associated with stroke among the male subgroup in the multivariate analysis after adjustment of the elevated level of total cholesterol, low-density lipoprotein-cholesterol, and triacylglycerols</p>	
Donahue et al (2009)	USA	To determine whether varicella vaccination is associated with increased risk of ischaemic stroke and encephalitis in children within 12 months of vaccination.	Case series	<p>1.14 million children who had the varicella vaccine.</p> <p>Age: 1.9 years (mean age at study entry).</p> <p>Gender: 51.4% male, 48.6% female.</p> <p>Ethnicity: not stated</p>	<p>2.09 million children without the varicella vaccine.</p> <p>Age: 7.9 years (mean age at study entry).</p> <p>Gender: 50.8% male, 49.2% female.</p> <p>Ethnicity: not stated</p>	-	<p>203 children has AIS within 12 months of the vaccine – incidence rate 1.2 per 100 000 person-years (95% CI 1.0-1.4)</p> <p>AIS more common in those who did not have varicella vaccine than those who did, even after adjustment for age. 0.008% vs 0.003%; p&lt;.0001)</p> <p>Of 203 children with AIS, 39 (19.2%) were vaccinated on/before their diagnosis, median interval ~4 y. 8 were within 12m of vaccination, 1 on day of vaccination, 1 other within 3m of vaccination. No temporal clustering.</p> <p>Adjusted hazard ratio for stroke not significantly elevated at any time within 12m after vaccination. HR 1.1 (95% CI: 0.1-9.2) in first 30 days, and 0.7 (95% CI: 0.1-5.7) in first 60 days.</p> <p>Risk factors for stroke not significantly different between vaccinated and unvaccinated groups.</p> <p>Conclusion: Varicella vaccine is not a risk factor for AIS</p>	Moderate

#### Investigations to identify underlying risk factors of AIS

Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Abram (1996)	USA	To assess the natural history, prognostic factors, and lipid and apolipoprotein abnormalities of idiopathic ischemic childhood stroke	Case series	42 children with AIS. Age: 6.8 (mean), range 9 months to 18 years. Gender: 60% male, 40% female. Ethnicity: Caucasian 86%, African American 14%.	NA	7.4 years (mean) range 1 to 19 years after presentation.	36/42 had both a fasting lipid and apolipoprotein analysis, findings were: a depressed apolipoprotein A-1B ratio (53%), elevated triglycerides (25%), an elevated total cholesterol (22%), an elevated low-density lipoprotein cholesterol (19%), and a depressed high-density lipoprotein cholesterol (17%). Twenty-eight percent had both an abnormal lipid value and a depressed apolipoprotein A-1B ratio, 25% just had a depressed ratio. Lipid abnormalities including an elevated triglyceride and low-density lipoprotein cholesterol, and a depressed high-density lipoprotein cholesterol were seen in one third of all patients. A depressed ratio of apolipoprotein A-1 to apolipoprotein B (using adult normative values) was seen in half of the entire cohort.	Low
Al-Sulaiman (1999)	Saudi Arabia	To report on the clinical features and neuroimaging correlates of stroke in Saudi children seen over a 5-year period.	Case series	31 children with stroke, 28 AIS, 2 ICH, 1 SAH. Age: 26.2 months (mean) range 3 months – 11 years. Gender: 18 male, 13 female. Ethnicity: Saudi.	NA	-	Diagnosed by CT or MRI. Baseline investigations included CBC; Hb electrophoresis; serum fibrinogen level; PT; PPT; serum immunoglobulins; liver function tests; random and fasting blood sugar; serum electrolytes; blood urea nitrogen; and serum mg, ca, ammonia, creat, creatine kinase, lactate, and pyruvate levels. Serologic tests, immunologic profile, muscle biopsy, skin biopsy for fibroblast characterization, and CSF evaluation of pyruvate and lactic acid levels were also performed when indicated. Other tests when indicated.	Low

Barnes (2004)	Australia	To determine the epidemiology and outcome of AIS in Australian children	Case series	144 children with AIS. Age: 4.8 years (mean) range 1 day – 19.3 years. Gender: 60 male, 35 female. Ethnicity: not stated	NA	-	Thrombophilic testing was performed in 33 patients (35%) at a mean duration of 44 days (range 0–690 days) after presentation. and thrombophilic markers were abnormal in six of these patients (18% of those patients tested). One patient had combined protein S and protein C deficiency and was heterozygous for factor V Leiden mutation. One patient had isolated protein C deficiency and one patient had isolated factor V Leiden mutation	High
Brush (2013)	Australia	To determine the prevalence of hypertension (HPT) in the acute phase after (IS) and explore its relationship to outcome.	Case series	90 children, 81 with AIS. Age: 3.8 years (median), range 1 month – 18 years. Gender: 54% male, 46% female Ethnicity: not stated	NA	-	Blood pressure readings recorded over the first 72 hours after diagnosis. Hypertension was defined as 2 consecutive readings of systolic blood pressure $\geq$ 95th percentile for age. 53/84 patients (63%) who had blood pressure readings available had at least 1 episode of hypertension (49/53 were AIS cases) and 19 (22%) had HPT on 3 consecutive days. HPT was more prevalent at both ends of the age spectrum and there was no statistically significant association between HPT and any of the risk factors or underlying conditions. The relative risk of 12-month mortality was 4.5 times higher (95% CI 0.6–34.5, $p = 0.096$ ) and relative risk of death in the hospital was 1.7 times higher (95% CI 1.4–2.0, $p = 0.05$ ) if the patient experienced HPT.	Moderate
Cardo (1999)	Spain	To study the association of hyperhomocysteinaemia with stroke in children.	Case-control	68 children with AIS and HS. Age: 2 months – 18 years.	100 children with epilepsy and no history of stroke.	-	Blood was collected between 2 weeks and 1 month after the stroke episode. Hyperhomocysteinaemia was defined as a homocysteine concentration above the	Low

				Gender: not stated Ethnicity: not stated	Age: 2 months – 18 years. Gender: not stated Ethnicity: not stated		95th percentile for the reference values. Significant differences were found in total homocysteine values of children with stroke and those taking anti-epileptic drugs compared with the reference values for similar ages, except for the adolescent group.	
Eltayeb (2015)	Egypt	To study some prothrombotic risk factors [activated protein C (APC) resistance, von Willebrand factor (vWF), antithrombin (AT), antithrombin (AT) antibodies and plasma homocysteine] in children with ischemic stroke, and to evaluate the role of aspirin and low molecular weight heparin (LMWH) in its management in relation to outcome.	Case-control	37 children with AIS. Age: 26.2 months (mean), range 1 month – 15 years. Gender: 20 male, 17 female. Ethnicity: not stated.	20 healthy age and sex-matched children.	-	There was a significant decrease in PTT, and significant increases in APC resistance, vWF, homocysteine and AT levels between cases and controls ( $p < 0.001$ for each). A total of eight cases (21.6%) had more than one prothrombotic risk factor.	Low
Ganesan (2011)	UK	To describe the frequency of cervical arterial abnormalities in children with AIS	Case series	60 children with AIS. Age: 5 years 3 months (median), range 1 month – 16 years. Gender: 31 male, 29 female. Ethnicity: White 43, Black 6, Indian or Arabic 11.	NA	-	MRI/MRA from aortic arch to include carotid bifurcations and intracranially. Catheter angiography performed at clinician's discretion. Infarction in the posterior circulation distribution significantly predicted the presence of cervical arterial abnormality (5/10) while infarction in the anterior circulation was only associated with cervical arterial abnormality in 9/49 cases. Overall the presence of cervical arterial abnormalities in 15/60 (25%) cases of childhood AIS was taken as supporting the Paediatric Stroke Working Group Recommendation that the cervical	High

							vasculature should be imaged in these patients.	
Gokben, (2007)	Turkey	To evaluate risk factors and outcome in children with arterial ischemic stroke.	Case series	31 children with AIS. Age: 4.5 years (mean) S.D. 3.1 years. Gender: 18 male, 13 female. Ethnicity: Turkish.	NA	-	'Old era' tests included: protein C, protein S, antithrombin, lupus anticoagulants, and anticardiolipin antibodies. 'New era' tests added 5 more tests: homocystine level, factor VIII level, mutations for factor V Leiden and prothrombin G20210A, and lipoprotein (a) level.  At least 1 risk factor was found in 5 of 13 children (38.5%) in the old era and in 8 of 18 (44.4%) in the new era. The extended battery for prothrombotic disorders revealed 7 risk factors in 4 children (22.2%) in the new era, whereas the limited battery identified a single risk factor in 1 child (7.7%) in the old era. For the correct etiologic identification, prothrombotic risk factors should be extensively evaluated in patients with arterial ischemic stroke.	Low
Goldenberg (2013)	USA	To assess whether acute findings of cerebral arteriopathy, large infarct, and acutely elevated plasma S-dimer levels are independently prognostic of poor long-term neurological outcome as measured at >1 year post-event in children with AIS	Cohort	61 children with AIS, 41 of whom completed follow-up. Age: 8 years (median), range 91 months to 19 years. Gender: 30 male, 31 female.	NA	1 year	Assessed acute arteriopathy and D-dimer levels. Cerebral arteriopathy and D-dimer levels >500ng/ml identified acutely in 41% and 31% of the cohort respectively. Acute cerebral arteriopathy and elevated D-dimer level were prognostic factors for poor outcome.	Moderate

				Ethnicity: (follow-up group only) 31 non-Hispanic, 10 Hispanic.			After adjustment for D-dimer, arteriopathy was an independent prognostic indicator (OR, 19.0; 95% CI, 1.6-229.8; P=.02)	
Yeon (2014)	Korea	To define angiographic course and outcome in children with unilateral arteriopathy and stroke	Case series	29 children with AIS. Age: 9.1 years (mean). Gender: 12 male, 17 female. Ethnicity: Korean.	NA	-	All included children had repeat vascular imaging (MRA and/or DSA). 17/25 reversible arteriopathy. 9 had initial worsening. 12/17 nearly normalised. 1 had recurrent stroke at 14 months. 5 had progressive arteriopathy – worsening within 6 months Only 3 had stable arteriopathy. Majority present with basal ganglia stroke.	Low

Role, modality and timing of imaging in assessment and monitoring AIS								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Beslow 2012	USA	To establish relationship of modASPECTS [modified Alberta Stroke Programme Early CT Score] to infarct volume in perinatal and childhood AIS and to establish the inter-rater reliability of the score.	Cross-sectional	71 children with AIS, perinatal group 31; childhood group 40. Age: (median childhood group) 3.7 years IQR 0.3 – 12 years. Gender: 42 male, 29 female. Ethnicity: 44 White (2 Hispanic), 20 Black, 3 Mixed race, 4 Unknown.	NA	-	Comparison of measurement of infarct volume by manual segmentation techniques with modASPECTS score. Assessment of infarct volume as larger volume associated with poorer outcome and increased risk of haemorrhagic transformation. ModASPECTS correlated well with infarct volume [Spearman rank correlation coefficient = 0.87 p<0.001 for perinatal group and 0.80 p<0.001 for childhood group. Intraclass correlation coefficients for 3 raters = 0.93 [95%CI 0.89 – 0.97, p<0.001] for neonates and 0.94 [95% CI 0.91-0.97, p<0.001] for childhood group.	Moderate

							<p>ModASPECTS score of 5 = differentiator for small v large volume stroke.</p> <p>In childhood group sensitivity and specificity of modASPECTS <math>\geq 5</math> for predicting large infarct were 80% [95%CI 65.4-90.4%] and 87% [95%CI 76.7-93.9%] respectively.</p> <p>Assessment of stroke volume of 5% or greater predicts increased risk of haemorrhagic transformation and poorer outcome at follow up by PSOM.</p>	
Buerki 2010	Switzerland	To describe neuroimaging patterns associated with AIS in childhood and to differentiate them according to stroke aetiology	Cohort	<p>79 children with AIS.</p> <p>Age: 5 years 3 months, range 2 months – 15 years 8 months.</p> <p>Gender: 48 male, 31 female.</p> <p>Ethnicity: not stated</p>	NA	-	<p>Stroke was confirmed in the acute period in 36 out of 41 children who underwent CT, in 53 of 57 who underwent T2-weighted MRI and in all 48 who underwent diffusion-weighted MRI.</p>	Low
Filippi 2015	USA	To describe computer assisted volumetry applied to diffusion imaging and compare to manual volume measurement techniques	Case series	<p>23 children with stroke.</p> <p>Age: 4.6 years (mean), range 0 to 17.6 years.</p> <p>Gender: 12 male, 11 female.</p> <p>Ethnicity: not stated.</p>	NA	-	<p>Manual and automated volume assessment equivalent in terms of measured volumes</p> <p>Automated technique significantly faster (<math>&lt;1\text{min}</math> v <math>7.3\text{ mins}</math> [<math>p&lt;.01</math>])</p> <p>Mean core volume = <math>75.7\text{ml}</math> in poor outcome and <math>7.4\text{ml}</math> in good outcome (<math>p&lt;.007</math>)</p>	Moderate
Ganesan 1999	UK	To investigate whether there is any diagnostic or therapeutic advantage to undertaking conventional cerebral angiography if MRA is available.	Case series	<p>128 children with AIS, 69 had MRA.</p> <p>Age: 6 years 7 months (median), range 9 months to 17 years.</p>	59 children who only had CA.	-	<p>MRA was diagnostic in 25 of 28 patients with large vessel occlusion, stenosis, or moyamoya.</p> <p>Angiogram was abnormal in four of nine patients with a normal MRA.</p>	Low

				Gender: (of the children who underwent MRA) 26 male, 43 female.			All patients with normal angiogram also had normal MRA. Conventional angiography, either diagnostic or yielding further information, altered management in five patients with arterial dissection, one patient with large vessel occlusion, one patient with large vessel stenosis, and four patients with arteritis.	
Ganesan 2006	UK	To report longitudinal data from the same patients on the rates of and risk factors for clinical and radiological recurrence.	Retrospective case series	212 children with AIS. Age: 5 years (median), range 21 days to 19.5 years. Gender: 115 male, 97 female. Ethnicity: 151 White, 41 Black, 19 Asian.	NA	-	131 children had received treatment to prevent another stroke; 50/131 (38%) had a clinical recurrence, compared with 29 (35%) of 81 who were untreated. After adjustment for the underlying and vascular diagnoses, neither aspirin nor anticoagulation significantly influenced the incidence of clinical recurrence compared with no prophylaxis, although there was a trend for an effect of aspirin (HR, 0.55; 95% CI, 0.26 to 1.16; P= 0.11 for aspirin; HR, 1.06; 95% CI, 0.45 to 2.51; P= 0.89 for anticoagulation).	High
Husson 2002	France and Belgium	To compare results of catheter angiography and MRA in childhood AIS	Cohort	24 children with AIS. Age: 6 months to 14 years. Gender: 13 male, 11 female. Ethnicity: Not stated.	NA	-	MRA and angiogram data similar in 26 large strokes MRA and angiograms concordant in 75% Discordant in 25 %: all MRA overestimations of degree of stenosis. Authors recommend that angiograms should still be considered in children with stroke where MRA normal, small vessel diseases suspected or uncertainties about differential diagnosis of ICA lesions.	Low
Jarus-Dziedzic 1999	Poland	To evaluate the usefulness of TCD in ischaemic stroke and to assess the	Case series	21 children with AIS.	NA	-	Asymmetry of 30 to 80% in cerebral blood flow velocity between right and left side was observed in 15 children, mainly with	Low

		compliance of TCD results with CT, MRI and angiography		Age: 12 years (mean). Gender: 13 male, 8 female. Ethnicity: not stated.			decreased cerebral blood flow velocity in the stroke area. Asymmetry in blood flow velocity exceeding 30% was observed in only one child out of 5 children with TIA. In all the patients, CT, MRI and cerebral angiography results revealed a correlation with TCD changes in blood flow velocities.	
Mackay 2010	Australia	To describe clinical and radiological features of childhood PCAIS to determine whether there are differences in infarct topography, vascular abnormalities, risk factors, and stroke subtypes when compared to adults.	Case series	27 children with AIS. Age: 7 years 11 months (mean), range 1 month to 16.5 years. Gender: 19 male, 8 female. Ethnicity: 23 White, 2 South East Asian, 2 East Indian.	NA	4 years 3 months (mean)	CA was performed in 11 children, intracranial MRA was performed at presentation in 25 of 27 children and in 25 children at follow-up. Contrast MRA of the neck vessels missed vertebral artery dissection in 2 children, overestimated the degree of stenosis in 2 children, and underestimated the degree of stenosis in 1. There was good correlation between CA and MRA in 6 cases. CA contributed considerable additional information over MRA – CA results were abnormal in 4/9 patients with normal MRAs and additional abnormalities not detected on MRA were found in 13 children, frequently altering management.	Low
Munot 2011	UK	To describe clinical and radiological characteristics of children with arterial ischemic stroke and normal MRA to compare them with children with arterial ischemic stroke and abnormal MRA.	Case series	40 children with AIS and no arteriopathy. Age: 4.6 years (median), range 2 months to 15.6 years. Gender: 24 male, 16 female. Ethnicity: not stated	82 children with AIS and arteriopathy Age: 6 years (median), range 1 month to 16 years. Gender: 40 male, 42 female.	22 months (mean)	Two children had a clinical recurrence 6 and 8 months after the index AIS (1 with acute myeloid leukemia, 1 with no RF and no patent foramen ovale) with new areas of infarction but vascular imaging remained normal. Of 28 follow-up scans in 24 children after a median of 12 months (range, 4 to 24 months), only these 2 showed new infarcts. MRA remained normal in all.	High

					Ethnicity: not stated.			
Zebedin 2013	Austria	To report the preliminary results of CT perfusion in cases of AIS	Case series	10 children with AIS. Age: 13 years (mean), range 8 to 17 years. Gender: 3 male, 7 female. Ethnicity: not stated.	NA	-	In 9/10 children perfusion CT showed no false positive or false negative results. In 1/10 children suffering from migraine focal hypo-perfusion was read as perfusion impairment potentially indicating early stroke, but MRI and MRA follow-up were negative. Overall, perfusion-CT with CT-DSA was rated very good in 80% of cases for the detection of perfusion disturbances and vessel anatomy.	Low

What is the safety and efficacy of thrombolytic agents/anticoagulants/antiplatelets for the acute treatment of children with AIS?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Alhaboob 2014	Pakistan	To study a cohort of children with (cPACNS); and evaluate efficacy and safety of their management	Observational cohort	68 children with AIS. Age: 7.4 years (median), range 1.5 to 16 years. Gender: 42 male, 26 female. Ethnicity: not stated.	NA	-	56/68 patients completed induction and carried on maintenance therapy as per the approved management protocol; 41 (73.21%) of them with Aspirin alone and 15 (26.79%) with combined Aspirin and Azathioprine. Mortality: 12 patient (17.64%), 11 normal (16.17%), 14 (20.59%) minor disabilities, 11 (16.17%) had moderate disabilities and 20 (29.41%) had severe disabilities. Mortalities included 7 M and 5 F, their neuroimaging studies showed 5 with haemorrhagic stroke, 5 with haemorrhagic infarct stroke and 2 with ischemic stroke with progressive arteriopathy. Eight of them had severe bilateral involvement of major cerebral arteries and/or massive parenchymal bleeding. No statistically significant differences were found for age, localization of (AIS) and occurrence of seizures in relation to morbidity and mortality. No secondary haemorrhages were observed among all the ischemic-infarcts patients who were treated initially with intravenous heparin and continued with oral anticoagulants	Low
Alshekhlee 2013	USA	To evaluate the mortality rate and the risk of intracerebral haemorrhage (ICH) in a large US sample of children. In addition, we evaluate the trend of	Cross sectional	9257 children from the KIDS inpatient database. Age: 8.22 years (mean), S.D. 7.51 years.	NA	-	67 children (0.7%) received thrombolysis treatment for AIS. Treated children were older, with the mean age 13.1+/-7.3 vs 8.18 +/-7.5, P < 0.0001. Other demographics were similar. Hospital stay was longer among the thrombolysis group	Moderate

		hospital utilization of thrombolysis in children.		Gender: 57% male, 43% female. Ethnicity: White 38.8%, Hispanic 16.4%, Black 15.4%.			(median: 11 vs 6 days, $P < 0.0001$ ). Overall mortality rate was 6.71%, but the rate was higher in the thrombolysis group (10.29% vs 6.19%). Bivariate analysis suggested a trend toward higher risks of hospital mortality (10.45% vs 6.14%; odds ratio [OR] 1.78; 95% CI 0.81-3.92; $P = 0.06$ ) and ICH (2.99% vs 0.77%; OR 3.95; 95% CI 0.94-16.45; $P = 0.08$ ) in the thrombolysis group. Adjusted analysis showed that intracerebral haemorrhage is predictive of a higher hospital mortality (OR 3.43; 95% CI 1.89-6.22), whereas thrombolysis was not (OR 1.78; 95% CI 0.86-3.64). The overall rate of thrombolysis per 3 years intervals had increased from 5.2 to 9.7 per 1000 children with acute ischemic stroke ( $P = 0.02$ ). This increase was mainly seen in non-children hospitals ( $P = 0.01$ ).	
Amlie-Lefond 2009	International (US/Canada)	To describe current practices and results of use of alteplase for acute arterial ischaemic stroke in children	Cohort	15 children given alteplase. Age: 8.9 (median), range 0.2 to 15 years. Gender: 6 male, 9 female. Ethnicity: 8 White, 3 Hispanic, 2 Mixed White/Hispanic, 2 Unknown.	NA	-	Alteplase given to 18 children – 15 as acute treatment; 9 IV and 6 intra-arterial, 1 had posterior circulation infarct. Death in 2 children – unrelated to alteplase. At discharge from hospital 1 healthy, 12 had neurological deficit – all 12 had motor deficit, 3 had speech impairment and 1 had cognitive impairment. 4 had intracranial haemorrhage – not symptomatic in any. None of those given IV alteplase was normal at discharge. Time to treatment was median 3.3 hr range 2 to 52 hr for IV and median 4.5 hr 93.8 to 24 hr for IA alteplase.	Moderate

Bernard 2009	USA/Germany	To investigate safety of extended anticoagulation in stroke with non-moyamoya arteriopathy	Cohort	37 children with AIS. Age: 5 years (median), range 6 weeks to 17 years. Gender: not stated. Ethnicity: not stated.	NA	-	Therapeutic anticoagulation was administered in 43% of patients and prophylactic anticoagulation in 57%. Median duration of anticoagulation was 6 months (range, 1 month to 4 years). No major bleeding episodes, 2 clinically relevant bleeding episodes, Cumulative probability of recurrent stroke at 1 year 14%. Anticoagulant Therapy Regimens used: Anticoagulation can be used safely.	Low
Eltayeb 2015	Egypt	To study some prothrombotic risk factors [activated protein C (APC) resistance, von Willebrand factor (vWF), anticardiolipin (ACL) antibodies and plasma homocysteine] in children with ischemic stroke, and to evaluate the role of aspirin and low molecular weight heparin (LMWH) in its management in relation to outcome.	Retrospective case series	37 children with AIS. Age: 26.2 months (mean). Gender: 20 male, 17 female. Ethnicity: not stated	20 apparently healthy children of matched age and sex. (NOT RELEVANT HERE)	-	Treatment with antithrombotic therapy Aspirin treatment group (n = 25), LMWH group (n = 12) Most of the cases (51.3%) were under 1 year of age with a significant difference (p = 0.015). Risk factors in relation to antithrombotic therapy. No significant differences between cases treated with aspirin and those treated with LMWH were found in all the studied parameters. Patients treated with aspirin showed a lower cognitive deficit than those treated with LMWH (16% versus 66 %) with p = 0.03.	Low
Goldenberg 2009	Canada	To describe frequencies and predictors of acute treatments and early outcomes in the International Paediatric Stroke Study (IPSS), a large	Multicentre observational cohort study	661 children with AIS. Age: 28 days to 19 years. Gender: 391 male, 270 female.	NA	-	Acute treatments included anticoagulation alone in 171 patients (27%), antiplatelet therapy alone in 177 (28%), antiplatelet and anticoagulation in 103 (16%), and no antithrombotic treatment in 189 (30%). After adjustment for significant covariates, subtypes associated with any use of	High

		international series of childhood AIS		Ethnicity: not stated.			<p>anticoagulation were dissection (OR 14.09, 95% CI 5.78–37.01; <math>p&lt;0.0001</math>) and cardiac disease (1.87, 1.20–2.92; <math>p=0.01</math>). Factors associated with non-use of anticoagulation included sickle-cell disease subtype (0.12, 0.02–0.95; <math>p=0.04</math>) and the enrolment centre being located in the USA (0.56, 0.39–0.80; <math>p=0.002</math>). By contrast, antiplatelet use was associated with moyamoya (4.88, 2.13–11.12; <math>p=0.0002</math>), whereas non-use was associated with dissection (0.47, 0.22–0.99; <math>p=0.047</math>), low level of consciousness (0.45, 0.31–0.64; <math>p&lt;0.0001</math>), and bilateral ischaemia (0.32, 0.20–0.52; <math>p&lt;0.0001</math>). Outcomes at hospital discharge included neurological deficits in 453 (74%) patients and death in 22 (3%). In multivariate analysis, arteriopathy, bilateral ischaemia, and decreased consciousness at presentation were prognostic of adverse outcome.</p>	
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Gupta 2001	Canada	To determine the safety and outcomes of thrombolysis with tissue plasminogen activator of intravascular thrombus	Retrospective Case series	80 children with AIS. Age: 6 months (median), range 2 day to 17.8 years. Gender: 43 male, 37 female. Ethnicity: not stated	NA	-	There were 65 arterial thrombi (56 after cardiac catheterization) and 15 venous thrombi treated with tPA at an average dose of tPA of 0.5 mg/kg/hour for a median duration of 6 hours. Complete resolution of the clot was noted in 52 patients (65%), partial resolution was noted in 16 patients (20%), and no change was noted in 12 patients (15%). Major complications associated with tPA therapy occurred in 32 patients (40%), minor complications occurred in 24 patients (30%), and no complications occurred in 24 patients (30%).	Low
Maltz 2009	USA	To examine the prescribing practices and to describe retrospectively bleeding, thrombotic, and other events occurring during clopidogrel use in a paediatric population at a single institution.	Retrospective cohort	90 children with AIS. Age: 6.7 years, range 11 days to 17.9 years. Gender: 53% male, 47% female. Ethnicity: not stated.	NA	-	Clopidogrel doses were limited to fractions of 75mg tablets and administered orally. The total daily dosage was a median of 1.3mg/kg/day (range 0.2-8.9 mg/kg/day). Doses were given daily or every other day. Loading doses (typically 2x the maintenance dose) were given 21.1% of the time. Other anticoagulants or antiplatelet agent were prescribed (81.1%) of the time at the time of first clopidogrel use. 58.9% were prescribed acetylsalicylic acid only, 11.1% prescribed a combination of acetylsalicylic acid and another anticoagulant or antiplatelet agent. Length of clopidogrel use was a median of 44.5 days (range = <1 day to 4 years).	Low

							Children with a history of thrombosis tended to have the shortest use (median 14 days) and those with abnormal vasculature with potential for low flow had the longest use (median = 78 days) 9 children had an event during clopidogrel use: 4 bleeding events (4.4%), 1 thrombotic event (1.1%), and 4 other (4.4%). Event rates were for minor bleeding 0.008 per month (95% CI 0.002-0.024), and for major thrombotic events 0.003 per month of exposure (95% CI 0-0.015).	
Nasr 2014	USA	to determine trends in the use of recombinant tissue plasminogen activator (rt-PA), treatment outcomes, and predictors of mortality for paediatric patients with acute ischemic stroke by using the Nationwide Inpatient Sample	Cohort identified from a database	99 children with AIS treated with rt-PA. Age: 12.4 years (mean), range 30 days to 17 years. Gender: 65% male, 35% female. Ethnicity: 67% White, other ethnicities not stated.	6944 children with AIS not treated with rt-PA. Age: 8.5 years (mean), range 30 days to 17 years. Gender: 56% male, 44% female. Ethnicity: 48% White, other ethnicities not stated.	5 years	329 (4.7%) children died in hospital. Rt-PA patients were older than non-rt-PA patients (12.4+-9.4 versus 8.5 +- 13.2, p<0.0001). There were no in-hospital deaths in the rt-PA group (0% versus 4.8%, p=0.02). rt-PA was associated with reduced risk of mortality in multivariate analyses (OR 0.00, 95% CI 0.00-0.24, p=0.0005).	Low
Pandey 2015	USA	To describe clinical presentation, imaging features, treatment strategies, and report clinical and imaging outcomes of CCADs at a large paediatric tertiary referral center.	Case series	42 patients with CCADs. Age: 14.8 years (mean), range 8 months to 25 years. Gender: 24 male, 18 female.	NA	-	31 of 42 (73.8%) patients had either medical or surgical/endovascular treatment. 22 had medical treatment only with antiplatelet therapy (aspirin and/or clopidogrel) or anticoagulation therapy (fractionated or unfractionated heparin or warfarin). Two patients failed medical	High

				Ethnicity: not stated.			management and developed recurrent symptoms one had a cervical ICA dissection leading to vessel occlusion, and one patient with vertebral artery dissection developed recurrent strokes on aspirin therapy. These patients were first started on anticoagulation with LMWH followed by warfarin. One patient presented with a cervical ICA dissection/occlusion and developed an intracranial haemorrhage while on heparin.	
Rafay 2006	Canada	To determine the frequency, identify the associated risk factors, determine the clinical presentation, imaging features, and treatment strategies and report the clinical and angiographic outcome of arterial dissection in the paediatric ischemic stroke population	Retrospective chart review.	16 children with dissection. Age: 9.4 years (median), range 6 months to 16.4 years. Gender: 8 male, 8 female. Ethnicity: not stated.	NA	6.4 years (mean)	Treatment: in the acute phase heparin was given to 9 (56%), LMWH in 5 (31%), and oral aspirin in 1 (6%). Follow up treatment consisted of LMWH or warfarin followed by aspirin in all except 2 or the 15 treated children. One child didn't have treatment because of an intra-abdominal haemorrhage, the other two children had (1) stroke recurrence on warfarin therapy and was treated with warfarin and aspirin with no subsequent stroke, and (2) recurrent dissections and ischaemic events was treated with long term LMWH followed by warfarin. No complications were noted with anticoagulation therapy. Follow-up angiography showed resolution of abnormalities in 60% of vessels. Total occlusion had the worst outcome for recanalization	Low

Rollins 2013	USA	To review experience with paediatric brainstem strokes examining issues impacting the timely diagnosis, practice patterns with respect to imaging and accuracy of non-invasive imaging at detecting vertebrobasilar pathology in children, and outcomes in a population treated with systemic anticoagulation.	Case series	15 children with AIS (brainstem). Age: 7.8 years (mean), range 9 months to 17 years. Gender: 10 male, 5 female. Ethnicity: not stated.	NA	-	Patients were systemically anticoagulated without haemorrhagic complications. One patient died. Paediatric Stroke Outcome Measures at 2-36 months is 0-5.0/10 (mean 1.25). Even with basilar artery occlusion and high stroke scales, outcome was good when systemic anticoagulation was started promptly.	Moderate
Schechter 2012	Canada	To evaluate the safety of protocol-based ACT in a longitudinal, prospectively enrolled sample of children diagnosed with AIS.	Prospective cohort	123 children with AIS treated with anticoagulant therapy. Age: 6.8 (mean), range 1 to 17.7 years. Gender: 64% male, 36 % female. Ethnicity: not stated.	75 children with AIS not treated with anticoagulant therapy. Age: 5.2 years (mean) 1 to 16 years. Gender: 48% male, 52% female. Ethnicity: not stated.	Length not given	Among 123 children receiving initial ACT within 7 days after AIS, 51 received a single ACT medication, 64 had 2 sequential ACT medications, and 8 had 3 sequential ACT medications during the treatment period. Seventy-two (58%) children switched ACT medication. HS rates were similar for each ACT regimen or combination. Median duration of ACT was 74 days (range, 1 day-6.4 years). Six children received ACT despite evidence of HS at diagnosis, either because the HS was minor (ECASS grade HI1) or the risk of recurrent thromboembolism was major. During anticoagulation, 14 (11%) children developed new or increased HS, all within 26 days from diagnosis. Long-term neurologic outcomes after ACT-associated HS in survivors were abnormal in 73% (8/11). 12 of 75 (16%) children treated without anticoagulation developed new or increased ICH on follow-up imaging	Moderate

							(P=0.3507). Authors concluded that ACT is relatively safe in children with AIS, with a 4% risk of symptomatic ICH.	
Shi 2008	China	To review cases of paediatric arterial ischemic stroke among Chinese subjects and thereby evaluate risk factors, clinical and neuroimaging features, and treatment, to establish a reasonable guideline for assessment and management of the disease.	Cohort series	157 children, 56 received thrombolytic therapy. Age: 32 months (median), range 4 to 192 months. Gender: 58.6% male, 41.4% female. Ethnicity: Chinese.	NA	-	56 (37.5%) patients received intravenous thrombolytic therapy upon confirmation of normal prothrombin time, activated partial thromboplastin time, and fibrinogen level (Urokinase- n=37, Streptokinase-n=19). The mean time between the first symptoms and application of thrombolytic agents was 6.8 days for urokinase and 8.0 days for streptokinase. The intravenous thrombolytic therapy was effective in all patients but one; that patient suffered from a haemorrhage as complication of the therapy. The efficacy of the treatment was reflected by improvement of symptoms and physical signs, such as increased myodynamia and disappearance of headache.	Low
Soman 2006	Canada	To assess the safety and tolerability of clopidogrel treatment in children with AIS.	Cohort	17 children with AIS. Age: 8.8 years (mean), range 1.5 to 17 years. Gender: not stated. Ethnicity: not stated.	NA	-	8 children treated with clopidogrel alone, 9 with aspirin as well. No children reported any major side effects during clopidogrel treatment alone. Significant intracranial haemorrhage was reported in 2 children (25%) on aspirin and clopidogrel combination. One of these had moyamoya and cerebral atrophy developed subdural haematoma 6 weeks after revascularisation surgery when aspirin and clopidogrel were restarted the other had Progeria and intracranial arterial stenosis also developed a subdural hematoma while on clopidogrel and ASA	Low

							combination. Both medications were withdrawn and no further progression of haemorrhage was noted.	
Strater 2001	Germany	To compare different antithrombotic secondary treatments (mainly medium-dose aspirin with low-dose low-molecular-weight heparin [LMWH]) in paediatric patients with a first ischemic stroke onset with regard to the risk of stroke recurrence.	Case series	135 children with AIS. Age: 7 years (median), range: 6 months to 18 years. Gender: 61% male, 39% female. Ethnicity: Caucasian.	NA	36 months (median)	Recurrent stroke occurred in 4 of 49 children treated with aspirin, 9 of 86 children treated with LMWH (OR 1.3, 95% CI 0.4-4.5, p=0.76, Fishers exact test). No patient in the aspirin group had drug associated side effects. No local or systemic haemorrhage or heparin induced thrombocytopenia was observed in the low molecular weight heparin arm.	Low
Tuckuviene 2010	Denmark	To study the incidence rate, clinical characteristics, risk factors and sequelae of AIS in children.	Cohort	211 children with AIS. Age: 0 to 18 years, no average given. Gender: 118 male, 93 female. Ethnicity: not stated.	NA	-	Anti-thrombotic treatment: given to 8% of infants, 56.4% of children and 75.9% of adolescents 89.4% received ASA with a median duration of 183 (IQR 53–561) days, (n = 29). Low molecular weight heparin was used in 11 patients with AIS for median 8 (IQR 6–18) days. Only one patient was treated with t-PA. Minor bleeding during antithrombotic therapy was relatively rare: Only 4 of 80 patients during ASA treatment, 2 of 33 patients during warfarin therapy (one got warfarin + ASA) and one patient experienced bleeding during thrombolytic therapy. No major or fatal bleeds were observed.	Low
Hulbert 2006	USA	To assess whether exchange transfusion as opposed to simple transfusion was more efficacious at preventing	Retrospective cohort study	137 children with SCD. Age: 6.3 years (mean), range 1.4 to 14 years.	NA	-	Recurrent stroke occurred in 57% (8/14) of patients with simple transfusion as opposed to 21% (8/38) of those having exchange transfusion. 5 fold greater risk of recurrent stroke with	Moderate

		stroke recurrence in a population of children with HbSS and stroke		Gender: 46% male, 54% female. Ethnicity: not stated.			simple exchange (95% CI 1.3-18.6) than those receiving exchange transfusions. Exchange transfusion gave greater protection against recurrent stroke compared with simple transfusion.	
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What is the safety and efficacy of medical interventions to prevent recurrence of AIS?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Ganesan 2006	UK	To report longitudinal data from the same patients on the rates of and risk factors for clinical and radiological recurrence.	Retrospective case series	212 children with AIS. Age: 5 years (median), range 21 days to 19.5 years. Gender: 115 male, 97 female. Ethnicity: 151 White, 41 Black, 19 Asian.	NA	-	131 children had received treatment to prevent another stroke; 50/131 (38%) had a clinical recurrence, compared with 29 (35%) of 81 who were untreated. After adjustment for the underlying and vascular diagnoses, neither aspirin nor anticoagulation significantly influenced the incidence of clinical recurrence compared with no prophylaxis, although there was a trend for an effect of aspirin (HR, 0.55; 95% CI, 0.26 to 1.16; P= 0.11 for aspirin; HR, 1.06; 95% CI, 0.45 to 2.51; P= 0.89 for anticoagulation).	High
Pandey 2015	USA	To describe clinical presentation, imaging features, treatment strategies, and report clinical and imaging outcomes of CCADs at a large paediatric tertiary referral center.	Case series	42 patients with CCADs. Age: 14.8 years (mean), range 8 months to 25 years. Gender: 24 male, 18 female. Ethnicity: not stated.	NA	-	31 of 42 (73.8%) patients had either medical or surgical/endovascular treatment. 22 had medical treatment only with antiplatelet therapy (aspirin and/or clopidogrel) or anticoagulation therapy (fractionated or unfractionated heparin or warfarin). Two patients failed medical management and developed recurrent symptoms one had a cervical ICA dissection leading to vessel occlusion, and one patient with	High

							vertebral artery dissection developed recurrent strokes on aspirin therapy. These patients were first started on anticoagulation with LMWH followed by warfarin. One patient presented with a cervical ICA dissection/occlusion and developed an intracranial haemorrhage while on heparin.	
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What is the safety and efficacy of medical interventions to prevent recurrence of AIS and progression of SCI in SCD?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Bishop 2011	USA	To determine the effect of chronic blood transfusion on the progression of cerebral vasculopathy in our paediatric cohort with sickle cell anaemia.	Retrospective review	34 children with SCA. Age: 6.5 years (mean). Gender: 53% male, 47% female. Ethnicity: not stated.	NA	7 years (median)	Patients experienced worsening vasculopathy, as measured by mean increases in their baseline MRI and MRA scores of +0.76 and +1.03. There was a significant difference in the mean change of MRI/MRA scores between patients who had cerebrovascular accident (CVA) and abnormal TCD (MRI; +1.23 vs. -0.08, $p=0.001$ and MRA; +1.54 vs. +0.08, $p=0.02$ ). Patients with abnormal baseline MRA had worsening scores compared to those with normal baseline MRA (54% vs. 9.5%, $p=0.01$ ). Also, patients who had CVA were more likely to have an abnormal baseline MRA and worsening scores compared to abnormal TCD patients.	Low
Brousse 2009	France	To assess evidence of MRI or MRA evidence of cerebrovascular disease in children with HbSS on long-term transfusion programmes as primary or	Retrospective cohort	18 children with SCD. Age: 7.6 years (mean), range 3 to 10.8 years.	NA	59.6 months	Standardised MRI scoring system was used. There was a progression of abnormal MRI scoring across the time frame despite the regular transfusion programme. In the 9 children with overt stroke the radiological scoring showed a significant	Low

		secondary stroke prevention.		Gender: 9 male, 9 female. Ethnicity: not stated.			deterioration: median total score 10 (2-22) at baseline increasing to 12 (3-26) P=0.27. No significant difference in the TCD group. Authors claim that the evidence suggests that effective transfusion programmes do not prevent progression of cerebrovascular disease in high risk children with HbSS.	
Bortolusso Ali 2011	Jamaica	To ascertain whether use of hydroxyurea in children with HbSS who had already had a stroke, could reduce the risk of recurrence	Cohort	43 children with SCD. Age: 7 years (mean), S.D. 3.9 years. Gender: 20 male, 24 female. Ethnicity: Afro Caribbean.	NA	111 person years	10 children (23.3%) agreed to start HU. 1/10 in HU group had a second stroke (incidence rate 2/100 person years) vs 20/33 in non-HU group (incidence rate 29/100 person years) Hazard ratio 9.4 (95% CI 1.3-70.6) P=0.03 No HU vs HU: Death 4 vs 0 53% vs 10% had mod/severe disability (P=0.017) 44% vs 20% SEN or too disabled to attend school.	Low
Hulbert 2006	USA	To assess whether exchange transfusion as opposed to simple transfusion was more efficacious at preventing stroke recurrence in a population of children with HbSS and stroke	Retrospective cohort study	137 children with SCD. Age: 6.3 years (mean), range 1.4 to 14 years. Gender: 46% male, 54% female. Ethnicity: not stated.	NA	-	Recurrent stroke occurred in 57% (8/14) of patients with simple transfusion as opposed to 21% (8/38) of those having exchange transfusion. 5 fold greater risk of recurrent stroke with simple exchange (95% CI 1.3-18.6) than those receiving exchange transfusions. Exchange transfusion gave greater protection against recurrent stroke compared with simple transfusion.	Moderate
Lagunju 2013	Nigeria	To compare the outcome after a first clinical stroke, following treatment with and without hydroxyurea (HU).	Cohort	13 children with SCD and stroke who received HU. Age: 7.9 years (mean), S.D. 1.7 years.	18 children with SCD and stroke who did not receive HU.	31.4 months (HU group), 30.5 months (non-HU group)	77.8% of the non-hydroxyurea treated group had recurrent stroke. Incidence rate 28/100 person years. 15.4% of the children treated with hydroxyurea had recurrent stroke. Incidence rate 7/100 person years. There was a significantly higher risk of	Low

				Gender: 8 male, 5 female. Ethnicity: African.	Age: 7.4 years (mean), S.D. 2.8 years. Gender: 13 male, 5 female. Ethnicity: African		stroke recurrence in the non-HU treated group ( $p=0.001$ , OR 3.808, 95% CI 1.556 to 9.317).	
Wang 2013	International	To assess risks and benefits of chronic blood transfusion regimens in people with sickle cell disease to prevent first stroke or recurrences.	Systematic Review	This SR included three eligible RCTs (n = 342, 130 - STOP Trials (60M/70F) 133 - SWiTC trial) children with (HbSS, SC, Sβ+ and Sβ0; proven by electrophoresis, with family studies or DNA tests as appropriate)	NA	-	Intervention with a chronic transfusion program produced a 90% relative risk reduction of first occurrence of stroke. Discontinuation after a minimum of 30 months was unsafe because of the likelihood of occurrence of abnormal TCD velocities or acute stroke. Transfusion and chelation vs hydroxyurea and phlebotomy SWiTC: Mortality - one death each in the transfusion and chelation, and the hydroxyurea and phlebotomy arms (OR 0.98, 95% CI 0.06-16.08). Incidence of stroke - 7 (10%) children in the hydroxyurea and phlebotomy arm and none in the transfusion and chelation arm had a stroke (OR 16.49, 95% CI 0.92-294.84). Transfusion related complications - at the final assessment median liver iron concentration was 17.3 (IQR 8.8-30.7mg/g) in the transfusion/chelation arm and 17.2 (IQR 10.0-30.6mg/g) in the hydroxyurea and phlebotomy arm. Incidence of TIA or silent infarct - 6 children in the hydroxyurea/phlebotomy arm and 9 in the transfusion/chelation arm had TIAs (OR 0.62, 95% CI 0.21-1.86). Haemoglobin level	High

							<p>and haemoglobin S percentage - median haemoglobin level was the same in both arms at the end of the trial (9.0 g/dL) (IQR 8.7-9.6 in h/p arm and 8.4-9.6 in t/c arm). Median haemoglobin S percentage was lower in the transfuse children (1.3% vs 19.5%)</p> <p>The use of hydroxyurea was associated with a greater (10%) risk of stroke recurrence than chronic transfusion for prevention of stroke recurrence, and the substitution of phlebotomy for iron chelation showed only equivalent efficacy in iron removal. Chronic transfusion and iron chelation is the appropriate management for patients at high risk for primary and secondary stroke. Blood transfusions significantly reduced the risk of recurrent stroke in children with stroke or high risk of stroke with HbSS. This is superior to hydroxyurea and ceasing transfusion after a fixed period does not prolong the protective effect.</p>	
Ware 1999	USA	To investigate daily hydroxyurea as an alternative to transfusion in prevention of stroke recurrence in SCD in children.	Cohort	<p>16 children with SCD and AIS.</p> <p>Age: 7.1 years (mean at first stroke), S.D. 4.4 years.</p> <p>Gender: 11 male, 5 female.</p> <p>Ethnicity: not stated</p>	NA	-	<p>1.) 6 children had minor painful events</p> <p>2.) 3 had new neurological events consistent with recurrent stroke,</p> <p>3.) Stroke recurrence rate 19%</p> <p>4.) No haemorrhagic event reported</p> <p>5.) All new neurological events 3-4m after discontinuing transfusion and before maximal benefit of HU could be obtained (dose)</p> <p>6.) Hydroxyurea therapy: mean haemoglobin concentration of 9.4 +/- 1.3g/dL (median 9.3 g/dL). Mean</p>	Low

							<p>corpuscular volume 112 +/- 9fL (median 110 fL). Mean %HbF is 20.6% +/- 8.0% (median 21.7%), mean %F cells 79.3% +/- 14.7% (median 85.7%).</p> <p>Phlebotomy regimen: 14 children had phlebotomy, initial median ferritin value = 2630 ng/mL which fell to 424 ng/mL, comparison of initial and latest serum ferritin showed significant reduction in response to phlebotomy , p=0.0015 by Wilcoxon Signed Rank Test.</p>	
Ware 2004	USA	To describe the clinical outcome and long-term follow-up for our entire cohort of paediatric patients with SCA receiving hydroxyurea therapy for prevention of secondary stroke.	Cohort	<p>35 children with SCD.</p> <p>Age: 11.9 years (mean), S.D. 4 years.</p> <p>Gender: 23 male, 12 female.</p> <p>Ethnicity: African American.</p>	NA	Unclear	<p>Children received hydroxyurea for 42 ± 30 months (range, 3-104 months).</p> <p>Hydroxyurea (26.7 ± 4.8 mg/kg per day) led to mild neutropenia (3.9 ± 2.3 3 109/L) with significant increases in haemoglobin concentration, mean corpuscular volume, and foetal haemoglobin. Stroke recurrence rate was 5.7 events per 100 patient-years, but children receiving overlapping hydroxyurea therapy had only 3.6 events per 100 patient-years. For 26 children with &gt;6 months of phlebotomy, 14,311 ± 12,459 mL blood (315 ± 214 mL/kg) was removed, with serum ferritin decreasing from a median of 2722 to 298 ng/mL.</p> <p>Among patients completing phlebotomy, liver biopsy documented normal histology and no excess iron deposition.</p> <p>Overlap between commencing hydroxyurea and discontinuing transfusions most effective in preventing stroke</p>	Low
Ware 2012	USA	To assess the efficacy of HU and phlebotomy vs	Multicentre RCT	134 children randomised into HU	66 children formed the	6 months	Stroke rate higher in the HU/phlebotomy arm 7/67 vs 0/66 but this was within the	Moderate

		transfusion with iron chelation for children with HbSS and stroke		and phlebotomy vs transfusion with iron chelation. Age: 13 years (mean), S.D. 4 years. Gender: 72 male, 62 female. Ethnicity: not stated.	comparison group. Age: 13.3 years (mean), S.D. 3.8 years. Gender: 31 male, 35 female. Ethnicity: not stated.		study's non-inferiority margin and was below the predicted 12% rate. The study was stopped because there was no significant difference in the arms with regards liver iron concentration. I.e. the HU/phlebotomy arm was not protective from this point of view 16.6 mg/g in the transfusion arm vs 15.7 mg/g in the hydroxyurea arm.	
Walters 2010	USA	To determine if children were protected from complications of SCD after successful bone marrow transplant	Prospective cohort	57 children with SCD, 29 had stroke. Age: <16 years. Gender: 33 male, 22 female (survivors only). Ethnicity: not stated.	NA	3.2 years (median MRI studies)	55 patients survived bone marrow transplant, 50 survived free of SCD. 4 patients died of transplant complications, 5 experienced graft rejection with recurrent SCD. Cumulative recurrence of SCD was 9% over 6.5 years. 8 children developed acute or chronic graft versus host disease, 3 died of it, it resolved in 5. 29 of the transplant patients had a stroke or other serious CNS that indicated transplant, 1 died. 25 patients with stroke who received a transplant had no subsequent stroke events. Any who experienced graft rejection were not protected from stroke. Lesions stabilised or evolved to a smaller size in 26 patients. Authors conclude that children who were treated by HLA-identical BMT have durable engraftment of donor cells and do not experience painful or other clinical events related to SCD. Findings strongly suggest that most individuals are also protected from subclinical progression of end-organ	Moderate

							pulmonary and CNS dysfunction that is associated with vaso-occlusion or other sickle-related pathophysiology.	
DeBaun 2014	US, Canada, France, UK	To establish with a transfusion programme prevents silent cerebral infarcts in children with HbSS.	Randomised single blind trial.	196 children with SCD undergoing transfusion. Age: 5 to 15 years. Gender: 54% male, 46% female. Ethnicity: 181 Black, 2 White, 13 Other.	97 children with SCD in the observation group. Age: 5 to 15 years. Gender: 60% male, 40% female. Ethnicity: 90 Black, 7 other.	3 years (median)	Incidence of silent stroke in the transfusion arm 2:100 person years and in supportive arm 4.8 per 100 person years. P=0.04 Relative risk reduction was 58%. Adding the TIA incidence to the silent stroke the results were 2 and 5.6 per 100 person years for transfusion and observation groups on entry scan. In the transfusion group, 6 of 99 children (6%) had an end-point event (1 had a stroke, and 5 had new or enlarged silent cerebral infarcts). In the observation group, 14 of 97 children (14%) had an end-point event (7 had strokes, and 7 had new or enlarged silent cerebral infarcts). The incidence of the primary end point in the transfusion and observation groups was 2.0 and 4.8 events, respectively, per 100 years at risk, corresponding to an incidence rate ratio of 0.41 (95% confidence interval, 0.12 to 0.99; P = 0.04).	High

In children with acute/chronic AIS what are the indications for referral to neurosurgery/interventional neuroradiology? What is the safety and efficacy of surgical interventions to treat acute AIS and prevent recurrence?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Bodey 2014	UK	To describe the authors' experience of mechanical thrombectomy in children in single centre.	Case series	4 children with AIS. Age: 5 to 15 years. Gender: 4 male, 0 female.	NA	-	Modified Rankin Scale 3, 2, 0 and 0 (no disability to moderate disability) in the 4 children at 6 months 3 were basilar occlusions, two of which presented with	Low

				Ethnicity: 3 Caucasian, 1 Asian.			established bilateral pontine infarcts on MRI.	
De Oliveira 2009	Brazil	To investigate the role of multiple cranial burr hole (MCBH) operations in the prevention of cerebral ischemic attacks in children with moyamoya.	Case series	7 children with moyamoya. Age: 8.4 years (mean), range 2 to 15 years. Gender: 2 male, 5 female. Ethnicity: not stated.	NA	4.5 years	Patients had no recurrence of ischemic attacks postoperatively. Neoangiogenesis was observed in both hemispheres. One patient developed a persistent subdural collection after surgery, requiring placement of a subdural-peritoneal shunt. Postoperative Barthel Index was significantly improved (P = 0.02).	Low
Ellis 2012	USA	To summarize the reported literature on the use of endovascular thrombolytic therapies in children with AIS and to address the potential role of endovascular techniques in the management of AIS in children.	Literature review	34 children with AIS. Age: 10.2 years (mean), range 2 to 18 years. Gender: 18 male, 16 female. Ethnicity: not stated.	NA	-	Mean time from symptom onset to endovascular therapy was 14.0 hours (range, 2–72). 1 patient underwent treatment with IV tPA prior to endovascular therapy. Endovascular therapies included IA thrombolysis alone (n=23), IA thrombolysis mechanical thrombolysis (n= 9), and mechanical thrombolysis alone (n=2). 1 patient underwent definitive treatment of primary vessel pathology using endovascular stent placement. Recanalization was complete in 12/34 cases (35.2%), incomplete in 13/34 cases (38.2%), and absent in 3/34 cases (8.8%); recanalization status was not reported in 6/34 cases (17.6%). Complications occurred in a total of 10/34 cases (29.4%). Postprocedural HS occurred in 8/34 patients (23.5%), although only 1 of these hemorrhages was symptomatic (2.9% of all cases). Calculated partial or complete recanalization rate of 74% and a complication rate of 29%.	Low

Funaki 2014	Japan	To examine the incidence of late cerebrovascular events after direct bypass for paediatric moyamoya disease.	Case series	58 children with moyamoya. Age: 6.4 years (mean), range 0 to 15 years. Gender: male:female ratio 1:1.4. Ethnicity: Japanese.	NA	986.6 person years	7.1% followed patients experienced at least one late cerebrovascular event during observation period. The mean interval between the initial surgery and the late cerebrovascular event was 13.0 years. One experienced an AIS after a head injury at 8 years of age. Three experienced HS at a mean age of 26 years (range, 24–29), an average of 16.8 years (range, 13.9–20.9) after surgery. One of the patients experienced a second HS, which resulted in a fatal outcome. In all patients with late-onset HS, the bypasses were still patent at the time of the HS. The incidence of overall late cerebrovascular events was 4/986.6 or 0.41 % per year (95 % CI, 0.15–1.08). The incidences of late AIS and HS events were 1/1004.7 or 0.10 % per year (95 % CI, 0.01–0.71) and 3/995.4 or 0.30 % per year (95 % CI, 0.10–0.93), respectively. The 10-year, 20-year, and 30-year cumulative incidences of late cerebrovascular events were 1.8 %, 7.3 %, and 13.1 %, respectively Conclusions: Despite the efficacy of surgical revascularization, paediatric patients remain at risk of future cerebrovascular events, especially HS, after reaching adulthood and thus require careful long-term follow-up.	Low
Golby 1999	USA	To present a single centre experience of direct anastomosis techniques in moyamoya.	Case series	12 children with moyamoya. Age: 5 to 17 years. Gender: 7 male, 5 female.	NA	-	Neurological condition stable or improved in all 12 patients after surgery. No new strokes clinically and no new ischaemic lesions seen on MRI. All grafts evaluated angiographically (in 10 patients) were patent. Post op CBF studies showed	Low

				Ethnicity: 2 Japanese, 2 Asian, 1 Indian, 7 European.			significantly improved blood flow (54.4 versus 42.5 ml /100g/min; $p = 0.017$ , $n=4$ ) and haemodynamic reserve compared with preoperative studies.	
Hankinson 2008	USA	To examine whether pial synangiosis reliably and durably protected children with sickle cell anaemia and moyamoya against cerebrovascular complication.	Case series	12 children with SCD and moyamoya. Age: 12.3 years (median), range 6.8 to 19.4 years. Gender: 4 male, 8 female. Ethnicity: 7 African American, 5 Hispanic.	NA	46.8 months (mean)	1. During the follow-up period, 2 patients (16.7%) suffered cerebrovascular events. One patient, who was stroke-free preoperatively, suffered a CVA 3 weeks after the procedure. The other patient suffered a single left lower-extremity TIA 18 months following right-sided EDAS. She returned to her neurological baseline condition and remains stable 53 months postoperatively. Seven patients underwent follow-up angiography or MR angiography, and evidence of revascularization was noted in all cases. At this time, no patient has developed progressive disease requiring a contralateral procedure after unilateral EDAS. 2. No immediate perioperative complications Conclusions: The EDAS procedure is a safe and effective treatment option in patients with SCA who develop moyamoya syndrome.	Low
Lee 2012	South Korea	To describe the functional and clinical outcome after decompressive craniectomy to control refractory high ICP due to non-traumatic acute stroke in paediatric patient.	Case series	5 children with AIS. Age: 34.6 months (mean), range 17 to 80 months. Gender: 3 male, 2 female. Ethnicity: not stated.	NA	-	The ICP of all patients were dropped to normal range within one and half days after operation. There were no surgical complications, even after cranioplasty. One AIS patient had a ventriculoperitoneal shunt operation because of post-stroke hydrocephalus. Based on regular follow up GOS scores, 5 patients had shown satisfactory recoveries:	Moderate

							4 good (GOS score of 5), and 1 moderate disability (GOS score of 4). There was no patient with severe disability or death. PCPCS scores: 4 patients received scores of 2, and only one patient scored 3. Authors conclude that decompressive hemicraniectomy can be lifesaving and can be safely performed in toddlers and pre-school children.	
Montgomery 2012	Australia	To describe four children with posterior circulation arterial ischemic stroke who required decompressive craniectomy.	Case series	4 children with AIS. Age: 6 to 10 years. Gender: 3 male, 1 female. Ethnicity: not stated.	NA	-	<p>1. No children died.</p> <p>2. Paediatric Stoke Outcome Measure 0.5, 0.5, 2, 3 in the 4 patients.</p> <p>3. Three manifested large, cerebellar hemispheric infarcts, and one manifested a large, temporo- occipital posterior cerebral artery infarct. Deterioration occurred within 72 hours of stroke onset. Two patients demonstrated minimal functional deficits at follow-up, and two demonstrated moderate deficits with functional limitations.</p> <p>Conclusions: Because decompressive craniectomy can be lifesaving in children with severe posterior circulation arterial ischemic stroke, early neurosurgical referral should be considered.</p>	Low
Ng 2012	UK	To describe experience of Surgical Revascularisation (SR) in children with moyamoya and subsequent outcome in a single centre in the UK.	Case series	73 children with moyamoya. Age: 4.7 years (mean), range 0.6 to 14.5 years. Gender: 31 male 42 female. Ethnicity: 64% White, 20% Black,	NA	34 months (median)	<p>134 SR were performed, 60 bilateral (120 hemispheres), 11 unilateral, 3 additional procedures.</p> <p>No peri-surgical mortality.</p> <p>In first 48 hours 7 children had TIA lateralising to the revascularised hemisphere, 5 were imaged and none had developed new areas of infarction.</p>	Moderate

				16% Asian, 1 East Asian.			<p>1 child who was anticoagulated with Warfarin had an extensive ICH 5 days after surgery.</p> <p>None of the children had further AIS in the revascularised hemisphere within 30 days of surgery.</p> <p>2 children with SCD had spontaneous ICH 1.5 and 11 months after surgery.</p> <p>5 children had clinical or radiological recurrence with clinical AIS in 3 and increasing TIAs in 2.</p> <p>AIS recurred in 2 out of 49 (4%) direct SR hemispheres versus 1 out of 82 (1.2%) indirect surgical revascularised hemispheres (p=0.289).</p> <p>Increasing TIAs occurred after 1 direct and 1 indirect surgical procedure respectively.</p> <p>Following surgery 79.2% had resolved or improved TIA symptoms, in the remaining 9, TIA symptoms were unchanged in 5, increased without infarction in 2, and increased with recurrent AIS.</p>	
Smith 2011	USA, Canada, UK	To evaluate the frequency of MMCAI and the use of decompressive craniectomy in children.	Case series	<p>10 children with malignant MCA infarction.</p> <p>Age: 9 years 10 months (median), range 10 months to 14 years.</p> <p>Gender: 8 male, 2 female/</p> <p>Ethnicity: not stated.</p>	NA	-	<p>Treatment and outcomes: Three patients who did not undergo decompression, all of whom had monitoring of intracranial pressure, developed intractable intracranial hypertension, and died.</p> <p>Seven patients underwent decompressive craniectomy (median time 54 hours after symptom onset, range 18-291H) and survived, with rapid improvement in their level of consciousness postoperatively.</p> <p>All seven survivors now walk independently with mild to moderate</p>	Moderate

							residual hemiparesis and speak fluently, even though four had left-sided infarcts.	
Tatum 2013	USA	To describe experience of mechanical thrombectomy in children.	Case series	4 children with large vessel occlusion. Age: 13 years (median), range 4 to 17 years. Gender: not stated. Ethnicity: not stated.	NA	90 days	Mean change in PaedNHSS: -3.5 Mean mRS at 90 days: 1 TICI score of 3 in most vessels. Long time between onset of symptoms and thrombectomy. One patient had a mRS 3 outcome; with little change in NHSS score pre and post. Significant infarct on DWI pre procedure. No complications attributable to the procedures.	Low
Scott 2004	USA	To report on the long-term outcomes of a neurosurgical revascularisation technique (pial synangiosis) in children with moyamoya	Case series	143 children with moyamoya. Age: 7.1 years (mean), range 0.5 to 21 years. Gender: 54 male, 89 female. Ethnicity: not stated	NA	5.1 years	Short term follow up: Eleven strokes (7.7% per patient) and 3 severe TIAs occurred within 30 days of surgery. Post-operative stroke occurred in patients with neurological instability although not all. 3 patients suffered strokes within 30 days postoperatively for no obvious reason and in an additional patient an acute subdural hematoma developed after a fall 20 days postoperatively. Chronic subdural hematomas developed in 3 patients 45-72 days postoperatively two of which required evacuation via burr hole. Long term follow up: In patients followed up for more than 1 year there were the following late onset neurological complications: stroke (4), severe reversible ischemic neurological deficit (1), severe persisting TIAs (2). Other long term complications were debilitating headaches with intermittent visual loss and extremity weakness (7 years post operation), intermittent leg weakness and aphasia	Moderate

							<p>aggravated by hyperventilation (2 years post operation), TIAs similar to those at presentation (1), lesser intensity and severity TIAs (6). Headaches of varying intensity frequently accompanied by typical migraine symptoms.</p> <p>In patients whom stroke alone was the primary symptom at presentation were evaluated long term (&gt;5years) and only 2 strokes developed in this group during long term follow-up period.</p> <p>Long term functional results: Were related to functional status at time of surgery.</p> <p>2 patients died: 21 year old woman died of a radiation induced invasive meningioma 5 years post-surgery, 12 year old boy died of recurrent haemorrhage secondary to a deep basal ganglia/third ventricular aneurysm on a moyamoya collateral vessel - this case must be considered a surgery related failure because his initial 1 year follow up angio showed only modest new operation induced collateral vessels. There were no deaths due to ischaemic stroke.</p> <p>1 year post-operative cerebral angiography and MR imaging/angiography in 102 patients showed 65% Grade A collateral circulation, 25% Grade B and 10% Grade C according to the grading method of Matsushima et al. 80% had at least 1 hemisphere demonstrating Grade A circulation. Visible collateral vessels to the brain at additional burr hole sites could be identified in 57% but only 28% of these vessels could be termed significant (filling</p>	
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							more than a small focal area at burr hole site).	
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## Chapter 7: Haemorrhagic Stroke

Risk factors for HS and HS recurrence								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Suh 2001	UK and France	To examine the aetiologies of ICH in children under 2 with neurovascular diseases.	Case series	165 children with vascular disease, 16 with HS. Age: < 2years. Gender: 7 male, 9–female. Ethnicity: not stated	NA	-	2 children had a HS resulting from aneurysm, 3 resulting from arteriovenous fistula, 5 resulting from arteriovenous malformation, 4 resulting from dural sinus malformation, 1 resulting from vascular malformation and 1 resulting from vein of galen aneurysmal malformation.	Low
Fullerton 2003	USA	To investigate the demographics of childhood stroke	Case series, database analysis	1111 children with HS. Age: 1 month to 19 years. Gender: 51% male, 49% female. Ethnicity: White, Black, Hispanic, Asian, Other.	NA	-	Risk factors: males vs females intracerebral haemorrhage RR 1.34 (95% CI 1.16-1.56) p=0.0001, subarachnoid haemorrhage RR 1.24 (95% CI 1.00-1.53) p=0.047 ICH Black vs White RR1.66 (95% CI 1.23-2.13) p=0.0001, Hispanic vs White RR 0.92 (95% CI 0.71-1.20) p=0.54, Asian vs White RR 1.05 (95% CI 0.81-1.37) p=0.66 SAH Black vs White RR 1.59 (95% CI 1.06-2.33) p=0.02, Hispanic vs White RR 0.92 (95% CI 0.71-1.20) p=0.54, Asian vs White RR 1.76 (95% CI 0.47-1.18) p=0.21 ICH 1-4y OR 1.41 (95% CI 0.69-2.87), 5-9y OR 1.37 (95% CI 0.69-2.72), 10-14y OR 1.72 (95% CI 0.89-3.32), 15-19y OR 2.11 (1.16-3.84) multivariate logistic regression. SAH 1-4y OR 1.63 (95% CI 0.50-5.30), 5-9y OR 1.04 (95% CI 0.32-3.37), 10-14y OR 0.58 (95% CI 0.18-1.92), 15-19y OR 0.49 (95% CI 0.16-1.50) multivariate logistic regression	Moderate
Elalfy 2010	Egypt	To discuss ICH in children with immune thrombocytopenic purpura,	Case series	10 children with HS. Age: 7.5 years (median).	NA	-	10 out of 1840 children with ITP had ICH (0.54%)	Low

		incidence, risk factors, management and outcome		Gender: 6 male, 4 female. Ethnicity: Egyptian.				
Nikoubashman 2015	France	To evaluate whether different cerebral cavernous malformation types are associated with different haemorrhage rates and provide a simple morphologic classification that reflects haemorrhage rates best.	Case series	70 children with cavernous malformations. Age: 8.9 years (mean), S.D. 4.5 years. Gender: 48 male, 22 female. Ethnicity: not stated	NA	-	Lifetime haemorrhage risk for all lesions was 4.5% per lesion year Annual haemorrhage rates based on the Zabramski Classification: CCM Type I 29.8%, type II 20.1%, type III 3.4%, type IV 1.3%, and for new proposed type V 23.1% Zabramski type I and II cavernous malformations had a significantly higher haemorrhage rate than type III and IV lesions. The presence of acute or subacute blood-degradation products was the strongest indicator for an increased haemorrhage risk (P=0.036, Cox regression).	Moderate
Pistracher 2012	Austria	To review the literature for primary angiitis of the central nervous system in childhood (cPACNS) presenting with haemorrhage	Systematic review	110 children with cPACNS. Age: 9.5 years (median), range 1 to 16 years. Gender: 55 male, 55 female. Ethnicity: not stated	NA	-	Out of 110 cases of cPACNS 7 had ICH (6.4%)	Low
So 2013	Hong Kong	To describe the incidence of ICH in children with immune/idiopathic thrombocytopenic purpura (ITP)	Case series	276 children with ITP, 8 with HS. Age: (HS only) 10 years (median), range 0.9 to 19 years. Gender: 2 male, 6 female. Ethnicity: Chinese	NA	-	Out of 276 children with ITP 8 (2.9%) children had 9 episodes of ICH.	Low
Proust 2001	France	To evaluate the causes of favourable and	Case series	22 children with aneurysms.	NA	-	Out of 22 children with aneurysms 21 had SAH (95.4%)	Low

		unfavourable treatment outcomes in children with intracranial aneurysms		Age: 13 years (mean) S.D. 2 years. Gender: 16 male, 6 female. Ethnicity: not stated				
Lv 2009	China	To report on patients with aneurysms treated using endovascular techniques	Case series	25 children with aneurysms. Age: 11.4 years (mean), range 4 to 17 years. Gender: 20 male, 5 female. Ethnicity: not stated	NA	-	Out of 25 patients with aneurysm 11 (44%) had an SAH	Low
Saraf 2012	India	To report on patients with aneurysms treated using endovascular techniques	Case series	23 children with aneurysms. Age: 13 years (mean), range: 2 months to 18 years. Gender: 17 male, 6 female. Ethnicity: not stated	NA	-	Out of 23 patients with aneurysm 14 (61%) had a HS, 13 (57%) had SAH and 1 (4%) had intracerebral haemorrhage	High
Sharma 2007	India	To review the aetiology, clinical characteristics, aneurysm morphology and surgical outcome in children with intracranial aneurysms	Case series	55 children with aneurysms. Age: 13.3 years (mean), range 7 months to 18 years. Gender: 38 male, 17 female. Ethnicity: not stated	NA	-	Out of 55 patients with aneurysm 43 (78.2%) presented with SAH.	High
Sheth 2014	USA	To evaluate the influence of angiographic features of AVMs on the rate of obliteration of gamma knife stereotactic radiosurgery	Case series	42 children with AVMs. Age: 12 years (mean) S.D. 4 years. Gender: 24 male, 18 female.	NA	-	Out of 42 patients with AVM, 26 (62%) had a haemorrhage	High

				Ethnicity: not stated				
Song 2011	China	To describe the clinical features and microsurgical treatment of children with cerebral cavernous malformations.	Case series	85 children with CM. Age: 13.1 years (mean), range 6 months – 17.9 years. Gender: 53 male, 32 female. Ethnicity: not stated	NA	4.2 years (mean)	Out of 85 patients with CCM 38 (44.7%) had a haemorrhage	Moderate
Abla 2010	USA	To review the surgical outcomes of children with cavernous malformations	Case series	40 children with CM. Age: 12.3 (mean), range 0.8 to 18.9 years. Gender: 19 male, 21 female. Ethnicity: 33 White, 6 Hispanic, 1 Asian.	NA	-	Out of 40 patients with CCM, 39 (97.5%) had a history of haemorrhage and 21 (53%) had had a haemorrhage within 6 weeks of surgery. During the observation period before surgery there was an annual re-haemorrhage rate of 44% per patient year.	Low
Anderson 2012	USA	To examine the incidence and behaviour of AVM associated aneurysms in children with AVMs.	Case series	77 children with AVM associated aneurysms. Age: 13.4 years (mean). Gender: 38 male, 39 female. Ethnicity: not stated	NA	-	48 out of 77 (62%) of children presented with haemorrhage. Of 11 children with AVM associated aneurysm in an arterial location, 10 (91%) presented with haemorrhage. There was a significantly higher initial haemorrhage rate with arterial aneurysms than those in children with isolated AVMs (35 of 55 (64%); $p=0.023$ ) or those with aneurysms only in other locations (3 of 11 (27%); $p=0.001$ )	Moderate
Bilginer 2014	Turkey	To examine demographic, clinical, radiological, management and follow-up in children with cavernous malformations	Case series	36 children with CM. Age: 8.7 years (mean) S.D. 5.7 years. Gender: 21 male, 15 female. Ethnicity: not stated	NA	-	Acute or sub-acute haemorrhage was evident in 63.9% of children with CM	Moderate

Bristol 2006	USA	To assess the outcomes of neurosurgery in children with AVMs	Case series	82 children with AVMs. Age: <18 Gender: not stated. Ethnicity: not stated.	NA	-	36 out of 82 (43.9%) children with AVM presented with haemorrhage	Low
Cohen-Gadol 2006	USA	To explore whether radio-surgery based AVM grading predicts chances of successful radiosurgery in children with AVMs.	Case series	38 children with AVMs. Age: 15 (median), range 7 to 18 years. Gender: 14 male, 24 female. Ethnicity: not stated	NA	42 months (median)	Out of 38 children with AVM 20 (53%) presented with haemorrhage.	Low
Aryan 2006	USA	To examine strategies for treating aneurysms in children	Case series	50 children with aneurysms. Age: 10.3 years (mean), range 5 months – 19 years. Gender: not stated. Ethnicity: not stated.	NA	-	Out of 54 aneurysms 35 were ruptured at time of diagnosis (64.8%).	Low
Liang 2011	China	To assess the clinical and radiological characteristics and look at the therapeutic strategies of intracranial aneurysms in adolescents	Case series	16 adolescents with aneurysms. Age: 16.8 years (mean) S.D. 1.18 years. Gender: 10 male, 6 female. Ethnicity: not stated	NA	19.2 months (mean)	Out of 16 patients with aneurysms, 8 (50%) had a SAH.	Low
Paramasivam 2013	USA	To describe children with congenital pial arteriovenous fistulas, focusing on embryological aspects, clinical features, angio-architecture, treatment indications, management options, with	Case series	16 children with congenital pial AVF. Age: <5 years. Gender: 7 male, 9 female. Ethnicity: not stated	NA	-	Out of 16 children with congenital pial AVF, 2 (12.5%) had an ICH.	Low

		emphasis on endovascular management						
Potts 2014	USA	To report on treatment of AVMs with stereotactic radiosurgery focussing on posttreatment complications and functional outcomes	Case series	80 children with AVMs. Age: 12.7 years (mean). Gender: 49 male, 31 female. Ethnicity: not stated.	NA	-	Out of 80 children 45 (56%) presented with haemorrhage.	Moderate
Li 2014 (1)	China	To provide prospective haemorrhage rate, haemorrhage risk and untreated prognosis in children with cerebral cavernous malformations.	Case series	85 children with CM. Age: 12.7 years (mean) S.D. 4 years. Gender: 59 male, 26 female. Ethnicity: not stated	NA	4.7 years (mean)	Out of 85 patients with CCM 67 (78.8%) had a previous haemorrhage.	Moderate
Griffiths 1998	Canada	To investigate early presentation and high mortality rates in children with AVM.	Case series	18 children with AVMs. Age: 10 years 8 months (median), range 11 months to 15 years 6 months. Gender: 6 male, 12 female. Ethnicity: not stated	NA	-	Out of 18 children with AVM, 17 presented with evidence of haemorrhage.	Low
Klinge 1999	Germany, Austria	To evaluate the prevalence and outcome of haemophiliacs, changes in prevalence and neurological outcome of ICH in haemophilia and additional risk factors correlated with adverse neurological outcome.	Case series	744 children with haemophilia, 30 with HS. Age: not stated. Gender: 100% male. Ethnicity: not stated.	NA	-	Out of 744 children with haemophilia, 30 (4%) had an ICH. Of those, 21 (70%) had haemophilia A and 9 (30%) had haemophilia B Prevalence was lower in haemophilia A than B but not significantly (3.5% vs 6.3%).	Moderate
Hetts 2009	USA	To characterise the clinical, imaging, treatment and	Case series	77 children with aneurysms.	NA	-	Out of 77 patients with aneurysms, 25 (32%) presented with SAH.	Moderate

		outcome data in patients diagnosed with intracranial aneurysms.		Age: 12 years (mean) S.D. 5 years. Gender: 37 male, 40 female. Ethnicity: not stated			Haemorrhage twice as likely to result from saccular aneurysm rupture than from fusiform or infectious aneurysms, occurring in >35% of cases.	
Vaid 2008	India	To discuss the epidemiology, clinoradiological profile, outcomes and management issues of children with aneurysms.	Case series	27 children with aneurysms. Age: 13.2 years (mean), S.D. 3.7 years. Gender: 14 male, 13 female. Ethnicity: not stated	NA	18.7 months (mean)	Out of 27 children with aneurysms, 23 presented with SAH (85.2%).	Low
Xia 2009	China	To discuss the clinical presentation, diagnosis, treatment and follow-up of children with cerebral cavernous malformations.	Case series	66 children with CM. Age: 11.6 years (mean), range 15 months – 17.8 years. Gender: 40 male, 26 female. Ethnicity: not stated.	NA	-	Out of 66 children with CM, 13 (20%) presented with HS.	Low
Yen 2010	USA	To analyse the long term imaging and clinical outcomes and complications of children with AVMs treated with gamma knife surgery	Case series	200 children with AVM. Age: 12.7 (mean), range 4 to 18 years. Gender: 98 male, 88 female. Ethnicity: not stated	NA	-	Out of 200 children with AVM, 133 (71.5%) presented with haemorrhage.	High
Lee 2008	South Korea	To describe the micro- and radiosurgical treatment of children with intracranial cavernous malformations	Case series	33 children with CM. Age: 11.1 years (mean), range 1 to 20 years. Gender: 18 male, 15 female. Ethnicity: not stated	NA	-	Out of 33 children with CM, 25 (75.8%) presented with HS.	Low

Levy 2000	USA	To describe the long term outcomes for children with AVM treated with radiosurgery.	Case series	53 children with AVMs. Age: 12 years (median), range 2 to 17 years. Gender: not stated Ethnicity: not stated	NA	36 months (median)	Out of 53 children with AVM, 34 (64%) presented with haemorrhage.	Moderate
Li 2014 (2)	China	To evaluate surgical outcomes of cavernous malformations and identify risk factors associated with post-operative full recovery and rebleeding	Case series	52 children with CM. Age: 12.2 (mean), S.D. 4.5 years. Gender: 37 male, 15 female. Ethnicity: not stated	NA	7.9 years (mean)	Preoperative annual haemorrhage rate was 12.3% (78 haemorrhages/633.0 patient-years, 95% CI 10%–15.1%).	Moderate
Kossorotoff (2014)	France	To report the characteristics of intracranial aneurysm or primary intracranial haemorrhage in a cohort of children with SCD and their relationship with the classic stenotic cerebral vasculopathy, in order to refine the description and give insights into the pathophysiological mechanisms and the treatment strategies.	Case series	251 children with SCD, 7 in the haemorrhage group. Age: (haemorrhage group) 10.5 years. Gender: 3 male, 4 female. Ethnicity: not stated	NA	-	7 out of 251 (2.8%) of the children had either previously had a HS or presented with HS.	Moderate
Liang 2009	China	To describe the clinical and radiological features and the therapeutic outcome and clarify the choice of therapeutic strategies for	Case series	24 children with aneurysms. Age: 8.8 years (mean) S.D. 2.7 years. Gender: 14 male, 10 female.	NA	-	Out of 24 patients with aneurysms. 11 (45.8%) patients had a history of SAH (Fisher grading 2-4).	Low

		paediatric intracranial aneurysms.		Ethnicity: not stated				
Lo 2009	USA	To analyse a national patient survey to determine the frequency of AIS and HS discharge and determine the risk factors.	Case series, database review	3015 children with stroke, 1215 in the sample which equates to 2022 in the national estimate. Age: >30 days to <20 years. Gender: 650 male, 546 female. Ethnicity: White 425, Black 150, Hispanic 234, Asian/Pacific Islander 25, Native American ≤10, Other 64, Missing 319.	NA	-	The odds for males compared with females with HS was 1.50 (95% CI: 1.35-1.68, P<.001) When stratified by age group, the odds for males compared with females aged 15 to 20 was 2.62 (95% CI: 2.23-3.11, P < .001). Co-existing risk factors in children with HS: congenital heart disease 276 (13.6%), AVM 272 (13.5), sepsis 191 (9.4%), arrhythmia 181 (9%), coagulation defect 155 (7.7%), hypertension 124 (6.1%), purpuric disorders 122 (6%), brain tumour 114 (5.6%), meningitis encephalitis 77 (3.8%), leukaemia 59 (2.9%), cardiac arrest 59 (2.9%), head trauma 58 (2.9%), autoimmune 52 (2.6%), acute lymphocytic leukaemia 42 (2.1%), sickle cell disease 31 (1.5%), cocaine 26 (1.3%), aneurysm 22 (1.1%), diabetes 20 (1%), cardiomyopathy 19 (0.9%).	Low
Lo 2008	USA	To determine whether the risk factors for ICH have changed and estimate the residual deficits in survivors.	Case series	85 children with HS. Age: 7 years (median) range 7 days to 17 years. Gender: 54 male, 31 female. Ethnicity: White 67, African American 10, South East Asian 1, Asian Indian 1, Other 1, Unknown 5.	NA	-	Risk factors present in children with ICH: brain tumour 13 (15%), congenital heart disease 14 (16%), AVM 11 (13%), cavernous malformation 7 (8%), venous angioma 2 (2%), aneurysm 2 (2%), moyamoya 2 (2%), herpes simplex virus encephalitis 1 (1%), sepsis (thrombocytopenia) 3 (4%), endocarditis 1 (1%), leukaemia or lymphoma 6 (7%), coagulation factor deficiencies 4 (5%), acute renal failure, aplastic anaemia or	Moderate

							LCHAD genetic 1 (1%), unidentified 13 (15%).	
Al-Jarallah 2000	USA	To analyse the clinical features, risk factors, and outcomes of children with ICH.	Case series	68 children with HS. Age: 7.1 years (mean) range 3 months – 18 years. Gender: 43 male, 25 female. Ethnicity: not stated.	NA	-	Risk factors: vascular malformation/fistula (23, 33.8%), cavernous malformation (2, 2.9%), aneurysm (4, 5.9%), brain tumour (9, 13.2%), sickle cell disease (3, 4.4%), thrombocytopenia (8, 11.8%), bone marrow transplant (1, 1.5%), Factor VIII deficiency (3, 4.4%), Factor XIII deficiency (1, 1.5%), liver failure (2, 2.9%), warfarin therapy (1, 1.5%), protein C deficiency (1, 1.5%), protein S deficiency (1, 1.5%), vitamin K deficiency (1, 1.5%), haemorrhagic infarct (6, 8.8%), spontaneous dissection (2, 2.9%), adrenocorticotrophic hormone (1, 1.5%), HIV (1, 1.5%), lupus (1, 1.5%), herpes encephalitis (1, 1.5%), no risk factors found (7, 10.3%).	Moderate
Xia 2008	China	To describe the characteristics of cerebrovascular disease in children.	Case series	204 children with HS. Age: 12.7 (mean boys), 13.1 (mean girls). Gender: 134 male, 70 female. Ethnicity: not stated.	NA	-	Risk factors present: AVM = 86, 42.2%, cavernomas = 33, 16.2%, aneurysms = 18, 8.8%, moyamoya = 12, 5.9%, complex vascular malformations (aneurysm + AVM) = 4, 2%, arteriovenous fistula = 2, 1%, venous malformations = 2, 1%, meningiomas = 2, 1%, telangiectasia 1, 0.5%, dural arteriovenous fistula = 1, 0.5%, unknown = 43, 21.1%.	Moderate
Kumar 2009	India	To determine the causes, course and outcome of HS	Case series	50 children with HS. Age: 13.8 years (mean) range 2 months to 17 years. Gender: 31 male, 19 female. Ethnicity: Indian.	NA	-	Risk factors: AVM 44%, aneurysm 34%, moyamoya 6%, tumour 4%, hematologic disorder 4%, cavernoma 4%, unknown 4%.	Low

Gumer 2014	Conducted in USA, international studies.	To examine the aetiologies of stroke and develop an initial diagnostic evaluation for a paediatric patient presenting in an emergency department	Systematic review	1457 children, 195 with HS. Age: 8.2 years (mean published age at time of illness). Gender: male: female ratio 1.3:1. Ethnicity: mainly non-Hispanic White followed by Afro-Caribbean/Black, Hispanic and Asian (total numbers not given).	NA	-	In patients with HS: 106 (54%) had vascular malformations of which 58 (30%) AVM, 23 (12%) cavernous haemangioma, 20 (10%) aneurysm, 4 (2%) SAH, 1 (0.5%) venous malformation. 18 (9%) had medical aetiologies, 5 (2.5%) had brain tumours, 2 (1%) had trauma/dissection, 64 (33%) were undetermined.	Low
Adil 2015	USA	To assess factors associated with mortality and targets for intervention.	Case series	1172 children with HS. Age: 1 to 18 years. (children who died) Gender: 59.1% male, 40.9% female Ethnicity: 34.8% White, 19.2% African American, 39.6% Hispanic, 6.4% other. (Children who survived) Gender: 57.1% male, 42.9% female. Ethnicity: 50.7% White, 15.2% African American, 21.5% Hispanic, 12.6% other.	NA	-	The most common comorbid conditions included coagulopathy (10.7%), brain arteriovenous malformations (17.6%), hypertension (11.4%), seizure (4.8%), deficiency anaemia (4.1%), renal failure (2.7%), and congenital heart disease (1.9%).	Moderate

de Ribaupierre 2008	Switzerland	To analyse the signs and symptoms of HS in children and their treatment.	Case series	22 children with HS. Age: 10.8 years (mean), range 2 months to 18 years. Gender: 9 male, 13 female. Ethnicity: not stated.	NA	35 months (mean)	Recurrence: 2 children who both had an AVM had a recurrent stroke.	Moderate
Proust 2001	France	To evaluate the causes of favourable and unfavourable treatment outcomes in children with intracranial aneurysms	Case series	22 children with aneurysms. Age: 13 years (mean) S.D. 2 years. Gender: 16 male, 6 female. Ethnicity: not stated	NA	-	Recurrence occurred in 11 children (52.4%) with aneurysms.	Low
Li 2014 (2)	China	To evaluate surgical outcomes of cavernous malformations and identify risk factors associated with post-operative full recovery and rebleeding	Case series	52 children with CM. Age: 12.2 years (mean) S.D. 4.5 years. Gender: 37 male, 15 female. Ethnicity: not stated	NA	8.4 years (mean)	Twenty-three patients (44.2%) with CM experienced a total of 26 re-haemorrhages during a cumulative symptom duration of 80.1 patient-years, and the calculated preoperative rebleeding rate was 32.5% per patient-year (26 haemorrhages/80.1 patient-years). Twenty-four patients were treated conservatively, all except 1 experienced prior symptomatic haemorrhage During a mean follow-up of 8.4 years (range 2.5–16.8 years), 8 haemorrhages occurred in 8 patients.	Moderate
Giroud 1997	France	To describe the clinical and etiological features of stroke	Case series	54 children, 23 with HS. Age: 9.5 years (mean). Gender: 12 male, 11 female. Ethnicity: White 22, Korean 1.	NA	-	Recurrent haemorrhage occurred in 3 cases (13%) with arterial malformations, 4 cases with hemidystonia (17%), and late epilepsy in all the 9 cases.	Low

Investigations to identify underlying risk factors of HS								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Al-Sulaiman (1999)	Saudi Arabia	To report on the clinical features and neuroimaging correlates of stroke in Saudi children seen over a 5-year period.	Case series	31 children with stroke, 28 AIS, 2 ICH, 1 SAH. Age: 26.2 months (mean) range 3 months – 11 years. Gender: 18 male, 13 female. Ethnicity: Saudi.	NA	-	Diagnosed by CT or MRI. Baseline investigations included CBC; Hb electrophoresis; serum fibrinogen level; PT; PPT; serum immunoglobulins; liver function tests; random and fasting blood sugar; serum electrolytes; blood urea nitrogen; and serum mg, ca, ammonia, creat, creatine kinase, lactate, and pyruvate levels. Serologic tests, immunologic profile, muscle biopsy, skin biopsy for fibroblast characterization, and CSF evaluation of pyruvate and lactic acid levels were also performed when indicated. Other tests when indicated.	Low
Cardo (1999)	Spain	To study the association of hyperhomocysteinaemia with stroke in children.	Case-control	68 children with AIS and HS. Age: 2 months – 18 years. Gender: not stated Ethnicity: not stated	100 children with epilepsy and no history of stroke. Age: 2 months to 18 years. Gender: not stated Ethnicity: not stated	-	Blood was collected between 2 weeks and 1 month after the stroke episode. Hyperhomocysteinaemia was defined as a homocysteine concentration above the 95th percentile for the reference values. Significant differences were found in total homocysteine values of children with stroke and those taking anti-epileptic drugs compared with the reference values for similar ages, except for the adolescent group.	Low
Saraf (2012)	India	To report on patients with aneurysms treated using endovascular techniques	Case series	23 children with aneurysms.	NA	-	MRI and angiographic findings were used to classify the aneurysms into saccular, dissecting, giant partially thrombosed, and infectious lesions.	High

				<p>Age: 13 years (mean), range: 2 months to 18 years.</p> <p>Gender: 17 male, 6 female.</p> <p>Ethnicity: not stated</p>			<p>Diagnosis of saccular aneurysm made on the basis of classic locations at bifurcations or the lesion configuration. Some patients with saccular aneurysms had associated coarctation of the aorta or visceral arteriovenous fistulas.</p> <p>Dissecting aneurysms were diagnosed by the “bead on a string” angiographic appearance of pre- and postaneurysmal narrowing with a fusiform shape in between.</p> <p>Giant partially thrombosed aneurysms were identified by the appearance of thrombus around the aneurysm on MRI and angiographic findings of fusiform appearance with contrast stasis, reservoir phenomenon, and displacement of arteries proximal and distal to the aneurysm.</p> <p>Patients with documented sepsis, meningitis, or infective endocarditis were considered to have infectious aneurysms. These lesions may show a fusiform dissecting appearance on angiograms.</p>	
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Role, modality and timing of imaging in assessment and monitoring HS								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Koelfen 1995	Germany	Explore the use of MRA in children	Case series	<p>140 children referred for MRA, 22 with AIS, 18 with HS.</p> <p>Age: 3 weeks to 18 years.</p> <p>Gender: 71 male, 69 female.</p>	NA	-	<p>MRA could visualised the following arteries at all ages: internal carotid (ICA, ACA, MCA, PCA, VA, and BA).</p> <p>Primary branches of posterior circulation (PICA, AICA, SCA) and the anterior and posterior communicating arteries were identified inconsistently but the number of</p>	High

				Ethnicity: not stated.			<p>arteries visualised increased up to the age of 6y</p> <p>Secondary branches of ACA, MCA and PCA could be seen up to the high cortical segments in some older children.</p> <p>The lenticulostriatae, thalamostriatae, and choroid artery were never visualized.</p> <p>MRA revealed anatomic variations in 21 patients (15%).</p> <p>In 22 of 32 children with malformations of the brain abnormal intracranial vasculature was seen.</p> <p>18 children with known or suspected vascular malformations were studied by MRA and were positive for intracerebral haemorrhage in 9 (50%).</p> <p>Delineation of all vascular territories wasn't possible due to limited size of imaging volume used.</p> <p>Complete definition difficult in complex AVM with multiple feeding arteries arising from different vascular distributions</p> <p>After haemorrhages, time of flight MRA was unreliable in the first examination because the high signal from the acute hematoma could not always be differentiated precisely from the high signal of the moving blood.</p> <p>In 6 children neither DSA nor MRA was able to demonstrate the cause of intracerebral haemorrhage seen on conventional MRI.</p> <p>In 3 children with AVMs, MRA was used after the operation/embolization for</p>	
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							controlling the results. No discrepancy was found between MRA and DSA findings.	
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What is the safety and efficacy of coagulation factor replacement for the acute treatment of children with HS?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Elalfy 2010	Egypt	To discuss ICH in children with immune thrombocytopenic purpura, incidence, risk factors, management and outcome	Case series	10 children with HS. Age: 7.5 years (median). Gender: 6 male, 4 female. Ethnicity: Egyptian.	NA	-	Seven children were on treatment prior to or at the time of occurrence of ICH and all were treated by pharmacotherapy - all received intravenous immunoglobulin G (10), as well as methylprednisolone (5), intravenous anti-D (5), platelet transfusion (3).  8 improved on therapy - 5 recovered completely and 3 had residual seizures.  Two children died shortly afterwards due to late referral to a specialized center.	Low
Aydinli 1998	Turkey	To describe the presenting clinical and laboratory features and outcome of late new-born haemorrhagic disease	Retrospective case series	11 children with HS. Age: 56 days (mean), range 30 to 119 days. Gender: 8 male, 3 female. Ethnicity: not stated.	NA	21.1 months (mean)	Bleeding tendency was treated in all patients with 1-2 mg vitamin K2 intravenously. Fresh frozen plasma was given to seven and packed red blood cells to six patients. One infant needed endotracheal intubation with mechanical ventilation.  The PT and PTT were corrected 6-12 hours after administration of vitamin K. An anticonvulsive therapy with phenobarbital or diphenylhydantoin seizures could be controlled with phenobarbital plus diphenylhydantoin. All were prescribed anticonvulsive therapy at discharge.  Dexamethasone and mannitol were administered in seven patients because of the suspicion of	Moderate

							intracranial hyper-tension. In two patients intracerebral haematomas of temporoparietal localization were surgically removed. cetazolamide therapy (30-50 mg/kg/day) was used in four patients during the acute phase. Follow-up: At the end of 1 year 3 children were normal, 8 were still prescribed anticonvulsive therapy, 3 suffered from West's Syndrome. 5 (46%) had cerebral palsy, 5 (46%) were microcephalic, visual disturbances were seen in 4 (36%). No children died.	
Nakar 2010	USA	Examine US experience of use of rFVIIa for treating intra- and extra-cranial haemorrhage in patients with severe congenital haemophilia with inhibitors	Retrospective case series	38 patients with HS. Age: 6.1 years (mean), range 0.1 to 41.3 years. Ethnicity: 10 White, 6 Black, 5 Hispanic White, 2 Hispanic Black, 1 Asian/Pacific Islander, 5 not specified.	NA	-	There were 11 HS 9/11 HS (82%) were treated effectively with rFVIIa. 6 bleeds were controlled within 24 hours and 1 within 72 hours 2 patients required surgery to evacuate haematomas, in both, haemorrhage was controlled with rFVIIa during the perioperative period. No serious adverse events reported with the use of rFVIIa. 1 patient died as a result of the bleeding despite reported control of bleeding. Neurological outcomes not collected.	Low
Heffren 2015	USA	To describe the treatment of cerebral vasospasm in children following multiple aetiologies of SAH. Also report clinical outcomes associated with therapy, including rebleeding episodes, incidence of vasospasm, evidence of	Retrospective electronic medical record review	12 children with HS. Age: 11.8 years (mean), range .5 to 17.3 years. Gender: 8 male, 4 female. Ethnicity: not stated.	NA	-	Aneurysm was responsible for the highest percentage (41.7%) of HS. The mean dose of oral nimodipine was 1 mg/kg every 4 hours and was associated with a high rate of hypotension requiring intervention or dose modification. Clinical outcomes while on nimodipine therapy varied; evidence of vasospasm was observed in 67%, new infarction in 33%, and rebleeding in	Moderate

		cerebral infarction, cognitive function, and mortality.					17%. Functional and cognitive deficits were minor in two-thirds and absent in the remaining individuals. All patients survived until hospital discharge.	
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What is the safety and efficacy of medical interventions to prevent recurrence of HS, including in SCD?								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Naderi 2014	Iran	To investigate ICH location, pattern, occurrence of complications, efficacy of treatment and recurrence in patients with F XIII deficiency.	Case series	38 patients with HS. Age: 17 years (median), range 3 to 43 (age at bleed under 18 for 35/38 patients). Gender: 17 male, 21 female. Ethnicity: not stated.	NA	-	Prophylaxis cryoprecipitate until 2011 then 10 IU/kg Fibrogammin every 4-6 weeks. The median duration of replacement therapy was 84 months (ranged from 24 to 192 months). Among the 38 patients, replacement therapy involved cryoprecipitate in 35 patients with the median duration of 18 months (3–70 months) and Fibrogammin in 37 patients with the median duration of 34 months (4–80 months). 94.7% of patients had good prophylaxis response without recurrent ICH. 37 patients had prophylactic treatment with 10 IU/kg Fibrogammin every 4-6 weeks, mean duration of treatment was 7 years (1-16 years).	Moderate
Kossorotoff 2014	France	Report the characteristics in intracranial aneurysms or primary intracranial haemorrhage in children with SCD.	Retrospective case series	7 children with SCD and HS. Age: 10.5 years (mean). Gender: 3 male, 4 female. Ethnicity: not stated.	NA	2 years	All children were assessed for intracranial aneurysms and 1 underwent coiling of multiple aneurysms. Three patients had small intracranial aneurysms not suitable for intervention and were followed closely, and one of these enlarged, requiring coiling. Two patients started on	Moderate

							hydroxyurea and four on regular transfusions.	
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**In children with acute/chronic HS, what are the indications for referral to neurosurgery/interventional neuroradiology?**

**What is the safety and efficacy of surgical interventions in the treatment of HS in children?**

<b>Author (date)</b>	<b>Country of origin</b>	<b>Study aim</b>	<b>Study type</b>	<b>Participants</b>	<b>Control group</b>	<b>Length of follow-up</b>	<b>Results</b>	<b>Quality assessment</b>
Li 2014 (1)	China	To provide prospective haemorrhage rate, haemorrhage risk and untreated prognosis in children with cerebral cavernous malformations.	Retrospective case series	85 children with HS. Age: 12.7 years (mean), S.D. 4 years. Gender: 59 male, 26 female.	NA	4.7 years (mean)	Reasons for recommending surgical treatment to the 51 patients included: lesion size $\geq$ 2cm, multiple haemorrhages, severe or progressive neurological dysfunction, significant mass effect, exophytic lesions or lesions abutting the pial membrane which is accessible via safe entry zones.	Moderate
Consales 2010	Italy	Report on paediatric patients with cerebral cavernomas	Case series	32 children with cavernous malformations. Age: 7.1 years (mean), range 2 days to 17 years. Gender: 17 male, 15 female. Ethnicity: not stated.	NA	4 years (median)	Twenty-eight out of 32 (87.5%) patients underwent surgery (21 with haemorrhage) Removal of the cavernous malformation was performed in all operated patients. No postoperative death occurred. A new transient neurological deficit was observed in two children, another child reported headache 48h post-operatively and a haematoma in the operative field which was surgically evacuated, resolving symptoms. At follow-up 22 out of 28 (78.6%) operated patients were in good condition with no focal neurological deficits. In one child the pre-surgical deficit (i.e., left hemiparesis) remained unchanged.	Low
Stiefel 2008	USA	To report on experience treating patients with ruptured cerebral	Case series	12 children with ruptured aneurysms.	NA	6 years	5 patients had endovascular therapy - 4 coil occlusion and 1 parent vessel occlusion.	Moderate

		aneurysms with both microsurgical and endovascular treatment.		Age: 5.1 years (mean), range 4 months to 16 years. Gender: 4 male, 8 female. Ethnicity: not stated.			After endovascular treatment 2 of the 4 coiled patients were independent (GOS >3), 1 was dependent (GOS 2-3) and 1 died (GOS 1). The patient who underwent parent vessel occlusion was independent (GOS >3). 8 (62%) of the ruptured aneurysms were treated surgically by clipping. 6 patients were independent (GOS >3) at follow-up, 1 was dependent (GOS 2-3), 1 died (GOS 1). No procedural complications were attributed to surgery. Some patients suffered vasospasm, hypervolemia, hemodilution, and hypertension but numbers affected are not given.	
Song 2011	China	To describe the clinical features and microsurgical treatment of children with cerebral cavernous malformations	Retrospective case series	85 children with cavernous malformations. Age: 13.1 years (mean), range 6 months to 17.9 years. Gender: 53 male, 32 female. Ethnicity: not stated.	NA	4.2 years (mean)	Among the 38 patients with ICH and preoperative neurological deficits symptoms improved in 27, unchanged in 9 and worsened 2 after surgery. No new neurological deficits appeared. No post-operative death occurred. 4-20 days post-surgery 3 patients suffered grand mal seizures and 6 had partial seizures. With the guidance of integrated neuronavigation images and fMRI all 10 lesions located in eloquent areas were removed totally, 1 patient suffered temporary aggravated neurological defect after surgery. Using DTI trajectory, the pyramidal tracts were preserved in 4 patients when resecting brain stem lesions. Follow-up: No post-operative re-haemorrhage, recurrence of any resected	Moderate

							<p>lesions or progression of residual lesions were detected on MRI.</p> <p>No patient suffered seizures.</p> <p>9 patients with post-operative neurological deficits gradually recovered after rehab treatment.</p> <p>Of the 4 patients who initially underwent conservative treatment 1 suffered from re-haemorrhage at 2 years and new formation of a lesion at 10 years and then underwent resection. The other 3 remained stable.</p>	
Scott 2004	USA	To report on the long-term outcomes of a neurosurgical revascularisation technique (pial synangiosis) in children with moyamoya	Case series	<p>143 children with moyamoya.</p> <p>Age: 7.1 years (mean), range 0.5 to 21 years.</p> <p>Gender: 54 male, 89 female.</p> <p>Ethnicity: not stated</p>	NA	5.1 years	<p>Short term follow up: Eleven strokes (7.7% per patient) and 3 severe TIAs occurred within 30 days of surgery.</p> <p>Post-operative stroke occurred in patients with neurological instability although not all. 3 patients suffered strokes within 30 days postoperatively for no obvious reason and in an additional patient an acute subdural hematoma developed after a fall 20 days postoperatively. Chronic subdural hematomas developed in 3 patients 45-72 days postoperatively two of which required evacuation via burr hole.</p> <p>There were no deaths due to ischaemic stroke.</p> <p>1 year post-operative cerebral angiography and MR imaging/angiography in 102 patients showed 65% Grade A collateral circulation, 25% Grade B and 10% Grade C according to the grading method of Matsushima et al. 80% had at least 1 hemisphere demonstrating Grade A circulation. Visible collateral vessels to the brain at additional burr hole sites could be</p>	Moderate

							identified in 57% but only 28% of these vessels could be termed significant (filling more than a small focal area at burr hole site).	
Sheth 2014	USA	To evaluate the influence of angiographic features of AVMs on the rate of obliteration of gamma knife stereotactic radiosurgery	Case series	42 children with AVM. Age: 12 years (mean), S.D. 4 years. Gender: 24 male, 18 female. Ethnicity: not stated.	NA	-	<p>SRS was first treatment modality for 74%, the remainder were treated first with embolisation (22%) or surgery (5%). SRS was the sole treatment for 67%. The median target volume for single-session SRS was 1.9 ml (range, 0.1–11 ml), with a median prescription dose of 18 Gy (range, 15–20 Gy).</p> <p>15 AVMs underwent staged SRS, with a median total target volume of 16.9 ml (range, 8–37 ml), median SRS dose of 17 Gy (range, 12–18 Gy), and median treated volume of 7.5 ml per stage (range, 4–15 ml), given over two (8) or three (7) stages with median interval between treatment of 3 months (3-5 months)</p> <p>3 year angiographic outcome measurements are available for 27 of the 42 patients</p> <p>Complete obliteration was achieved in 8 (30%) patients. Partial obliteration was achieved in 18 and no response was seen in 1.</p> <p>2 patients with partial response were retreated with SRS and one with surgery. One achieved complete obliteration.</p> <p>All patients who achieved complete obliteration had single dose SRS, Complete obliteration was associated with higher SRS dose. There was no significant relationship between pre-treatment</p>	High

							<p>Spetzler-Martin grade and angiographic outcome.</p> <p>7 (17%) patients had haemorrhage after SRS 1-12 years after treatment, 2 resulted in death. 5 of these had 3-year angiographic follow-up which showed partial response in all.</p> <p>Other complications included new onset seizure (7, 17%), significant nausea (1), and headache (15, 37%).</p>	
Soltanolkotabi 2013	USA	To assess the safety and efficacy of Onyx embolization in the treatment of intracranial AVMs in paediatric patients.	Case series	<p>25 children with AVM.</p> <p>Age: 10.5 years (mean), range 4 months to 17 years.</p> <p>Gender: 17 male, 8 female.</p> <p>Ethnicity: not stated.</p>	NA	6 months	<p>Onyx embolization resulted in complete obliteration of the AVM in 12% and partial obliteration in 88%. 23 patients underwent surgical treatment. One patient was treated with radiosurgery following Onyx embolization. 10 complications occurred in 38 procedures (26.3%). None of the complications resulted in permanent neurological morbidity. The rate of transient neurological complications was 10.5% and the rate of transient non-neurological complications was 5.3%. The remaining 4 complications were clinically silent (rate of 10.5%).</p> <p>There were no procedure-related deaths.</p> <p>There was no significant difference in patients with and without complications in terms of demographic characteristics, AVM grade, or embolization features (<math>p \geq 0.2</math>).</p>	Moderate
Yen 2010	USA	To analyse the long term side imaging and clinical outcomes and complications of children with AVMs treated with SRS.	Case series	<p>200 children with AVM.</p> <p>Age: 12.7 years (mean), range 4 to 18 years.</p>	NA	98 months	<p>Spetzler- Martin grading at the time of initial SRS was Grade I in 23 (12.4%), Grade II in 55 (29.6%), Grade III in 87 (46.8%), Grade IV in 20 (10.8%), and Grade V in 1 (0.5%).</p>	High

				<p>Gender: 98 male, 88 female.</p> <p>Ethnicity: not stated.</p>			<p>Following a single SRS procedure, 69 patients (37.1%) had a residual nidus. In 92 patients (49.5%), total obliteration was confirmed on follow-up angiography 10 patients (5.4%) had a subtotal obliteration (no visible nidus; however, an early filling draining vein was still present). 41 underwent additional SRS for AVMs that remained patent.</p> <p>After 1 or more SRS sessions, a complete obliteration was confirmed in 109 (58.6%) and subtotal obliteration in 9 (4.8%) patients, 49 (26.3%) still had a patent residual nidus.</p> <p>The actuarial angiographic obliteration rate was 34% at 2 years, 46% at 3 years, and 51% at 5 years.</p> <p>The number of angiographic obliteration based on Spetzler-Martin grading were: Grade I 12 (52.2%), Grade II 36 (65.5%), Grade III 56 (64.4%), Grade IV 5 (25%), Grade V 0 (0%)</p> <p>The number of non-haemorrhage related neurological complication based on Spetzler-Martin grading were: Grade I 0 (0%), Grade II 1 (1.8%), Grade III 3 (3.4%), Grade IV 2 (10%), Grade V 0 (0%).</p> <p>5 patients has post-SRS haemorrhage</p> <p>2 patients had radiation induced changes associated with permanent neurological deficits, 2 were incapacitated by large AVM with persistent shunting, 2 by medically refractory seizures and 2 with ongoing personality disorder.</p>	
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Kano 2012	USA	To describe the outcomes of patients with AVMs treated with SRS.	Case series	135 children with AVM. Age: 12 years (median), range 2 to 17 years. Gender: 75 male, 60 female. Ethnicity: not stated.	NA	71.3 months (median)	<p>Post radiosurgery obliteration rates based on either angiography or MR imaging criteria were 45%, 64%, 67%, and 72% at 3, 4, 5, and 10 years, respectively.</p> <p>In 8 patients (6%) an AVM haemorrhage after radiosurgery occurred at a median of 41 months (range 13-118months), and 1 patient died.</p> <p>The rates of AVM haemorrhage after SRS were 0%, 1.6%, 2.4%, 5.5%, and 10.0% at 1, 2, 3, 5, and 10 years, respectively. No patient bled after AVM obliteration.</p> <p>Eight patients had adverse radiation effects after SRS at a median of 6.6months (2.8-13.2m). Permanent neurological deficits developed in 2 patients (1.5%), one developed a visual field cut after 13 months, the other developed a trochlear nerve palsy. The remaining 6 had transient adverse radiation effects including hemiparesis (3), seizures (2), and headache (1), these were successfully managed with corticosteroids and/or anticonvulsants. No radiation related neoplasms were detected during the follow-up period.</p> <p>After one or more radiosurgery procedures the obliteration rate was 81%.</p>	Moderate
Potts 2014	USA	To describe SRS treatment of AVMs and focus on posttreatment complications and functional outcomes.	Case series	80 children with AVM. Age: 12.7 years (mean). Gender: 61% male, 39% female. Ethnicity: not stated.	NA	-	<p>SRS was primary treatment for 84% of patients, in remaining patients prior treatments included sub-total resection and endovascular embolisation, 3 patients had undergone SRS at another institution and 8 had undergone treatment with multiple modalities.</p> <p>Complete obliteration was seen in 34% of</p>	Moderate

							<p>patients.</p> <p>Post-SRS complication was seen in 48%, post treatment haemorrhage seen in 20%, cumulative post treatment haemorrhage at 5 years was 25%.</p> <p>31% of patients underwent subsequent treatment for residual AVM.</p> <p>Good functional outcomes were seen for 78% of patients.</p>	
Zabel-du Bois 2006	Germany	To evaluate the clinical outcome and obliteration rates after linac-based radiosurgery.	Case series	<p>22 children with AVM.</p> <p>Age: 11.8 years (mean), range 4.4 to 16.4 years.</p> <p>Gender: 11 male, 11 female.</p> <p>Ethnicity: not stated</p>	NA	3.1 years (median)	<p>Complete obliteration rate 64% and was higher after single doses &gt;18Gy.</p> <p>Post-surgery haemorrhage occurred in 23%.</p> <p>There was no increased bleeding risk after SRS in patients who had bled before. The annual bleeding risk observed following SRS was 9.1% in the first and 13.6 % in the second year. Large AVM over 3cm diameter showed intracranial haemorrhage in 50% vs none in AVM under 3 cm. No new onset of neurological or visual deficits was seen during the follow-up period. No significant side effects were observed, no focal necrosis and no radiation induced malignancy.</p>	Moderate
Levy 2000	USA	Present the long term outcomes for children undergoing radiosurgery	Case series	<p>53 children with AVM.</p> <p>Age: 12 years (median), range 2 to 17 years.</p> <p>Gender: not stated.</p> <p>Ethnicity: not stated.</p>	NA	36 months (minimum)	<p>93% of children returned to their previous activity levels after surgery.</p> <p>Four patients experienced intracranial haemorrhage one of whom died. One child died from leukaemia.</p> <p>50% who presented with seizures were free of seizures at follow-up.</p> <p>Two of three children who presented with headache were free of headache at follow-up.</p>	Moderate

							There were no treatment related deaths or acute morbidity. No patient had a haemorrhage after obliteration.	
Lee 2008	South Korea	To report experience of managing cavernous malformations in children.	Case series	33 children with cavernous malformations. Age: 11.6 years (mean), range 1 to 20 years. Gender: 18 male, 15 female. Ethnicity: not stated.	NA	5.8 years (mean)	Microsurgery: performed in 25 (75.8%) of patients All but 1 patient survived without neurologic deficits. Lesions were completely removed in 23 patients, the remaining were stable at the time of writing and lesions had not recurred Surgical complications were transient dysphasia (1) which resolved 1 week after surgery. Radiosurgery: performed in 8 patients (24.2%). There were no complications associated with radiosurgery. Follow-up MRI showed lesion stability in 4 and decreased lesion size in 4 patients 1 patient died from rebleeding 1 day after radiosurgery.	Low
Di Rocco 2000	Italy	To report the authors' experience with 37 parenchymal AVMs.	Retrospective case series	37 children with AVMs. Age: 8.15 years (mean), range 1 month to 15.2 years. Gender: 21 male, 16 female. Ethnicity: not stated.	NA	64.7 months (mean)	Treatment: Surgery 62.2% Endovascular+surgery 10.8% Surgery+ radiosurgery 2.7% Radiosurgery 8.1% Endovascular + radiosurgery 5.4% No treatment 10.8% 4 patients died after surgical treatment, complete AVM exclusion was confirmed by angiography in 16 out of 23 surgically treated children, one patient had a minimal remnant of his AVM which underwent spontaneous thrombosis.	Moderate

							<p>Total disappearance of the AVM was seen on angiography in the 4 children who were operated on after partial AVM embolisation and in the patient who received radiosurgery after sub-total AVM removal.</p> <p>AVM was reduced in size in the 3 children who underwent radiosurgery as the only treatment modality and in the 2 patients who had combined radiosurgery and endovascular treatment.</p> <p>After follow-up: 67.7% had no neurological deficits, 25.8% had mild neurological deficits, 6.4 had severe neurological deficits.</p>	
Kalani 2014	USA	To evaluate the outcomes of patients with complex aneurysms using cerebral revascularisation alone or in conjunction with endovascular or microsurgery.	Case series	<p>27 children with aneurysms.</p> <p>Age: 11.5 years (mean), range 1 to 17 years.</p> <p>Gender: 19 male, 8 female.</p> <p>Ethnicity: not stated.</p>	NA	46 months (mean)	<p>Three cases were previously treated using microsurgery (n = 2) or an endovascular procedure (n = 1).</p> <p>A total of 28 revascularization procedures. 24 (82.7%) aneurysms were obliterated at 46months clinical follow-up, 1 (3.4%) was residual, 1 (3.4%) was recurrent, and 3 (10.3%) were unknown</p> <p>Perioperative stroke occurred in 4 patients, but only one remained dependent (Glasgow Outcome Scale [GOS] score 3).</p> <p>Five patients had documented occlusion of the bypass graft. There were 5 cases of post-operative graft occlusion, none had a cerebrovascular accident, 1 patient experienced permanent blindness, 1 patient suffered a post procedural iliac pseudoaneurysm after endovascular treatment.</p>	Low

							At follow-up 26 patients had a good outcome (GOS score 4 or 5). There were no deaths.	
Darsaut 2011	USA	To present the authors' experience of treating AVMs to define the natural history and results of treatment.	Case series	120 children with AVM. Age: 11.7 years (mean), range 2.7 to 17.7 years. Gender: 61 male, 59 female. Ethnicity: not stated.	NA	9.2 years (mean)	Annual risk of haemorrhage from presentation to initial treatment was 4.0%, decreasing to 3.2% after treatment initiation until confirmed obliteration. Initial single-modality therapy led to AVM obliteration in 51 of 67 low-grade (76%) and 3 of 34 high-grade (9%) AVMs, improving to 58 of 67 (87%) and 9 of 34 (26%), respectively, with further treatment. Surgery alone cured 19 (95%) of low grade AVM, stereotactic radiosurgery alone cured 5 (42%) low grade AVM but none of the high grade AVM, endovascular treatment alone cured 2 (100%) of the low grade AVM. For dual modality treatment, endovascular treatment then surgery cured 17 (100%) low grade AVM and 2 (100%) of the high grade AVMs. Endovascular treatment then stereotactic radiosurgery cured 4 (67%) of low great AVM, and none of the high grade AVM, surgery then stereotactic radiosurgery cured 3 (43%) of the low grade AVM. For multimodal treatment endovascular treatment then surgery then stereotactic radiosurgery cured 1 (33%) of low grade AVM and 1 (13%) of high grade AVM. Treatment for residual AVM; repeat stereotactic radiosurgery cured 1 (17%) of high grade AVM, dual modality treatment	Moderate

							<p>cured 4 (57%) of low grade AVM and none of the high grade AVM, multimodality treatment cured 3 (75%) of the low grade AVM and 5 (50%) of the high grade AVM. Mean time to obliteration was 1.8 years for low-grade and 6.4 years for high-grade AVMs.</p> <p>Disabling neurological complications occurred in 4 of 77 low-grade (5%) and 12 of 43 high-grade (28%) AVMs.</p> <p>At the final clinical follow-up 48 of 67 patients (72%) with low-grade lesions had a modified Rankin Scale score (mRS) of 0 to 1 compared with 12 of 34 patients (35%) with high-grade AVMs.</p> <p>On multivariate analysis, significant risk factors for poor final clinical outcome (mRS <math>\geq 2</math>) included baseline mRS <math>\geq 2</math>, left-sided location, and high AVM grade.</p> <p>The authors also emphasise the value of a delayed post treatment angiogram 3-6 months after treatment in confirming whether obliteration has genuinely been achieved even if the immediate post treatment angio suggests it has.</p>	
Proust 2001	France	Evaluate the causes of favourable and unfavourable treatment outcomes in children with intracranial aneurysms	Case series	<p>22 children with aneurysms.</p> <p>Age: 13 years (mean), range 7 to 16 years.</p> <p>Gender: 16 male, 6 female.</p> <p>Ethnicity: not stated.</p>	NA	2 to 10 years	<p>Endovascular treatment—performed alone or in combination with other procedures—was used in five patients. In three patients, the endovascular approach consisted of parent vessel occlusion, which conferred no clinical consequences because of a distal recanalization of the vessel by the circle of Willis or leptomeningeal anastomosis. The two other patients underwent aneurysm sac exclusion, but died from the</p>	Low

							severity of the initial SAH. Postoperative angiography revealed vasospasm in eight children (36.4%).	
Saraf 2012	India	To report on patients with aneurysms treated using endovascular techniques	Case series	23 children with aneurysms. Age: 13 years (mean), range 2 months to 18 years. Gender: 17 male, 6 female. Ethnicity: not stated.	NA	3 years (mean)	Treatment: Endovascular treatment was performed in all patients. Angiograms showed cure or stasis in partially thrombosed aneurysms in 22 (96%) patients. There was no improvement in 1 case in which partial flow reversal was performed. Outcomes: MRA was performed in all children; DSA was performed in 6 children. 20 (87%) had a good outcome (GOS 5), 1 (4.3%) had a mild residual deficit (GOS 4), 1 (4.3%) had moderate residual deficit (GOS 3), 1 (4.3%) had significant residual morbidity (GOS 2), no patients died. Complications: 4 patients had procedural complications, 2 had good outcome at 3 month follow-up, 1 was recovering slowly and 1 had poor outcome - quadriplegia and mute.	High
Sharma 2007	India	To review aetiology, clinical characteristics, aneurysm morphology and surgical outcome in children with intracranial aneurysms	Retrospective case series	55 children with aneurysms. Age: 13.3 years (mean), range 7 months to 18 years. Gender: 38 male, 17 female. Ethnicity: not stated.	NA	-	Patients undergoing surgery were Hunt and Hess grades I-IV (10, 17, 10, 3 respectively) 48 aneurysms in 40 patients were treated surgically 5 aneurysms were unclipped - they had not bled in patients with multiple aneurysms. Surgical procedures in 40 patients were: clipping (35), trapping (2), wrapping (1), wrapping with proximal ligation (1), STA-MCA bypass (1). 4 patients underwent endovascular coiling of the aneurysm including the patient that	High

							<p>was Hunt and Hess grade V.</p> <p>Of the remaining 11 patients, 3 had rebleeding from the aneurysm and died after the second event while awaiting treatment, 2 patients with mycotic aneurysms were treated with antibiotics, 2 had small intracavernous aneurysms and were followed-up without treatment, 1 patient had poor neurological status and was never a surgery candidate, 1 patient was lost to follow-up, 2 had thrombosed aneurysms and were not treated.</p> <p>Outcomes: vasospasm 10 (25%) which was responsible for infarct in 2 (5%), perforator infarct 1 which led to monoplegia, death 2 (5%)</p> <p>GOS 5 n=31 (77.5%), GOS 4 n=5 (12.5%), GOS 3 n=2 (5%), GOS 1 n=2 (5%) at discharge</p> <p>Follow-up ranged from 3 months to 6 years with a mean of 9.5 months. At follow-up 26 patients were in GOS 5 and 5 were in GOS 4.</p>	
Abla 2010	USA	To review the surgical outcomes of children with cavernous malformations	Case series	<p>40 children with cavernous malformations.</p> <p>Age: 12.3 years (mean).</p> <p>Gender: 19 male, 21 female.</p> <p>Ethnicity: 33 White, 6 Hispanic, 1 Asian.</p>	NA	31.9 months (mean)	<p>Based on the location of the lesion and the 2-point method, standard cranial base approaches were used: suboccipital (including 2 telovelar approaches) (11) far lateral (4)</p> <p>retrosigmoid (10) orbitozygomatic (4)</p> <p>lateral supracerebellar infratentorial (8)</p> <p>combined supra- and infratentorial suboccipital (transtentorial suboccipital) (1)</p> <p>combined orbitozygomatic/supracerebellar-infratentorial (1)</p>	Low

							<p>retrolabyrinthine (1)</p> <p>Two procedures were staged: 1 patient underwent an orbitozygomatic craniotomy followed by a supracerebellar-infratentorial approach, and 1 patient underwent a supracerebellar-infratentorial approach twice during the same hospitalization. The second procedure was via the same approach, and craniotomy was repeated to access residual cavernoma in the thalamus.</p> <p>19 patients experienced new or worsened neurological deficits, these resolved in 9 patients and were new permanent morbidity in 10 (25%) patients.</p> <p>Complications included: percutaneous gastrostomy (4), tracheostomy (3), clinically significant cerebrospinal leaks (3), pneumonia (2), meningitis/ventriculitis (2) and fungal sepsis (1).</p> <p>1 patient returned to surgery for resection of residual CCM</p> <p>Mean GOS at discharge was 4.05 +/- 0.9.</p> <p>Mean GOS at last follow-up was 4.5 +/- 0.9.</p> <p>16 (40%) patients reported resolution or amelioration of presenting symptoms.</p> <p>Temporary post-operative deficits 22.5%.</p> <p>New permanent post-operative deficits 25%.</p> <p>Recurrence (true recurrence or residual that had grown) was seen in 6 patients, 5 patients rebled.</p> <p>Rebleed rate was 5.25% per patient year after surgery.</p>	
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Ahn 2012	South Korea	To investigate the clinical features and role of bypass surgery in children with moyamoya who presented with bleeding	Case series	13 children with moyamoya. Age: 11 years (mean), range 4 to 18 years. Gender: 6 male, 7 female. Ethnicity: not stated.	NA	50.3 months (mean)	<p>The surgical procedure consisted of bilateral encephaloduroarteriosynangiosis (EDAS) either with or without bifrontal encephalogaleo (periosteal)synangiosis in most cases.</p> <p>No cases were associated with surgical morbidity or mortality</p> <p>Overall clinical outcome was measured by the Paediatric Stroke Outcome Measure (PSOM). 9 patients had a good outcome (being normal or having only mild deficit), and 4 had poor outcome (with a moderate or severe deficit).</p> <p>Three out of four patients with prior history of infarct or haemorrhage had poor outcome with deficits that persisted after surgery.</p> <p>Ten of 13 patients were evaluated for haemodynamic changes after surgery with SPECT. Postoperative SPECT of entire brain showed favourable outcome in 6/10 patients.</p> <p>Post-operative angiogram was performed in 9 out of 13 patients and showed that the degree of moyamoya vessels decreased in 7 patients and was unchanged in 2</p> <p>Progression of the occlusion or stenosis in the internal carotid artery was observed in 7 cases and was unchanged in 2.</p> <p>Patients with history of infarct or haemorrhage showed no favourable degree of revascularisation on follow-up angioigram.</p> <p>Rebleeding occurred in 1 patient.</p>	Low
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Anderson 2012	USA	Examined the incidence and behaviour of AVM associated aneurysms in children with AVMs	Case series	77 children with AVM. Age: 13.4 years (mean). Gender: 38 male, 39 female. Ethnicity: not stated.	NA	Not stated.	11 (14%) children were treated with surgical excision alone, 16 (21%) by radiosurgery alone, 43 (56%) with endovascular occlusion followed by surgical excision, 4 (5%) with endovascular occlusion followed by radiosurgery, 2 (3%) by radiosurgery and excision, and 1 (1%) using only embolization. There were no children who suffered haemorrhage after presentation or treatment.	Moderate
Bilginer 2014	Turkey	To examine demographic, clinical, radiological, management and follow-up in children with cavernous malformations.	Case series	36 children with cavernous malformations. Age: 8.7 years (mean), S.D. 5.7 years. Gender: 21 male, 15 female. Ethnicity: not stated.	NA	6.9 years (mean)	Surgery was the treatment of choice is the CM was symptomatic and accessible 86.1% underwent surgical excision of CM, 5 were followed conservatively 26 CMs were removed totally (81.2%). There was no mortality or permanent morbidity associated with surgery. 1 patient had right arm monoparesis and 1 had frequent seizures following surgery but both had recovered or were being managed effectively with anti-epileptic drugs at follow-up. Outcomes: Rehaemorrhage did not occur in either surgically or conservatively treated patients. 66.7% had GOS 5 (excellent), 27.8% had GOS 4 (good), 5.5% GOS 3 (fair). 90.9% of patients presenting with seizures were seizure free at last follow-up (Engel class I). 9 out of 15 (60%) of patients with focal neurological deficits had complete resolution and 6 improved over time.	Moderate

Bristol 2006	USA	To present the outcomes of neurosurgery in children with AVMs.	Case series	82 children with AVM. Age: under 18 (no average given). Gender: not stated. Ethnicity: not stated.	NA	3 months	<p>Final lesion obliteration rate was 77.5% for the 78 surviving patients.</p> <p>Complete radiosurgical obliteration of residual AVM was achieved in 7 patients (43.8%).</p> <p>2 patients with resected brainstem lesions suffered haemorrhages.</p> <p>Recurrence rate of AVM was 5.6%.</p> <p>33 patients underwent preoperative embolisation, 4 (12.1%) exhibited neurological changes after treatment, all except 1 of these deficits had resolved by 3 month follow-up.</p> <p>79 patients underwent resection, 19 (24.1%) experienced a post-operative deficit.</p> <p>There were 8 occurrences of major complications (infarction, intracranial hypertension, wound infection, lumbar drain breakage, and renal failure) and 12 occurrences of minor complications (CS fluid leakage, sepsis, ventriculitis, UTI, pneumonia, C difficile infection, pneumothorax, decubitus ulcer, and duodenal ulcer).</p> <p>Complication rate was 19%</p> <p>Perioperative mortality rate was 3.7%</p> <p>One patient died 4 years after resection of brainstem aneurysm.</p>	Low
Cohen-Gadol 2006	USA	To explore whether radio-surgery based AVM grading predicts chances of successful radiosurgery in children with AVMs.	Case series	38 children with AVMs. Age: 15 years (median), range 7 to 18 years.	NA	42 months (median)	<p>Obliteration rate on MRI 66%.</p> <p>Angiographic cure rate 53%.</p> <p>Combining angiographic and MRI obliteration showed an overall cure rate of 68%. Complications: 1 patient had intraventricular haemorrhage 26 months</p>	Low

				Gender: 14 male, 24 female. Ethnicity: not stated.			after radiosurgery and recovered without new neurological deficit. No patient who underwent only 1 radiosurgical procedure experience radiation related complication. 1 patient experienced temporary hand numbness after repeated radiosurgery At last follow-up 26 (68%) had excellent outcomes (complete obliteration and no new deficits), 12 (31.6%) remained unchanged (incomplete obliteration and no new deficits). In univariate analyses patients with a radiosurgery-based AVM score of 1 or lower had an excellent outcome more frequently than patients with an AVM score higher than 1 (88% compared with 52%, $p=0.03$ )	
Liang 2011	China	To assess the clinical and radiological characteristics and look at the therapeutic strategies of intracranial aneurysms in adolescents	Retrospective case series	16 children with aneurysms. Age: 16.8 years (mean), range 15 to 18 years. Gender: 10 male, 6 female. Ethnicity: not stated.	NA	19.2 months (mean)	8 patients underwent endovascular therapy - GDC coiling (5), parent artery occlusion (2), cover stent in pseudoaneurysm (1) 4 patients were treated by microsurgical technique - aneurysmal neck clipping (2), extra-intracranial bypass (2) The remaining 4 did not receive surgery - one of whom died before treatment could be given. Glasgow Outcome Scale after treatment: grade 5 (8), grade 4 (7), grade 1 (1)	Low
Liu 2016	China	To report the clinical, angiographic and long term surgical outcomes of haemorrhagic and	Retrospective case series	374 children with moyamoya (30 with HS).	NA	6.4 years (mean)	All patients underwent bilateral revascularization surgery. 15 (50%) patients underwent digital subtraction L61angiography in the follow-up (mean interval, $6.5\pm 1.1$ months; range, 5–9	Low

		ischaemic moyamoya patients.		Age: 12.6 years (mean HS), range 4 to 16 years. Gender: 10 male, 20 female. Ethnicity: not stated.			months). Postoperative digital subtraction angiography results showed that good collateral circulation in 12 patients and fair collateral circulation in 3 patients. Moyamoya vessels were decreased in 11 patients (73%) and were unchanged in 4 patients (27%). 1 (3.3%) patient had a recurrent intracranial haemorrhage and died 6 complained of ischaemic symptoms (headache and limb weakness). Of the 29 surviving patients 25 (83%) had no disability (mRS score 0 and 1), 3 (10%) had mild or moderate disability (mRS score 2 or 3), and 1 (3.3%) had unfavourable outcome (mRS score 4).	
Paramasivam 2013	USA	To review children with congenital pial arteriovenous fistulas, focusing on embryological aspects, clinical features, angio-architecture, treatment indications, management options, with emphasis on endovascular management.	Retrospective case series	16 children with arteriovenous fistulae. Age: < 5 years. Gender: 7 male, 9 female. Ethnicity: not stated.	NA	1 day to 18 months	All cases were managed with N-butyl-cyanoacrylate (NBCA) embolization and coils in 10 cases (63%) to reduce flow before NBCA embolization. In no instances were coils alone used to close the feeders. In 72% of fistulas NBCA with a concentration of 50e90% was used, while in 28% a more dilute NBCA was used. Flow-guided coils were used in five cases and other detachable coils in six cases. Following treatment, four cases developed de novo dural arteriovenous fistula (25%). Reactive angiogenesis in the vicinity of the treated fistula was seen in six cases (37%). 87% of patients were followed with MRI and digital subtraction angiography. Outcome was excellent (12/16 or 75%)	Low

							when there was no residual shunt and no additional neurological deficit, good (3/16 or 19%) when there was minimal residual shunting with no additional neurological deficit and all others were considered poor outcome (1/16 or 6%).	
Hetts 2009	USA	Characterise the clinical, imaging, treatment and outcome data in patients diagnosed with intracranial aneurysms	Retrospective case series	77 children with aneurysms. Age: 12 years (mean), range 3 months to 18 years. Gender: 37 male, 40 female. Ethnicity: not stated.	NA	23 months (mean)	Used selective coiling, endovascular parent artery occlusion, selective clipping, surgical trapping, and conservative observation. Mortality low 1.3% Morbidity 8% infarction and 4% new onset seizures 6 had new aneurysms or enlargement of existing ones.	Moderate
Vaid 2008	India	Discuss the epidemiology, clinicoradiological profile, outcomes and management issues of children with aneurysms	Retrospective case series	27 children with aneurysms. Age: 13.2 years (mean), S.D> 3.7 years. Gender: 14 male, 13 female. Ethnicity: not stated.	NA	18.7 months (mean)	23 children (85.18%) presented with SAH. 7 giant aneurysms and 8 posterior circulation aneurysms At follow-up there were 21 (77.77%) patients with favourable outcome and 3 patients died.	Low
Xia 2009	China	Discuss the clinical presentation, diagnosis, treatment and follow-up of children with cerebral cavernous malformations	Retrospective case series	66 children with cavernous malformation. Age: 11.6 (mean), range 15 months to 17.8 years. Gender: 40 male, 26 female. Ethnicity: not stated.	NA	39.1 months (mean)	Sixty-two children underwent microsurgical operations, and with the help of neuronavigation (19 cases), intraoperative ultrasonography (6 cases), and neuronavigation combined with intraoperative ultrasonography (3 cases). There was no major morbidity or mortality from surgical procedures. In 46 operated children, the long-term post-treatment results were satisfactory: 73.9% no sign or symptom associated with CMs,	Low

							19.6% improved obviously, only 1 (2.2%) boy with unrestored paraplegia incurred by spinal cord CM, and 2 boys (4.3%) with controllable seizures occurring after initial 5 symptom free years (one without need of antiepileptic drugs, AEDs).	
Li 2014 (2)	China	To evaluate surgical outcomes of cavernous malformations and identify risk factors associated with post-operative full recovery and rebleeding	Case series	52 children with cavernous malformations. Age: 12.2 years (mean), range 1 to 17 years. Gender: 37 male, 15 female. Ethnicity: not stated.	NA	7.9 years (mean)	Gross-total resection and subtotal resection (STR) were achieved in 49 (94.2%) and 3 (5.8%) patients, respectively. There were no surgery related deaths. Surgery related morbidity developed in 25 (48.1%) of patients. Overall, deterioration, stabilization, and improvement of neurological function were detected in 3 (5.8%), 31 (59.6%), and 18 (34.6%) patients, respectively. After follow-up 42 patients (80.8%) still had neurological deficits. Ten patients (19.2%) demonstrated complete recovery with an mRS score of 0, 35 patients (67.3%) lived independently and presented with mild deficits (mRS score of 1), 5 patients (9.6%) were able to perform self-care activities (mRS score of 2), and the remaining 2 patients (3.8%) were completely dependent and presented moderate to severe deficits (mRS score of 3). Postoperative recovery was significantly associated with age (HR 0.230, 95% CI 0.066–0.800; p =0.021), number of preoperative haemorrhages (HR 0.124, 95% 0.016–0.979; p = 0.048) and preoperative mRS score (HR 0.197, 95% CI 0.042–0.926; p =	Moderate

							0.040) 2 patients rebled after surgery.	
Liang 2009	China	To describe the clinical and radiological features and the therapeutic outcome and clarify the choice of therapeutic strategies for paediatric intracranial aneurysms.	Case series	24 children with aneurysms. Age: 8.8 years (mean), range 1 to 14. Gender: 14 male, 10 female. Ethnicity: not stated.	NA	13.6 months	15 patients underwent endovascular therapy. 4 patients were treated by using a microsurgical technique, 3 by aneurysmal neck clipping, and 1 by parent artery ligation. 5 patients (six aneurysms) received conservative therapy. 22 patients had a favourable outcome and 2 patients had an unfavourable outcome. There was 1 death owing to thrombosis in the basilar artery and 1 patient whose aneurysm reruptured preoperatively and had the parent artery occluded.	Low
Aryan 2006	USA	To examine strategies for treating aneurysms in children.	Retrospective case series	50 children with aneurysms. Age: 10.3 years (mean), range 5 months to 19 years. Gender: not stated. Ethnicity: not stated.	NA	Not clear. Study carried out over 15 years.	Treatments: Clipping (28), Clip–circulatory arrest (1), Re-clipping (2), Trapping (1), Trap–bypass (2), Clip–wrap (5), Wrapping (1), Hunterian ligation (3), Excision (7), Embolization (4). Intraoperative complications: Rupture (6), Progressive cerebral oedema (2), Perforating arterial injury (4), Postoperative complications: Cranial nerve palsy (3), Delayed ischaemic stroke (3), Hemiparesis (2) Monoparesis (2), Infection (2). Postoperative angiography showed excellent to good results in 36 and fair in two. Long-term outcome was excellent in 22 patients, good in 20 and poor in nine, with one death and two cases lost to follow-up.	Low

Zheng 2014	China	To describes patients with AVM and their treatment and outcomes	Cohort	127 children in total, 66 with AVM that received treatment. Age: 13.2 years (mean), range 3 to 18 years. Gender: 77 male, 50 female. Ethnicity: not stated.	NA	9.6 months (mean)	Treatment: 61 patients treated with microsurgery, radiosurgery, or a combination. Initial complete obliteration at the end of all embolisation was achieved in 14/66 patients (21.2%) after a mean follow-up of 9.6 months (6-48 months) there was 1 angiographic recurrence at 5 months. Complete obliteration rate of 19.7%. Treatment related complications: complication rate 7.3% (9 embolisation procedures), no permanent neurological deficit or morbidity, no deaths, no significant differences between patients who did and did not experience complications in sex, age, AVM location, number of pedicles embolised, Spetzler-Martin grade, deep venous drainage, and devascularization percentage ( $p>0.05$ ). In patients who had radiosurgery 22 had no complications, 2 had small interval haemorrhage 6 months after radiosurgery with no permanent clinical sequelae. MRA or angiography showed complete obliteration after radiosurgery in 12 patients.	Moderate
Mehrotra 2012	India	To describe management of children with aneurysms	Cohort, database review	57 children with aneurysms. Age: 12.7 years (mean), S.D. 3.8 years. Gender: 26 male, 31 female. Ethnicity: not stated.	NA	18.6 months (mean)	Treatment: 73 aneurysms, 69 clipped, 2 wrapped because of difficulty dissecting the aneurysm neck, 2 were trapped because of difficulty defining the aneurysm neck. 7 underwent ventriculoperitoneal shunt placement due to significant ventriculomegaly, 3 patients had infarcts and 2 of these underwent decompression,	Low

							wound infection developed in 2, transient diabetes insipidus developed in 2, vasospasm developed in 11 (19.29%). At latest outcome 44 (77.19%) had favourable outcome, 13 had unfavourable outcome, 5 (8.77%) died. Among the 52 who survived 36 (69.23%) were able to perform normal activities without any special care, 8 (15.38%) had mild to moderate restrictions and 8 had moderate to severe restrictions.	
Kumar 2009	India	To determine the causes, course and outcome of HS.	Case series	50 children with HS. Age: 13.8 years (mean), range 2 months to 17 years. Gender: 31 male, 19 female. Ethnicity: Indian.	NA	3.1 years (mean)	Treatment: excision of AVM 30%, clipping of aneurysm 26%, 18% managed conservatively because of poor neurological status, haematoma evacuation 14%, tumour excision 4%, cavernoma excision 4%, embolisation and superficial temporal artery to MCA bypass 2%. Outcomes: 44% had good outcomes, 30% moderately disabled, 12% severely disabled, 8% vegetative state, 6% died. All patients who presented <6h after the onset of symptoms had good outcomes. Significant association was found between location of bleed and outcome ( $p<0.05$ )	Low
Lv 2009	China	To report on patients with aneurysms treated using endovascular techniques	Case series	25 children with aneurysms. Age: 11.4 years (mean), range 4 to 17 years. Gender: 20 male, 5 female. Ethnicity: not stated.	NA	23.5 months (mean)	Selective coil embolisation: 5 were treated with selective coil embolisation of the aneurysmal sac. Complete occlusion was achieved in 4 and neck remnant was evident in 1. 1 late thrombus formation and 1 recanalisation of embolised A1 aneurysm on the follow-up studies which were retreated with surgical clipping. Parent artery occlusion: 16 patients (8 VA,	Low

							<p>4 PCA, 4 MCA, 1 ICA aneurysms) had parent artery occlusion. Angiograms obtained immediately after treatment showed occlusion of the aneurysm and retrograde filling of the vessel. One had partial thrombosis. On follow-up angiograms, occlusion of the parent artery remained stable and none of the aneurysms refilled by a retrograde or leptomeningeal supply.</p> <p>No patient that underwent selective coil embolisation developed neurologic deficits related to the procedure.</p> <p>No patient who underwent parent artery occlusion developed neurologic deficits after treatment.</p> <p>Follow-up: 23 (92%) patients had a good Glasgow Outcome Scale of 5, 1 (4%) patient had a Glasgow Outcome Scale of 4, and 1 died, leaving an overall favourable outcome of 96%.</p>	
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## Chapter 8: Discharge from hospital

Discharge								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Ball (2013)	UK	To explore the process of reintegration into school of children with ABI and to consider the role of EPs within the local authority in supporting this process	Qualitative interviews	Interviews conducted with professionals in two specialist settings. Age: unknown. Gender: unknown. Ethnicity: British.	NA	-	<p>There was a need for improved communication between health and education staff, and a need for more training for education staff in ABI.</p> <p>There are no nationally agreed processes to record ABI by severity to aid communication.</p> <p>Discharge from hospital key transition point for exchange of information between professionals.</p> <p>There is a role for educational psychologists to attend discharge meetings as they remain involved with child through school life.</p> <p>Communications between hospital schools and mainstream schools seen as important.</p> <p>Another role of educational psychologist would be to translate medical jargon into practical information but this require training.</p> <p>There is a need to train individuals working with the child about rehab and brain injury so they can maximise potential for rehab of cognitive skills as well as ongoing training as child moves through school system.</p> <p>Educational psychologists should have a role in monitoring child progress and educating staff and families about changing needs.</p>	Low

Glang (2008)	USA	To examine factors that influence identification and service practices for students with TBI.	Cross sectional/qualitative interviews	56 families of young people with TBI. Age: 12.48 years (mean), range 4.8 to 18.1 years Gender: 68% male, 32% female Ethnicity: 89.3% White, 7.1% Hispanic, 1.8% Asian, 1.8% unknown.	NA	-	For children with severe injuries, 81.5% received additional support at school. For children with mild/moderate injuries, 51.7% received additional support at school.  Children who received hospital to school transition services were 16 times more likely to get additional support at school. Schools are open to providing support, if parents and hospital staff help them understand what's needed. 49.1% of families said they received no information or guidance on transition back to school from the hospital team.  Results from chi-square and logistic regression analyses suggest that injury severity and hospital-school transition services (e.g., written or verbal communication between hospital and school) were related to the provision of formal special education or 504 services. A critical factor contributing to the identification of students with TBI for special education is the link between hospital and school. Parents were just as happy with informal support as with formalised support at school.	Moderate
Lindsay (2015)	Reviewers were in Canada (but reviewed studies worldwide)	To inform the development of effective hospital-to-school reintegration programs.	Systematic review	350 children. Age: 4 to 19 years. Gender: not stated. Ethnicity: not stated.	Varies by study	-	The included studies investigated several different types of intervention, including arts-based activities, problem-solving activities, clinician-led information sessions, behavioural and cognitive interventions, family or social support interventions, online interventions, and multi-component interventions. 14/17	Low

							<p>studies reported at least one significant improvement in cognitive, social, psychological, or behavioural functioning or knowledge of ABI. Effect sizes are calculated but these are not then used directly to identify which interventions are considered successful.</p> <p>Common components of successful interventions included one-on-one sessions led by a trained clinician or educator, homework activities, and parental involvement.</p>	
Sharp (2006)	Australia	To understand the influence of services and support on the school return following ABI	Qualitative interviews	<p>8 families with a child with ABI.</p> <p>Age: 14 to 19 years.</p> <p>Gender: 5 male, 3 female.</p> <p>Ethnicity: not stated.</p>	NA	-	<p>Findings suggest the need for:</p> <ul style="list-style-type: none"> <li>a) Early and ongoing communication amongst the adolescent, their family, the rehabilitation team and schoolteachers regarding return to school support strategies and services;</li> <li>b) Appropriately targeted education of schoolteachers and peers regarding the impact of ABI;</li> <li>c) Selection of a suitable range of support interventions which meet the particular needs of the adolescent and implementation of these interventions appropriately;</li> </ul>	Moderate

							<ul style="list-style-type: none"> <li>d) Recognition of family variability in the type and extent of parental involvement in return to school;</li> <li>e) Recognition that organizing the school return is just as important as actually returning to school.</li> </ul>	
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## Chapter 9: Rehabilitation

Framework for evaluation of rehabilitation needs in children with stroke								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Anderson 2014	Australia	To investigate the impact of age at brain insult on functional outcome and the influence of insult and environmental factors on cognitive and behavioural outcomes.	Retrospective observational	138 children with MRI evidence of focal brain insult sustained from the first trimester of pregnancy to adolescence. Age: 13 years 1 months (mean), range 10 years to 16 years. Gender: 76 male, 62 female.	NA	-	Focal insult before the age of 3 years was associated with poorer outcomes than insult after the age of 3 years across all domains. For IQ outcomes(WASI: Verbal IQ: 9.46 (3.60–15.32, P<0.01), WASI: Performance IQ 8.19 (1.54–14.83, P,0.05), WASI: Full-scale IQ 6.87 (0.37–13.83, P<0.01), BRIEF: Global Executive Composite score 7.63 ( 11.70-3.53, P<0.01), WMS: total score 5.68 (0.09–11.27, P<0.05), SDQ: total difficulties score 3.35 (5.70- 0.99, P<0.01). Insult characteristics: Right hemisphere lesion and Bilateral lesion were predictive of lower verbal IQ. Seizures were highly predictive of lower IQ outcomes.	Moderate
Bedell 2002	USA	To describe the extent of readiness for participation in home, school and community life at discharge from inpatient rehabilitation	Cross sectional	65 children with ABI. Age: 9.8 years (mean), range 9 months to 18.9 years. Gender: 60% male, 40% female. Ethnicity: 75% Caucasian, 11% African American, 8% Hispanic.	NA	-	Children discharged home had higher participation readiness scores than children discharged to other rehab settings. Children aged 15+ had the highest readiness scores; children aged 5-7 had the lowest scores. Between a third and a half of children were rated as having moderate or severe restrictions in each area of participation at discharge.	Low

Boardman 2005	UK	To define stroke lesion topography and evaluate motor outcomes in neonatal and childhood stroke to assess whether (1) early topographic predictors of hemiparesis after unilateral MCA stroke are the same in neonates and older children and (2) compare prevalence of dystonia and loss of independent finger movements between the two age groups	Cohort	28 neonates and 43 children with MCA infarct. Age: neonates median gestational age 40.3 weeks, range 38 to 42.3 weeks, children median age 3.6 years, range 0.3 to 15.5 years. Gender: neonates 18 male, 10 female, children 28 male, 15 female. Ethnicity: not stated.	NA	-	Hemiparesis more common following childhood stroke (56%) than neonatal stroke (24%). Childhood group: children with all these regions affected developed hemiparesis but also if 1 or 2 site involvement (but less likely if infarct affected BG only) [OR 0.162; 95% CI 0.036-0.729]. Dystonia seen in 15/24 childhood group with hemiparesis but not seen in neonatal onset group. In both groups upper limbs more affected than lower limbs. 75% neonatal infarcts involved left MCA but left sided preponderance not seen in childhood group [17 LMCA; 26 RMCA]	Moderate
Braga 2005	Brazil	To explore the relative effectiveness of clinician-delivered vs family-supported interventions for children with chronic impairment after TBI.	RCT	38 children with TBI. Age: 97.66 months (mean), S.D. 29.61 months. Gender: 20 male, 18 female. Ethnicity: not stated.	34 children with TBI. Age: 96.95 months (mean), S.D. 30.3 months Gender: 19 male, 15 female Ethnicity: not stated.	-	Parents in the family-supported intervention sample efficiently acquired the skills needed to deliver physical and cognitive interventions within the context of everyday routines of the child's life at home; family education level was not a factor. IFS group showed stat. sig. improvement on WISC III 91.4 (SD 15.6) compared to DCD 85.3 (SD15.2) P= 0.05 and SARAH 3.1 (SD 0.8) compared to 2.6 (SD1.1) in the DCD group P=0.018.	Moderate
Bulder 2011	Netherlands	To compare paediatric stroke outcome obtained from the PSOM and outcome obtained from the combination of mRS and information on type of school attendance; to	Cross-sectional	40 children with AIS. Age: 5.6 years (median at stroke), range 0.3 to 15.9 years.	NA	-	In 35/40 children (88%), outcome classification was concordant between the two outcome measures (24 good and 11 poor outcome according to both measures). Five children had a poor outcome according to the PSOM and good outcome with the mRS including school	Low

		assess if the classification into good and poor outcome, according to both outcome measures, correlated with quality of life reported by the child and parents, and with the intuitive assessment of overall functioning of the child, by parents and investigators.		Gender: 23 male, 17 female. Ethnicity: not stated.			performance. In these patients, mRS outcome classification agreed better with the impression of the investigators, as reflected by VAS scores $\geq 7.5$ . For both the PSOM and mRS in combination with school performance, patients with a good outcome had significantly higher PedsQL and VAS scores than those with a poor outcome ( $p$ values $<0.01$ for all comparisons). VAS scores of investigators and parents correlated significantly with PedsQL.	
Chen 2004	USA	To gain knowledge of type and quantity of inpatient rehab provided to children who received inpatient rehab services.	Retrospective cohort	814 children. Age: 125 months (mean) S.D. 64. Gender: 465 male, 346 female. Ethnicity: 522 Caucasian, 182 African-American, 65 Hispanic American.	NA	-	Occupational therapy and physical therapy were the primary rehabilitation services received by patients across impairment groups (98% and 99%, respectively). Children improved more in self-care if they were more than 7 years of age, had lower self-care measures at admission, had traumatic injuries, and received more occupational therapy. Children improved more in mobility if they were more than 7 years of age, had lower mobility measures at admission, had traumatic injuries, and received more physical therapy. Children improved more in cognition if they were more than 7 years of age, had lower cognition measures at admission, had traumatic injuries, and received more speech therapy.	Moderate
Chevignard 2010	France	To describe a comprehensive model of care devoted to children with acquired brain injuries; and to provide descriptive	Case series	Children hospitalized in the department ( $n = 116$ ), children assessed by the	NA	-	Inpatients: Mean GOS had improved (2.15; SD = 0.74). Improvement was dramatic, with most children being in the more favourable outcome categories. Most children (90%) were	Moderate

		data analysing the characteristics of children followed up, the type/amount of services provided and general outcomes.		<p>'assessment, academic and vocational guidance unit' (n = 131) and the children followed up by the outreach programme (n = 268).</p> <p>Age: Hospitalised children: mean 7.3 years (mean), SD 4.6 years,</p> <p>Outreach programme (children's team) 11.08 years (mean), (adolescent team) 18.58 years (mean),</p> <p>Assessment, academic unit age range not reported.</p> <p>Gender: Inpatients: 71 male, 45 female.</p>			walking independently upon discharge. Analysis of children's discharge destinations and rehabilitation organization for the year 2006 confirms all children had a well-established schooling project and rehabilitation programme upon discharge, allowing a large majority of children to return home, with appropriate help. Children of school age either returned to their previous school, most of the time with special educational help or adaptations in the classroom; or were admitted in specialized classes settled within regular schools. Most of the children were discharged with ongoing rehabilitation.	
Cnossen 2010	Netherlands	To study functional outcome in children aged 1 month to 18 years after paediatric arterial ischaemic stroke (PAIS) and to identify risk factors influencing their quality of life.	Case series	<p>76 children with AIS.</p> <p>Age: 2 years 6 months (median at diagnosis), range 1 month to 17 years 2 months.</p> <p>Gender: 35 male, 41 female.</p> <p>Ethnicity: not stated.</p>	NA	-	Significant risk factors at presentation for a poor neurological outcome were Younger age at onset of PAIS was correlated with a higher mRS (modified Rankin Scale) at 12 months after onset (Spearman's $r=0.27$ , $p=0.02$ ) and had thus a poorer outcome, infarction in the right middle cerebral artery territory, and fever at presentation. Proportional odds regression analysis revealed that younger age at onset, fever, and stroke in the right MCA territory were	High

							the strongest predictors of a poor neurological outcome at 12 months after onset of PAIS. 54% of children had severe neurological impairments at 12 months after PAIS, and at last follow-up more than half needed remedial teaching, special education, or institutionalization. HRQOL questionnaires showed a significantly lower HRQOL in all age groups. Children with a longer follow-up had a lower HRQOL in the cognitive functioning domain.	
Davis 2010	Australia	To determine the reliability of the AHA when used with children and youth who have unilateral motor impairment following ABI	Retrospective cohort	26 children with unilateral motor impairment and ABI. Age: 6.8 years (mean), range 22 months to 16.5 years. Gender: 14 male, 12 female. Ethnicity: not stated.	NA	-	Interrater reliability ICC 0.85-0.93 (domain scores) 0.97 (0.93-0.99 95%CI) (total scores) most variation for 'chooses assisting hand' (0.55) in categories of somewhat effective or ineffective. And 'moves forearm' (0.59) in all categories (except does not do). Intrater reliability ICC 0.94-0.97 (domain scores) and 0.99 (0.97-0.99 (95%CI)(total score) Item responses: grasps and calibrates more variation. But Chooses assisting hand (low in interrater) —>excellent intrarater (0.84); Moves forearm —> good (0.67).	Low
Engelmann 2012	USA	to assess the standardized outcome measures currently used in paediatric stroke studies	Systematic review	34 studies that included children from birth to 18 years of age with AIS, HS, or both, had > 5 subjects, and evaluated children for neurological or	NA	-	19 studies were focused on AIS only, five were focused on haemorrhagic stroke only, and ten included both types of stroke. The most commonly applied outcome measure was the age-appropriate form of the Wechsler Intelligence Scale (WIS), used in 34% of studies. Second-most prevalent was the Paediatric Stroke Outcome Measure (PSOM), utilized in seven studies (21%).	Low

				functional outcome status with a recognized outcome measure.			Notably, 24 of 38 outcome measures were used in one included study each (63%). Only PSOM and mRES have been validated in paediatric stroke population.	
Friefeld 2004	Canada	To examine parent and child perspectives on QOL and examine factors that correlate with reduced QOL for child survivors of stroke.	Prospective single-center cohort	100 children with AIS and CSVT. Age: 8.4 years (mean), range 4 to 12 years. Gender: 56 male, 44 female. Ethnicity: not stated.	NA	-	The parent-proxy and child self-report HRQOL scores were significantly reduced (72.07, SD 18.60, t-value -5.46, P<.01), (71.48, SD 16.95, t-value -5.58, P<0.01) compared with normative data of healthy children. Multivariate analysis showed that of neurological deficits after stroke was a significant predictor of poor HRQOL (P<.05).	Moderate
Galvin 2011	Australia	To describe functional abilities of children following ischemic stroke using a validated outcome measure (Paediatric Evaluation of Disability Inventory)	Case series	18 children with AIS. Age: 7.9 years (mean), S.D. 4.3 years. Gender: 9 male, 9 female. Ethnicity: not stated.	NA	-	All children demonstrated lower functional skills and required more caregiver assistance than would be expected for their age. These findings were seen across all functional areas; however, self-care was more affected than mobility and social functions.	Low
Max 2004 (1)	USA	To assess the impact of laterality of lesion on neuropsychological function.	Cohort	29 children with stroke. Age: Early stroke 11.8 years (mean), S.D. 3.6 years, late stroke 13.2 years (mean), SD 4.2 years. Gender: 18 male 11 female. Ethnicity: 27 Caucasian, 1 Hispanic, 1 Asian.	Children with congenital clubfoot and children with scoliosis according to age of onset of stroke (i.e., early vs. late), gender, ethnicity, socio-economic	-	Laterality of insult does not significantly impact on neuropsychological function suggesting significant plasticity. Accuracy in detection of both appearing and disappearing stars was significantly worse in the children with stroke. RT was also significantly longer for this group compared with the control group, although only for disappearing stars. Accuracy performance on the Starry Night task was related to lesion size (both area and volume) in both the sensory-orienting	High

					status, and age within 1 year.		and alerting networks, but not in the executive network. Both Starry Night measures remained significantly associated with lesion size in the sensory orienting network, but not with lesion size in the alerting network. Significantly poorer detection of both appearing and disappearing stars in the early onset stroke subgroup when compared with either the controls or the later onset stroke subgroup.	
Max 2004 (2)	USA	To investigate attentional outcome after childhood stroke.	Case control	29 children with focal stroke (HS and AIS) lesions. Age: 12.6 years (mean), S.D. 3.9 years. Gender: 18 male, 11 female. Ethnicity: 27 Caucasian, 1 Hispanic, 1 Asian.	Matched children with clubfoot or scoliosis. Age: 12.4 years (mean), S.D. 3.9. Gender: 18male, 11 female.	-	Post stroke psychiatric disorder was more common than post orthopaedic diagnosis psychiatric disorder (17029; 59% vs. 4029; 14%; Fisher Exact Test $\leq .001$ ). Children with stroke lesions performed significantly more poorly regarding attention function compared with controls. Performance on the Starry Night, a test demanding alerting and sensory-orienting but not executive attention function, was significantly associated with lesion size in the alerting and sensory-orienting networks but not the executive attention network. Furthermore, earlier age at lesion acquisition was significantly associated with poorer attention function even when lesion size was controlled.	Low
Oddson 2006	Canada	To assess the acceptability, validity and reliability of the Mayo-Portland Adaptability Inventory in rehabilitation after paediatric acquired brain injury.	Retrospective cohort	335 children with ABI. Age: 9 years 8 months (median), range 1 to 19 years. Gender: 215 male, 120 female.	NA	-	98% of children had some level of impairment reflected in their total MPAI score. For patients admitted as in-patients, there was a correlation between age at injury and MPAA total score, such that older children showed more impairment ( $r_s=0.23$ , $p=0.023$ , $n=102$ ). MPAA total	Low

				Ethnicity: not stated.			<p>scores taken during in-patient admission correlated negatively with GCS (<math>r_s = -0.36</math>, <math>p = 0.002</math>, <math>n = 72</math>), indicating that low GCS (more serious injury) was associated with high subsequent disability. MPAl total scores correlated positively with days of PTA (<math>r_s = 0.44</math>, <math>p &lt; 0.001</math>, <math>n = 57</math>). MPAl total scores from first outpatient visits correlated negatively with GCS scores (<math>r_s = -0.33</math>, <math>p &lt; 0.001</math>, <math>n = 195</math>). Days of PTA did not correlate with MPAl total scores in this sample (<math>r_s = -0.08</math>, <math>p = 0.220</math>, <math>n = 216</math>), although days of ventilation did (<math>r_s = 0.22</math>, <math>p &lt; 0.001</math>, <math>n = 320</math>), both these correlations being significantly less than those for in-patient MPAl total scores as reported above.</p>	
Schatz 1999	USA	To further examine the relationship between the location and volume of cerebral infarcts and neuropsychological deficits in children with sickle cell disease.	Cohort	<p>28 children with SCD. Age: 12.8 years (mean), S.D. 3.7 years. Gender: not stated. Ethnicity: not stated.</p>	<p>17 siblings of the intervention group. Age: 12.2 years (mean), S.D. 4.0 years. Gender: not stated. Ethnicity: not stated.</p>	-	<p>Children with anterior cerebral infarcts (<math>n = 7</math>) showed deficits in attention and executive skills, whereas children with more widespread cerebral infarcts (<math>n = 18</math>) showed additional deficits in spatial skills. The volume of cerebral infarction was associated with spatial and language performance, but minimally related to performance in other cognitive domains. The location and volume of cerebral infarction are both important for defining the type and magnitude of cognitive sequelae in childhood stroke. Anterior lesions produced problems in attention and executive skills. Extensive lesions resulted in additional problems in spatial skills.</p>	Moderate

Studer 2014	Switzerland	To examine the influence of age, lesion characteristics, seizures, NI, and functional outcome on cognitive outcome in a population-based group of children 2 years after an AIS occurrence.	Prospective Cohort	99 children with AIS. Age: 9.45 years (mean), S.D. 4.87 years. Gender: 71 male, 28 female. Ethnicity: not stated.	NA	-	Younger children poorer outcome, cortical and subcortical damage combined leads to poorer outcome. Presence of seizures negative prognostic indicator. Correlation between cognitive and neurological outcome.	Moderate
West 2014	England	To explore the ability of the School Function Assessment (SFA) to identify levels of participation in school-based functional tasks and demonstrate progress for pupils with an ABI in a residential rehabilitation setting.	Cohort	70 children with ABI. Age: 12.8 years (median), range 4.7 to 17.2 years. Gender: 42 male, 28 female. Ethnicity: not stated.	NA	-	54/70 students improved their scores on school participation between assessments. Teachers found the SFA useful and Ofsted thought it was a good thing. For individuals the scores were used to plan interventions in the setting and to inform the suggestions when students were discharged. As a whole setting the school could see where students were making most and least progress, and could adapt the curriculum to encourage better progress in those areas.	Low

Components and effectiveness of rehabilitation interventions for children with stroke								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Antonini 2014	USA	To report findings from a pilot randomized clinical trial (RCT) comparing the efficacy of an online positive parenting skills intervention program focused on young children with TBI with access to Internet resources in increasing positive parenting	Pilot RCT	20 children with TBI (parenting skills intervention). Age: 5.6 years (mean), S.D. 2.1 years. Gender: 14 male, 6 female. Ethnicity: 2 Caucasian American/White	17 children with TBI (internet resources). Age: 5.2 years (mean),	-	Positive parenting skills improved in the intervention group. Improvements were correlated with the number of sessions completed. Child compliance following indirect commands: children across groups were more compliant at the follow-up visit than at the baseline visit (RR = .78, p = .017).	Moderate

		behaviours and reducing child behaviour problems.		8 African American/Black/Multiracial.	S.D. 2.1 years. Gender: 11 male, 6 female. Ethnicity: 11 Caucasian American/White 6 African American/Black/Multiracial		There were no changes in Parent Ratings of Child Behaviour on ECBI.	
Backeljauw 2014	USA	To gain an understanding of the current state of the evidence for management of attention problems after traumatic brain injury (TBI) in children, determine gaps in the literature, and make recommendations for future research.	Systematic Review	<p>Inclusion criteria: English, human studies, published 1993-2013, age range 0-18 years, TBI and other ABI in children</p> <p>Exclusion criteria: book, case study, dissertation or review article, primary or secondary outcome measure specific to attention was not used, average age of sample over 18 years, not an intervention, did not measure attention before intervention administered.</p>	NA	-	Methylphenidate is recommended as a first line treatment for P-ADHD and demonstrates benefits in S-ADHD. Cognitive training appears to be beneficial when targeting attention or attention and memory specifically rather than mixing with other behavioural or cognitive interventions. Larger multi-center studies are needed to determine which interventions or combinations of interventions are most likely to improve S-ADHD. Future research should evaluate factors that may influence treatment response, for targeted individualized management.	High

Bloom 2010	USA	To measure whether chronic daily use of biofeedback of muscle electrical activity might promote improved use of the upper extremity in children with cerebral palsy and upper extremity motor deficits.	Case series	11 children with poor motor function in upper extremity. Age: 10 years (mean), S.D. 2.8 years. Gender: 5 male, 6 female. Ethnicity: not stated.	NA	-	All children showed improvement by a mean of 4.7 points (SD = 2.6, $P < .0001$ on 1-sided matched pairs t test, $N = 10$ ), and excluding subjects 1, 7, and 8 because they had botulinum toxin injected into their affected upper extremity, they gave a mean improvement of 4.1 points (SD = 2.5, $P < .001$ , $N = 7$ ).	Low
Braga 2005	Brazil	To explore the relative effectiveness of clinician-delivered vs family-supported interventions for children with chronic impairment after TBI.	RCT	38 children with TBI. Age: 97.66 months (mean), S.D. 29.61 months. Gender: 20 male, 18 female. Ethnicity: not stated.	34 children with TBI. Age: 96.95 months (mean), S.D. 30.3 months Gender: 19 male, 15 female Ethnicity: not stated.	-	Parents in the family-supported intervention sample efficiently acquired the skills needed to deliver physical and cognitive interventions within the context of everyday routines of the child's life at home; family education level was not a factor. IFS group showed stat. sig. improvement on WISC III 91.4 (SD 15.6) compared to DCD 85.3 (SD15.2) $P = 0.05$ and SARAH 3.1 (SD 0.8) compared to 2.6 (SD1.1) in the DCD group $P = 0.018$ .	Moderate
Braga 2012	Brazil	To evaluate the efficacy of an intervention program based on social mediation, cooperative learning and metacognition (Metacognitive Dimension) in preadolescents with acquired brain injury (ABI).	RCT	14 children with ABI. Age: 9 to 13 years. Gender: 9 male, 5 female. Ethnicity: Brazilian.	15 children with ABI. Age: 9 to 13 years. Gender: 12 male, 3 female. Ethnicity: Brazilian.	-	After 3 months, the experimental group presented higher averages than the control group in both the Self Concept Scale for Children and Evaluation Scale of Elementary School Learning Strategies. Behavioural Rating Inventory of Executive Function was used to compare the differences between the parents' rating in the two groups, pre and post-intervention. No differences between the groups were observed.	High

Charles 2006	USA	To examine the efficacy of a modified form of Constraint Induced Movement therapy on involved upper extremity function in children with hemiplegic CP.	Single blinded randomised control study	11 children with CP. Age: 6 years, 8 months (mean), S.D. 1 year 4 months (all children). Gender: 5 male, 6 female. Ethnicity: not stated.	11 children with CP. Age: not reported separately. Gender: 9 male, 2 female. Ethnicity: not stated.	-	Both groups improved in movement efficiency but intervention group improved more and improvement maintained at 6 months, control group returned to baseline. Both improved speed dexterity. Environmental (functional) use: greater improvement in use perceived in intervention group. Quality of movement improved in both groups; but continued to improve in intervention group and decreased between 1-6 months in control group. Impairment results No significant differences across any group ( $p>0.05$ ). None of the children were out of their sling for more than 15 minutes during any 6-hour session.	Low
Corn 2003	Australia	To investigate the effectiveness of Second Skin lycra splints to improve the quality of upper limb movement for children with spasticity.	Case series	4 children with a neurological disorder. Age: 8, 11, 13, 16 years. Gender: 2 male, 2 female. Ethnicity: not stated.	Participants are their own controls.	-	Long-term wearing of a Second Skin lycra splint for one child with CP was associated with a decline in the quality of his upper limb movement. For one new user with ABI, a significant improvement was found while wearing the splint initially but was not maintained over time. Two other participants showed no change in their quality of movement while wearing the splint.	Moderate
Eliasson 2015	Sweden	To investigate whether or not a single block of mCIMT (2h/d for 2mo) at age 2 to 3 years influences the course of development of bimanual hand function at around 8 years of age.	Cohort Study	26 children with CP. Age: 27.9 months (mean), S.D. 11 months. Gender: 15 male, 11 female. Ethnicity: not stated.	19 children with CP. Age: 37.2 months (mean),	-	Children who were receiving mCIMT had an upper limit of development of bimanual hand function that was 8.5 AHA units higher than in the reference group ( $p=0.022$ ). When controlling for brain lesion characteristics and baseline in a subgroup	Moderate

					S.D. 14.6 months. Gender: 9 males, 10 females. Ethnicity: not stated.		of 32 children, the difference was considerably smaller and no longer significant.	
Fasoli 2008	USA	To examine the feasibility and effects of robotic therapy for children with cerebral palsy and upper limb hemiplegia.	Cohort	12 children with CP or ABI. Age: 4 to 12 years. Gender: 7 male, 5 female. Ethnicity: not stated.	NA	1 month	Significant improvements in upper limb coordination and quality of movement were found on the two primary outcome measures, with moderate to large effect sizes found on two of the QUEST sub scores (dissociated movements and weight bearing) as well as on the QUEST total score and FMA. A review of individual scores revealed the greatest improvement on the shoulder and elbow items of the FMA and QUEST. Significant improvements with small to moderate effect sizes were found for the Modified Ashworth Scale and isometric elbow strength. Robotic therapy had a smaller impact on muscle spasticity and strength, as compared with quality of arm coordination and motor function. The parent questionnaire revealed gains in the quantity and quality of paretic arm use during daily activities at the end of the 8-wk therapy trial (discharge)..	Low
Fasoli 2010	USA	To develop robot assisted movement therapy that was engaging and cognitively challenging for children that	Case report (n=1) and feasibility study (n=12)	One additional child with CP to add to the study above. Age: 8.5 years.	Children included in Fasoli 2008	1 month	Upper limb coordination and quality of movement statistically significant in n=12 sample (ANOVA and main effect). Moderate-large effect scores for QUEST	Low

		provided intensive sensorimotor practice during goal directed reaching activities		Gender: female. Ethnicity: not stated.			subscores of dissociated movement and weight bearing as well as QUEST total score and FMA. Parent questionnaire: large gains in quantity and quality of paretic arm use at end of 8 weeks ( $p<0.001$ ) which dropped but remained higher than baseline at 1 month post.	
Fehlings 2001	Canada	To evaluate which baseline characteristics of the child predict a positive functional response to the BTX-A injections within our randomized controlled trial.	RCT	14 children with spastic hemiplegia. Age: 2.5 to 10 years. Gender: not stated Ethnicity: not stated.	15 children with spastic hemiplegia. Age: 2.5 to 10 years. Gender: not stated. Ethnicity: not stated.	-	RCT results (previously published): 14 in BTX-A group. Two way ANOVA QUEST scores favoured Rx group: $F=4.69$ , $DF\ 1,83$ , $p=0.039$ PEDI also improved $F=4.68$ , $df=1,82$ , $p=0.04$ Current study analysis: Baseline grip strength was significantly higher in the responder group $p=0.001$ (60-84mmHg vs 30-52mmHg at baseline). After adjusting for possible effects of age on grip strength with an analysis of covariance procedure, the difference in baseline grip strength remained significant with a P-value of 0.002.	Moderate
Frascarelli 2009	Italy	To assess whether robot mediated therapy (RMT) can yield positive outcomes in children with acquired or congenital upper extremity movement disorders.	Case series	12 children with hemiplegia. Age: 10.5 years (mean), range 5 to 15 years. Gender: not stated. Ethnicity: not stated.	NA	-	Pre-post clinical evaluation revealed statistically significant gains for all primary and secondary metrics. Parent's Questionnaire high level of satisfaction- better use of the arm during the activity daily life. Clinically, children were better able to move their paretic arm in reaching movement and to control the coordination of shoulder, elbow and wrist. RMT led to spasticity decreases in chronic cases. It led to improved trunk-upper	Low

							extremity postural attitude, and it was well accepted by parents and children.	
Galvin 2010	Australia	To identify the functional tasks of concern to children and parents following paediatric stroke, and to investigate the use of the COPM and PEGS in a paediatric stroke population.	Cross-sectional study	26 children with AIS. Age: 9 years 1 month (mean), S.D. 61 months. Gender: 14 male, 12 female. Ethnicity: not stated.	NA	-	Children and families report concerns across all functional domains. Nearly half of the concerns identified for both pre-school (45%) and school aged (46%) were related to the performance of self-care skills.  Pre-school-aged children, the second highest area of concern was productivity such as learning and fine motor tasks. Leisure concerns were more readily identified for school aged children, followed by productivity concerns. School age children were also concerned about social abilities and activities outside the home.	Low
Gordon 2007	UK	The aim of this pilot study was to investigate feasibility, tolerability, and effect of modified constraint-induced movement therapy (mCIT) in children with hemiparesis after arterial ischaemic stroke (AIS).	Case series	6 children with AIS. Age: 12 years 3 months (median), range 6 years 10 months to 15 years 2 months. Gender: 1 male, 5 female. Ethnicity: not stated.	NA	-	Level of motor impairment changed in only one participant, who was rated severe prior to therapy and moderate immediately after and 1 month later, and who made a significant improvement as rated by the Melbourne Assessment. Participant 4 appeared to show improvement in sensory impairment from severe to mild over the course of the study. There was no change in sensory impairment in the rest.  There was no significant change in quality of movement of the affected upper limb after the therapy intervention All participants improved by at least one increment in each of their three goals. All parents thought that mCIT had been beneficial to their child, with improved	Moderate

							awareness of and confidence in upper limb use. Parents reported that mCIT was not as intrusive or disruptive as anticipated. Children reported improved use and control of their upper limb and thought the therapy sessions were fun, but would have preferred not to wear the splint. The importance of the child–therapist relationship was a common theme for both parents and children. The model preferred by parents and children, if having further mCIT, was home-based, therapist-delivered intervention during school holidays.	
Gygax 2011	Switzerland	To test the effectiveness and feasibility of mirror therapy in children with hemiplegia by performing a pilot crossover study in 10 participants	A pilot crossover study	10 children with spastic hemiparesis split into 2 groups of 5 – intervention and control. Demographic details not reported separately. Age: 6 to 14 years. Gender: 5 male, 5 female. Ethnicity: not stated.	10 children with spastic hemiparesis is split into 2 groups of 5 – intervention and control.	-	Testing of grasp strength behind the mirror improved performance by 15% ( $p=0.004$ ). Training with the mirror significantly improved grasp strength (with mirror +20.4%, $p=0.033$ ; without +5.9%, $p>0.1$ ) and Upper limb dynamic position (with mirror +4.6%, $p=0.044$ ; without +1.2%, $p>0.1$ ), Training without a mirror significantly improved pinch strength (with mirror +6.9%, $p>0.1$ ; without +21.9%, $p=0.026$ ).	Low
Chan 2011	Hong Kong	To investigate the effects of an explicit problem-solving skills training programme based on metacognitive principles for children with acquired brain injury (ABI) who attend mainstream schools.	RCT	16 children with ABI. Age: 12.4 years (mean), range 3 years. Gender: not stated. Ethnicity: not stated.	16 children with ABI. Age: 12.4 years (mean), range 3 years.	-	Significant differences in post-test scores were found for all measurements between children in the experimental group and those in the comparison group, using the baselines of dependent variables, years of schooling and the full IQ scores as the covariates.	Moderate

					Gender: not stated. Ethnicity: not stated.			
Lundine 2015	USA	To examine whether carbonated thin liquids improved swallowing compared to non-carbonated thin liquids for children with neurogenic dysphagia.	Non-randomised, cross over controlled trial	30 children with a neurological diagnosis (results for 24). Age: 13.7 years (mean), range 5 to 18 years. Gender: 13 male, 11 female. Ethnicity: not stated.	NA	-	Carbonation shows promise in reducing penetration/aspiration in neurogenic dysphagia Pre-swallow pooling significantly less often on carbonated liquids than on non-carbonated liquids. Penetration/aspiration occurred less often with carbonated liquids than non-carbonated Scores on Penetration/Aspiration Scale significantly lower (improvement) for carbonated liquid Post-swallow residue - no significant difference The 3 stroke patients showed little difference between the 2 conditions on any variable.	Moderate
Missiuna 2010	Canada	To explore the use of CO-OP with children with ABI.	Cohort	6 children with ABI. Age: 6 to 15 years. Gender: 5 male, 1 female. Ethnicity: not stated.	NA	-	An improvement in score was observed from the pre- to immediately post intervention period. Most children also continued to improve from post intervention to the follow-up. Of the six CO-OP enabling principles four principles were identified by therapists in their logs as being useful when working with children with ABI: making it fun, taking one thing at a time, working towards independence, and guided discovery. Children did not seem to remember or apply the executive strategy	Moderate

							from week to week and had difficulty formulating cognitive strategies independently.	
Mitchell 2012	Australia	To systematically review the literature for effectiveness and utility of virtual reality interventions on increasing physical activity capacity and performance in young people with cerebral palsy.	Systematic Review	4 studies were identified. Age: 6 to 18 years. Interventions included: 1. Mitti (Move it to improve it) 2. Wii Sports 3. Sony Playstation 2 and Eye Toy 4. Gesture Tek's Interactive Rehabilitation and Exercise system software	NA	-	Only one of the studies looked primarily at physical activity performance following virtual reality intervention. Others looked at gross motor or upper limb function, and balance or impairment measures, and included a measure of physical activity as a secondary outcome.  Large effects were seen for functional strength outcomes following Mitii training, though only side-steps and sit-to-stand were significant	High
Morgan 2004	Australia	To document the clinical characteristics of acute dysphagia in a group of paediatric patients after traumatic brain injury.	Case series	14 children with TBI. Age: 7.1 years (mean), S.D. 11 months. Gender: 7 male, 7 female. Ethnicity: not stated.	NA	-	a) cognitive rating – 8/14 RLA score III, 3/14 IV, 2/14 V, 1/14 II. b) 14/14 severe oral= motor impairment on VMPAC. c) 14/14 had deficits in all oromotor categories of the FDA – including reflex, jaw, lip and tongue function. d) 14/14 had oral-motor dysfunction for puree and semi-solid foods on SOMA. e) Feeding trial results: >50% had cognitive/behavioural deficits; oral sensitivity affected in 1/3rd; abnormal reflexes noted in majority of patients f) 9/14 had severe dysphagia on PHAD, 5/14 moderate dysphagia.	Low
Morgan 2007	UK	To investigate the effectiveness of eelectropalatography in	Case series	3 children with TBI. Age: 15, 14, 15 years.	NA	-	Perceptual improvement was noted for phoneme precision and length. Spatial EPG measures confirmed increased precision of	Low

		treating the articulatory component of dysarthria post-TBI.		Gender: 2 male, 1 female. Ethnicity: not stated.			phoneme production. No clear pattern of change for phoneme duration occurred. Intelligibility increased at word and sentence level, with little change reported in everyday speech intelligibility.	
Morgan 2012	Australia	To examine the effectiveness of interventions for oropharyngeal dysphagia in children with neurological impairment.	Systematic review	3 studies found. Age; under 18. Inclusion criteria: randomised controlled trials and quasi-randomised controlled trials for children with oropharyngeal dysphagia and neurological impairment.	NA	-	For the physiological function of swallowing, no significant differences were found between experimental and control groups for eating time, clearing time after swallows, or duration of meal times. No significant change in oral motor function was reported in the experimental group in one study. There were no significant differences found for any group on the ability to advance to a more solid food texture. No significant differences were reported for weight between the intervention and control group. It is not possible to reach definitive conclusions on the effectiveness of particular interventions for oropharyngeal dysphagia based on these studies.	High
Morgan 2013	Australia	To appraise the effectiveness evidence about enriched environments for improving the motor outcomes of infants at high risk of cerebral palsy.	Systematic review	7 studies included. Inclusion criteria: RCT, infants with a confirmed diagnosis of CP, designated "at high risk" of CP, 25% 2 years of age or younger, interventions: infant's environment was enriched via parent training or coaching, or therapists provided intense, targeted	NA	-	Five of 7 included studies compared an EE intervention with standard care and were clinically homogeneous for meta-analysis. When combined, the 5 studies included a total of 150 participants. The standard mean difference was 0.39 (95% confidence interval 0.05–0.72; I <sup>2</sup> = 3%; P = .02), indicating a small positive effect favouring enrichment over standard care on motor outcomes.	High

				motor skill practice aimed at enhancing plasticity.				
Raghavendra 2013	Australia	To investigate the effectiveness of tailored one-on-one support strategies designed to facilitate social participation of youth with disabilities through the use of the Internet for social networking.	Cohort	18 children with physical disabilities. Age: 13.7 years (mean) Gender: 12 male, 6 female. Ethnicity: not stated.	NA	-	Youth with disabilities can learn to use the Internet to build social networks with their peers, family and friends using Facebook, Skype and email.  Intensive one-to-one tailored intervention is needed to facilitate social participation. Families need support and training in use of the computer and Internet literacy, and awareness of the potential benefits of assistive technologies. Youth with disabilities may have basic literacy issues that need to be addressed to increase their successful Internet use.	Moderate
Karch 2013	Germany	To summarise the efficacy of studies to date—both CBT based and computer-aided—in the form of a meta-analysis to answer the questions Do cognitive therapies lead to improvement in functions promoting cognition, and do they enhance behaviour, intelligence, and school performance?	Systematic review	22 included studies. Age: under 18. Inclusion criteria: ABI, ADD/ADHD	NA	-	The overall effects of cognitive training on attention were small. A relatively strong effect was found on memory performance but with marked heterogeneity. The largest effect was found in the area of behaviour and but this was derived mainly from studies that lacked an active control group.	Moderate
Taub 2007	USA	To report on two RCTs of the use of CI therapy with children with CP with asymmetric upper extremity motor deficits and with hemiparesis consequent to prenatal, perinatal or early	RCT	Number of children not clear. Age: 8 months to 8 years across both studies. Gender: not stated. Ethnicity: not stated.	NA	-	The results in children with CP are better than those obtained in adults. Marked changes were observed in the quality of movement in the laboratory scored by masked observers from videotape; actual amount of use of the more affected arm in the life situation; active range of motion;	Moderate

		antenatal stroke, compare the results from adult and paediatric CI therapy, the special problems associated with carrying out CI therapy with young children and what some of the limits of paediatric CI therapy are.					and emergence of new classes of behaviour never performed before, such as in individual cases, fine thumb-forefinger grasp, supination, and use of the more affected extremity in crawling with palmar placement and rhythmic alteration. In the second experiment, the control group, after receiving usual and customary care for 6 months, was crossed over to receive CI therapy and exhibited results that were as good as those for the children receiving CI therapy first. Retention of treatment gains was approximately 70% at 6 months after the end of treatment.	
Ross 2011	UK	To answer the questions: Are there effective interventions for 1) cognitive effects, and 2) psychosocial effects, of paediatric ABI?	Systematic review	11 included studies. Inclusion criteria: (1) intervention studies addressing cognitive or psychosocial outcomes, (2) participants aged up to 18 years, and (3) peer-reviewed journal articles.	NA	-	Only two of the nine studies were rated as high quality. There was limited evidence for effective interventions for cognitive outcomes (attention, memory, and learning difficulties). For psychosocial outcomes, there was evidence that interventions can alleviate internalizing symptoms.	High
van Rhijn 2005	Belguim	To assess the effect of BTX-A to treat spasticity in children and adolescents with an acquired brain injury.	Case series	21 children with ABI. Age: 2 years 7 months to 19 years 8 months. Gender: 15 male, 6 female. Ethnicity: not stated.	NA	-	Improvement in spasticity (MAS) was demonstrated in all groups following treatment with BTX-A. Improvements in range of motion were initially demonstrated in all groups. By month 3, five patients had a worsening of movement. Patients with upper limb spasticity (Group 2) responded best to treatment with BTX-A with respect to MAS, goniometry and overall treatment goal assessments. Group 1 (spastic quadriplegia patients) also	Low

							obtained benefits from BTX-A treatment, with this being most evident up to 3 months post-injection. Group 3 patients (lower limb spasticity) showed the least improvement following BTX-A treatment, although both goniometry, MAS and overall treatment goal assessments did show some initial improvements.	
Wade 2006 (1)	USA	To describe a family-centred problem-solving intervention (FPS) for paediatric traumatic brain injury (TBI), and to assess the efficacy of the intervention in a randomized clinical trial.	RCT	16 children with TBI. Age: 10.9 years (mean), S.D. 2.6 years. Gender: not stated. Ethnicity: 19% African American, 81% Caucasian.	NA	-	Parents and children with TBI rated the program as extremely helpful and all indicated that they would recommend the program to others. Eighty percent of parents (12/15) and 75% of children reported that they had reached the problem-solving goals that they had set when they began the program. All parents reported that they understood the child's injury better and knew strategies for improving their child's behaviour. Nearly all parents (>90%) also reported that they knew strategies for improving their child's attention and had a plan for handling future problems. Most children with TBI and their siblings indicated that they understood TBI better (85% and 83%, respectively), knew strategies for paying attention (92% and 100%, respectively), and had a plan for handling future problems (69% and 89%, respectively). All parents, 85% of children with TBI, and 89% of siblings receiving FPS reported improved parent-child relationships.	High
Wade 2006 (2)	USA	To examine the feasibility and efficacy of online FPS therapy in improving child	RCT	20 children with TBI. Age: 10.9 years (mean), S.D. 2.5 years.	20 children with TBI.	-	The FPS group reported better child self-management/compliance at follow-up than did the IRC group. The child's age and	Low

		outcomes following paediatric TBI.		Gender: 11 male, 9 female. Ethnicity: 20% African American, 80% Caucasian.	Age: 11 years (mean), S.D. 3.9 years. Gender: 12 male, 8 female. Ethnicity: 30% African American, 70% Caucasian.		socioeconomic status moderated treatment effects, with older children and those of lower SES who received FPS showing greater improvements in self-management and behaviour problems, respectively.	
Willis 2002	USA	To assess whether restraint of the unimpaired arm would improve the function of the paretic arm in children with chronic hemiplegia (>1year).	RCT	12 children with hemiplegia. Age: (2x) 3 years, (4x) 4 years, (2x) 5 years, (4x) 6 years. Gender: not stated. Ethnicity: not stated.	13 children with hemiplegia. Age: (2x) 1 year, (6x) 2 years, (1x) 4 years, (1x) 5 years, (1x) 7 years, (2x) 8 years. Gender: not stated.	-	The 12 treatment (casted) children improved 12.6 PDMS points after 1 month of casting; the 13 control children improved 2.5 points. Improved PDMS scores persisted 6 months later when 7 treatment children returned. Similar results were obtained in the crossover when 10 control children received casts. Parental report corroborated improvement in casted children (22 of 22 parents) and its persistence at follow-up (21 of 22 parents). Receiving ongoing physical/occupational therapy did not seem to account for these results: control children received more (2.1 visits/week) than treatment children (1.4 visits/week).	Low

					Ethnicity: not stated.			
Yang 2013	Canada	To identify from the literature a potential critical period for the maturation of the corticospinal tract (CST) and report pilot data on an intensive, activity- based therapy applied during this period, in children with lesions to the CST.	Literature review and cohort study	5 children with CP. Age: 1.5 years (mean) range 1.0 to 1.9 years. Gender: 2 male, 3 female. Ethnicity: not stated.	NA	-	Preliminary results with training children younger than 2 years showed improvements in walking that exceeded all previous reports. Further, techniques for measuring motor and sensory pathways to and from the legs were refined, so that changes can be measured at this young age.	Low
Yasukawa 2006	USA	To describe functional hand and arm skills in children admitted into a rehabilitation program subsequent to use of Kinesio Taping.	Case series	15 children with decreased muscle strength of the upper extremity. Age: 4 to 16 years. Gender: 5 male, 10 female. Ethnicity: not stated.	NA	-	Analysis of variance was used to compare the Melbourne Assessment scores across the 3 time periods. Melbourne Scores improved over time, $F(2, 14) = 17.7, p < .001$ . Further, the improvement from pre- to post taping was statistically significant, $F(1, 14) = 18.9, p < .02$ .	Moderate
Van't Hooft 2005	Sweden	Test effectiveness of a cognitive training programme in children and adolescents with attention and memory deficits after ABI.	RCT	18 children with ABI. Age: 11.7 years (mean), S.D. 2.3 years. Gender: 12 male, 6 female. Ethnicity: not stated.	20 children with ABI. Age: 12.6 years (mean), S.D. 2.6 years. Gender: 10 male, 10 female. Ethnicity: not stated.	-	Significant improvements in the majority of neuropsychological tests of sustained and selective attention as well as in memory performance were shown in the treatment group as compared to controls.	Low

Needs of families and the role of the voluntary sector in planning care and rehabilitation.								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Antonini 2014	USA	To report findings from a pilot randomized clinical trial (RCT) comparing the efficacy of an online positive parenting skills intervention program focused on young children with TBI with access to Internet resources in increasing positive parenting behaviours and reducing child behaviour problems.	Pilot RCT	20 children with TBI (parenting skills intervention). Age: 5.6 years (mean), S.D. 2.1 years. Gender: 14 male, 6 female. Ethnicity: 2 Caucasian American/White 8 African American/Black/Multiracial.	17 children with TBI (internet resources). Age: 5.2 years (mean), S.D. 2.1 years. Gender: 11 male, 6 female. Ethnicity: 11 Caucasian American/White 6 African American/Black/Multiracial	-	Positive parenting skills improved in the intervention group. Improvements were correlated with the number of sessions completed. Child compliance following indirect commands: children across groups were more compliant at the follow-up visit than at the baseline visit (RR = .78, p = .017). There were no changes in Parent Ratings of Child Behaviour on ECBI.	Moderate
Ball 2013	UK	To explore the process of reintegration into school of children with ABI and to consider the role of EPs within the local authority in supporting this process	Qualitative interviews	8 adults reporting on their work with children. Age: not stated. Gender: not stated. Ethnicity: not stated.	NA	-	1. Need improved communication between health and education staff which was ad hoc. 2. Need more training for education staff in ABI 3. Discharge from hospital key transition point for exchange of information between professionals Educational psychologists remain	Low

							involved with child through school life and are key for communicating information about the injury to future settings and translating medical jargon into practical information.	
Bykova 2013	Russia	To uncover some particularities of psychological support for children with severe TBI.	Case series	30 children with TBI. Age: 11 to 16 years. Gender: not stated. Ethnicity: not stated.	NA	-	52% of parents whose children survived severe TBI could adequately integrate into the process of their child's recovery. In these families, the level of expectations is reasonable, rehabilitation goals are correctly planned at every stage, and there is an observable awareness of "here and now." 34% of parents view their participation in the rehabilitation process as a formality, whereby they feel responsible solely for the provision of nurture, while holding others (including doctors) accountable for their child's recovery. 14% of parents entirely ignore their child's needs during his recovery after severe TBI.	Low
Ehrenfors 2009	Sweden	To investigate which assessments were widely used in the rehabilitation of schoolchildren with ABI and to examine which components those assessments addressed, using the ICF model as a framework.	Qualitative study	70 professionals. Age: not stated. Gender: not stated. Ethnicity: not stated.	NA	-	Most of the assessments (two-thirds) were linked to the body functions. No assessments were linked to facilitators/barriers in the community. 175 formal assessments identified with little coherence nationally. 43 were widely used.	Moderate
Galvin 2010	Australia	To identify the functional tasks of concern to children and parents following paediatric stroke, and to investigate the use of the	Cross-sectional study	26 children with AIS. Age: 9 years 1 month (mean), S.D. 61 months. Gender: 14 male, 12 female.	NA	-	Children and families report concerns across all functional domains. Nearly half of the concerns identified for both pre-school (45%) and school aged (46%) were related to the performance of self-care skills.	Low

		COPM and PEGS in a paediatric stroke population.		Ethnicity: not stated.			Pre-school-aged children, the second highest area of concern was productivity such as learning and fine motor tasks. Leisure concerns were more readily identified for school aged children, followed by productivity concerns. Children and families reported similar concerns School age children were also concerned about social abilities and activities outside the home.	
Law 2006	Canada	To describe comprehensively the participation of children with physical disabilities in day to- day formal and informal activities.	Cohort	427 children with physical disabilities. Age: 10 years (mean), S.D. 2 years 4 months Gender: 229 male, 198 female. Ethnicity: 28 Asian (east and southeast), 8 Asian (Arab/west), 28 Black, 345 Caucasian, 9 Hispanic, 6 Native, 3 Missing.	NA	-	Children participated in proportionately greater participation in informal activities rather than formal activities. Proportionately, there are fewer activities completed in the active physical and skill-based scales. Participation intensity in formal activities was lower than intensity in informal activities. Females participated in significantly more social ( $p=0.001$ ) and skill-based ( $p<0.001$ ) activities. Analysis by age indicated that overall participation was significantly lower for children 12 years and older ( $p<0.001$ ), owing to a significantly lower participation in informal ( $p<0.001$ ) and recreational activities ( $p<0.001$ ).	Low
Limond 2009	UK	To present a preliminary examination of quality of life following TBI and also to obtain parents' views on services.	Retrospective cross sectional study.	47 children with TBI. Age: 10.5 years (mean), S.D. 3.6. Gender: not stated. Ethnicity: not stated.	NA	-	Children with TBI were 13x more likely to have significantly impaired QoL compared to general population. 57% of parents reported that they received the right amount of information about what had happened to their child	High

							<p>during hospital admission and about the difficulties their child may have after leaving hospital.</p> <p>60% felt that they received enough information about who to contact if having concerns after leaving hospital. 23% felt they had received enough information about voluntary or other services.</p> <p>11% of children currently received extra support at school.</p> <p>Contact with follow-up services was rated as just right by 32% of the group. 45% of parents felt they did not receive enough support.</p>	
McDougall 2006	Canada	<p>To evaluate the utility of PABICOP (Paediatric Acquired Brain Injury Community Outreach Programme) in</p> <ul style="list-style-type: none"> <li>-improving knowledge</li> <li>-facilitating empowerment</li> <li>-increasing successful integration</li> <li>-and other secondary outcome measures</li> </ul>	Non-randomised controlled trial.	<p>64 children with ABI.</p> <p>Age: 9.8 years (mean).</p> <p>Gender: 44 male, 20 female.</p> <p>Ethnicity: not stated.</p>	<p>32 children with ABI.</p> <p>Age: 11.1 years (mean), S.D. 4.6.</p> <p>Gender: 25 male, 7 female.</p> <p>Ethnicity: not stated.</p>	1 year	<p>Parents/caregivers with more than 10 contacts with PABICOP scored significantly higher on an ABI knowledge quiz than parents/caregivers with 10 contacts or less or the comparison group at post-test and follow-up.</p> <p>Parents/caregivers with 10 contacts or less with PABICOP reported significantly greater improvements in children's school and total competence on the CBCL than either parents/caregivers with more than 10 contacts or the comparison group at post-test and follow-up.</p>	Low
Morgan 2013	Australia	To appraise the effectiveness evidence about enriched environments for improving the motor outcomes of infants at high risk of cerebral palsy.	Systematic review	<p>7 studies included.</p> <p>Inclusion criteria: RCT, infants with a confirmed diagnosis of CP, designated "at high risk" of CP, 25% 2 years of age or younger.</p>	NA	-	<p>Five of 7 included studies compared an EE intervention with standard care and were clinically homogeneous for meta-analysis</p> <p>When combined, the 5 studies included a total of 150 participants. The standard mean difference was 0.39 (95%</p>	High

							confidence interval 0.05–0.72; I <sup>2</sup> = 3%; P = .02), indicating a small positive effect favouring enrichment over standard care on motor outcomes.	
Rietdijk 2012	Australia	To describe the effectiveness of using telehealth programs to provide training or support to family members of people with traumatic brain injury.	Systematic review	16 studies included. Inclusion criteria: 1) any telehealth intervention involving family members of a person with TBI 2) Any age 3) at least 50% of sample had to be family members of people with TBI 4) Telehealth defined as any intervention delivered at a distance using technology incl. telephone, websites and videoconferencing	NA	-	29–38% of family members across 5 studies stated they believed a face-to-face intervention would have been preferable or more helpful. Telehealth could be used to increase access to services for families in rural areas, to train family members in the skills required to facilitate recovery after TBI, to provide appropriate and timely intervention for problems arising at home, or to create a forum for peer support without needing to share the same location. Several studies demonstrated that participants reported training to be beneficial over the long-term after program completion, or that improvements in outcomes were maintained over time.	Moderate
Wade 2014 (1)	USA	To test the efficacy of Counsellor-Assisted Problem Solving (CAPS) versus an internet resources comparison (IRC) condition in reducing behaviour problems in adolescents following traumatic brain injury (TBI).	RCT	65 children with TBI. Age: 12 to 17 years. Gender: not stated. Ethnicity: not stated.	67 children with TBI. Age: 12 to 17. Gender: not stated. Ethnicity: not stated.	6 months	Post hoc ANCOVA, controlling for pre-treatment scores, was used to examine group differences in behaviour problems in the entire sample and among older (n=59) and younger adolescents (n=53). Among older but not younger adolescents, CAPS resulted in greater improvements on multiple dimensions of externalizing behaviour problems than did IRC.	High

Wade 2014 (2)	USA	The purpose of the current study is to examine the efficacy of Counsellor-Assisted Problem Solving (CAPS) in improving caregiver adaptation following traumatic brain injury (TBI).	RCT	Families of 65 children with TBI. Age: 12 to 17 years. Gender: not stated. Ethnicity: 20% Caucasian.	Families of 67 children with TBI. Age: 12 to 17. Gender: not stated. Ethnicity: 19% Caucasian.	-	Computer experience moderated post intervention improvements in caregiving self-efficacy following CAPS, Specifically, parents in CAPS with low levels of prior use reporting the greatest improvements. CAPS participants who completed 5 or more sessions reported greater reductions in depression than did the IRC; however, the groups did not differ on global distress.	Moderate
Wade 2011 (2)	USA	To describe the benefits of web based coaching for parents of children with TBI.	Cohort	13 parents. Age: children between ages of 3 and 9. Gender: not specified. Ethnicity: includes African American and Appalachian but numbers not specified.	NA	-	9/13 parents preferred the web-based coaching to traditional treatment; they liked its ease of use and doing it at home. Therapists liked coaching over the web despite the need to address boundaries and troubleshoot technological difficulties. Therapeutic alliance was comparable to traditional therapy with nearly all families expressing a strong connection to the therapist. Individuals with less computer experience particularly liked the program because it gave them access to the web and a sense of empowerment.	Moderate
Eccleston 2012	USA	To evaluate the effectiveness of psychological therapies that include coping strategies for parents of children/adolescents with chronic illnesses.	Systematic review	45 papers with 3214 participants. Age: under 19 years.	NA	-	Across all treatment types, psychological therapies that included parents significantly improved child symptoms for painful conditions immediately post-treatment. Across all medical conditions, cognitive behavioural therapy (CBT) significantly improved child symptoms and problem solving therapy significantly	Moderate

							improved parent behaviour and parent mental health immediately post-treatment. There were no other effects at post-treatment or follow-up.	
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## Chapter 10: Long term care: transfer and transition

Managing educational and social-care transition								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Backhouse (1999)	Australia	To examine the perceptions and experiences of adolescents with ABI and their parents in relation to their school to work transition	Qualitative	<p>14 Participants (7 young people with ABI plus 7 parents of young people with ABI).</p> <p>Age: at injury (6 to 13), age at participation (14 to 18).</p> <p>Gender: unknown.</p> <p>Ethnicity: unknown.</p>	NA	-	Most of the young people appeared to have had a general lack of support from allied health and educational professionals throughout the continuum of hospital to school, and school to work transitions. All parents reported high levels of stress related to their child's schooling and future employment, and many young people also reported vast unmet needs related to both the present and the future.	Moderate
Wehman (2014)	America	To analyse the relationships between the transition planning process and post-school employment for youth with TBI using the NLTS-2	Prospective longitudinal study	<p>200 students with an educational disability of TBI.</p> <p>Age: unknown.</p> <p>Gender: 73% male, 27% female.</p> <p>Ethnicity: 74% white, 13% African-American, 11% Hispanic, and 2% others.</p>	NA	-	Among youth with TBI, 51% held current employment at the time of interview and 73% had been employed at any time after high school. Findings showed that students with TBI who had transition goals for postsecondary education were more likely to be employed at some point since leaving high school. The findings also support active student engagement & leadership in the transition planning process, and the inclusion of outside organizations and individuals.	High

The transition of a young person into adult health care								
Author (date)	Country of origin	Study aim	Study type	Participants	Control group	Length of follow-up	Results	Quality assessment
Latzman (2010)	America	To assess the general feelings and attitudes regarding transition of health care in patients with SCD, and the effectiveness of a transitional sickle cell clinic model with regard to psychological outcomes.	Cross-sectional survey	71 African-American patients aged 14 to 26-years with SCD. Age: 14 to 26 years. Gender: 40% female (group 1), 55.6% female (group 2), 41.7% female (group 3). Ethnicity: African-American	NA	-	The number one area of concern for pre-transition patients was meeting new caregivers. Caregivers of pre-transition patients identified leaving behind the previous doctor as the number one area of concern. The most important concern for patients both in the transitioning and adult clinic was being seen in the adult emergency room. Compared to both pre-transitioning and adult clinic patients, transitional patients reported significantly lower levels of negative affect (fear and sadness; $p < 0.001$ ), and higher levels of positive affect for joviality ( $p < 0.01$ ).	Low
Young (2009)	Canada	To examine the issue of clinical transition from the perspectives of individual patients with mild, moderate, and severe CP, SB, and ABIC and their parents, to better understand the scope of this issue and to assist with the development of evidence-based health care transition programs	Qualitative study	15 youths and 15 adults who had a primary diagnosis of CP, SB, or ABIC. Age: 14 to 18 years (mean 17.8 years). Gender: unknown. Ethnicity: unknown.	NA	-	All participants identified challenges in transition, including: lack of access to health care; lack of professionals' knowledge; lack of information and uncertainty regarding the transition process. Two solutions were identified: early provision of detailed information and more extensive support throughout the clinical transition process. Six key themes emerged from the qualitative analysis. These themes included four barriers and two potential solutions: Barriers: 1 Lack of access to health care by 78% of sample 2 Lack of professional knowledge 56% 3 Lack of information provided 55% 4 Uncertainty regarding the transition process 60% Solutions: (A) More information	High

							throughout transition process 52: (B) More support throughout transition process 50%	
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# Appendix 4d: List of included studies

## Chapter 3: Acute diagnosis of stroke in childhood

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## Chapter 7: Haemorrhagic Stroke

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