

**Supplemental Table 3.** Pre- and post-workshop weighted scores for all statements/recommendations.

Statement	Pre Weighted score	Post Weighted score	Post % for ≥4
<b>Recognition of stroke-like episodes</b>			
1. All patients suspected to be suffering a stroke-like episode due to underlying mitochondrial disease should be discussed or referred to a mitochondrial disease specialist in the acute setting.	4.6	5.0	100%
2. The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.	4.3	5.0	100%
3. The recognised features associated with stroke-like episodes:			
• Acute/subacute onset, evolving neurological symptoms	4.7	5.0	100%
• Altered conscious level/encephalopathy	4.4	4.8	90%
• Headache	4.7	4.6	90%
• Visual field defect	4.5	4.6	90%
• Focal motor seizures (including epilepsy partialis continua)	4.5	4.5	90%
• Generalised seizures	4.3	4.5	90%
• Non-convulsive status epilepticus	4.1	4.5	90%
• Elementary visual hallucination e.g. coloured flashing light	4.2	4.4	90%
• Nausea and vomiting	4.0	4.3	90%
• Formed, complex visual hallucination	3.9	4.3	80%
• Focal motor weakness	4.3	4.3	90%
• Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	4.0	4.1	90%
• Focal sensory symptoms	4.1	4.1	80%
• Dysphasia	4.0	4.1	80%

• Apraxia	4.1	4.1	80%
4. Diagnosis of a stroke-like episode requires the combination of clinical assessment, MRI head and EEG	64%	100%	-
5. Definition for the mitochondrial stroke-like episodes: A mitochondrial stroke-like episode is a subacute, evolving brain syndrome driven by seizure activity in genetically determined mitochondrial disease. These potentially treatable encephalopathic episodes can present at any age with neurological and/or psychiatric symptoms typically associated with cortical/subcortical MRI changes and EEG abnormalities.	N/A	4.9	100%
6. Stroke-like episodes should be suspected irrespective of patient's age, although it is more common under age of 40.	4.4	4.8	100%
7. All patients (or their carers) with the mitochondrial disease and previous history of stroke-like episodes should be given an alert card and emergency care plan regarding the recognition and management of stroke-like episodes and associated complications.	4.8	5.0	100%
8. Carriers of genetic mutations that put them at significant risk of developing stroke-like episodes should be given an alert card regarding the recognition and management of stroke-like episodes and associated complications.	4.6	4.5	90%
<b>Assessment and investigations</b>			
9. Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.	4.2	4.5	100%

10. A systemic enquiry and general examination should be performed to identify any potential triggers such as infection, gut dysmotility, dehydration, prolonged fasting and adherence to the anti-epileptic drug(s).	4.7	4.9	100%
11. A full neurological examination should be performed with a special attention to the level of consciousness, visual field testing, and evaluation of speech and signs of apraxia.	4.8	5.0	100%
12. The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes:			
• Full blood count	4.6	5.0	100%
• Urea and creatinine (kidney function)	4.6	4.9	100%
• Liver function test (LFT)	4.6	4.9	100%
• Random glucose	4.7	4.9	100%
• Serum lactate (without tourniquet applied)	4.5	4.4	100%
• C-reactive protein (CRP)	4.4	4.9	100%
• Urinalysis and urine culture (septic screen)	4.5	4.7	90%
• Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	4.0	4.6	90%
• Coagulation screen (for patients with <i>POLG</i> mutations)	3.9	4.4	80%
• Creatine kinase (CK)	4.0	4.3	80%
• HbA1c (for known diabetic)	3.7	4.3	90%
• Blood culture (septic screen)	3.3	4.1	80%
• Arterial blood gas (ABG)	3.8	3.8	70%
13. The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/ <i>POLG</i> mutation.			
• Blood tests (as outlined in Q12)	4.8	5.0	100%
• Chest radiography (if aspiration pneumonia suspected)	4.7	4.9	100%

• Abdominal x-ray (if intestinal pseudo-obstruction suspected)	4.5	4.9	100%
• Electrocardiogram (ECG)	4.6	4.8	90%
• Lumbar puncture (LP)	3.2	3.6	60%
• Electroencephalogram (EEG)	4.8	5.0	100%
• MRI head (unless there is contraindication, then CT head)	4.9	5.0	100%
14. A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.	4.2	4.6	90%
15. Proposed MRI head sequences for investigating stroke-like episodes:			
• T2		5.0	100%
• FLAIR		5.0	100%
• DWI		5.0	100%
• T1		4.9	100%
• ADC		4.7	90%
• DTI (diffusion tensor imaging)		3.3	30%
• T2 gradient echo		3.2	20%
• MR angiogram		2.7	0
• MR venogram		2.5	0
16. If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, the following tests should be considered repeating to help guide clinical management:			
• Electroencephalogram (EEG)	4.9	5.0	100%
• MRI head (unless there is contraindication, then CT head)	4.6	5.0	100%
• Blood tests (as outlined in Q12)	4.4	4.6	100%
• Chest radiograph	3.7	3.7	50%
• Abdominal x-ray	3.8	3.7	60%
• Electrocardiogram (ECG)	3.4	3.5	60%
• Lumbar puncture (LP)	3.2	3.3	50%

### Management

17. Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.	4.6	4.8	100%
18. At the initial hospital presentation, if a stroke-like episode is suspected and focal seizures are evident, how would you manage this? (more than one option is permitted)			
• Intravenous anti-epileptic drug	100%	5.0	100%
• Oral anti-epileptic drug	45%	3.8	70%
• Intravenous L-arginine	18%	2.6	10%
• Oral L-arginine	9%	2.3	0
• Anti-epileptic drug is not routinely used in my practice	0	1.1	0
19. At the initial hospital presentation, if seizures and/or encephalopathy are evident, levetiracetam (20-40mg/kg, max 4500mg) is the preferred first-line intravenous anti-epileptic drug.		4.8	80%
<i>Other second-line choices: phenytoin, phenobarbitone, lacosamide</i>			
20. At the initial hospital presentation, if a stroke-like episode is suspected due to a new neurological deficit (e.g. hemianopia) but no clear seizure activity is evident, how would you manage this?			
• Intravenous anti-epileptic drug	27%	4.1	70%
• Oral anti-epileptic drug	27%	3.8	60%
• Intravenous L-arginine	18%	2.5	10%
• Oral L-arginine	9%	2.2	0
• Anti-epileptic drug is not routinely used in my practice	0	1.3	0
• Observation and supportive care only (e.g. hydration, management of constipation)	36%	2.5	20%
21. Sodium valproate is contra-indicated for patients with recessive <i>POLG</i> mutations, and should also be avoided in patients with mitochondrial	4.7	4.8	100%

epilepsy caused by other genotypes if another alternative drug is available.			
22. After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.	4.3	4.8	100%
23. Nasogastric tube (NGT) insertion should be performed for administering usual AEDs and other medications if oral route is not reliable due to encephalopathy or vomiting.	4.5	4.7	90%
24. <i>POLG</i> mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.	4.4	4.7	100%
25. In patients with previous history of stroke-like episodes, when they report of symptoms suggestive of a new episode or seizure, advice should be given to consider early commencement in the pre-hospital setting of intermediate or long-acting benzodiazepine for example clobazam.	4.2	4.3	80%
26. If the patient develops generalised, convulsive status epilepticus, further management such as escalation to intensive care setting should follow the local status epilepticus guidelines (e.g. NICE Clinical Guidelines 137, SIGN guidelines 143, EFNS guidelines 2010), except sodium valproate is contra-indicated.	4.8	5.0	100%
27. Indications for intensive care unit admission (more than one option is permitted):			
• Convulsive (generalised) status epilepticus	100%	100%	-
• Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)	91%	100%	-

• Severe encephalopathy (with breakthrough focal motor or generalised seizures) with a high risk of aspiration	73%	100%	-
• Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs	64%	90%	-
• Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs	46%	80%	-
28. Midazolam is the first choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes.		4.5	-
29. There is a potential for worsening pre-existing lactic acidosis or increase the risk of developing of propofol infusion syndrome (PRIS) with prolonged use (>24-48 hours) in the maintenance of anaesthesia, therefore, we should avoid using propofol infusion.	3.6	3.3	40%
<i>It is not contraindicated for using propofol to treat refractory status epilepticus associated with stroke-like episodes; it should be decided on the case by case basis.</i>			
30. Continuous EEG monitoring should be performed to ensure that seizure activity has been suppressed, and no breakthrough seizures (including non-convulsive seizures) occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals (at least daily) for the duration of anaesthesia.	4.3	4.8	100%
31. Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.	3.9	4.7	100%

32. Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.	N/A	3.7	70%
33. Some patients may manifest with excessive anxiety, aggressiveness, agitation or psychosis (auditory or visual hallucination) if stroke-like lesions involve frontal, temporal or limbic lobe.	4.5	4.7	90%
34. It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.	4.1	4.9	100%
35. Which of the following antipsychotic medications would you consider using to manage the acute psychiatric complications related to stroke-like episodes? (more than one option is permitted)			
• Haloperidol	45%	90%	-
• Benzodiazepine	73%	80%	-
• Quetiapine	64%	80%	-
• Olanzapine	45%	70%	-
• Risperidone	45%	60%	-
• Do not use any anti-psychotic drug	9%	10%	-
36. Monitoring for the development of arrhythmia with the introduction of an antipsychotic drug may be necessary especially in patients with the m.3243A>G mutation or other rare mtDNA point mutations and pre-existing pre-excitation syndrome (e.g. Wolff-Parkinson-White syndrome).	3.8	4.4	100%
37. Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.	4.1	4.4	100%
38. Maintenance intravenous fluid should be administered for patients who are at risk of	4.8	5.0	100%



dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

39. The preferred fluid choices are 5% dextrose and 0.9% saline; Ringer's solution (e.g. Hartman's) is not recommended because of the theoretical risk of exacerbating lactic acidemia in patients with mitochondrial disease.	3.8	4.1	90%
40. Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.	4.7	4.9	100%
41. Careful monitoring of fluid balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.		4.9	100%
42. Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes?	55%	70%	-
43. Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.	4.1	4.6	100%
44. Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.	4.1	4.3	100%
45. Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.	4.7	4.8	100%
46. Nutrition: Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ).	4.4	4.6	100%

47. Nutrition: Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds.	4.3	4.7	100%
48. Gastroparesis and small bowel intestinal pseudo-obstruction can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction.	4.6	4.8	100%
49. Drip and suck: Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach content can be achieved with the insertion of the wide-bore nasogastric tube.	4.4	4.8	100%
50. Concomitant constipation and/or faecal impaction should be treated.	4.6	4.8	100%
51. Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.	4.5	4.6	100%
52. Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.	4.1	4.5	100%
53. Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.	3.9	4.9	100%
54. Early consultation with the nutritional team is recommended during admission for stroke-like episodes.	4.3	4.5	90%
55. IV L-arginine is not routinely used by the participants of the workshop for the acute management of stroke-like episodes.	82%	80%	-

56. Oral L-arginine is not routinely used by the participants of the workshop for the acute management of stroke-like episodes.	82%	80%	-
57. There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.	4.3	4.6	100%
58. Oral co-supplementation of citrulline and L-arginine has been shown to increase nitric oxide production in patients with the diagnosis of MELAS syndrome. However, there is currently no clinical study demonstrating its efficacy in treating acute stroke-like episodes.	4.2	4.6	100%
59. Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.	4.4	4.6	100%
60. Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.		4.6	100%
61. Other supplements such as riboflavin and creatine have been assessed in small trials but have not been proven to provide benefit in general or in relation to stroke-like episodes.	4.6	4.6	100%
62. Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.	4.2	4.6	100%
63. Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.	4.5	4.7	100%
64. Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.	4.6	4.9	100%
65. Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid	4.3	4.7	100%

replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

### Genetic testing

66. Urgent genetic testing for the mitochondrial disease should be considered in patients presenting with suspected stroke-like episodes because of their implications for the clinical management.	N/A	4.7	90%
67. At least two tissue samples should be sent for the genetic studies because the m.3243A>G mutation (or other mtDNA mutations) may not be detectable in the blood sample.	N/A	4.7	100%
68. Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?			
• Urine	82%	100%	-
• Blood	82%	80%	-
• Muscle	64%	70%	-
• Buccal	27%	40%	-
• Fibroblast	18%	20%	-
69. Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	91% (Yes)	90% (Yes)	-
<i>We would recommend to quantify the mutant heteroplasmy levels of m.3243A&gt;G and other mtDNA mutations.</i>			
70. Whole mtDNA sequencing of non-invasive tissue (such as urine epithelial cells) should be considered before the muscle biopsy in patients present with classical stroke-like episodes (after excluding m.3243A>G and <i>POLG</i> ).	3.4	4.0	90%
71. Muscle biopsy should be considered after excluding m.3243A>G and <i>POLG</i> mutations.	4.0	4.4	100%
72. A detailed family pedigree should be obtained and the genetic testing should be offered to at-	4.6	4.7	90%

risk individuals where a pathogenic mutation has been identified.			
73. In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?	2.5	2.9	40%
74. The prophylactic use of an anti-epileptic drug should be considered in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.	3.4	3.9	70%
<i>We do not reach a consensus to recommend the prophylactic use of an anti-epileptic drug in mtDNA mutation carriers who are deemed at high risk of developing stroke-like episodes.</i>			
75. The prophylactic use of an anti-epileptic drug should be considered in patients harbouring <i>POLG</i> recessive mutations who are deemed at high risk of developing stroke-like episodes.	3.6	4.2	90%