#1

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Thursday, March 29, 2018 6:40:46 AM
Last Modified:	Thursday, March 29, 2018 7:03:47 AM
Time Spent:	00:23:01
IP Address:	79.36.61.52

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Strongly agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Strongly agree**
Formed, complex visual hallucination	**Strongly agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Strongly agree**
Focal sensory symptoms	**Strongly agree**
Dysphasia	**Agree**
Apraxia	**Agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Strongly agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Strongly agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Agree**
Creatine kinase (CK)	**Strongly agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Agree**
Coagulation screen (for patients with POLG mutations)	**Agree**
Urinalysis and urine culture (septic screen)	**Agree**
Blood culture (septic screen)	**Agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Disagree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Strongly agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Agree**
MR venogram	**Disagree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Neither disagree nor agree**
Abdominal X-ray	**Agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Neither disagree nor agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Strongly agree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**4**
Phenobarbitone (15mg/kg)	**5**
Lacosamide (200-400mg)	**3**
Other	**2**

Q20 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?

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Neither disagree nor agree**
Intravenous L-arginine	**Agree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Disagree**
Comments:	empirical treatment also without epileptic discharges considering the pathogenesis of SLEs

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**
Comment:	Meaning not necessary increasing the previous AED -if the blood concentration is already high, but eventually adding a new AED

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Strongly agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):	**Convulsive (generalised) status epilepticus** , **Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)** , **Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs** , **Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs** , **Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**2**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Strongly agree**

Q30 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.

(no label)	**Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Intravenous magnesium

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Neither disagree nor agree**
Comments:	no experience

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**
Comment:	catatonia like syndrome!

Q36 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)

Benzodiazepine,
Haloperidol,
Quetiapine,
Olanzapine,
Risperidone

Q37 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).

(no label)	**Strongly agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)	**Agree**
Comment:	Theoretically yes. Unofrtunately most of the psychiatrists do not know MELAS. An awareness campaign with these specialists is warranted

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)	**Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label)	**Strongly agree**

Q41 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.

(no label)	**Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **No**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)	**Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)	**Strongly agree**
Comment:	we should probably also provide a guide on how much and for how long we can use iv sodium bicarbonate, considering its long term toxicity in renal and liver dysfunction

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)	**Strongly agree**

Q46 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).

(no label)	**Strongly agree**

Q47 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.

(no label)	**Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label)	**Strongly agree**

Q49 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.

(no label)	**Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label)	**Strongly agree**
Comment:	how? is there any evidence of a first choice drug for that?

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label)	**Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label)	**Strongly agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label)	**Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label)	**Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **Yes**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **Yes**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label)	**Strongly agree**
Comment:	I would suggest to be cautious here (MMS JAMA Guidelines!)

Q58 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.

(no label)	**Strongly agree**
Comment:	I would suggest to be cautious here (MMS JAMA Guidelines!)

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label)	**Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label)	**Strongly agree**
Comment:	should we also mention here ubiquinol?

Q61 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.

(no label)	**Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label)	**Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label) **Strongly agree**

Q67 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.

(no label) **Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

Urine,

Other (please specify):

In chronic settings we also expand the study in other tissues. But in acute setting no time to expand the analysis

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

No,

Comments:

we do estimate, but not routinely quantify

Q70 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 POLG).

(no label) **Strongly agree**

Comments:

only if the facilities are able to provide answers within a week. Otherwise I suggest to say: "if the facilities are not able to provide results within a week, muscle biopsy for histological and immunohystochemistry markers for mt dysfunction (i.e. RRFs, COX neg f., SSVs) should be promptly performed.

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Strongly agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Strongly disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Strongly agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Strongly agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**LEvetiracetam**
For women of childbearing age	**LEvetiracetam**
For children	**LEvetiracetam**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#2

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Thursday, March 29, 2018 4:40:28 PM
Last Modified:	Thursday, March 29, 2018 5:14:04 PM
Time Spent:	00:33:35
IP Address:	144.82.48.96

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Strongly agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Strongly agree**
Formed, complex visual hallucination	**Strongly agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Agree**
Focal sensory symptoms	**Agree**
Dysphasia	**Agree**
Apraxia	**Agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Strongly agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Strongly agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Strongly agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Strongly agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Strongly agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Neither disagree nor agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Neither disagree nor agree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Strongly agree**
Abdominal X-ray	**Strongly agree**
Electrocardiogram (ECG)	**Neither disagree nor agree**
Lumbar puncture	**Strongly agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**2**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**1**
Phenobarbitone (15mg/kg)	**3**
Lacosamide (200-400mg)	**4**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Neither disagree nor agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Strongly agree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Agree**

Q25 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.

(no label)	**Strongly agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):	**Convulsive (generalised) status epilepticus** , **Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)** , **Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs** , **Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs** , **Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**2**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Agree**

Q30 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.

(no label)	**Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)	**Ketogenic diet or similar diet ,** **Intravenous methylprednisolone,** **Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation) ,** **Ketamine,** **Hypothermia**

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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)	**Benzodiazepine,** **Haloperidol,** **Quetiapine,** **Olanzapine,** **Risperidone**

Q37 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).

(no label) **Agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Strongly agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Agree**

Q47 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.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q58 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.

(no label) **Agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Agree**

Q61 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.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label)	**Agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label)	**Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)	**Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label)	**Strongly agree**

Q67 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.

(no label)	**Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?	**Blood,** **Urine,** **Fibroblast,** **Muscle**

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	**Yes**

Q70 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 POLG).

(no label)	**Agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Neither disagree nor agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Neither disagree nor agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

Respondent skipped this question

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#3

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Friday, March 30, 2018 6:55:51 AM
Last Modified: Friday, March 30, 2018 7:19:26 AM
Time Spent: 00:23:35
IP Address: 81.131.226.243

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Agree**
Formed, complex visual hallucination	**Strongly agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Strongly agree**
Focal sensory symptoms	**Strongly agree**
Dysphasia	**Strongly agree**
Apraxia	**Strongly agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Strongly agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Strongly agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Agree**
Liver function test (LFT)	**Agree**
Serum lactate (without tourniquet applied)	**Disagree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Neither disagree nor agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Strongly agree**
Coagulation screen (for patients with POLG mutations)	**Neither disagree nor agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Neither disagree nor agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Neither disagree nor agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Neither disagree nor agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Neither disagree nor agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Neither disagree nor agree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Agree**
Abdominal X-ray	**Agree**
Electrocardiogram (ECG)	**Agree**
Lumbar puncture	**Neither disagree nor agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**2**
Phenobarbitone (15mg/kg)	**4**
Lacosamide (200-400mg)	**3**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Neither disagree nor agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Strongly disagree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Strongly agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus ,

Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs) ,

Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs ,

Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs ,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**1**
Midazolam	**2**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Neither disagree nor agree**

Q30 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.

(no label)	**Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)	**Intravenous immunoglobulin ,** **Intravenous methylprednisolone,** **Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation)**

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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,** **Quetiapine,** **Olanzapine,** **Risperidone**

Q37 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).

(no label)	**Strongly agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Strongly agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Strongly agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q58 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.

(no label) **Strongly agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Strongly agree**

Q61 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.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)	**Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label)	**Strongly agree**

Q67 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.

(no label)	**Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?	**Blood,** **Urine**
Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	**Yes**

Q70 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 POLG).

(no label)	**Agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Strongly agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Strongly agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**Leviteracetam**
For women of childbearing age	**Leviteracetam**
For children	**Leviteracetam**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#4

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Thursday, April 05, 2018 6:49:24 AM
Last Modified: Thursday, April 05, 2018 7:58:14 AM
Time Spent: 01:08:50
IP Address: 193.143.201.115

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Agree**
Nausea and vomiting	**Agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Agree**
Generalised seizures	**Agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Strongly agree**
Formed, complex visual hallucination	**Strongly agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Agree**
Focal sensory symptoms	**Agree**
Dysphasia	**Agree**
Apraxia	**Agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Agree**

Q10 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).

(no label)	**Agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Strongly agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Agree**
Arterial blood gas (ABG)	**Agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Disagree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Disagree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Agree**
Chest radiograph	**Agree**
Abdominal X-ray	**Agree**
Electrocardiogram (ECG)	**Agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**
Other (please specify):	Selection of tests repeated depends on the particular changes in clinical picture (e.g., abdominal X-ray); however EEG and brain MRI should always be considered repeated if neurological deficit worsens.

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Disagree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**5**
Phenobarbitone (15mg/kg)	**4**
Lacosamide (200-400mg)	**2**
Other	**3**

Q20 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?

Oral anti-epileptic drug	**Neither disagree nor agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Disagree**
Comments:	As this presentation suggests underlying epileptic activity very likely I would administer iv antiepileptic drug and order EEG plus brain imaging.

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Neither disagree nor agree**
Other (please specify):	Depends on medication and expected duration of treatment. In acute setting I would replace with iv AEDs, NGT insertion if prolonged condition and/or usual medication that is not available in iv format (e.g. zonisamide, perampanel).

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):	**Convulsive (generalised) status epilepticus** , **Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)** , **Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs** , **Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs** , **Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**2**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Neither disagree nor agree**
Comment:	Consider changing the GA agent if prolonged anaesthesia is indicated. There are also important problems with thiopental anaesthesia and the use of ketamine.

Q30 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.

(no label)	**Agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Neither disagree nor agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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)

Benzodiazepine,
Haloperidol,
Quetiapine,
Olanzapine,
Risperidone

Q37 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).

(no label)	**Agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q58 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.

(no label) **Strongly agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Strongly agree**

Q61 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.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)	**Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label)	**Strongly agree**

Q67 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.

(no label)	**Agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?	**Blood,** **Urine,** **Buccal,** **Muscle**
Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	**Yes**

Q70 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 POLG).

(no label)	**Agree**
Comments:	If available in local practice.

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Strongly agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Disagree**
Comment:	At present unfortunately not - a lot of work remains to be done!

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Neither disagree nor agree**
Comments:	What means "at high risk"? If no previous SLEs or epilepsy and thus only based on e.g. high heteroplasmy level I think not. However in some instances may be justified, on case by case basis.

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Agree**
Comments:	Occasionally, yes.

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**levetiracetam as first choice, if no psychiatric issues**
For women of childbearing age	**same**
For children	**same**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

I think this is very useful and important work. Many thanks.

#5

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Thursday, April 05, 2018 2:50:58 PM
Last Modified: Thursday, April 05, 2018 4:18:05 PM
Time Spent: 01:27:07
IP Address: 194.176.105.171

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Strongly agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Strongly agree**
Formed, complex visual hallucination	**Neither disagree nor agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Agree**
Focal sensory symptoms	**Agree**
Dysphasia	**Strongly agree**
Apraxia	**Strongly agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Strongly agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Strongly agree**
Coagulation screen (for patients with POLG mutations)	**Agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Agree**
Arterial blood gas (ABG)	**Disagree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Disagree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Disagree**
MR angiogram	**Disagree**
T2 gradient echo	**Disagree**
MR venogram	**Disagree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Agree**
Chest radiograph	**Neither disagree nor agree**
Abdominal X-ray	**Neither disagree nor agree**
Electrocardiogram (ECG)	**Disagree**
Lumbar puncture	**Disagree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Neither disagree nor agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Other (please specify):	we don't know if L arginine works. Should NOT delay effective Rx with AEDs Should get IV AEDs but could load with HIGH dose oral agents. Don't want agreement with 'oral AEDs' to suggest can use low dosages

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**2**
Phenobarbitone (15mg/kg)	**4**
Lacosamide (200-400mg)	**3**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Neither disagree nor agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Disagree**
Comments:	IV AED if clearly a NEW deficit in known mito patient - AND no symptoms suggestive of other pathology - eg SOL or vascular stroke

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Agree**
Other (please specify):	But AEDs via IV route preferable - if vomiting may vomit AEDs anyway and CIPO may limit absorption.

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Strongly agree**

Q26 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.

(no label)	**Strongly agree**
Comment:	NB for Q19 (choice of AEDs) - I would usually give IV lorazepam just before/with loading dose of AED. Wasn't an option on list

Q27 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus ,

Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs) ,

Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs ,

Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs ,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration ,

Other (please specify):

ITU admission not necessarily thiopentone coma. Note options 3 and 4 (focal motor and occ seizures) is a difficult call - depends on scenario. ITU/HDU admission worth considering to allow midazolam infusion or phenobarbitone

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**2**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label) **Neither disagree nor agree**

Q30 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.

(no label) **Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label) **Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet ,

Intravenous methylprednisolone,

Intravenous magnesium,

Ketamine,

Hypothermia

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label) **Agree**

Comments: no evidence - ltd experience - 'agree' as little to lose in some scenarios

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label) **Agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label) **Agree**

Q36 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)

Benzodiazepine,
Haloperidol,
Quetiapine,
Olanzapine

Q37 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).

(no label) **Agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Strongly agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Strongly agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q58 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.

(no label) **Strongly agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Strongly agree**

Q61 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.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label) **Strongly agree**

Q67 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.

(no label) **Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?

Blood,

Urine,

Muscle,

Other (please specify):

muscle for mtDNA sequencing if 3243 and POLG -ve from blood/urine

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?

Yes

Q70 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 POLG).

(no label)	**Disagree**
Comments:	Main urgency is confirming mito - histo from Bx is quicker. Actual mutation can come later

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Strongly agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Strongly disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Strongly agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**Keppra**
For women of childbearing age	**LMT or Keppra**
For children	**not paediatric**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Thanks - well done!

#6

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Saturday, April 07, 2018 1:37:36 PM
Last Modified:	Saturday, April 07, 2018 2:29:18 PM
Time Spent:	00:51:41
IP Address:	31.51.236.204

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Agree**
Generalised seizures	**Agree**
Non-convulsive status epilepticus	**Agree**
Elementary visual hallucination e.g. coloured flashing light	**Agree**
Formed, complex visual hallucination	**Agree**
Visual field defect	**Agree**
Focal motor weakness	**Agree**
Focal sensory symptoms	**Agree**
Dysphasia	**Agree**
Apraxia	**Agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Neither disagree nor agree**
Comment:	If we could identify those with m.3243A>G or POLG mutations who are more likely to develop stroke-like episodes I would strongly agree. Until we have better estimation of the risk I would not give it to all carriers of m.3243A>G or POLG.

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Strongly agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Neither disagree nor agree**
Comment:	Until we have recommendations I would not restrict the possibility of performing a routine MRI.

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Agree**
DTI	**Agree**
MR angiogram	**Disagree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Disagree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Neither disagree nor agree**
Abdominal X-ray	**Neither disagree nor agree**
Electrocardiogram (ECG)	**Agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Agree**

Q18 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)

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**2**
Phenobarbitone (15mg/kg)	**3**
Lacosamide (200-400mg)	**4**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Strongly agree**
Intravenous anti-epileptic drug	**Neither disagree nor agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Neither disagree nor agree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus

,

Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)

,

Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs

,

Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs

,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**1**
Propofol	**4**
Midazolam	**2**
Ketamine	**3**
Other	**5**

Q29 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.

(no label) **Agree**

Q30 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.

(no label) **Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label) **Agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Other (please specify):

I haven`t tried any of these yet.

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label) **Agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label) **Strongly agree**

Q36 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)	**Benzodiazepine,** **Haloperidol,** **Quetiapine**

Q37 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).

(no label)	**Agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)	**Agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label)	**Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label)	**Agree**

Q41 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.

(no label)	**Agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes?	**Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label)	**Agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label)	**Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label)	**Strongly agree**

Q46 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).

(no label)	**Agree**

Q47 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.

(no label)	**Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Agree**

Q49 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.

(no label) **Agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q58 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.

(no label) **Agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Agree**

Q61 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.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label) **Strongly agree**

Q67 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.

(no label) **Agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,** **Urine,** **Buccal,** **Fibroblast,** **Muscle**

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q70 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 POLG).

(no label) **Agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**Levetiracetam**
For women of childbearing age	**Levetiracetam+folic acid**
For children	**I don`t treat children**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#7

COMPLETE

Collector:	Web Link 1 (Web Link)
Started:	Tuesday, April 17, 2018 5:58:50 AM
Last Modified:	Tuesday, April 17, 2018 6:31:49 AM
Time Spent:	00:32:58
IP Address:	129.177.166.2

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Agree**
Generalised seizures	**Agree**
Non-convulsive status epilepticus	**Agree**
Elementary visual hallucination e.g. coloured flashing light	**Agree**
Formed, complex visual hallucination	**Agree**
Visual field defect	**Agree**
Focal motor weakness	**Agree**
Focal sensory symptoms	**Neither disagree nor agree**
Dysphasia	**Neither disagree nor agree**
Apraxia	**Neither disagree nor agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Strongly agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Agree**
Random glucose	**Agree**
HbA1c (known diabetic)	**Agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Neither disagree nor agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Neither disagree nor agree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Agree**
Chest radiograph	**Agree**
Abdominal X-ray	**Agree**
Electrocardiogram (ECG)	**Agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Strongly agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**4**
Phenobarbitone (15mg/kg)	**3**
Lacosamide (200-400mg)	**2**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Neither disagree nor agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Disagree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):	**Convulsive (generalised) status epilepticus** , **Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)** , **Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs** , **Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**2**
Propofol	**1**
Midazolam	**4**
Ketamine	**3**
Other	**5**

Q29 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.

(no label)	**Disagree**

Q30 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.

(no label)	**Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet ,

Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation) ,

Intravenous magnesium,

Ketamine,

Hypothermia,

Folinic acid

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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)

Benzodiazepine,

Haloperidol

Q37 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).

(no label)	**Agree**
Comment:	Also in POLG

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Comment: Limited effect

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Agree**

Q46 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).

(no label) **Agree**

Q47 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.

(no label) **Agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q58 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.

(no label) **Agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Agree**

Q61 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.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)	**Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label)	**Strongly agree**

Q67 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.

(no label)	**Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?	**Blood,** **Urine,** **Muscle,** Other (please specify): Blood - POLG the others for 3243

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	**Yes**

Q70 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 POLG).

(no label)	**Agree**
Comments:	agree with comments made i meeting

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Agree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**KEP**
For women of childbearing age	**KEP**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#8

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Friday, May 25, 2018 12:39:58 PM
Last Modified: Friday, May 25, 2018 1:19:28 PM
Time Spent: 00:39:30
IP Address: 2.24.139.30

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Agree**
Nausea and vomiting	**Agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Agree**
Elementary visual hallucination e.g. coloured flashing light	**Agree**
Formed, complex visual hallucination	**Agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Strongly agree**
Focal sensory symptoms	**Agree**
Dysphasia	**Agree**
Apraxia	**Agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Neither disagree nor agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Neither disagree nor agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Strongly agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Agree**
Electrocardiogram (ECG)	**Neither disagree nor agree**
Lumbar puncture	**Neither disagree nor agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Neither disagree nor agree**
DTI	**Neither disagree nor agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Neither disagree nor agree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Agree**
Chest radiograph	**Neither disagree nor agree**
Abdominal X-ray	**Disagree**
Electrocardiogram (ECG)	**Disagree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Agree**

Q18 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)

Oral anti-epileptic drug	**Disagree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**3**
Phenobarbitone (15mg/kg)	**2**
Lacosamide (200-400mg)	**4**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Agree**
Intravenous L-arginine	**Disagree**
Oral L-arginine	**Disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Disagree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Agree**

Q25 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.

(no label)	**Neither disagree nor agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):	**Convulsive (generalised) status epilepticus** , **Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)** , **Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs** , **Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs** , **Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration**

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**2**
Propofol	**3**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Neither disagree nor agree**

Q30 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.

(no label)	**Agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)	**Intravenous immunoglobulin ,** **Plasma exchange ,** **Intravenous methylprednisolone,** **Hypothermia**

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.	**Respondent skipped this question**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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)	**Do not use any antipsychotic drug**

Q37 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).

(no label)	**Agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)	**Strongly agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Do not know**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Strongly agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Agree**

Q49 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.

(no label) **Agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Neither disagree nor agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Agree**

Q58 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.

(no label) **Agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Agree**

Q61 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.

(no label) **Agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label) **Agree**

Q67 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.

(no label) **Agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Urine,** **Buccal,** **Muscle**

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q70 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 POLG).

(no label) **Agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Agree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label) **Neither disagree nor agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**Levetiracetam**
For women of childbearing age	**Levetiracetam**
For children	**Levetiracetam**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

There are clear guidelines (RCPCH / NICE) for the investigation of strokes in children. The investigation and management of SLEs derived from this workshop should be presented to their working group for consideration of incorporation into their guideline.

#9

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Friday, June 01, 2018 10:15:13 AM
Last Modified: Friday, June 01, 2018 10:40:20 AM
Time Spent: 00:25:07
IP Address: 88.202.59.15

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Strongly agree**
Nausea and vomiting	**Strongly agree**
Altered conscious level/ encephalopathy	**Strongly agree**
Focal motor seizures (including epilepsia partialis continua)	**Strongly agree**
Generalised seizures	**Strongly agree**
Non-convulsive status epilepticus	**Strongly agree**
Elementary visual hallucination e.g. coloured flashing light	**Strongly agree**
Formed, complex visual hallucination	**Strongly agree**
Visual field defect	**Strongly agree**
Focal motor weakness	**Strongly agree**
Focal sensory symptoms	**Strongly agree**
Dysphasia	**Strongly agree**
Apraxia	**Strongly agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Strongly agree**

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Strongly agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Agree**
Coagulation screen (for patients with POLG mutations)	**Strongly agree**
Urinalysis and urine culture (septic screen)	**Strongly agree**
Blood culture (septic screen)	**Strongly agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Strongly agree**
Arterial blood gas (ABG)	**Strongly agree**

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Strongly agree**
MR angiogram	**Disagree**
T2 gradient echo	**Strongly agree**
MR venogram	**Disagree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Strongly agree**
Abdominal X-ray	**Strongly agree**
Electrocardiogram (ECG)	**Agree**
Lumbar puncture	**Disagree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Strongly agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Strongly disagree**
Oral L-arginine	**Strongly disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**2**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**1**
Phenobarbitone (15mg/kg)	**4**
Lacosamide (200-400mg)	**3**
Other	**5**

Q20 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?

Oral anti-epileptic drug	**Agree**
Intravenous anti-epileptic drug	**Agree**
Intravenous L-arginine	**Strongly disagree**
Oral L-arginine	**Strongly disagree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Strongly agree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Strongly agree**

Q25 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.

(no label)	**Strongly agree**

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus ,

Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs) ,

Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs ,

Occipital status epilepticus (and at risk of developing cortical blindness) failing to respond to benzodiazepine and two IV AEDs ,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**3**
Propofol	**2**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label) **Disagree**

Q30 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.

(no label) **Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label) **Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Ketogenic diet or similar diet ,
Neurostimulation (e.g. vagal nerve stimulator, transcranial magnetic stimulation, transcranial direct current stimulation) ,
Folinic acid

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label) **Agree**

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label) **Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label) **Strongly agree**

Q36 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)

Benzodiazepine,
Haloperidol,
Quetiapine,
Olanzapine,
Risperidone

Q37 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).

(no label) **Strongly agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label) **Strongly agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Yes**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Strongly agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Strongly agree**

Q46 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).

(no label) **Strongly agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Strongly agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **No**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **No**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q58 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.

(no label) **Strongly agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Strongly agree**

Q61 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.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label) **Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label) **Strongly agree**

Q67 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.

(no label) **Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis? **Blood,** **Urine,** **Buccal,** **Muscle**

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations? **Yes**

Q70 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 POLG).

(no label) **Strongly agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label) **Strongly agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label) **Strongly agree**

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label) **Disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label) **Agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label) **Agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**Lev**
For women of childbearing age	**Lev**
For children	**Lev**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question

#10

COMPLETE

Collector: Web Link 1 (Web Link)
Started: Friday, June 01, 2018 4:28:38 PM
Last Modified: Friday, June 01, 2018 5:10:48 PM
Time Spent: 00:42:10
IP Address: 138.245.1.1

Page 2: SECTION A: Demographic Data

Q1 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.

(no label)	**Strongly agree**

Page 3: SECTION B: Defining Stroke-like Episodes

Q2 The entity of stroke-like episodes requires better definition because it is crucial to improving recognition and acute management.

(no label)	**Strongly agree**

Q3 Which of the following are recognised clinical features of a stroke-like episode in your opinion?

Acute/subacute onset, evolving neurological symptoms	**Strongly agree**
Headache	**Neither disagree nor agree**
Nausea and vomiting	**Neither disagree nor agree**
Altered conscious level/ encephalopathy	**Neither disagree nor agree**
Focal motor seizures (including epilepsia partialis continua)	**Neither disagree nor agree**
Generalised seizures	**Neither disagree nor agree**
Non-convulsive status epilepticus	**Neither disagree nor agree**
Elementary visual hallucination e.g. coloured flashing light	**Neither disagree nor agree**
Formed, complex visual hallucination	**Neither disagree nor agree**
Visual field defect	**Neither disagree nor agree**
Focal motor weakness	**Neither disagree nor agree**
Focal sensory symptoms	**Neither disagree nor agree**
Dysphasia	**Neither disagree nor agree**
Apraxia	**Neither disagree nor agree**
Neuropsychiatric symptoms (e.g. agitation, behavioural disturbance)	**Neither disagree nor agree**
Other (please specify):	Unclear formulation of question: all of these Symptoms can be part of a SLE but only the first symptom is indispensable in my opinion

Q4 How do you diagnose a stroke-like episode in your current clinical practice?	**Clinical assessment plus MRI head plus EEG**

Q5 Do you agree with the following statement provides a better definition of 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.

(no label)	**Strongly agree**

Q6 Stroke-like episodes should be suspected irrespective of patient's age , although it is more common under age of 40.

(no label)	**Strongly agree**

Page 4: SECTION C: Alert Card and Emergency Care Plan

Q7 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.

(no label)	**Strongly agree**

Q8 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.

(no label)	**Strongly agree**

Page 5: Section D: Clinical Assessment

Q9 Hyper-acute onset, dense facial weakness and/or hemiparesis is highly unusual in the context of stroke-like episodes.

(no label)	**Strongly agree**

Q10 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).

(no label)	**Strongly agree**

Q11 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.

(no label)	**Strongly agree**

Page 6: Section E: Investigations

Q12 The following blood and laboratory tests should be considered in any patients presenting with (suspected) stroke-like episodes.

Full blood count	**Strongly agree**
Urea and creatinine (kidney function)	**Strongly agree**
Liver function test (LFT)	**Strongly agree**
Serum lactate (without tourniquet applied)	**Strongly agree**
C-reactive protein (CRP)	**Strongly agree**
Creatine kinase (CK)	**Strongly agree**
Random glucose	**Strongly agree**
HbA1c (known diabetic)	**Strongly agree**
Coagulation screen (for patients with POLG mutations)	**Neither disagree nor agree**
Urinalysis and urine culture (septic screen)	**Neither disagree nor agree**
Blood culture (septic screen)	**Neither disagree nor agree**
Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable	**Neither disagree nor agree**
Arterial blood gas (ABG)	**Neither disagree nor agree**
Other (please specify):	septic screens only if suggested by clinical symptoms

Q13 The following investigations should be considered for any suspected stroke-like episodes in patients with known mtDNA/POLG mutation.

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph (if aspiration pneumonia suspected)	**Strongly agree**
Abdominal X-ray (if intestinal pseudo-obstruction suspected)	**Strongly agree**
Electrocardiogram (ECG)	**Strongly agree**
Lumbar puncture	**Strongly agree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Q14 A standardised MRI head protocol should be used for any patients presenting with (suspected) stroke-like episodes.

(no label)	**Agree**
Comment:	A standardised MRI head protocol is recommendable. If this is not implemented, however, a minimal MRI (most importantly T2 and/or FLAIR) is already extremely valuable for clinical judgement.

Q15 If we were to develop standardised MRI protocol, which of the following sequences that are essential in your opinion?

T1	**Strongly agree**
T2	**Strongly agree**
FLAIR	**Strongly agree**
DWI	**Strongly agree**
ADC	**Strongly agree**
DTI	**Neither disagree nor agree**
MR angiogram	**Neither disagree nor agree**
T2 gradient echo	**Neither disagree nor agree**
MR venogram	**Neither disagree nor agree**

Q16 If the clinical picture continues to evolve, for example developing new or worsening neurological deficit following the initial investigations, which of the following tests would you consider repeating to help guide your clinical management?

Blood tests (as outlined in Question 22)	**Strongly agree**
Chest radiograph	**Neither disagree nor agree**
Abdominal X-ray	**Neither disagree nor agree**
Electrocardiogram (ECG)	**Neither disagree nor agree**
Lumbar puncture	**Disagree**
Electroencephalogram (EEG)	**Strongly agree**
MRI head (unless there is contraindication, then CT head)	**Strongly agree**

Page 7: Section F: Treatment for Seizures

Q17 Non-availability of EEG or MRI head should not deter or delay treatment of patients with (suspected) stroke-like episodes.

(no label)	**Strongly agree**

Q18 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)

Oral anti-epileptic drug	**Strongly agree**
Intravenous anti-epileptic drug	**Strongly agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**

Q19 At the initial hospital presentation, if seizures and/or encephalopathy are evident, and you decide to administer an IV AED, what would be your preferred choice? (please rank your preference):

Levetiracetam (20-40mg/kg, maximum 4500mg)	**1**
Phenytoin (15-18mg/kg) or fosphenytoin (15-20mg/kg)	**3**
Phenobarbitone (15mg/kg)	**5**
Lacosamide (200-400mg)	**4**
Other	**2**

Q20 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?

Oral anti-epileptic drug	**Strongly agree**
Intravenous anti-epileptic drug	**Agree**
Intravenous L-arginine	**Neither disagree nor agree**
Oral L-arginine	**Neither disagree nor agree**
Anti-epileptic drug is not routinely used in my practice	**Strongly disagree**
Observation and supportive care only (e.g. hydration, management of constipation)	**Strongly disagree**

Q21 Sodium valproate is contra-indicated for patients with recessive POLG mutations, and should also be avoided in patients with mitochondrial epilepsy caused by other genotypes if another alternative drug is available.

(no label)	**Strongly agree**

Q22 After a stroke-like episode needing IV AEDs, the patient should be discharged on an increased AED regime.

(no label)	**Strongly agree**

Q23 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.

(no label)	**Strongly agree**

Q24 POLG mutations are more often associated with pharmaco-resistant epilepsy than the m.3243A>G-related stroke-like episodes.

(no label)	**Agree**

Q25 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.

(no label)	**Neither disagree nor agree**
Comment:	unclear formulation

Q26 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.

(no label)	**Strongly agree**

Q27 Indications for intensive care unit admission (more than one option is permitted):

Convulsive (generalised) status epilepticus ,

Intrusive, frequent focal motor seizures with breakthrough generalised seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)

,

Severe encephalopathy (with breakthrough focal motor or generalised seizures) with high risk of aspiration

Q28 What is your choice of general anaesthetics (GA) agent for treating refractory status epilepticus associated with stroke-like episodes? (please rank your preference)

Thiopentone (thiopental)	**2**
Propofol	**3**
Midazolam	**1**
Ketamine	**4**
Other	**5**

Q29 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.

(no label)	**Agree**
Comment:	but propofol may be a good choice for short-term use, in view of its fast onset of action and good controllability

Q30 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.

(no label)	**Strongly agree**

Q31 Burst suppression is the commonly used EEG target of GA agents and should be maintained for at least 48 hours.

(no label)	**Strongly agree**

Q32 What other non-conventional treatments have you previously tried to manage refractory stroke-like episodes? (More than one option is permitted)

Intravenous methylprednisolone

Q33 Hypothermia may provide neuroprotection and should be considered as part of the management of refractory stroke-like episodes in the ICU setting.

(no label)	**Neither disagree nor agree**
Comments:	I have no specific experience on that.

Page 8: Section G: Treatment of Neuropsychiatric Complications

Q34 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.

(no label)	**Strongly agree**

Q35 It is important to consider non-convulsive seizures as the cause of new-onset neuropsychiatric symptoms in stroke-like episodes.

(no label)	**Strongly agree**

Q36 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)

Benzodiazepine,

Haloperidol,

Quetiapine,

Olanzapine,

Risperidone,

Other (please specify):

almost all psychopharmaka can be considered if necessary

Q37 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).

(no label)	**Strongly agree**

Q38 Liaison psychiatric service should be consulted to guide assessment, treatment and to monitor the progress.

(no label)	**Agree**

Page 9: Section H: General Medical Treatment

Q39 Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those with encephalopathy or those presenting with vomiting due to intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q40 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 acidaemia in patients with mitochondrial disease.

(no label) **Neither disagree nor agree**

Q41 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.

(no label) **Strongly agree**

Q42 Do you recognise hyponatraemia (<130) in the setting of acute stroke-like episodes? **Do not know**

Q43 Mild to moderate lactic acidosis often responds well to rehydration and does not require any buffering agent.

(no label) **Strongly agree**

Q44 Buffering agent such as sodium bicarbonate is often only required for symptomatic, severe lactic acidosis.

(no label) **Agree**

Q45 Blood sugar level should be closely monitored during an acute stroke-like episode and managed accordingly.

(no label) **Agree**

Q46 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).

(no label) **Strongly agree**

Q47 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.

(no label) **Strongly agree**

Page 10: Section I: Treatment for The Intestinal Pseudo-obstruction (IPO)

Q48 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.

(no label) **Strongly agree**

Q49 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.

(no label) **Strongly agree**

Q50 Concomitant constipation and/or faecal impaction should be treated.

(no label) **Strongly agree**

Q51 Serum lactate may not be a reliable marker for sepsis or tissue ischaemia in patients with mitochondrial disease.

(no label) **Strongly agree**

Q52 Total parenteral nutrition (TPN) should be considered early if prolonged fasting is anticipated for patients with refractory IPO.

(no label) **Strongly agree**

Q53 Bowel resection surgery is very rarely indicated in the management of intestinal pseudo-obstruction.

(no label) **Strongly agree**

Q54 Early consultation with the nutritional team is recommended during admission for stroke-like episodes.

(no label) **Agree**

Page 11: Section J: Specific Therapies for Stroke-like Episodes

Q55 Do you routinely use IV L-arginine for the acute management of stroke-like episodes? **Yes**

Q56 Do you routinely use oral L-arginine as a prohylactic agent for stroke-like episodes? **Yes**

Q57 There is no robust scientific evidence to support the use of L-arginine either in the acute or chronic settings.

(no label) **Strongly agree**

Q58 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.

(no label) **Strongly agree**

Q59 Dichloroacetate has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits.

(no label) **Strongly agree**

Q60 Supplementation of ubiquinone has not been demonstrated a benefit for patients presenting acutely/subacutely with stroke-like episodes.

(no label) **Strongly agree**

Q61 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.

(no label) **Strongly agree**

Page 12: Section K: Other Considerations for Acute Hospital Admission

Q62 Antiplatelet therapy is not indicated for patients presenting with typical stroke-like episodes.

(no label) **Strongly agree**

Q63 Deep vein thrombosis (DVT) prophylaxis: usual guidelines for DVT prophylaxis should be followed. Low molecular weight heparin is not contraindicated in mitochondrial disease.

(no label) **Strongly agree**

Q64 Swallowing assessment: encephalopathy, cerebellar disease and focal deficits may increase the risk of aspiration pneumonia.

(no label) **Strongly agree**

Q65 Cardiac disease: lactic acidosis, electrolyte disturbances, anti-epileptic drugs and fluid replacement may exacerbate or unmask pre-existing cardiac conduction defects or ventricular impairment.

(no label)	**Strongly agree**

Page 13: Section L: Genetic Studies for The First Presentation of Stroke-like Episode

Q66 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.

(no label)	**Neither disagree nor agree**
Comments:	clinical management more driven by the phenotype; even very fast genetic testing comes too late for the acute treatment

Q67 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.

(no label)	**Strongly agree**

Q68 Which tissue(s) do you use (preferentially) to confirm a genetic diagnosis?	**Blood,** **Urine**

Q69 Do you routinely quantify the mutant heteroplasmy level of m.3243A>G and other mtDNA mutations?	**Yes**

Q70 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 POLG).

(no label)	**Agree**

Q71 Muscle biopsy should be considered after excluding m.3243A>G and POLG mutations.

(no label)	**Agree**

Q72 A detailed family pedigree should be obtained and the genetic testing should be offered to at-risk individuals where a pathogenic mutation has been identified.

(no label)	**Neither disagree nor agree**
Comment:	depends on the age of at-risk individuals and many other factors

Page 14: Section M: Rehabilitation After Stroke-like Episodes

Q73 In general, do you find patients with stroke-like episodes receive appropriate rehabilitation and support in the community?

(no label)	**Strongly disagree**

Page 15: Section N: Role of Prophylactic Anti-epileptic Drug

Q74 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.

(no label)	**Agree**

Q75 The prophylactic use of an anti-epileptic drug should be considered in patients harbouring POLG recessive mutations who are deemed at high risk of developing stroke-like episodes.

(no label)	**Agree**

Q76 If your answer is either 'Agree' or 'Strongly agree' for questions 74 and 75, what would be your preferred choice of AED?

For men	**LEV**
For women of childbearing age	**LEV**
For children	**LEV**

Page 16: SECTION O: Your Comments

Q77 Please feel free to write any comments about any topics listed above or other issues that you think would be helpful to include in the manuscript regarding the consensus-based recommendation.

Respondent skipped this question