Endocrinology in the time of COVID-19: Clinical management of neuroendocrine neoplasms (NENs)

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Disclaimer

Due to the emerging nature of the Covid-19 crisis this document is not based on extensive systematic review or meta-analysis, but on rapid expert consensus. This document should be considered as guidance only; it is not intended to determine an absolute standard of medical care. Healthcare staff needs to consider individual circumstances when devising the management plan for a specific patient.
Abstract

In viral pandemics, most specifically Covid-19, many patients with neuroendocrine neoplasms (NENs), including phaeochromocytomas, paragangliomas and medullary thyroid carcinoma, may develop Covid-19 in a mild or severe form, or be concerned about the influence of viral infection relative to their anti-tumoral therapy. In general, newly-presenting patients should be assessed, and patients recently receiving chemotherapy, targeted therapy or radionuclide therapy, or showing tumour growth, should be closely followed. For previously diagnosed patients, who have indolent disease, some delay in routine follow-up or treatment may not be problematic. However, patients developing acute secretory syndromes due to functional neuroendocrine neoplasms (such as of the pancreas, intestine or lung), phaeochromocytomas and paragangliomas, will require prompt treatment. Patients with life-threatening Covid-19-related symptoms should be urgently treated and long-term anti-tumoral treatments may be temporarily delayed. In patients with especially aggressive NENs, a careful judgement should be made regarding the severity of any Covid-19 illness, tumour grade, and the immunosuppressant effects of any planned chemotherapy, immunotherapy (e.g. interferon-alpha), targeted therapy or related treatment. In other cases, especially patients with completely resected NENs, or who are under surveillance for a genetic disorder, a telephone or delayed consultation may be in order, balancing the risk of a delay against that of the possible development of Covid-19.
Introduction:

- SARS CoV2 viruses (Covid-19) bind to angiotensin converting enzyme-2 (ACE2), a cell-surface receptor, and a potential interaction between Covid-19 and the renin-angiotensin-aldosterone system has been reported [1] [2] [3] [4]. However, such interactions between Covid-19 or other SARS viruses and receptors expressed on neuroendocrine neoplasms (NENs), such as somatostatin receptors (SSRs) and histamine receptors (H1 and H2 receptors), have not been reported.

- The specific effects of Covid-19 infection in patients with NENs have not as yet, to our knowledge, been reported.

- Neuroendocrine neoplasms (NEN) are rare neoplasms arising from cells of the diffuse endocrine system, mainly dispersed throughout the digestive system and respiratory tract. Most NENs grow slowly and symptoms may be related to tumour mass (non-functioning, NF-NENs) and/or to the hypersecretion of hormones (functioning, F-NENs). Histo-pathologically, most NENs are well-differentiated (WD) tumours grade 1 (G1, Ki67 ≤2%), grade 2 (G2, Ki67 3-20%) or grade 3 (G3, Ki67>20%), whereas a small fraction are defined as poorly-differentiated (PD) neuroendocrine small-cell or large-cell carcinoma (NEC) with a Ki67 >20%[5][6].

- Patients with NENs and severe infections causing respiratory difficulties or gastrointestinal (GI) symptoms (e.g. diarrhoea, nausea and vomiting) are likely to present to hospital. Such ill patients may not be able to take their prescribed medication (e.g. analgesia, anti-diarrhoeals, proton pump inhibitors, oral chemotherapy drugs, targeted drugs), or the medication may not be absorbed, and these patients may require admission for treatment.

- Some patients presenting with Covid-19 infection may have an underlying undiagnosed NEN, and this possibility should be considered in those patients whose
symptoms, e.g. diarrhoea, or wheeze with shortness of breath, are not resolving, or whose symptoms were chronic.

Management of patients with NENs and Covid-19 infection:

- There are currently no drug-treatments or vaccines available for Covid-19, and therefore managing patients with NENs alongside Covid-19 is likely to be an ongoing challenge for many months.

General measures:

- The general measures for treatment are the same as in any other patient with Covid-19 infection and should involve acute management of airway, breathing and circulation.

Specific measures:

- Specific emergency treatments may need to be directed to the NEN (Table 1).
- Surgery (or endoscopic removal) is the only curative option for localised NENs[7]. For those patients with compressive symptoms or acute complications, surgery may need to be considered during the Covid-19 pandemic (Figure 1). For patients with localised disease who are asymptomatic, surgery could be reasonably delayed for 8-12 weeks.
- Patients with NENs who have had prior treatments (e.g. surgery, chemotherapy, everolimus, sunitinib, or radionuclide therapy) may have developed sequelae such as diabetes mellitus, or be on glucocorticoids, or be immuno-
compromised, which will make them vulnerable to the severe complications of Covid-19 infection.

- NENs may arise in any organ, and those occurring in the respiratory tract (referred to as carcinoids), gastrointestinal (GI) tract and pancreas (referred to as GEP-NENs), thyroid, and adrenal (Table 1).

- NENs may occur with other tumours in patients with heritable endocrine tumour syndromes, such as multiple endocrine neoplasia (MEN) and von Hippel-Lindau disease (VHL). There are four major forms of MEN. In MEN1, pancreatic and lung (and rarely thymic) NENs occur with parathyroid tumours and anterior pituitary adenomas (8). In MEN2 (previously MEN2A), medullary thyroid carcinoma (MTC) occurs with phaeochromocytoma and parathyroid tumours, while in MEN3 (previously MEN2B) parathyroid tumours are rare, and the occurrence of MTC and phaeochromocytoma is found in association with a marfanoid habitus, mucosal neuromas, medullated corneal fibers, and intestinal autonomic ganglion dysfunction leading to megacolon (9). In the very rare MEN4, parathyroid adenomas, pituitary adenomas, and pancreatic NENs occur in association with gonadal, adrenal, renal and thyroid tumours. In VHL pancreatic NENs and PPGL occur in addition to haemangiblastomas and renal cell carcinoma.

- Based on our experience/knowledge gained from the consequences of other severe infections in patients with NENs, and on expert opinion, a brief overview of NENs for the non-specialist is given together with specific management recommendations for individual conditions (Figures 1 and 2) and service provision during the Covid-19 pandemic.
i) Neuroendocrine Neoplasms of the Respiratory Tract and Thymus

**Bronchial carcinoids**

- Bronchial carcinoid tumours can secrete serotonin, vasoactive substances and other hormones directly into the systemic circulation (Table 1) [8].
- Bronchial carcinoids may present with bronchial obstruction, cough, haemoptysis, weakness, nausea, weight loss, and neuralgia, or incidentally on chest imaging.
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), can also cause acute respiratory symptoms and may be difficult to differentiate from Covid-19 infection on chest x-ray or conventional cross-sectional imaging. We advise prioritising Covid-19 testing for such patients. If viral testing is negative, a biopsy to provide a definitive diagnosis should be considered.

- Thymic neuroendocrine neoplasms
  - Thymic NENs may cause compression of the trachea and mediastinal blood vessels and may secrete hormones.

ii) Gastrointestinal neuroendocrine neoplasms (GI NENs)

- GI NENs may be asymptomatic or they may present with obstructive symptoms (pain, nausea, vomiting), or with symptoms due to hormonal secretion.
- For major NEN surgery prophylactic perioperative treatment with intravenous (i.v.) octreotide, a somatostatin analogue (SSA), at a starting dose of 50–100
μg/h, is used to prevent carcinoid crisis [9] (see below), and drugs that stimulate the sympathetic nervous system or cause histamine release such as morphine and D-tubocurarine are avoided. Well-differentiated grade 3 GI NENs with a Ki-67<55% should be treated as for grade 1 and 2 GI NENs unless there is evidence of rapid tumour growth, in which case they should be treated as for poorly differentiated NECs[10].

- Irrespective of Covid-19 risk, NECs should be treated urgently with appropriate chemotherapy [11][10].
- NEC patients being treated with chemotherapy may be immunocompromised and therefore at high-risk for Covid-19.
- If a NEC is discovered in a patient with severe Covid-19, the respiratory illness should be treated first, followed by early and appropriate chemotherapy following recovery.

**Small intestinal (SI) NENs**

- SI NENs, which can produce serotonin and other vasoactive substances, may present with loco-regional disease or distant metastatic disease and are associated with estimated five-year survival rates of 65% and 35%, respectively [8].
- Loco-regional disease may present with abdominal pain due to mesenteric venous insufficiency, auto-infarction with tumour necrosis and haemorrhage, serotonin-induced retroperitoneal fibrosis, hydronephrosis or small bowel obstruction, which may require surgical intervention as an emergency.
- Metastatic and systemic disease may result in features of the carcinoid syndrome, which occurs in approximately 20% of SI NENs. Features of
carcinoid syndrome include facial flushing, angioedema, diarrhoea, wheeze, ascites, pellagra and symptoms of right-sided heart failure caused by fibrosis of right-sided heart valves, so-called carcinoid heart disease (CHD). Some patients have lacrimation, rhinorrhoea, and episodic palpitations when they flush.

- The first-line therapy for patients with metastatic carcinoid is a long-acting SSA (e.g. octreotide LAR or lanreotide autogel) which has anti-proliferative and anti-secretory benefits in NENs [12][13]. Anti-diarrhoeal drugs (e.g. loperamide, codeine phosphate) and anti-histamines (blocking histamine 1 (H1) and 2 receptors (H2) for flushing may help some patients.

- At present there is no evidence to suggest that SSAs increase the risk of Covid-19 infection.

- SSAs can cause QT prolongation, and choice of anti-microbial and/or cardiac monitoring should be carefully considered for patients with Covid-19 taking SSAs [14] (Table 1).

- Treatment with telotristat ethyl may be considered in some centres for the management of refractory diarrhoea in patients with carcinoid syndrome.

- A carcinoid crisis is a medical emergency caused by the sudden release of serotonin and other vasoactive substances into the systemic circulation, and is characterised by intense flushing, bronchospasm, tachycardia, labile blood pressure (hypertension or profound hypotension) [15]. A carcinoid crisis may look like an anaphylactic attack, but adrenaline must not be given as it will provoke, not help, carcinoid attacks (see below and Table 1) [15][16]

- Common precipitants of a carcinoid crisis include: i) intra-operative handling of the primary tumour; ii) biopsy or ablative therapies of a tumour; iii) anaesthetic induction; and iv) specific medications such as cyclizine, long-
acting vasopressors (e.g. noradrenaline) and drugs which stimulate histamine release (e.g D-tubocurarine) (Table 1).

- Treatment for a carcinoid crisis comprises an i.v. bolus of octreotide (25-500 μg) followed by an i.v. infusion of octreotide at a starting dose of 50–150 μg/h, together with i.v. fluids and appropriate cardiovascular measures to treat the likely intracardiac hypovolaemia and decreased pulmonary artery pressure[8][7] [16]

- At present, there are no data regarding the risk of a carcinoid crisis in patients with carcinoid syndrome who develop acute viral infections, but patients with carcinoid heart disease may suffer significant decompensated heart failure.

**Large intestinal (LI) NENs**

- LI NENs may present with obstructive symptoms (pain, nausea, constipation and diarrhoea), weight loss, or rectal bleeding, loco-regional disease similar to SI NENs, and rarely carcinoid syndrome (see above)[8].

**iii) Pancreatic NENs**

- PNENs may secrete endogenous hormones or be non-hormone secreting (non-functioning) (Table 1).

- Surgery is the treatment of choice for non-metastatic PNENs measuring 2cm or greater in size, as it is often curative[7][9].

**Insulinomas**
• Hypoglycaemia in association with neuroglycopenia symptoms that are relieved by administration of glucose are the cardinal features (Whipple's triad) (Table 1)[9][17].

• The combination of hypoglycaemic symptoms with documented hypoglycaemia (blood glucose <2.2mmol/L) with hyperinsulinaemia (>30pmol/L) and inappropriately increased circulating C-peptide (>300pmol/L), in the absence of sulphonylurea or related drugs, in the plasma and urine is pathognomonic of insulinoma.

• Hydroxychloroquine as a treatment for Covid-19 can cause hypoglycaemia, which should be differentiated from hyperinsulinaemic hypoglycemia.

• Hypoglycaemia is an emergency. Initially in a conscious and cooperative patient, glucose 10-20g (e.g. 2-4 teaspoons (or 3-6 lumps) of sugar, 150-200ml of pure fruit juice, or 5-7 tablets of dextrose) can be given orally. In an unconscious patient intravenous (i.v.) administration of glucose is required (e.g. 50ml of 20% glucose (dextrose) infusion over 10 minutes, into a large vein through a large-gauge needle since this concentration is irritant especially if extravasation occurs). Glucagon 1mg i.m. may be used as an alternative.

• Frequent meals (or enteral feeding via nasogastric tube) with diazoxide can be started before proceeding more definitive treatment, e.g. surgery.

• Somatostatin analogues (SSAs) can be effective, but need careful monitoring as they can worsen the hypoglycemia. Corticosteroids may benefit some patients.

_Gastrinomas_
• Gastrinomas, which are most often located in the duodenum, but also occur in the pancreas, are associated with marked gastric acid production and severe peptic ulcers that are multiple and recurrent (Zollinger-Ellison syndrome). Some patients may also have diarrhoea (steatorrhoea)[9].

• Patients with severe haematemesis may need blood transfusions and i.v. fluid resuscitation, but for patients with Covid-19 and clinical or radiological evidence of pulmonary congestion, caution with i.v. fluid resuscitation is warranted.

• Medical treatment, which is directed to reducing gastric acid production, comprises high-dose proton pump inhibitors, which in severe cases may need to be combined with H2 blockers.

Other PNENs

• The diagnosis and treatments of other PNENs is detailed in Table 1.

iv) Phaeochromocytoma and paragangliomas

• Phaeochromocytomas and paragangliomas (PPGL) may present with paroxysmal or sustained hypertension, and attacks of palpitations, tremor, perspiration, headache and anxiety[18]

• Patients with previously-treated PPGL should perform interval home monitoring of blood pressure and can be advised that their risk of Covid-19 is not increased. Regular review in asymptomatic patients can be delayed (Figure 2).
• If admitted with Covid-19, no special requirements should be necessary, but plasma and urinary metanephrines may be grossly elevated during severe disease so should not necessarily be indicative of recurrent tumour.

• If a patient with Covid-19 is suspected of harbouring a PPGL and this has been biochemically proven, α-adrenoreceptor blockade should be instituted (oral with phenoxybenzamine or doxazosin, or intravenous phenoxybenzamine) with monitoring of blood pressure, and may be considered for β-adrenoreceptor blockade after adequate α-adrenoreceptor blockade[18].

• With adequate and appropriate sympathetic blockade, PPGL surgery could be postponed during an acute Covid-19 crisis (Figure 1).

v) Medullary thyroid carcinoma (MTC)

• MTC may present as a palpable mass in the neck, which may be asymptomatic or associated with symptoms of pressure, dysphagia, diarrhoea or flushing.

• Diagnosis of MTC is based on histopathology (high calcitonin and or CEA may help but are not diagnostic)

• MEN2 patients with MTC may also have phaeochromocytoma, which must be excluded before undertaking any surgical intervention[19].

• Ectopic ACTH production by MTC may cause Cushing’s syndrome.

• Metastatic MTC can be treated with limited surgical resection, external beam radiotherapy in certain situations, tyrosine kinase inhibitors (TKIs), SSAs or other agents.
vi) Specific recommendations for the management of NENs during Covid-19

i. Multi-disciplinary meetings (MDT)

- Specialist NEN MDT meetings will be crucial during this period to ensure ongoing governance and appropriate decision making. For each case, the risk of the proposed intervention, diagnostic procedure or treatment should be weighed up against the risk of hospital attendance and Covid-19.
- MDT meetings should have options for videoconference and virtual meetings.

ii. Surgery for NENs

(See Figure 1)

iii. Clinical review for NEN patients

- Non face-to-face consultations including phone or video consultations for suitable patients is recommended (Figure 2).
- Non-essential clinic consultations should be postponed (Figure 2).
  Clinical review should be carried out with necessary safety precautions in place (Figure 2).

iv. Radiological surveillance for NEN patients

- Cross-sectional imaging should be considered for patients with suspected disease progression, based on clinical symptoms, biochemistry or anticipated tumour biology.
- Routine surveillance in asymptomatic patients, in whom suspicion of disease progression is low, could be delayed.
• Access to nuclear imaging may be limited by Covid-19 pandemic, and patients considered for peptide receptor radionuclide therapy (PRRT) with $^{177}$Lutetium-dotatate should be prioritised for somatostatin receptor imaging (SRI).

v. **Endoscopic procedures for NENs**

• Endoscopy department closure or restriction may affect diagnosis of and interventions for NENs. SRI may be considered as an alternative to endoscopy-guided biopsy in certain cases. Individual centres should discuss alternative planning for emergency endoscopic procedures for patients with NENs during Covid-19.

vi. **Therapy for NENs**

• Management of acute presentations due to secretory NENs is reviewed in Table 1.

• Patients with Covid-19 have an increased risk of venous thromboembolism (VTE)[20]. We recommend that patients with NEN and Covid-19 receive VTE prophylaxis in accordance with local protocols unless there is a significant contraindication, in which case careful discussion with a haematology specialist is advised.

• Conservative fluid resuscitation is generally recommended for patients with Covid-19 [21], but we advise that the intravenous fluid requirements for patients with Covid-19 and secretory NENs (e.g patients with VIPoma and PPGL) is guided by careful clinical assessment, blood pressure, electrolytes and invasive monitoring when necessary.
• For patients on active therapy who develop Covid-19, we recommend that
treatment is withheld during the illness with the exception of SSAs for
symptomatic secretory NENs.

• Options for home administration of SSA should be explored with patients and
family.

• SSA therapy should be commenced in the absence of confirmatory SRI when
delayed during the Covid-19 pandemic.

• SSA therapy can be considered as a bridge to a postponed curative surgery in
asymptomatic patients with localised well-differentiated and non-secretory
NENs.

• High-dose SSA therapy may be considered as a potentially safer alternative to
PRRT, targeted therapy, or chemotherapy in patients with progressive well-
differentiated GEP NENs [22]

• PRRT with $^{177}$Lutetium- dotatate therapy and other radionuclide therapies (e.g.
$^{131}$I-Metaiodobenzylguanidine ($^{131}$I-MIBG)) should be discussed at specialist
NEN MDTs. Radionuclide therapies should be strictly performed according to
international protocols, and if cytopaenia develops treatment cycles may need
to be delayed or postponed.

• Monitoring for patients receiving PRRT and other radionuclide therapies
should continue according to local guidelines.

• Patients may develop treatment-related fevers, leucopenia and lymphopenia
post-PRRT and $^{131}$I-MIBG therapy. The differential diagnosis of Covid-19
should be considered and testing prioritised to exclude this diagnosis.

• Cytotoxic chemotherapy should be discussed at specialist NEN MDTs and
alternative lower risks options considered for each patient.
- Local ablative therapies should be considered as an alternative to surgery or systemic chemotherapies in suitable patients.
- External beam radiotherapy should only be considered in patients with symptomatic bone metastases not responding to conventional analgesia.

**vii. Discussing resuscitation status for NEN patients**
- Discussions regarding resuscitation and escalation of care for patients with NENs and Covid-19 should, when possible, involve NEN specialists for advice on treatments, prognosis and end-of-life measures related to the underlying NEN.

**viii. Support and educational resources**
- Advice and support for NEN patients and families is provided at: www.amend.org.uk, www.netpatientfoundation.org, and paradifference.org.

**ix. Collecting data on patients with NENs and Covid-19**
- We recommend recruiting patients with a diagnosis of NEN and COVID-19 to a dedicated registry (e.g. https://endo-ern.eu/ese-and-endo-ern-launch-an-initiative-to-collect-data-on-patients-with-rare-endocrine-conditions-and-covid-19/) in order to better inform future management of this patient group during the Covid-19 pandemic.

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Figure 1: A suggested approach to surgical decision making during the Covid-19 pandemic for patients with NENs

* = The patient's prognosis and life-expectancy from the underlying NEN must be considered in each case and discussed with the patient, family and surgical team
** = Locally ablative therapies e.g. RFA, radio-embolisation or PRRT could be considered as an alternative to surgery in select patients
*** = This is not an exhaustive list but designed as a guide and all non-emergency surgical cases should be discussed at a specialist NEN MDT
**** = Age over 60, pre-existing cardiovascular disease, pre-existing respiratory disease

CHD: Carcinoid heart disease
PPGL=Phaeochromocytoma/paraganglioma
pNEN= Pancreatic neuroendocrine neoplasm
SI NEN=small intestine neuroendocrine neoplasm
PRRT=Peptide receptor radionuclide therapy
SSA= somatostatin analogues
RFA=Radiofrequency ablation
GEP= Gatro-enteropancreatic

Figure 2: A suggested approach to the timing of clinical assessment during Covid-19 for new and follow-up patients with NENs

*=The timelines and type of surveillance should follow local and ENETS guidelines where possible
**=The diagnosis may be based on limited biochemical and radiological data and clinical judgement should be applied

PPGL=Phaeochromocytoma/paraganglioma
pNEN= Pancreatic neuroendocrine tumour
PRRT=Peptide receptor radionuclide therapy
SSA= somatostatin analogues
NEC=neuroendocrine carcinoma
MTC= medullary thyroid carcinoma
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|                | Category 1 | Category 2 | Category 3 |
|----------------|------------|------------|------------|
| **Clinical urgency** | High | Moderate | Low |
| **Time-frame** | Emergency surgery needed within 24-72 hours | Elective surgery needed within 4-6 weeks | Elective surgery can be delayed for 10-12 weeks |
| **Rationale** | Life threatening condition requiring emergency life saving surgery* | Potentially curative surgery required because of severity of symptoms, or biological priority  
Or  
Palliative surgery required because of the severity of symptoms in the setting of failed medical therapy with a life expectancy> 12 months ** | Surgery in patients with low or moderate biological priority and low risk of complications in the interim |
| **Patient cohort** | SI NENs complicated by small bowel obstruction or perforation, mesenteric ischaemia or haemorrhage  
Bronchial carcinoid complicated by life threatening haemopulysis  
Acute duodenal perforation due to a gastrin secreting NEN | Symptomatic catecholamine secreting PPGL  
Secretory pNENs (localised or metastatic) inadequately controlled by medical therapy**  
Primary SI NENs causing intermittent obstruction  
Thymic NEN | Symptomatically well controlled primary SI/G2 GEP NENs  
Non-secretory PPGL  
Elective valve surgery for CHD  
Primary asymptomatic bronchial carcinoid |
| **Additional considerations** | Intra-operative i.v. SSA prophylaxis for emergency SI NEN surgery  
COVID-19 screening for emergency surgery should follow local guidance | The need for ICU/HDU admission post-operation  
Other co-morbidities which may place patients at risk if they develop COVID-19 **** | |

254x190mm (72 x 72 DPI)
**New diagnosis of:**
- Functioning pNEN
- Carcinoid syndrome
- Secretory PPGL
- Bronchial carcinoid
- Thymic NEN
- G3 NEN
- NEC
- Symptomatic non-secretory NEN
- Symptomatic metastatic MTC
- A symptomatic hereditary endocrine neoplasia syndrome gene carrier

**Surveillance of:**
- Patients receiving radionuclide therapies
- Patients with secretory NENs awaiting surgery e.g. insulinoma, PPGL
- Patients treated by cytotoxic chemotherapy, targeted therapy or immunotherapy in the last 6 weeks
- Patients with progressive NENs (clinically, biochemically, or radiologically)
- All symptomatic patients

**New diagnosis of:**
- Non-functioning pNEN 2 cm
- Localised asymptomatic G1/G2 small bowel NEN (Ki67<10%) or radiological evidence of slow progression
- Non-functioning PPGL
- Incidental G1/G2 NEN identified on post-op histology with evidence of nodal or suspicion of distant disease
- New diagnosis of localised MTC

**Surveillance of:**
- Metastatic NEN stable on SSA therapy
- Patients > 4 weeks post completion of PRRT without deterioration in plasma biomarkers
- Patients who recently underwent uncomplicated surgery for a localised NEN
- Patients > 4 weeks post ablative therapy for a secreting NEN who is asymptomatic

**New diagnosis of:**
- Hereditary endocrine neoplasia gene carriers (asymptomatic)
- Incidental G1/G2 NEN identified on post-op histology without evidence of nodal or distant disease

- Hereditary asymptomatic endocrine gene carriers with stable imaging within the last 12 months
- Patients undergoing post-operative surveillance with stable imaging in the past 12 months
- Patients with asymptomatic metastatic G1/G2 NENs, stable on therapy and with stable imaging over the past 12 months

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Figure 2: A suggested approach to the timing of clinical assessment during Covid-19 for new and follow-up patients with NENs

*The timelines and type of surveillance should follow local and ENETS guidelines where possible

**The diagnosis may be based on limited biochemical and radiological data and clinical judgement should be applied

PPGL=Phaeochromocytoma/paraganglioma
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Table 1: Clinical manifestations, investigations and first line treatments for NENs

| NEN                  | Clinical Manifestations                  | Secreted Hormones / Compounds | Basic* Tests (Special tests)                  | Emergency Treatments                                                                 | Contraindicated Drugs |
|----------------------|-----------------------------------------|-------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------|-----------------------|
| Bronchial As, CS, Ob | H, S, ACTH                               | PICgA, SHIAA, ACTH, CT scan   | SSA/H1/H2 SX                                | Has, as often aggressive clinical behaviour needing prompt resection                  | Aspirin NSAID         |
| (Cushing syndrome)   |                                         |                               |                                             |                                                                                       |                       |
| Thymic As, CS, Ob    | H, S, ACTH                               | PICgA, ACTH CT scan, SRI      | SX, as often aggressive clinical behaviour needing prompt resection                      |                                                                                       |                       |
| (Cushing syndrome)   |                                         |                               |                                             |                                                                                       |                       |
| Pancreatic Gastrinoma| Haematemesis, epigastric pain, PU, diarrhea | Gastrin Hb, U&E, LFTs, Ca++, gastrin, PICgA endoscopy, CT scan, MRI, SRI | PPI H2 Transfusion SX Glucose (p.o. or i.v.) Diazoxide, SSA, SX                         | Aspirin NSAID         |
| Insulinoma Whipple’s Triad | Insulin C-peptide | Glucose (overnight fast), (insulin, C-peptide), PICgA, U&E, LFTs, FBC CT scan, MRI, EUS, SRI | SSA# SX |                                                                                       |                       |
| Glucagonoma Wt loss, anaemia, stomatitis, rash-NME, venous thrombosis | Glucagon | Hb, U&E, LFTs, glucose, (glucagon), PICgA, CT scan, MRI, EUS, SRI | SSA# SX |                                                                                       |                       |
| VIPoma WDHA | VIP | Hb, U&E, LFTs, PICgA CT scan, MRI, (VIP), EUS, SRI | SSA# SX |                                                                                       |                       |
| NF (PPoma) As, Wt loss, Ob | PP or none | Hb, U&E, LFTs, (PP), PICgA, CT scan, MRI, EUS | SSA# SX | Cyclizine, Adrenaline, Noradrenaline, D-tubocurarine, Atracurium, Morphine |                       |
| Small Intestinal As, CS, Ob, Wt loss | H, S, Cg A/B | Hb, U&E, LFTs, PICgA, CT scan, MRI SRI, Urinary SHIAA, Echo | SSA# / H1 / H2 / SX |                                                                                       |                       |
| Appendix As, CS, Abdo pain | H, S, Cg A/B | Hb, U&E, LFTs, PICgA, CT scan, MRI SRI | SX |                                                                                       |                       |
| Colo-rectal As, CS, Ob, Wt loss | H, S, Cg A/B | Hb, U&E, LFTs, PICgA, CT scan, MRI SRI | SSA# / H1 / H2 / SX |                                                                                       |                       |
| Phaeochromocytoma □BP, headaches, palpitation, sweating, As | Adr, Nor | Hb, U&E, LFTs, Pl or Ur metanephrines, CT scan, MRI | Alpha Blockade (p.o. or i.v.) / SX | Beta adrenoreceptor blockade (unopposed), Metoclopramide, Naloxone |                       |
| □BP, headaches, palpitation, sweating, palpitiation, As, Lump(s) | Adr, Nor | Hb, U&E, LFTs, Pl or Ur metanephrines, CT scan, MRI, SRI | Alpha Blockade / SX | Beta adrenoreceptor blockade (unopposed) |                       |
| Parangangioma | Neck lump, As, Dysphagia, Diarrhoea, Flushing, (Cushing’s syndrome) | Calcitonin (ACTH) | calcitonin, CEA, Hb, U&E, LFTs, TFT’s Ultrasound scan, CT scan, MRI | SX +/- systemic therapy |                      |
| MTC                                                                                                                                                                                                 |                       |
NEN, Neuroendocrine neoplasm; VIPoma, vasoactive intestinal peptide (VIP) tumor; NF, Non-functioning; PPoma, pancreatic polypeptide (PP) tumor; MTC, medullary thyroid carcinoma; As, asymptomatic; CS, carcinoid syndrome – facial flushing and edema, diarrhea, abdominal pain, telangiectasia, carcinoid heart disease, wheezing, pellagra-like skin lesions; Ob, obstruction; PU, peptic ulcer; Whipple’s triad, hypoglycemic symptoms, blood glucose <2.2mmol/L, relief of symptoms following ingestion of glucose; Wt, weight; NME, necrolytic migratory erythema; WDHA, watery diarrhea, hypokalemia, achlorhydria; Abdo, abdominal; BP, hypertension; H, histamine; S, serotonin; ACTH, adrenocorticotropic hormone; CgA, chromogranin A; Adr, adrenaline; Nor, noradrenaline; CT, computed tomography; PlCgA, plasma CgA; 5HIAA, 5-hydroxyindoleacetic acid; SRI, somatostatin receptor imaging; Hb, haemoglobin; U&E, urea and electrolytes; LFTs, liver function tests; Ca++, plasma calcium; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; Pl, plasma; Ur, urine; SSA, somatostatin analogue (eg, octreotide or lanreotide); HI, histamine receptor 1 blocker (anti-histamine); H2, histamine receptor 2 blocker (eg, ranitidine or cimetidine); SX, surgery; PPI, proton pump inhibitor (e.g. lansoprazole or omeprazole); alpha blockade e.g. phenoxybenzamine or phentolamine; NSAID, non-steroidal anti-inflammatory drugs;

8QT prolonging drugs should be avoided in patients taking SSA therapy including medications which may be used as part of the treatment of Covid-19 e.g.; macrolides, azole anti-fungals, antimalarials, pentamidine, ciprofloxacin and moxifloxacin. If there are no alternatives to these medications, careful cardiac monitoring is required.