A NEUROLOGIST’S APPROACH TO THE IMMUNOSUPPRESSED PATIENT
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It is not unusual to be asked for a neurological assessment of a patient with some form of immune suppression. Most patients will have an acquired disorder of the immune system and are the focus of this review (table 1). We shall not discuss the neurological consequences of HIV, as this is the subject of a separate article in this supplement (see p i29), nor those with rarer inherited immune deficiency as their investigation and treatment is such a highly specialised area.

ACQUIRED IMMUNE SUPPRESSION

Acquired immune suppression may be a deliberate goal of medical treatment where the aim is to reduce an inappropriate immune response, such as treating myasthenia with steroids and azathioprine. It may be a recognised undesired effect of treatment for another condition—for example, in a patient on anti-neoplastic chemotherapy. Less obviously immunosuppression can occur in disorders that impair the effectiveness of the immune system—for example, systemic lupus erythematosus (SLE), diabetes, renal failure. In all these situations the condition being treated with immunosuppression, or the process causing the immune suppression, may have their own inherent neurological manifestations additional to suppression of the immune response. Examples include non-metastatic effects of malignancy, such as limbic encephalitis, or a systemic condition such as SLE that leads to direct involvement of the central nervous system (CNS) presenting as neuropsychiatric illness. Alternatively, treatments for malignancy also have direct and unwanted effects on the CNS and neuromuscular system—for example, the neurotoxic side effects of cytotoxic drugs.

Immunosuppression changes the normal relationships to the microorganisms so:

- innocuous organisms in the immune competent individuals become pathogenic
- infections evolve rapidly
- the usual clinical and laboratory manifestations and markers of infection may not be seen or detected.

This alters the clinical presentation and features of infection, both systemic and neurological. Immunosuppressed patients are susceptible to a variety of general medical problems relating to the underlying illness, systemic infection, adverse effects of drugs, poor nutrition, and the medical interventions to which they are exposed.

Thus, in the immunosuppressed patient with neurological involvement there are three inter-related areas to consider. First, has whatever caused the immunosuppression either directly or indirectly affected the nervous system? Second, are such problems due to an infection of the nervous system? And last, are there any medical complications that might produce a neurological disturbance? In assessing immunosuppressed patients, the clinician must remember that more than one of these factors may be involved in the neurological presentation.

These patients are often overtly unwell and obtaining information from other medical attendants, the general practitioner, other health professionals, and the patient’s family is essential for proper evaluation. You will often be dealing with a condition or treatment with which you will have little familiarity. Therefore discussion with the microbiologist, oncologist, haematologist, clinical immunologist, other specialists involved in the care of the patient, as well as with the hospital pharmacist/drug information service is required.

Some questions to ask yourself at the bedside are given in box 1.

CAUSES OF IMMUNE SUPPRESSION: HOST FACTORS

The classification of immune deficient conditions is given in table 1. We shall focus, using the clinical approach outlined in box 2, on the more common acquired immune conditions and discuss each of these in turn, although many of the principles apply across all immunodeficient states.
Table 1 Classification of immune deficient conditions

<table>
<thead>
<tr>
<th>Primary/inherited immune deficiency states</th>
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<tbody>
<tr>
<td>Antibody deficiency</td>
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<tr>
<td>Combined antibody and cellular immunodeficiency</td>
</tr>
<tr>
<td>Complement deficiency</td>
</tr>
<tr>
<td>Secondary/acquired immune suppression (non-HIV)</td>
</tr>
<tr>
<td>Extremes of age</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
</tr>
<tr>
<td>Connective tissues disease</td>
</tr>
<tr>
<td>Organ failure (renal failure, hepatic failure)</td>
</tr>
<tr>
<td>Malignancy (especially haematological and lymphoreticular)</td>
</tr>
<tr>
<td>Iatrogenic</td>
</tr>
<tr>
<td>- chemotherapy</td>
</tr>
<tr>
<td>- radiotherapy</td>
</tr>
<tr>
<td>- transplantation</td>
</tr>
<tr>
<td>Asplenism/splenic dysfunction (primary or secondary—for example, sickle cell disease, trauma)</td>
</tr>
</tbody>
</table>

DIABETES

Patients with diabetes have an increased risk of cerebral vascular disease. Diabetes is associated with various types of neuropathy (see Llewelyn1 in this series) and causes retinopathy. In addition there are complications associated with more acute metabolic disturbance related to hypoglycaemia and hyperglycaemia. Patients with diabetes are prone to infections which may be related to high circulating levels of glucose and to compromised vascular circulation. Two uncommon but well recognised and typical infections of the head in diabetes are rhinocerebral mucormycosis and malignant otitis externa.

Rhinocerebral mucormycosis

Fifty per cent of rhinocerebral mucormycosis fungal infection occurs in the context of diabetes, and in half of these the presentation is in the context of ketoacidosis. The infection can involve nose, paranasal sinuses, orbit, and brain. Facial and ocular pain are commonly present and the patient may develop orbital swelling with proptosis and ophthalmoplegia. Necrotic lesions on the palate are characteristic. The infection tends to spread along vascular channels. Diagnosis is usually confirmed with biopsy (fig 1). Surgical treatment combined with amphotericin is recommended. Some authorities have suggested hyperbaric oxygen treatment.

Malignant otitis externa

Malignant otitis externa is an infection which starts in the skin and the external ear canal. The majority (80%) of patients are diabetic. The infection may then spread from the ear to the soft tissues and bone of the skull base. Cranial nerve palsies VII through to XII may result. The infecting agent is usually *Pseudomonas aeruginosa*. Patients present with otalgia and evidence of infection in the external auditory canal. The extent of spread may be shown with computed tomography (CT) or magnetic resonance imaging (MRI) with views of the skull base. Debridement followed by appropriate antibiotics (penicillin with cephalosporins such as cefazidine).

CHRONIC ALCHOLISM

Patients with chronic alcoholism often have poor nutrition and can have reduced granulocyte function with consequent susceptibility to nutritional syndromes and bacterial infections. In addition they may have clotting disorders.

Box 1: Some questions to ask yourself at the bedside

- Is this patient immune suppressed?
  - Sometimes this will be obvious but in other patients a review of the past medical history may be an important starting point. As outlined above, the spectrum of illness associated with immune suppression is wide and that the patient is immunosuppressed may not be immediately obvious.

- What is the neurological problem?
  - Again this may not be easy. Patients may be unwell and have multiple medical problems. The neurologist is sometimes called in when the clinicians in charge are in difficulties. The context of the examination may be unfamiliar to you—for example, in the transplant unit, making an assessment more difficult with the patient attached to complex equipment.

- Is this a general medical problem?
  - It is important to exclude metabolic disturbance, hypoxia, sepsis, or organ failure as a primary cause. It is always worth considering prompt administration of intravenous vitamin supplements (thiamine, riboflavin, and pyridoxine) in the malnourished patient.

- Is this some treatable infection?
  - Clearly this is something not to be missed. When investigations are requested it is essential to involve the microbiologist so that correct samples are sent and appropriately processed. Awareness that certain types of infection may be signatures of particular illnesses is helpful. An example would be rhinocerebral mucormycosis in diabetics.

- Is this a neurosurgical problem?
  - Again, not to be missed. Is there evidence of a cerebral mass lesion or evidence of cord compression? Scanning of patients who are unwell, restless, and agitated can be problematic. Enhanced imaging with contrast may be useful and engaging the radiologist in discussing the problem helpful.

- Is the clinical picture caused by the underlying medical condition?
  - Could recurrent malignancy or a paraneoplastic syndrome explain the problem? Is the problem a recognised presentation of the underlying medical problem, such as vasculitis?

- Is this a direct side effect of therapeutic agents?
  - There are adverse effects, other than immune suppression associated with chemotherapy and radiotherapy. Some of these drugs may be unfamiliar to you. Checking them with the pharmacy or your drug information service is advisable.

Box 2 A clinical approach to the immune suppressed patient

Consider

- The specific complications of the primary diagnosis
- The potential side effects of its treatment
- The complications of an impaired immune response
  - unusual presentation of infection with common pathogens
  - infection with unusual pathogen (opportunist infections)
- The general medical health of the patient
- The specific nature of infection, as some are anticipated in particular conditions (for example, malignant otitis externa in diabetes).
Connective tissue diseases can affect the nervous system in a variety of ways (table 2). This may be by direct involvement in the inflammatory process, such as vasculitis, or indirect involvement mediated by circulating antibodies. The presence of anti-phospholipid antibodies is associated with a prothrombotic tendency and increased risk of cerebral or retinal ischaemia. These antibodies may be found in SLE or as part of the primary anti-phospholipid antibody syndrome (APS). Patients with SLE may have multiple complement deficiencies with consequent risk of infection. Furthermore, neurological complications may be secondary to treatment with steroids or other immunosuppressants (see later).

ORGAN FAILURE

Renal failure

Dialysis dysequilibrium syndrome is caused by an osmotic gradient between plasma and brain occurring with dialysis and resulting in cerebral oedema and encephalopathy (box 3). Patients develop headache and may go on to develop coma, seizures, and myoclonus. Dialysis encephalopathy is a progressive central nervous system (CNS) disorder which may be related to aluminium accumulation. Patients develop ataxia, myoclonus, and progressive cortical dysfunction (dyspraxia, dysphasia, dysgraphia) and later convulsions. Treatment consists of prevention of aluminium exposure and chelation in established cases.

In common with other conditions causing poor nutrition, Wernicke’s encephalopathy can be seen in patients with renal failure. Dialysis and glucose loading may precipitate acute thiamine deficiency.

Uraemia, combined with anticoagulation for treatment, may lead to bleeding such as subdural haematoma.

Transplantation encephalopathy may be seen in the early months post-transplantation, presenting with headache, constitutional symptoms, and sometimes seizures. This is thought to be a self-limited illness with an immunological basis.

Complications of the immunosuppressive agents used in transplantation—infecions and secondary malignancy (typically lymphoreticular)—are discussed later.

Box 3: Neurological complications of organ failure

- Renal failure
  - Dialysis complications (dysequilibrium syndrome, dialysis encephalopathy)
  - Nutritional syndromes
  - Complications of anticoagulation
  - Transplantation encephalopathy
  - Uraemic encephalopathy

- Hepatic failure
  - Hepatic encephalopathy
  - Coagulation defects
  - Nutritional defects

Box 4: Treatments causing immune suppression

- Steroids
- Other immune suppressant drugs
- Anti-neoplastic drugs
- Monoclonal (anti-lymphocyte) antibodies
- Radiotherapy
- Transplantation
Hepatic failure
Patients with impaired liver function may develop encephalopathy. Shunting from the portal into the systemic circulation may contribute to this. This can come on quickly and resolve rapidly. Foetor, a metabolic limb flap, and triphasic EEG waves may help in the diagnosis.

Coagulation defects may lead to bleeding complications. Patients with hepatic dysfunction may be particularly prone to nutritional deficiency. Although the B vitamins are the most common cause of neurological syndromes, patients with gastrointestinal malabsorption may develop vitamin E deficiency which is associated with ataxia, ophthalmoplegia, and peripheral neuropathy.

COMPLICATIONS OF IMMUNOSUPPRESSIVE TREATMENT
The drugs that either intentionally or unintentionally produce immunosuppression (box 4) can have other adverse effects on the nervous system. These need to be recognised and distinguished from complications of immunosuppression.

Corticosteroids (steroids) and other immune suppressants
Steroids can be administered orally as prednisolone or dexamethasone or intravenously as dexamethasone or methylprednisolone. Adverse effects are shown in box 5.

A variety of immune suppressant drugs are used, often with steroids, to modify an abnormal immune response. Azathioprine is perhaps the most frequently used drug in neurological practice, but other commonly used drugs include methotrexate, cyclophosphamide, and cyclosporin. Some of these drugs have direct neurological complications (table 3).

Antineoplastic drugs
The adverse effects of antineoplastic drugs are given in table 3.

Radiotherapy
Radiation therapy causes neurological complications in a number of ways. The effects will depend to an extent on dose, fractionation, and radiation field. Radiotherapy given widely may affect the immune system by damaging the bone marrow and other immunologically active tissues. Specific problems from CNS irradiation may be acute or delayed. Below are some of the more commonly encountered problems:

- Drowsiness, anorexia, and nausea are common in patients undergoing cranial irradiation
- Acute encephalopathy may be seen with cerebral swelling giving headache and progressive neurological deterioration. Treatment with steroids is helpful
- Delayed cranial nerve damage may be seen including optic neuropathy and sensori-neural deafness. Pituitary failure can also develop similarly
- Subacute demyelination occurring within months of treatment and presenting with neurological deterioration may again be helped by steroids
- Radiation necrosis may present years after treatment and differentiation from tumour can be difficult. The cause is uncertain but pathological changes occur in small blood vessels
- Long term white matter damage can present with progressive neurological and cognitive decline. This presentation may be more common in patients who also received chemotherapy. The imaging features are of progressive atrophy and diffuse white matter change.

Transplantation
The success of organ transplantation requires effective immunosuppressive chemotherapy. The complications of renal transplantation have already been discussed. There are more specific, common complications associated with bone marrow transplantation. Fifty per cent of patients who undergo bone marrow transplant have neurological complications and a significant number (5–10%) will die from these. The neurological complications are shown in box 6 in order of incidence.

**Table 2** Neurological complications of connective tissue diseases

<table>
<thead>
<tr>
<th>Connective tissue disease</th>
<th>Brain</th>
<th>Neuro-psychiatric</th>
<th>Cord</th>
<th>Peripheral neuropathy</th>
<th>Muscle</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>Nodules causing compression</td>
</tr>
<tr>
<td>RA</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Trigeminal neuropathy, myositis</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>Myositis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

**Box 6: Neurological complications of bone marrow transplantation**

- Metabolic encephalopathy
  - hypoxia
  - hepatic failure
  - renal failure
  - electrolyte imbalance
- Infection
  - early (< 1 month): bacterial, viral, fungal
  - late (1–12 months): viral, parasitic
- Cerebrovascular complications
- secondary to infective or non-infective endocarditis
- Malignancy
- Post-transplantation lymphoproliferative (Epstein-Barr virus induced) disorders
- Recurrence of original tumour

**Box 5: Complications of steroid treatment**

- Diabetes
- Immune suppression
- Electrolyte disturbance
- Psychosis/depression
- Myopathy
- Osteoporosis
- Avascular necrosis of the hips
CNS Infection

The approach to the diagnosis of infection in immunosuppressed patients differs from that in usual clinical practice. Presentations may be subtle or atypical because of an altered inflammatory response, and some of the investigations will be of limited utility. An elevated white cell count may not be seen in patients who are neutropenic or immunosuppressed. The erythrocyte sedimentation rate (ESR) may be of little use as this is a crude measure of fibrinogen which may be reduced in hepatic disease and in patients with coagulopathy. Treatment should be based on identification of the organism and selective appropriate antibiosis; however, this may not be possible in the first instance in a patient who is severely unwell, and empirical treatment may be required so knowledge of the likely infecting pathogen(s) is useful. In this situation advice from the microbiologist is invaluable. Bacteria, viruses, fungi and parasitic infections need to be considered and investigated (Box 7).

CNS Infection by Location

It is useful clinically to consider the likelihood of the pathogen depending on the clinical syndrome (Table 4).

Some Specific Infections

Candida albicans

Candida albicans is a common infection in patients with defective granulocytes. Disseminated infection may affect many organs including the CNS. Clinical presentation may sometimes be similar to bacterial sepsis with systemic manifestations. CNS infection may be introduced by instrumentation including lumbar puncture (LP). C albicans may cause meningitis and cerebral abscess with a high mortality rate.

Cryptococcus neoformans

Cryptococcus neoformans is a common cause of fungal meningitis in immunocompromised patients, especially in those with cell mediated immune deficits such as organ transplantation, lymphoma, or HIV. Onset may be insidious and headache is often present; however, fever may not be a feature. CSF is usually clear and typically reveals a lymphocytosis, low glucose, and elevated protein level. A definitive diagnosis relies on positive culture; however, cryptococcal infection can be suspected earlier by direct examination of the CSF on India ink stain, which has a sensitivity of 50%, or, if capsular antigen is present, on latex agglutination testing, which has a sensitivity of 95%. Treatment is with combined amphotericin B and 5 fluoro-cytosine. C neoformans may also cause cerebral or spinal abscess.

Listeria monocytogenes

Listeria monocytogenes infection is often diagnosed after delay. The bacteria may cause meningitis, meningoencephalitis, infection of the brain stem (rhomboencephalitis), and rarely cerebritis or abscess formation. Recurrent or relapsing listeriosis can occur in immunocompromised individuals. Diagnostic delay is often caused by lack of clinical suspicion or the organisms being dismissed as laboratory contaminants. Here the peripheral white cell count may be misleadingly normal.

Clinical presentation of listeria meningitis is as a febrile illness with impairment of consciousness in most cases (Box 8). In about 75% of cases, CSF shows a predominant neutrophilia but frequently with a mixed lymphocytic and monocytic picture. In the remaining 25% lymphocytes or monocytes predominate. CSF glucose is often normal, but the protein usually raised. The organism may be cultured from blood in 75% and CSF in 80% of cases. Repeated blood cultures can be helpful in establishing the diagnosis. Serum antibody titres for listeria are unreliable as these can be present at high levels in individuals with no active infection.

Treatment is normally with ampicillin for at least two weeks (in immunocompromised patients three to four weeks with an additional two weeks in immunocompetent patients). CSF contamination including lumbar puncture (LP) is used in the diagnosis and is a common infection in patients with impaired immune function. Definitive diagnosis relies on positive culture; however, cryptococcal infection can be suspected earlier by direct examination of the CSF on India ink stain, which has a sensitivity of 50%, or, if capsular antigen is present, on latex agglutination testing, which has a sensitivity of 95%. Treatment is with combined amphotericin B and 5 fluoro-cytosine. C neoformans may also cause cerebral or spinal abscess.
Other antibiotics, including co-trimoxazole and vancomycin, have been used where penicillin sensitivity exists. In the pre-antibiotic era mortality exceeded 66%, and the mortality remains high despite current antibiotics at 20–30%; 10% of survivors have neurological deficits which may improve further after resolution of the infection.

INVESTIGATION OF SUSPECTED INFECTION IN THE IMMUNOSUPPRESSED PATIENT

Investigation of CNS infection

After imaging to exclude a mass lesion, CSF should be examined (box 9) provided there are no other contraindications (for example, disordered coagulation). Often the laboratories will have to be directed to look for the specific organisms depending on clinical suspicion. The differential may be wide and may include malignancy. It is often useful to store extra CSF that can be re-examined later for additional specific tests. Repeat LP may be useful for detecting malignant cells or monitoring response to treatment.

Further investigation

It is important to look for systemic manifestations of CNS infection such as atypical pneumonia. A thorough history and physical examination should help, including auroscopy and skin examination. Patients should have swabs, culture, and biopsy of any skin lesions. Also a chest x-ray, blood cultures, serology, throat swabs, and urine culture are essential.

GENERAL MEDICAL CAUSES OF NEUROLOGICAL COMPLICATIONS

Remember that many patients who present neurologically may have a general medical condition. These are listed in box 10 and can be a useful checklist when no specific neurological features can be found.

APPROACH TO THE ENCEPHALOPATHIC PATIENT

Perhaps one of the most common clinical problems is the encephalopathic patient who is confused and drowsy and may have other neurological features such as seizures. The clinical approach is similar to the general scheme outlined above and is summarised in fig 2. Having excluded general medical type problems the neurological aspects of the case need to be interrogated. Cerebral imaging (preferably MRI with gadolinium contrast) is helpful. It is often difficult to obtain good quality scans in confused and agitated patients. If thought normal, scans may need to be reviewed by a specialist neuroradiologist or repeated depending on other investigations and clinical progress. In the immune suppressed patient the picture can change quickly.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Pathogens based on CNS location</th>
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<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td><strong>Fungi</strong></td>
</tr>
<tr>
<td>Meningitis</td>
<td>Listeria, enteric bacilli</td>
</tr>
<tr>
<td></td>
<td>Pneumococcus</td>
</tr>
<tr>
<td></td>
<td>Meningococcus</td>
</tr>
<tr>
<td>Haemophilus</td>
<td></td>
</tr>
<tr>
<td>Meningoencephalitis</td>
<td>Listeria</td>
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<tr>
<td></td>
<td>Legionella</td>
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<tr>
<td></td>
<td>Enteric bacilli</td>
</tr>
<tr>
<td>Abscess</td>
<td>Nocardia</td>
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<tr>
<td></td>
<td>Enteric bacilli</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus</td>
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<tr>
<td></td>
<td>Streptococcus</td>
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</tbody>
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**Box 9: CSF examination in the immunocompromised patient**

- Opening pressure
- Protein
- Red blood cell/white blood cell (cell type and count)
- Glucose (and blood glucose)
- Cytology
- Bacterial stains and culture
- Fungal stains and culture
- AFB (acid fast bacilli)
- Cryptococcal antigen
- Viral PCR (polymerase chain reaction) and culture
- Immunocytochemistry (when malignancy suspected)

**Box 10: General medical causes of neurological complications**

- **Metabolic**
  - electrolyte or acid/base imbalance
  - hypoxia/hypercapnia
  - hyperglycaemia/ hypoglycaemia
- **Cardiac**
  - endocarditis (infective or sterile)
- **Respiratory**
  - atypical pneumonia
  - pulmonary emboli
- **Gastrointestinal**
  - hepatic failure
  - pancreatic encephalopathy
  - malabsorption/nutritional syndromes
- **Musculoskeletal**
  - osteomyelitis
  - septic arthritis
- **Inflammatory/autoimmune diseases**
  - connective tissue diseases
  - vasculitides
- **Malignancies**
  - especially haematological and lymphoreticular
- **Endocrine**
  - phaeochromocytoma/carcinoid
  - Addison’s disease
  - thyroid disease
  - parathyroid disease
- **Toxicity**
  - drugs and drug withdrawal—prescribed or illicit
contraindication to CSF examination this should be done. In collaboration with the clinical microbiologist, analysis for usual and opportunistic infections should be carried out and include PCR examinations (for example, herpes simplex) and antigen tests (for example, cryptococcal antigen). Fresh samples for cytological examination should be taken. Again, in pursuit of a diagnosis, the CSF examination may need to be repeated.

CONCLUSION
Diagnosis of the neurological complications in immunosuppressed patients can be a challenging but rewarding task for the neurologist. Knowledge of the likely causes with aggressive treatment of defined or suspected infection is warranted, as these patients can deteriorate rapidly. In those who elude diagnosis, medical complications or specific effects of treatment should be considered. Seeking specialist help from colleagues in other disciplines is invaluable in the diagnosis and management.

ACKNOWLEDGEMENTS
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1 Llewelyn JG. The diabetic neuropathies: types, diagnosis and management. J Neurol Neurosurg Psychiatry 2003;74(suppl II):i1–2.
3 This paper summarises infections in the immunosuppressed host with HIV or post-transplantation. The summary tables and diagnostic utility of investigations are particularly helpful.
5 This paper emphasises the timing of likely pathogens post-transplantation and discusses each of the infecting pathogens.
8 This paper highlights the frequency of neurological complications in bone marrow transplant patients.
12 An invaluable reminder of the neurological complications of renal disease.
14 This paper reviews the pathogens that cause meningitis and addresses the question of who should go on to have further immunological testing.
16 A useful overview of the specific and general complications of the commonly used immunosuppressants.
18 For reference only, but one for the library or to borrow from your microbiologist’s shelf.