Infectious Complications of Transplantation

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Post-transplant infection is a common cause of graft deterioration, morbidity and mortality. It is also responsible for delayed discharge, multiple, often prolonged admissions and thus a significant clinical challenge. Infections can be donor derived, pre-existing in the recipient, nosocomial and opportunistic. For each of these categories, it is often possible to significantly reduce the hazard and thus the adverse consequences by first identifying patients at high risk. As always, clinical vigilance is vital, but equally important is the establishment of robust clinical systems for prevention, screening and rapid treatment.

Donor Infections

A variety of infections can be transmitted from the donor to the recipient of a kidney transplant with outcomes that range from mildly troublesome to fatal. To avoid this unpleasantness, transplant programmes institute a variety of screening procedures (see Table 71.1), but this screening is not watertight. Therefore, careful clinical assessment is critical and interpretation of risk is key; recipient serology is also crucial in assessing risk. Serum accompanies the donor organ and thus can be tested by the receiving unit for any serology felt to be relevant.

Recipient Infections Pre-transplant: Treatment, Vaccination and Prophylaxis

For the same infectious agent, there tends to be a hierarchy of virulence post-transplant with primary infections being worse than reinfections, which are more virulent than reactivations. Risk stratification is therefore highly important; identification and eradication or control of infection as well as vaccination pre-listing and appropriate prophylaxis post-transplant is not always done as well as it might be.

Table 71.2 shows infections that should be treated or controlled pre-transplant and vaccinations either recommended or to be considered on the grounds of common sense. In addition, non-specific clinical features such as unexplained splenomegaly, lymphadenopathy, persistently raised CRP, eosinophilia, polyclonal gammopathy (in the absence of autoimmunity) all need explaining before listing. In patients who have previously received high doses of immunosuppression or chemotherapy or in those with recurrent viral (e.g. herpes) or bacterial infections, it is important to check immunoglobulin levels and lymphocyte subsets. It is worth noting that immunosuppression post-transplant reduces seroconversion rates to around 50 % of that achieved by control patients, and the evidence suggests that a second dose of vaccine such as H1N1 offers no benefit [1]. Nonetheless, it is clear that vaccination has benefit, saves lives and should be built into any transplant programme [2]. Whenever possible vaccinations should be undertaken predialysis; in particular live or attenuated vaccines must be given before immunosuppression as cannot be given post-transplant.

There are several sets of guidelines recommending post-transplant prophylaxis, and Table 71.3 illustrates the main recommendations. As with pre-transplant vaccinations, units are frequently inconsistent about some areas of post-transplant prophylaxis such as TB prevention, culture of

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Table 71.1 Donor screening

History of donor	At risk behaviour, country of origin and travel
History from donor hospital	Presenting illness (NB: beware undiagnosed meningoencephalitis or flaccid paralysis[a]), evidence of undiagnosed nosocomial infection (CRP, WBC), treated nosocomial infection (UTI, pneumonia, bacteraemia – virulent vs. non-virulent, antibiotic history and duration – discuss with microbiology in donor hospital if not clear). Blood cultures, MSU/CSU, respiratory viral PCR screen, line and wound swabs, post-mortem findings
CXR	Active consolidation (or previous TB). Review other imaging
Minilaparotomy	Mostly to exclude malignancy but also gross infection/lymph nodes
Perfusion fluid	Cheap and important test especially if virulent organism (e.g. candida or Staphylococcus aureus is cultured – may lead to mycotic aneurysm)
Viruses:	
1. HIV 1 and 2 Ab	Seroconversion window – HIV RNA not routinely available. Some HIV donors may be suitable for HIV recipients if infection is controlled and resistance history readily available
2. Hepatitis B surface and core Ab	Seroconversion window – hepatitis B DNA not routinely available
3. Hepatitis C Ab	Seroconversion window – hepatitis C RNA not routinely available potential donors for Hepatitis C recipients
4. HTLV 1 and 2 Ab	Proviral DNA or RNA not routinely available. NB: caution if Ab positive and signs of disease
5. CMV Ab	Routinely checked on all donors
6. EBV Ab	Not routinely done, assume >95 % adult donors positive (can be done at recipient centre)
7. HSV Ab	Not routinely done but essential if encephalitis (check for HSV DNA in CSF)
8. VZV Ab	Assume >95 % adult donors positive
9. HHV-8 Ab	Not routinely done, possible merit in donors from endemic regions (e.g. North African countries)
10. HHV-6 Ab	Not routinely done
11. BKV serology	Not routinely done, assume 70 % seropositive
12. West Nile virus (WNV)	Consider screening (nucleic acid testing) in endemic areas, especially if undiagnosed encephalitis
Bacteria:	
1. Syphilis serology	Old vs. current infection vs. yaws, if in doubt treat
2. Tuberculosis	Inferferon-gamma release assays rarely done on donors but worth considering in live donors if from endemic regions
Fungi:	
1. Histoplasmosis cruzi Ab	Consider in donors from endemic regions: Africa, Australia, Eastern Europe, North America
2. Coccidioides Ab	Consider in donors from endemic regions: Central, South America, Southern USA
Parasitic:	
1. Toxoplasma Ab	Routine screening
2. Strongyloides Ab	Consider in endemic regions: sub-Saharan Africa, Southeast Asia, Central and S. America, Eastern Europe
3. Trypanosoma cruzi Ab	Consider in donors from endemic regions: Central and South America
4. Leishmania	Consider screening donors from endemic regions
5. Malaria	Consider screening donors in or recently from endemic regions

Communication between recipient hospitals: a unit identifying an infection acquired from a donor has a duty to relay this rapidly to other recipient units
Ab antibody
[a]Donor transmission of rabies, WNV, and LCMV has an extremely poor outcome

perfusate and hepatitis B follow-up. A robust system to ensure that patients are appropriately considered for post-transplant prophylaxis in line with local policy is critical to ensure patient safety.

Timeline for Post-transplant Infections

Although not absolute there is a clinically helpful timeline for infections post-transplant expounded by Rubin [3].

0–2 weeks: infections are mostly a direct result of surgery, i.e. chest and wound infection, line-associated sepsis and occasionally bacterial infection derived from the donor (positive perfusate culture, donor UTI, donor bacteraemia or unexplained meningoencephalitic illness).

1–4 weeks: predominantly nosocomial infections related to stay and hospitalisation, i.e. UTI, line- and PD catheter-associated infection, and *Clostridium difficile*. Oral and oesophageal candidiasis is also common at this stage especially in patients on steroids. Of the herpes viruses, primary HSV is unusual in presenting at this early stage. Other viruses such as transmitted WNV can also present at this time.

4–26 weeks: this is the period dominated by opportunistic infections related to the heaviest period of

Table 71.2 Pre-treatment and vaccination

Hepatitis C RNA positive	Erstwhile attempt to eradicate infection with pegalated interferon and ribavirin before listing. Consider newer direct-acting antivirals pre-transplant
Hepatitis B	Universal vaccination of nonimmune CKD patients (and ESRD), pre-listing assessment and stable virological control of hepatitis B with antivirals
HIV Ab positive	Undetectable viral load and CD4$^+$ >200 for 6 months prior to listing
VZV Ab negative	Vaccination (live vaccine) of the 3 % of ESRF population negative for VZV with live vaccine. Prophylaxis with acyclovir if transplanted within 2 weeks of vaccination
Influenza and H1N1	Annual vaccination
MMR (live vaccine)	If not previously vaccinated, vaccinate 1 month pre-transplant. Testing and vaccination of all women of child-bearing age pre-listing if rubella IgG negative
Diptheria, tetanus and pertussis	If not previously vaccinated vaccinate pre-transplant and routine boosters 5–10 yearly
Polio (inactivated)	Routine vaccination if not given, can be given post-transplant but *not live vaccine*
Human papillomavirus	Girls eligible for local vaccination programme should be strongly encouraged. No evidence yet for a benefit in older females to prevent CIN or prevent anogenital warts in women or men, but worth considering especially in those likely to receive high levels of immunosuppression
CMV	Early vaccine studies looking encouraging, large-scale studies pending
Pneumococcal	Vaccination according to national guidelines ideally pre-transplant
Haemophilus influenzae B	Consider pre-transplant in those with pulmonary pathology (can also be given post-transplant)
Meningococcal meningitis B&C	Vaccination according to national guidelines
Recurrent UTI	Patients with recurrent UTI before transplantation are highly likely to have significant urosepsis after transplantation; where possible the cause should be identified and treated pre-listing. NB: persistent pyuria also needs explaining even if not associated with overt sepsis
Tuberculosis	Screening in patients with ESRF by Mantoux or interferon-ϒ assays often negative due to diminished T-cell response
Strongyloides Ab positive	If treatment history not clear, especially if eosinophilia, treat with two doses of ivermectin 200 mch/kg/day for 2 days
Schistosomiasis Ab positive	Treat with two doses of praziquantel

immunosuppression. Most herpes viruses (reactivation and primary infection), e.g. CMV (in the absence of prophylaxis typically at 40 days), EBV, HSV, VZV (shingles) and HHV-8/7/6. Respiratory viruses may present with chest involvement. Invasive fungal infections such as candida or aspergillus tend to present in this period as may mycobacterium TB. Parasitic infections such as reactivation of strongyloides or toxoplasmosis tend to occur early. UTIs remain very common and, in the absence of prophylaxis, PCP presents in this period.

>26 weeks: periodic viral reactivation of HSV or VZV (shingles) can occur at any stage, and a small proportion of patients develop very high levels of EBV viraemia often many years post-transplant. Viral warts are also common in the first year. Late-onset CMV presents usually within the 8 weeks following cessation of prophylaxis (orogenital HSV may also recur). Incidental infections such as listeria, legionella and respiratory viral infection can occur at any time. CMV-, EBV-, VZV- and HSV-negative patients can acquire primary infection many years post-transplant particularly if they have a young family or become exposed to young children. MTB tends to present relatively early in the course of a transplant, while Non-tuberculous mycobacteria (NTM) tends to present later.

Cryptococcus tends to present late and PCP can occur at any stage, although risk diminishes with time. NB: hepatitis B and C reactivation can occur at any time especially after cessation of prophylaxis in hepatitis B and can be promoted by the use of steroids.

Urinary Tract Infection

UTI post-transplant is very common and associated with a significant morbidity, hospitalisation and graft loss and by definition constitutes 'complicated UTI'. UTI post-transplant is covered in more detail in Chap. 34, but it is worth emphasising that (a) patients with abnormal anatomy and recurrent UTI pre-transplant are likely to have significant problems with urosepsis post-transplant unless the underlying cause is resolved; (b) as transplant UTIs are by definition 'complicated', short courses of antibiotics may result in partially treated and recurrent infections (with high risk of generating multiple admissions and highly resistant organisms); and (c) patients with recurrent or severe urosepsis need prompt assessment in a urolo-radio nephrology MDT.

Table 71.3 Infection prophylaxis post-renal transplantation

CMV	Pre-emptive monitoring or prophylaxis (see text). Valgancyclovir 900 mg daily if normal renal function (450 mg possibly as effective and less side effects), dose adjusted if GFR <60
HSV Ab negative	*Essential* if not receiving valgancyclovir prophylaxis for CMV. Valacyclovir 500 mg twice a day or acyclovir 200 mg three times a day for 1 month regardless of donor HSV status
HSV Ab positive	If history of recurrent cold sores pre-transplant, likely to be worse post-transplant. Acyclovir 200 mg o.d. prophylaxis
VZV Ab negative	Administer varicella zoster immunoglobulin if significant exposure to chicken pox or shingles (within 7 days of exposure)
Hepatitis B core Ab positive donor	HBV immunoglobulin (HBIG) at transplant (HBIG 4,000 IU IV stat and measure HBs Ab levels at day 7 and repeat dose if levels are <500 IU/L); start lamivudine 2–3 days before or at least on the day of transplant; monitor HBsAg regularly
Hepatitis B core Ab positive recipient	Lamivudine prophylaxis 2–3 days before or immediately after transplantation. Monitor HBsAg regularly
Hepatitis B surface Ag positive donor	HBV vaccination for recipients pre-transplant. HBIG (HBIG 4,000 IU IV stat) at transplant, measure HBsAb levels at day 5 and repeat dose if levels are <500 IU/L. Monitor HBsAb levels weekly and repeat HBIG to maintain levels >500 IU/L during the first month post-RT. Start antiviral prophylaxis 2–3 days before or immediately after transplantation. Preferred drug is entecavir. Obtain donor HBV treatment status if available and modify antiviral prophylaxis accordingly if there is a risk of drug resistance. Monitor HBsAg regularly
Hepatitis B surface Ag positive recipient	Start antiviral therapy preferably 2–3 weeks prior to or at least immediately after transplantation. Entecavir is the preferred option if no concerns about resistance
Wound prophylaxis	Local policy
UTI prophylaxis	Septrin (as part of universal *Pneumocystis jirovecii* prophylaxis), some units give additional UTI prophylaxis (see Chap. 35)
Bacterial growth in perfusate	Treatment on the basis of culture, but consider long course if virulent organism, e.g. *Staphylococcus aureus*, *Pseudomonas*
Mycobacterium	6 months of isoniazid 300 mg o.d. and pyridoxine 10–25 mg o.d. in high risk, no need to treat those who have fully completed treatment course. Prophylaxis against NTM not currently recommended
Pneumocystis jirovecii	First choice: trimethoprim-sulphonamide 480 mg o.d. or 960 mg 3× per week for 3–6 months or until CD4$^+$ count >200 if depleting antibodies or late immunosuppression (*also gives co-prophylaxis against toxoplasmosis*, *nocardia*, *listeria and UTI*). Allergy to TMP-SM/s second line (no norcardia/UTI prophylaxis afforded by these agents): monthly nebulised pentamidine 300 mg, dapsone 50–100 mg daily (if not G6PD deficient) (addition of pyrimethamine 50–75mg/week to dapsone provides toxoplasm prophylaxis), atovaquone 1,500 mg daily (also has anti-toxoplasma activity). Prophylaxis is recommended for recipients exposed to cases of PCP
Candida sp.	Fluconazole 200–400 mg daily, itraconazole 200 mg twice a day, voriconazole 200 mg twice a day
Coccidioides immitis	Fluconazole 200–400 mg if past history or positive serology

NB: perfect aseptic technique for line/catheter insertion, prompt line drain and catheter removal, chest physiotherapy and early mobilisation, as well as appropriate isolation and infection control measures for inpatients

A robust system is needed for identifying patients with communicable infections such as shingles and viral respiratory tract infections and for seeing them in isolation in outpatients

Specific Infectious Agents: Guidelines [4]

HHV-5 Cytomegalovirus (CMV)

CMV is a beta herpes virus and the most common opportunistic infection post-transplant: about 40–50 % of renal transplants develop viraemia, and it represents a significant challenge in some organ transplant recipients.

CMV has a seroprevalence of 45–100 % with higher rates in Africa, lower rates in Northern Europe and USA, and increasing prevalence with age. Transmission can be via saliva, urine, sexual contact, breast-feeding, placental transmission, blood transfusion or transplantation. In the immunocompetent host primary infection is usually asymptomatic, although it can present as a mononucleosis-like illness,

following which the virus undergoes a prolonged period of latency but can become reactivated by a variety of mechanisms including 'stress', sepsis and immunosuppression. For example, TNF-alpha released by rejection or infection can activate the major immediate early promoter (MieP) of CMV and induce intracellular replication. Transplant recipients (and occasionally, it is worth remembering, patients immunosuppressed for autoimmune conditions) can have a primary infection (D+/R−), reinfection (with a different strain) (D+/R+) or reactivation (D−/R+).

The risk of viraemia is very strongly associated with D+/R− status, but in addition the use of depleting antibody induction, acute rejection, poor graft function and older donor age are known risk factors. In renal transplants predominantly induced with anti-IL2-R mAb and no prophylaxis,

Table 71.4 Clinical characteristics of CMV infection post-transplant

CMV viraemia	Often asymptomatic. Commonly associated with leucopenia or myelosuppression before developing CMV syndrome
CMV syndrome	Temperature >38 °C for at least 2 days in the absence of another cause, plus CMV DNA viraemia and either neutropenia, thrombocytopenia, lymphocytosis, myalgia, headache or arthralgia
Pneumonitis	Interstitial pneumonitis with early desaturation. Can be rapidly progressive and may have co-infections such as PCP
Upper GI	Gastritis/duodenitis common symptoms in early primary infection, mouth ulcers and oesphagitis
Lower GI	Colitis – often bloody and may be fulminant
Hepatitis	Raised transaminases and flu-like illness
Pancreatitis	Asymptomatic with raised amylase to fulminant pancreatitis
Encephalitis/meningitis	Usually late feature
Retinitis	Usually a late manifestation in profoundly immunocompromised patients
Myocarditis	Usually late
Nephritis	Relatively rare but can result in graft failure or native kidney loss. May have characteristic 'owl's eye' appearance in biopsy
Cystitis	Relatively rare following SOT but can occur post-BMT

NB: peripheral blood is usually, but not always, positive for CMV DNA in the presence of end-organ disease

viraemia occurred in 70 % of D+/R−, 53 % D+/R+, 44 % of D−/R + and none of the D−/R−. The peak viral load is also significantly higher in the D+R− patients [5].

Clinical characteristics: many patients who have viraemia are asymptomatic, but there is a strong correlation between viral load and symptoms. The clinical characteristics of CMV infection in the immunocompromised are shown in Table 71.4. Viraemia and clinical features usually occur between 4 and 12 weeks (typically 6) post-transplant, but it is easy to be caught out by disease occurring outside this period (a) following treatment of late rejection, (b) cessation of prophylaxis (c) and in D−/R− transplants following primary exposure sometimes years later.

The kinetics of viral replication has clinical relevance; primary infection is associated with a doubling time of 1.5 days vs. 2.7 days for reactivation. This means that a CMV naïve patient can go from asymptomatic with a low detectable viral load to significant end-organ disease within a week. A patient with primary infection often presents with the so-called CMV syndrome (high fever without localising physical signs) that can progress rapidly to gastritis, colitis (often bloody), pneumonitis and other end-organ involvement. This is usually associated with very high viral loads. Patients with reactivation or reinfection *may* have a less fulminant course with isolated colitis or pneumonitis without an obvious full-blown viral syndrome. Either way, end-organ damage can progress rapidly and can occur with only low-level viraemia or very rarely in the absence of viraemia; therefore, a high index of suspicion is required. CMV is immunosuppressive in its own right and often 'opens the door' to other opportunistic infections such as HHV-6 and HHV-4 (EBV) and PCP.

The clinical characteristics of CMV infection Table 71.4.

The diagnosis of CMV infection is based on the detection of virus either by antigenaemia or detection and quantification of CMV nucleic acid testing by real-time quantitative PCR. In practice most laboratories now use real-time PCR

and should adhere to universal diagnostic standards. This technique is highly reproducible, and concerns that PCR would result in false positives have not been our experience.

Although viraemia is common, with modern management clinical disease affects only about 8 % of renal transplant recipients, and the vast majority of this is CMV syndrome; however, when end-organ disease occurs, it can be devastating and rapidly progressive. Pneumonitis may present with shortness of breath and oxygen desaturation post-exercise and may progress swiftly from mild dyspnoea to marked desaturation particularly after mild exertion. Chest X-ray (see Fig. 71.1) or CT scan may show signs of an interstitial lung disease, but there is a wide differential so it is essential to get samples, rapidly, (ideally a bronchoalveolar lavage) where possible or treat blindly (covering CMV) or both. It is important to note that CMV infection predisposes to other infections, and viral pneumonitis can coexist with *Pneumocystis* pneumonitis. Meningitis and encephalitis may present with classic symptoms and signs, or epilepsy and impaired cognition. It can be diagnosed from PCR on CSF, so ensuring the appropriate sample is taken at the time of lumbar puncture is important. Where possible, with tissue-invasive disease such as gastritis, colitis (Fig. 71.2) and nephritis (Fig. 71.3), biopsy, culture and PCR are critical. However, the pancreas and retina are less-appealing biopsy targets: ophthalmologists can normally make a firm clinical diagnosis, and CMV pancreatitis is usually, therefore, a presumptive diagnosis based on viraemia and clinical findings.

In short, it is important to have a high index of suspicion in any transplant with end-organ disease, with rapid requesting and processing of blood or any other tissue for CMV PCR, and if possible/appropriate, ensure that a biopsy is sent to virology as well as histopathology departments.

Beyond the direct effects of the virus, CMV infection has been implicated in several indirect consequences including
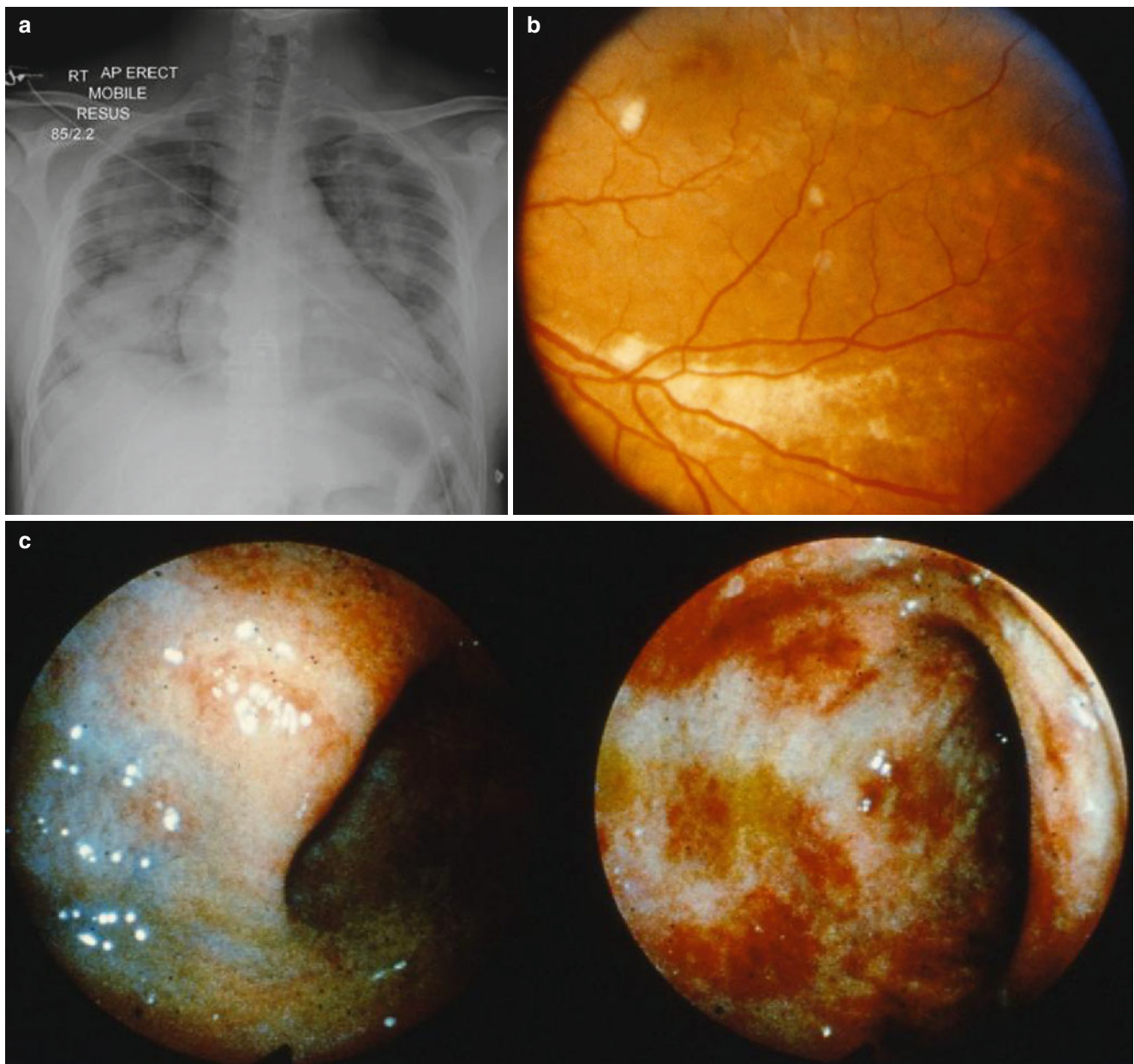
Fig. 71.1 (**a**) CMV pneumonitis in a renal transplant recipient. The patient had minimal constitutional illness, a dry cough and presented severely hypoxic. The differential is large including pulmonary oedema, but the peripheral sparing goes against this despite the cardiomegaly. There were very low levels of CMV viraemia, but BAL was positive and there was a very rapid improvement in clinical condition with IV gancyclovir. (**b**) Early CMV retinitis. (**c**) CMV colitis in a renal transplant recipient presenting with abdominal pain and bloody diarrhoea. This patient also had only low levels of viraemia and the diagnosis was made on biopsy

(a) increased cellular rejection, (b) increased infection by other microbes, (c) increased mortality and (d) worse graft survival [6, 7]. This is not without controversy. For instance, studies showing an association with acute cellular rejection have not always differentiated cause of effect, and a significant proportion (80 % in our experience) of acute rejection precedes CMV viraemia, so much of this association may simply be a response to increased immunosuppression. CMV viraemia is immunomodulatory and predisposes to EBV and HHV-6 viraemia, as well as an increase in fungal infections, although again CMV viraemia may also be a biomarker of over immunosuppression. Some studies have shown increased mortality, and worse 4-year graft survival has also been shown [8]; however, a UK study based on serology in 10,000 transplants showed no effect on patient or allograft survival [9]. A detailed analysis is beyond the scope of this chapter, but what is clear is that overt CMV disease is nasty and best avoided.

Fig. 71.2 Herpes simplex virus (**a**) herpetic whitlow, (**b**) herpes ophthalmitis, (**c**) perineal HSV and (**d**) extensive labial HSV

Fig. 71.3 Herpes zoster reactivation (shingles)

There are a variety of recommendations on the prevention and treatment of CMV post-transplant [4, 10, 11], and the 2011 BTS guidelines nicely summarise the current evidence [12]. For kidney transplantation most guidelines favour universal prophylaxis (for D+/R− or any positive recipients), especially following depleting antibodies. This is, in part based on meta-analyses of prophylaxis studies demonstrating a benefit in all cause mortality with prophylaxis [13]. Most of the studies in the meta-analyses have short follow-up and very few patients in the pre-emptive arm. Guidelines mostly acknowledge that pre-emptive therapy is probably equally appropriate if the logistics can be robustly managed (the case for pre-emptive over prophylaxis is eloquently argued by Thomas Reischig [14]) and there is some suggestion that the prevailing opinion is moving towards equal recommendation for pre-emptive and prophylaxis.

The main advantages of universal prophylaxis include ease of administration and co-prophylaxis against viruses (such as primary HSV), with disadvantages including drug side effects (especially leucopenia) and the concern of late-onset disease. The advantages of pre-emptive approach include limiting drug exposure to those that need it, encouraging immunity, and the near complete absence of late disease. The disadvantages of pre-emptive therapy include the extra vigilance required and the lack of co-prophylaxis.

Table 71.5a Universal prophylaxis (especially if received depleting antibodies). Valgancyclovir 900/450 mg daily (dose adjusted for GFR)

D+/R−, D+/R+ and D−/R+: 200 days for D+/R−, 100 days for R+	Late-onset disease biggest hazard. Ensure robust monitoring on cessation of prophylaxis. Resistant CMV and non-compliance may rarely result in disease in prophylactic period if no routine monitoring. Leucopenia common side effect
Partial prophylaxis (if not received depleting antibodies)	
D+/R− 200 days, no prophylaxis for R+	Numerically, D+/R+ and D−/R+ account for more viraemia than D+/R- so requires good monitoring of CMV PCR for R+ group and the ability to safely run two different approaches
D−/R−	No prophylaxis for CMV, but HSV-negative recipients must have at least 1 month of anti-HSV prophylaxis and irradiated blood products

Table 71.5b Pre-emptive therapy

D+/R−, D+/R+ and D−/R+: no prophylaxis	1. HSV prophylaxis in HSV-negative recipients for at least 1 month (e.g. valacyclovir) 2. Robust monitoring (guidelines at least weekly) ideally twice weekly especially in D+/R− and those receiving depleting antibodies for the first 3 months from transplant or treated rejection episode. Rapid turnaround time and reporting (e.g. e-mail alerts to transplant pool) 3. Twice weekly monitoring for those with viraemia and in those successfully treated 4. System to ensure patients admitted to other hospitals or units are identified and monitored appropriately 5. Issue patients with 3-day starter pack of valgancyclovir to take if develops viraemia 6. Start treatment at any positive for D+/R− and at local threshold for R+ (e.g. 3,000 copies per ml)
Hybrid (if received depleting antibodies or high immunological risk)	
D+/R−: no prophylaxis initially, prophylaxis following treatment of viraemia	D+/R− patients with primary infection following depleting antibody are highly likely to relapse following treatment as are those who have had rejection and cannot safely tolerate ISR. For these patients it may be worth considering prophylaxis after successful treatment

To summarise the current guidelines [4, 10–12] on prevention, most recommend prophylaxis with valgancyclovir (superior to acyclovir, valacyclovir or oral gancyclovir) starting within 10 days of transplant for D+/R− and R+ patients. Based on the findings of the IMPACT study [15] which showed a reduced rate of late-onset CMV disease with 200 compared to 100 days treatment (16 % vs. 37 %), the guidelines tend to favour treatment for 200 days in D+/R− and in those who have received depleting antibodies such as ATG. The dose recommended for those with normal renal function is 900 mg per day, but 450 mg appears to be as effective, causes much less leucopenia but potentially increases the risk of resistance [16]. Further dose reduction for renal impairment is required. The risk of CMV disease in D−/R− is so low as to not require CMV prophylaxis but does therefore mandate anti-HSV prophylaxis. Clinicians need to be vigilant to CMV post-prophylaxis and have a system of monitoring patients at this time as well as being alert to the possibility of viral resistance or non-compliance during prophylaxis.

Our experience of the pre-emptive approach has been very positive with CMV syndrome developing in only 4.9 %, end-organ disease in approximately 1 % and only 2.3 % of late-onset viraemia (first episode after 90 days) [5]. There are some important cautions included in Table 71.5a and 71.5b. Pre-emptive therapy relies on robust monitoring and reporting as well as a good relationship with your virology

department. Because of the rapid doubling time of primary infection, we ensure twice weekly CMV monitoring for the first 8 weeks (longer if there has been an episode of viraemia) and weekly for a further 4 weeks. An e-mail reporting service to the transplant team, with clear lines of responsibility, works well and we give D+/R− patients 3 days of valgancyclovir on discharge to start if viraemia is detected as an outpatient. Patients admitted to other hospitals or under other teams may be at risk as monitoring and reporting can breakdown, and it is important to have a strategy for these patients.

Finally, it is clear that some patients such as those D+/R− who have viraemia after depleting antibodies or who are high immunological risk (i.e. have had early rejection) and therefore cannot risk immunosuppression reduction (ISR) are highly likely to have recurrent viraemia after completion of treatment, and it may be worth considering converting to prophylaxis after treatment with the advantage that the recipient will have developed some immunity with the first viraemia.

Treatment. In asymptomatic serologically positive R+ patients with viral counts below 3,000 genomes/ml, our practice is to reduce the overall burden of immunosuppression (CNI if level high, anti-proliferative if not). We treat reactivation if viraemia is >3,000 genomes/ml or if there is evidence of end-organ disease. As a unit that practises preemptive therapy, CMV naïve patients with a positive donor are discharged with 3 days of valgancyclovir (starter pack)

Table 71.6 Risk factors for the development of Kaposi's sarcoma post-transplant

Serostatus of donor/recipient	Data suggesting that both reactivation and primary infection at transplant are significant risk factors
Geographical location	Mediterranean, Middle East, Eastern Europe and sub-Saharan Africa
Burden of immunosuppression	Overall burden of immunosuppression is important especially depleting mAb
Age of recipient	>50 years
Homosexual males	Multiple partners
Transfusion	In high-prevalence areas

to take if there is a single positive PCR of any level to avoid delay in treatment (also worth considering post-prophylaxis).

First-line treatment of significant viraemia or CMV disease should be with valgancyclovir or IV gancyclovir (especially the latter if any doubt about absorption) dose adjusted for eGFR (see Table 71.6). In patients who have not recently undergone rejection, it is advisable to reduce any anti-proliferative agent or consider stopping altogether if serious disease. Treatment of CMV disease should be continued for at least 2 weeks even if early elimination of viraemia and our practice is to continue treatment until two negative PCRs in everyone. Relapse is common, especially in the D+/R− and in those who have received depleting antibodies. There is insufficient evidence to support the use of IVIg (CMV Ab enriched or otherwise), which is expensive and a scarce resource, but it is likely to be relatively harmless and might be worth considering in a tight corner if the patient is not responding to antivirals. It is important to ensure PCP prophylaxis continues, and GCSF can be helpful in the face of neutropenia.

Viral resistance is much more common in the D+/R− subgroup (up to 10 %) with prolonged treatment and the use of depleting antibodies. Apart from this high-risk group, a strong indication of resistance is failure to clear the virus by 3 weeks, and mutation analysis should be requested in this setting. Mutations of UL97 kinase and UL54 DNA polymerase are the currently recognised markers of resistance, and it is important to note that as gancyclovir, cidofovir and foscarnet all target UL54 DNA polymerase, resistance to gancyclovir can lead to cross resistance to cidofovir and foscarnet. The latter two drugs are reserved as second-line drugs and generally reviled by nephrologists because of their high rate of nephrotoxicity. Nonetheless they can be life-saving in extreme disease (doses for both need to be carefully adjusted for GFR and pre-hydration essential).

Leflunomide and mTOR inhibitors theoretically both have anti-CMV properties, and there are case reports of some success using leflunomide to treat resistant CMV in SOT. However, there is likely to be reporting bias, and as yet no RCTs to support the use of leflunomide as treatment.

The circumstantial evidence in favour of a clinically relevant anti-CMV effect of mTOR inhibitors is more convincing, and there are many studies that show significantly reduced rates of CMV infection in de novo kidney transplants receiving

mTOR inhibitors [17]. The evidence that mTOR inhibitors are helpful in treatment of CMV infection again degenerates to anecdote with small cases series. Our experience, and a niche that may prove important, is in those patients with persistent or resistant CMV who cannot tolerate further reduction in immunosuppression. Swapping tacrolimus for sirolimus or adding sirolimus to tacrolimus in high immunological risk patients with dose reduction of the CNI can be effective as clearing CMV and simultaneously avoiding rejection.

With modern management, CMV disease (the majority being CMV syndrome) affects only about 8 % of renal transplants. In our experience of a pre-emptive approach, treatment was required in 63 % of D+/R−, 22 % of D+/R+ and 18 % of D−/R + for viraemia, and end-organ disease occurred in only 1 %.

Herpes Simplex Virus: HSV 1 and 2

Reactivation of HSV in the form of nasolabial cold sores or genital ulcers is relatively common but can be very aggressive in the significantly immunocompromised (see Fig. 71.2). Patients may give a history of previous cold sores and, if frequent pre-transplant, are highly likely to recur post-transplant. This can be prevented with ready access to topical acyclovir or low-dose oral acyclovir prophylaxis (e.g. 200 mg daily). Treatment with oral acyclovir, valacyclovir or famcyclovir is highly effective but should start early, and dose adjustment for GFR is important. HSV can also affect the cornea and conjunctiva presenting as a red eye/keratitis and progressing to a dendritic ulcer with potential sight loss (Fig. 71.2), and any painful red eye should have viral swabs and rapid ophthalmology review.

Very rarely, seronegative patients can develop a fulminant primary HSV infection. This has been reported with both HSV1 and HSV2 and has a very high mortality. A high fever is universal, but skin lesions are present in only half the patients, which may explain delay in diagnosis. The patient may seem better than their fever would imply initially, but without treatment pancytopenia, gastric ulceration and acute hepatitis (CT imaging may appear as abscesses) rapidly progress to encephalopathy, coagulopathy and death. The diagnosis can be made by detecting HSV DNA in blood, CSF, swabs

and biopsies. However, onset to death is short, so a high index of suspicion is important and early empirical treatment critical. CMV prophylaxis with valgancyclovir is essentially protective against primary HSV, but in those HSV-negative patients not having CMV, prophylaxis should be given either as acyclovir or valacyclovir (regardless of donor status). There is no consensus on duration of prophylaxis, but our practice is to give valacyclovir 500 mg b.i.d for the first month of transplant. HSV is very sensitive to acyclovir and, as mentioned above, any suspicion of fulminant HSV should prompt rapid IV treatment (10–12.5 mg/kg t.i.d.), reduction in anti-proliferatives and placement on a high dependency unit.

HHV-3 (Varicella zoster virus (VZV))

Reactivation with herpes zoster (shingles) is markedly more common in transplant recipients (10×) than the general population, occurring in roughly 10 % of patients in the first 5 years (Fig. 71.3) [18] but more commonly still in those receiving lymphocyte-depleting antibodies. As neuralgia precedes the rash, the diagnosis can be initially missed and should be considered in anyone with new onset severe, otherwise unexplained pain. Treatment is with acyclovir or valacyclovir for 7 days, analgesia, surveillance for secondary infection and usually reduction in anti-proliferatives.

Primary infection is potentially life-threatening in solid-organ transplant recipients, and about 3 % of the adult population are VZV naïve; others bear a similar risk if hypogammaglobulinaemic. Identification of naïve patients on the waiting list is mandatory, and vaccination should be robustly embedded in any pre-transplant programme, although the evidence is that as a community we are very poor at doing this. The vaccine is usually given as two doses, 4–8 weeks apart, and as it is a live vaccine, we offer acyclovir to any patient receiving a transplant within 2 weeks of the vaccination. Patients unlucky enough to get primary varicella infection while under the influence of significant immunosuppression can present with pneumonitis, hepatitis, ulcerative gastritis and colitis. Pancreatitis, encephalitis, meningitis and DIC can follow swiftly and have a mortality of 30 %. Treatment of primary chickenpox should be with rapid initiation of IV acyclovir (10–12.5 mg/kg t.i.d. adjusted for GFR) for 7–10 days, usually until all the lesions have crusted over. Treatment may need to be continued longer (2–3 weeks) for CNS involvement or disseminated infection. Of course, it is more desirable to avoid the risk of a primary infection so that seronegative patients should be identified pre-transplant, advised to avoid exposure and given clear (written) advice on what to do if exposed either to chickenpox or shingles (often unwittingly in the transplant clinic waiting room). If pre-transplant serostatus is not known, an urgent VZV IgG test is required to establish VZV immune status.

1. Attend hospital within 24 h (up to 7 days of exposure) for varicella zoster immune globulin (VZIG; 1,000 mg IM adult dose). If a second exposure occurs after 3 weeks, a further dose may be required.
2. If VZIG is unavailable or the exposed patient cannot be given an IM injection (contraindicated in bleeding disorders), IVIg can be used (0.2 g per kg body weight).
3. Consider acyclovir/valacyclovir or famcyclovir prophylaxis in household contacts.

HHV-4 Epstein-Barr Virus (EBV)

EBV is gamma-herpes virus with 95 % world seroprevalence, mostly acquired asymptomatically in childhood or as infectious mononucleosis (IM) in 25 % during puberty. It immortalises B-cell lines and remains mostly latent with occasional lytic cycles and shedding mostly in saliva in healthy individuals. Given the prevalence of EBV infection, primary infection following transplantation is common in a seronegative recipient. Viraemia is common post-transplant occurring in roughly 50 % of all patients, but this is usually asymptomatic. Occasionally patients may present with IM or non-specific viral illness, but the greatest concern is the propensity for EBV to induce post-transplant lymphoproliferative disorder (PTLD). Ninety percent of early PTLDs are EBV positive, and a primary infection post-transplant confers a 10–75-fold risk of PTLD (greater still if concomitant CMV infection and/or the use of depleting antibodies). There is also data to support EBV viraemia preceding development of PTLD; however, recent guidelines make the reasonable point that there is no evidence to support the routine monitoring of EBV levels post-renal transplant [19].

The Renal Association Guidelines [20], however, do recommend EBV PCR monitoring in D+/R- patients for the first year and following treatment for rejection. Despite the lack of evidence, risk stratification is key and it is worth considering monitoring: (1) D+/R− patients (especially if they received depleting antibodies), (2) patients who are viraemic pre-transplant (usually previous transplants), (3) those with previous EBV +ve lymphoma, (4) following treatment of rejection and (5) possibly at annual review as a surrogate marker of over immunosuppression – a small percentage of patients develop very high levels asymptomatically with increasing time post-transplant. In the absence of convincing evidence, it is our practice to monitor the above groups. Stable patients with viraemia are monitored as follows:

Levels of <10,000 monitor 3 monthly
Levels of 10,000–50,000 monitor 6–8 weekly and consider immunosuppression reduction
Levels of >50,000 gentle ISR monitor 4 weekly

While it is common sense, and our practice, to reduce immunosuppression in the presence of persistent high-level EBV viraemia, there is negligible evidence to support ISR in the absence of lymphoma and there is a risk of late rejection so it should be undertaken cautiously. There is no convincing evidence in favour of antiviral prophylaxis.

The management of post-transplant lymphoproliferative disorder requires a specialist multidisciplinary approach and is discussed in chapter 70.

HHV-6

The prevalence of HHV-6 infection is very high with >90 % of the population infected in early childhood. Reactivation of HHV-6 is very common in the early post-transplant period often as a co-infection with CMV and HHV-7 [21] with clinical manifestations from asymptomatic viraemia, self-limiting viral illness, to a more disseminated disease with pneumonitis, encephalitis lymphadenopathy and bone marrow suppression. As most units do not screen for HHV-6 and the vast majority of patients are either asymptomatic or settle spontaneously, treatment is not usually required, but there are case reports of death secondary to HHV-6, and it is worth considering as a diagnosis in a patient with unexplained viral illness. Treatments if required are gancyclovir or valgancyclovir, exclusion of co-existent CMV and reduction in ISR.

HHV-7

Reactivation of childhood-acquired virus may occur early post-transplant either asymptomatically or with a non-specific viral illness, but severe disease is extremely rare. Management involves exclusion of more likely infections, then immunosuppression reduction and, if necessary, treatment with foscarnet or cidofovir.

HHV-8

The main clinical manifestation of HHV-8 primary infection, reactivation or reinfection in solid-organ transplants is the development of Kaposi's sarcoma. Although HHV-8 infection does occur sporadically, there is a significant geographical bias in the seroprevalence of HHV-8 with the Mediterranean, Eastern Europe, the Middle East and sub-Saharan Africa having high rates. The role of immunosuppression is profound in that the prevalence of KS in SOT is 500 times that of the general population, occurring in 0.5 % of transplant recipients from North-West Europe and up to 5 % of transplant recipients in Saudi Arabia. Known risk factors for post-transplant KS are shown in Table 71.6 [22].

Clinical presentation is predominantly cutaneous involvement with red/purple/black nodules (see Fig. 71.4) typically on the lower body, initially often associated with lower limb oedema which may precede the development of skin lesions. Visceral involvement may also occur including lymphadenopathy, pulmonary nodules, chylous pleural effusions and gastrointestinal involvement. Clinical presentation is usually within the first year, but it is not unusual for the diagnosis of visceral KS to be delayed particularly in the setting of GI involvement. The mortality associated with KS particularly with visceral involvement is around 10 %, and graft loss is common as a consequence of ISR.

Serology is rarely helpful in the diagnosis and donors are not currently screened; however, it might be worth considering donor and recipient screening in high-prevalence areas to identify risk. Histology is the gold standard for diagnosis; any suspicious lesion should be biopsied, and a high index of suspicion is important particularly for gastrointestinal involvement. PCR for HHV-8 may be considered as a tool to monitor response to treatment for visceral KS, although it will not be helpful in the absence of viraemia.

Treatment is with reduction in immunosuppression or complete cessation if life-threatening visceral involvement or progressive disease. The reduction of immunosuppression required to induce remission often results in graft loss, and conversion from CNI to mTOR inhibitor (which possesses anti-VEGF activity) has had some significant success [23], although this is not universal. With aggressive, unresponsive disease, antivirals (foscarnet, cidofovir) and chemotherapy such as bleomycin, adriamycin and taxols have been tried with variable success.

Our practice is to stop the anti-proliferative agents initially and if no response within 2–4 weeks or significant visceral involvement convert non-proteinuric patients from their CNI to an mTOR inhibitor. If intolerant of mTOR inhibitor, then proceed with a stepwise reduction in CNI, ideally with slow small cuts rather than large cuts, if the disease permits [24].

KS has a high risk of recurrence in a second transplant; we aim to avoid heavy induction and plan for an early switch to an mTOR inhibitor if possible.

Polyoma Viruses: Polyomavirus hominis 1 (BK) and 2 (JC)

BK and JC are usually picked up in childhood remaining latent in the presence of a normal immune system but can cause significant nephropathy (polyoma virus-associated nephropathy, PVAN) in renal transplant (although very rarely in other transplants), and JC virus is the causative agent in multifocal leucoencephalopathy.

Fig. 71.4 (**a–e**) Multiple cutaneous manifestations of Kaposi's sarcoma

BKV

It is a double-stranded DNA virus, acquired mostly in childhood with seroprevalence in excess of 85 %. It remains latent in the renal tract, and 5–10 % of immunocompetent individuals intermittently shed virus, but there is no evidence of pathological consequences of BK infection in the general population. In RTR, infection results in nephropathy in 1–10 % of recipients with high risk of graft loss, as well as causing ureteric strictures and haemorrhagic cystitis (usually in BMT).

The incidence of PVAN seems to have genuinely increased in the last 30 years, and registry data from the US organ procurement and transplant network suggests current rates of 6 % PVAN by 5 years (the vast majority occurring in the first

2 years) [25]. The main risk factor appears to relate to the total burden of immunosuppression (use of depleting antibodies, treatment of acute rejection and combination of tacrolimus and mycophenolic acid). However, it is extremely rare to get PVAN in other SOT with much higher levels of IS in part because the renal tract is the site of latency for BKV. In addition, other known risk factors such as D+R−, episodes of acute rejections, deceased donor, ureteric stent and viral co-infection may all contribute to infection and tubular cell injury/division necessary for BKV growth. It is also possible that some serotypes are more virulent and may cause a reinfection. There is a clinically important natural history to PVAN; 20–40 % of RTRs have viruria which precede the 5–15 % of those that get viraemia by 4–6 weeks and diagnosis of PVAN by 12 weeks [26], thus offering a window for detection and prevention.

There are usually no clinical features associated with BKV infection in RTR except a deterioration in renal function or ureteric obstruction, so screening and biopsy are critical.

Urine PCR for BKV DNA has a sensitivity of about 50 % but given the high rates of viruria lack specificity for PVAN. In plasma >10^4copies/ml of BKV DNA is a sensitive and specific marker of PVAN with a high negative predictive value. Consequently the KDIGO guidelines recommend screening plasma for BKV DNA, monthly for 3 months, followed by 3 monthly for 12–24 months [4]. An alternative to plasma DNA is to use urine cytology (Papanicolaou stain) to identify the viral cytopathic effect in 'decoy cells' (detached tubular epithelial cells with viral nuclear inclusions). This has a lower positive predictive value than viraemia (similar to DNA screening of urine) but is cheaper than nucleic acid testing [27]. Urine positive for viral cytopathic effect should prompt plasma BKV DNA screening. Plasma BKV DNA screening should also be done in the context of an unexplained rise in creatinine or ureteric obstruction. Not everyone with viraemia develops PVAN so the gold standard for diagnosis is histological evidence of polyoma virus with viral cytopathic changes, nuclear inclusion, interstitial infiltrate and tubulitis. Granulomas may also be present (Fig. 71.5). It is confirmed by positive simian virus large T-antigen staining (SV40). However, the infection is patchy and the disease may be missed early on especially if the biopsy is small or superficial. In addition, initial views of the biopsy may appear identical to the tubulitis of acute cellular rejection so all biopsies with a cellular infiltrate should be stained for SV40 with urgency to avoid increasing IS when reduction is necessary.

Treatment

It is important to note that there is no substantial data in support of any treatment of PVAN apart from ISR. Although not the subject of a RCT, pre-emptive ISR has been associated with viral clearance in 80–95 % and a reduction in
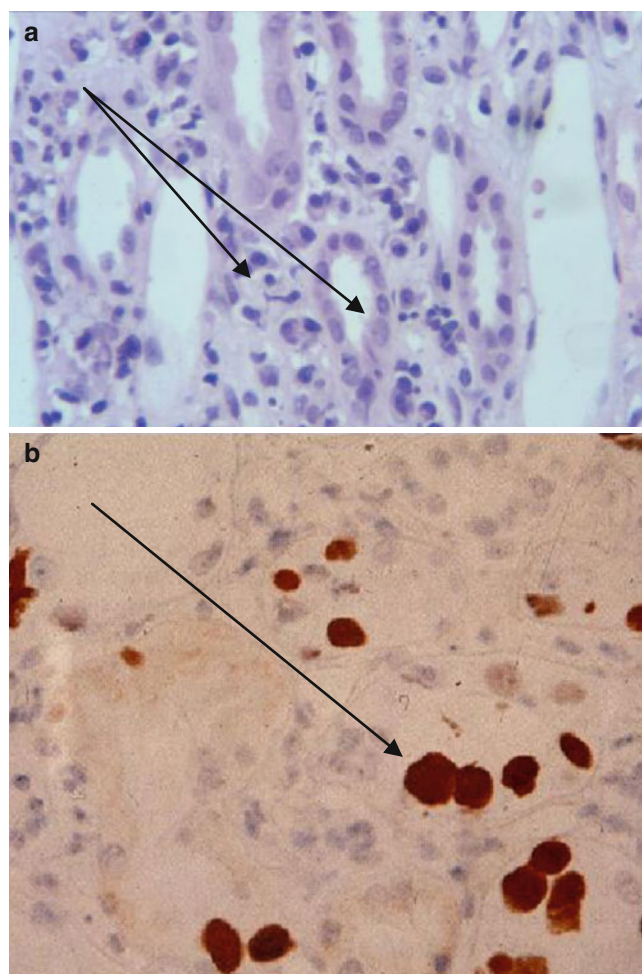
Fig. 71.5 BKV. Nephropathy showing cellular infiltrate and nuclear inclusions (**a**). Diagnosis of BKV confirmed by positive SV40 staining (**b**)

death-censored graft survival. A variety of protocols have been suggested for ISR in the face of viraemia [26, 28], but essentially start with halving either mycophenolic acid or azathioprine, and if no reduction in viraemia, then either reduction in CNI or stopping the anti-proliferative altogether. Rapid and abrupt cuts in IS are more likely to be associated with rejection, and differentiating the main pathological process even with SV40 staining can be very difficult.

A variety of drugs have been tried on the basis of theoretical or in vitro anti-polyoma activity and reported mostly as small case series and nonrandomised trials [26, 29]. These include leflunomide (usually at a dose of 20–60 mg/day), cidofovir (0.25 mg/kg with probenecid every 2 weeks), fluoroquinolones, IVIg and mTOR inhibitors. The use of leflunomide is out of the comfort zone for most nephrologists; drug monitoring is not available to most units and judging the appropriate dose is therefore tricky. Cidofovir has very considerable nephrotoxicity, pre-hydration with IV fluids is necessary, and the subsequent deterioration in renal function causes further diagnostic difficulty. There is

a little evidence that fluoroquinolones reduce viraemia, but no evidence currently of improved clinical outcomes. Given the high prevalence of BKV infection, IVIg would seem a harmless therapeutic option, but it is a scarce resource without an evidence base, and it is not clear what significance humoral immunity has in clearing an intracellular virus. The data for conversion to mTOR inhibitors as treatment is also poor, but there is quite a lot of circumstantial evidence that mTOR inhibition may reduce the risk of PVAN by roughly a half that of other IS regimens [25] possibly by inhibiting cell cycle progression and not disabling BKV-specific T-cell responses to the same degree. In short there is a severe lack of decent evidence to support treatment of PVAN when appropriate ISR has failed. Our practice and that of some others [28] if PVAN persists following ISR or there has been a rejection episode is to introduce an mTORi (if proteinuria <0.5 g/l), ultimately aiming for mTORi monotherapy.

Original reports recounted grim outcomes in terms of graft survival, and roughly 50 % of grafts with PVAN were lost; however, greater awareness and better screening seem to be improving the outcome. A histological grading system (A–C) for PVAN has been devised based on the amount of cellular involvement and the extent of interstitial fibrosis and atrophy (reviewed in 28). The take-home message is that grade A is associated with 13 % graft loss, but grade C 100 % graft loss, i.e. early detection and ISR are likely to be dramatically more helpful than applying toxic medication for advanced disease. Limited data suggests a recurrence rate of about 20 %, but loss of second graft seems rare. There seems no evidence to remove the failed graft, but persistent viraemia is a likely risk factor, and removal of IS until an immune response suppresses viraemia would seem very prudent.

JC viral infection is commonly acquired asymptomatically early in life reaching 50 % seroprevalence by middle age, viruria can be detected in normal individuals, and viraemia has been detected in 5 % of transplant patients. Despite this, clinically apparent reactivation in the form of progressive multifocal leucoencephalopathy (PML) is very rare in transplantation. A caveat here is that the risk of PML is clearly related to the burden of immunosuppression; cases have been reported in patients with SLE following rituximab and in transplants following belatacept as well as less-specific depleting antibodies. PML has a wide differential and may be confused with CNI toxicity. The treatment is with staged immunosuppression reduction mindful of immune reconstitution syndrome (IRIS) with rapid withdrawal resulting in a vigorous immune response and worsening of clinical features as a consequence. Cidofovir has been used with limited success. The issue of re-transplantation is a moot point, often PML from whatever cause is an absolute contraindication, but it might be considered once there is good evidence of immune recovery in the absence of further depleting antibodies and following counselling.

Respiratory Viruses

A number of respiratory viruses infecting RTR (see Table 71.7) can cause asymptomatic or minor infection sometimes with prolonged shedding, but can also result in devastating respiratory illness and death. For most of these viruses, there is either no effective antiviral, or antivirals that have only modest efficacy. Management therefore relies on good housekeeping in terms of annual influenza vaccination (measles vaccination if not previously done), ensuring staff and patient hand hygiene is taught (and practised) and the ability to isolate potentially infectious patients. Rapid nucleic testing of nasopharyngeal swabs or aspirates is important to avoid inappropriate antibiotics and admitting an infectious patient into an open transplant ward.

Table 71.7 Respiratory viruses in renal transplant recipients

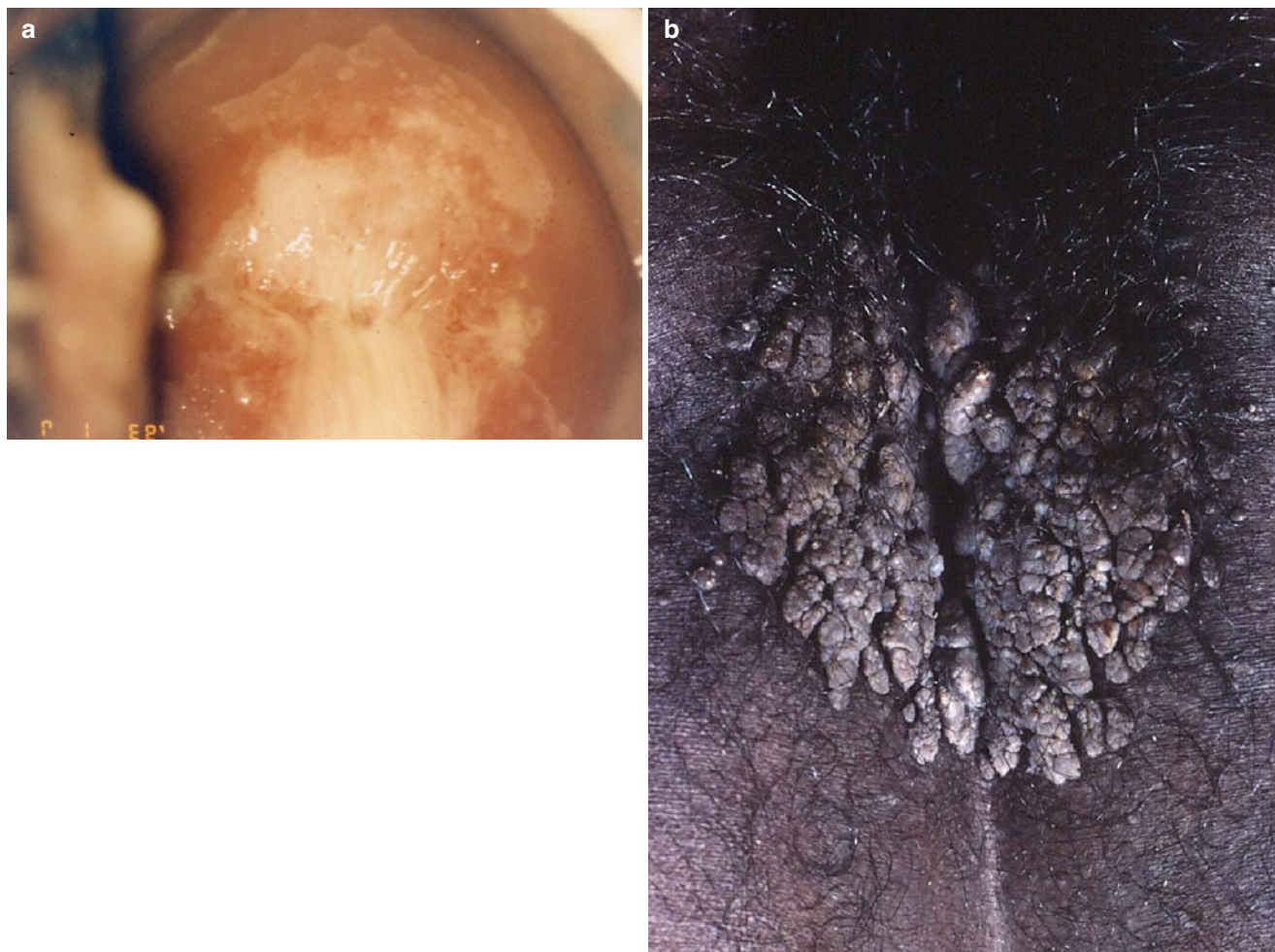|	
Respiratory syncytial virus (paramyxovirus)	Common respiratory infection post-SOT can progress to pneumonitis/bronchiolitis. Ribavirin (IV or inhaled) can be used (no RCTs) alone or with IVIg and reduction in immunosuppression. Consider palivizumab
Coronavirus (SARS coronavirus)	Coronavirus can cause URTi and LRTi, relevant in heavily immunosuppressed patients. SARS coronavirus carries a significant risk of ARDS and mortality. Currently no treatment for coronaviridae infections so emphasis on avoidance, ISR and supportive care
Adenovirus	May be shed for long periods from upper airway. Serotypes 1 and 2 associated with pneumonia. Supportive and reduction in IS (cidofovir can be used for disseminated infection)
Rhinovirus	Predominantly URTi but can cause LRTi, currently no effective treatment
Parainfluenzae virus	URT and LRT infection as well as asymptomatic shedding, no effective treatment
Influenza A and B (orthomyxovirus)	Influenza A H1N1 2009 pandemic responsible for considerable morbidity among SOT. Vaccination effective in SOT (less so in first 6 months post-transplant) and should be offered annually. Widespread resistance to M2 inhibitors (amantadine and rimantadine), some resistance to neuraminidase inhibitors (oseltamivir and zanamivir), but primary treatment oseltamivir 75 mg b.i.d. for 5 days. Prophylaxis should be considered for significant RTR contacts (oseltamivir 75 mg o.d. for 10 days)
Metapneumovirus	URTi and LRTi currently no effective treatment
Bocovirus	URTi, clinical relevance unclear
Enteroviruses	URTi and LRTi as well as meningitis and encephalitis

Fig. 71.6 (**a**) Colposcopy showing CIN3 in a 30-year-old renal transplant patient with human papillomavirus infection. (**b**) Perianal warts secondary to human papillomavirus infection in a renal transplant recipient

Beyond specific antivirals therapy is supportive care, treating secondary bacterial infections and immunosuppression reduction. IVIg has been used in patients with severe infections and worth considering in patients with severe infections and worth considering in life-threatening disease.

Parvovirus B-19

Parvovirus B-19 is a single-stranded DNA virus acquired by respiratory transmission, although it can be transmitted via transfusion or with the donor organ. Acute infection is with fever, arthritis and rash and sometimes with an acute aplastic crisis with marked anaemia (thrombocytopenia and leucopenia also common). Nephrotic syndrome secondary to a collapsing focal segmental glomerulopathy is also reported. Diagnosis can be made serologically with IgM, but PCR for viral DNA is more sensitive and permits monitoring of response. Viraemia can persist and treatment of aplastic anaemia or glomerulonephritis is with IVIg 0.4 g/Kg over 5 days.

Human Papillomavirus HPV

It is an important cause of morbidity post-transplant both in terms of viral cutaneous and anogenital warts as well as skin, vulval and perianal malignancy (Fig. 71.6). The skin manifestations and management of viral warts are discussed in chapter on renal skin disease, and it is worth remembering that HPV has been detected in the majority of post-transplant squamous cell and basal cell carcinomas [30]. Post-transplant patients have much higher incidence of HPV infection with pro-oncogenic serotypes 16 and 18. Registry data shows a substantial excess of cervical and anal precancer (approximately ×10) and a 50–100-fold increase in vulval premalignancies; most alarmingly the average age of vulval premalignancy in this group is 37, almost 25 years earlier than the general population. HPV vaccination of school girls may help reduce the incidence in women, but as yet there is no data to support the routine vaccination of patients on the waiting list. Many countries have guidelines recommending

annual cervical screening post-transplant, but in the UK the evidence is that the uptake is extremely poor at around 10 % and is something we could improve [31].

Hepatitis E

Hepatitis E is an RNA virus transmitted by the faecal oral route, particularly from undercooked meat (predominantly genotype 3 in Western countries) and associated with high mortality with acute hepatic failure in patients with pre-existing chronic liver disease or pregnancy. Recent data suggests, however, that it may be associated with chronic subclinical hepatitis in solid-organ transplants. In France the seroprevalence pre-transplant is 14 %, but reactivation has not been demonstrated. >50 % of de novo cases post-transplant are asymptomatic with the rest having hepatitis. Approximately 40 % of these patients clear the virus spontaneously, but 60 % do not and go on to have chronic infection with abnormal LFTs but occasionally rapid progression to cirrhosis. However, the overall prevalence of chronic infection is not known, and making the diagnosis is important as clearance of the virus may prevent cirrhosis and, if suspected, the diagnosis can be made on RNA from blood or stool. Treatment is with ISR or, failing that, success has been reported with pegalated interferon or ribavirin [32].

Bacteria

Legionella

Cell-mediated immunity appears particularly important in the defence against *Legionella pneumophila*, and consequently SOT recipients are at substantial risk if exposed (usually from contaminated air-conditioning systems or water tanks and in outbreaks). High fever and cough with flu-like symptoms are the norm. The CXR may show focal, nodular, lobar or diffuse consolidation sometimes with cavitation. Urine legionella antigen testing is quick (but does not detect the 10–30 % of serogroups that are not pneumophila such as micdadei) unlike paired legionella serology which is rarely helpful in real time. As with mycoplasma and chlamydia, PCR for legionella can be done on BAL samples.

Treatment is with macrolides (ideally azithromycin as it causes less inhibition of cytochrome p450), fluroquinolones, rifampicin (marked inducer of cytochrome p450) or dual therapy in sick patients.

Since tests may not be diagnostic, 'atypical' pathogen cover should be considered (ideally with a macrolide) for SOT recipients with a lower respiratory tract infection.
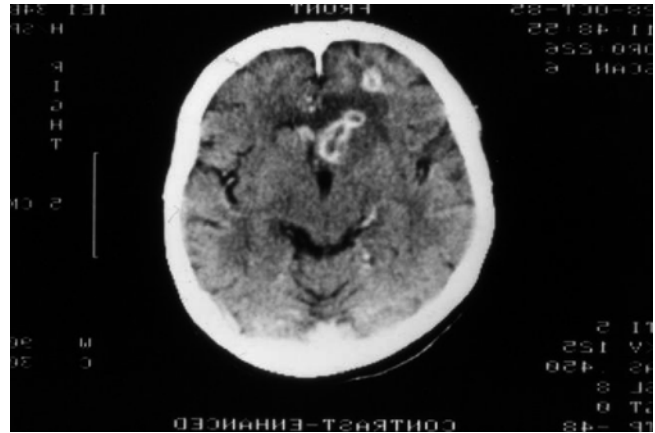

Fig. 71.7 Listeria causing a ring-enhancing space occupying lesion (SOL) in a recipient 6 years post-transplant

Listeriosis

Listeria monocytogenes is an environmental gram-positive bacillus, contracted orally from pets, domestic animals or unpasteurised or poorly kept foods and consequently can occur in outbreaks as well as sporadically. Listeria infection is associated with a high mortality especially in the immunocompromised as it is intracellular and normally eradicated by cell-mediated immunity which is disabled in SOT. It is the most common cause of bacterial meningitis in SOT and in addition has tropism for brain parenchyma. Incubation is within 24 h of ingestion, and symptoms develop within a week. Clinically presentation is non-specific: fever possibly following a diarrhoeal illness, malaise, meningitis (50 %) or encephalitis with abscess (10 %) (Fig. 71.7) [33]. Diagnosis is typically made on blood culture or examination of CSF.

Treatment is with intravenous ampicillin (2 g every 4 h). Gentamycin (3 mg/kg in three divided doses) is usually added in for immunocompromised patients. Trimethoprim-sulphamethoxazole (septrin) is an alternative for penicillin-allergic patients.

Nocardia

Nocardia is a rare but serious opportunistic infection post-transplant caused by actinomycetes nocardia species, mostly acquired by inhalation, occasionally via skin inoculation. The incidence in the reported literature is around 1 %, but this probably represents reporting bias, and the evidence is that it is less common in part because of universal prophylaxis with septrin. A review of the English literature case reports following renal transplantation shows a huge variation in onset from 4 weeks to 22 years [34].
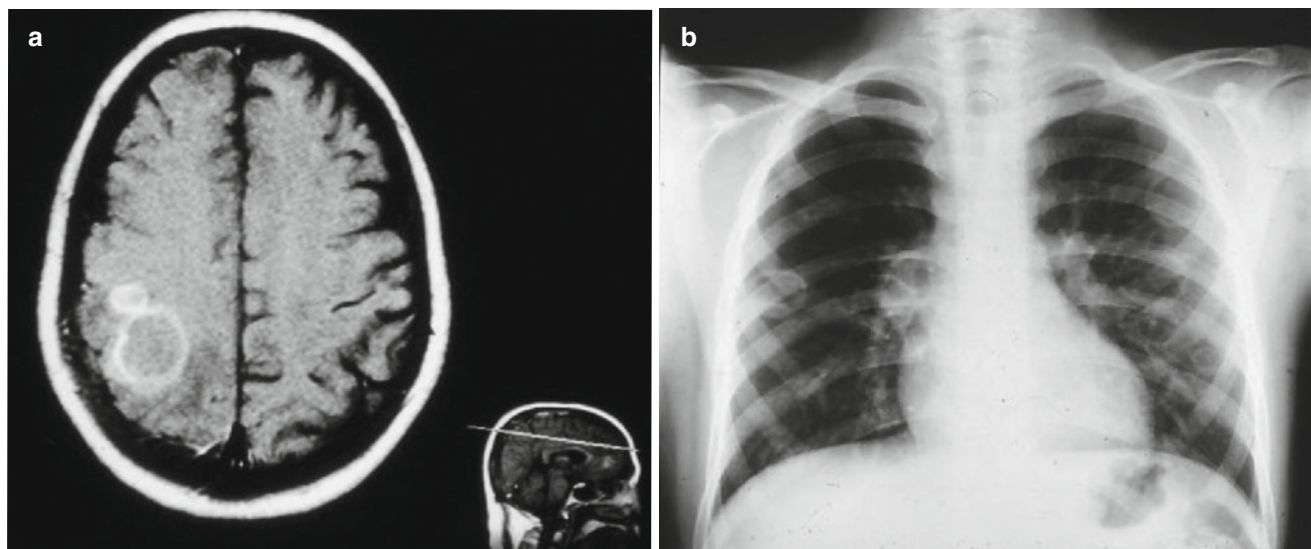
Fig. 71.8 Nocardia causing a ring-enhancing SOL on CT (**a**) and multiple cavities on CXR (**b**)

The vast majority of cases present with or have primary pulmonary involvement, and a significant proportion of these go on to have disseminated disease with a predilection for brain and cutaneous involvement (Fig. 71.8). Pulmonary involvement does not typically present as classical pneumonia, but fever, lung nodules and cavities are common. Cerebral involvement may be insidious and non-specific with headaches, confusion, focal neurological signs and is also associated with a fever [34].

Norcardia, especially disseminated disease, is associated with a significant mortality (17 %), and early diagnosis with biopsy of unexplained skin nodules or other accessible lesions is essential. Treatment for early pulmonary disease is with sulphonamides usually trimethoprim-sulphamethoxazole 15 mg/kg/day. For severe pulmonary or any cerebral involvement, imipenem and amikacin are added in, with the caveat that some nocardia species have resistance, and biopsy with culture and sensitivities is very important. Treatment must be prolonged to 6–12 months for pulmonary and 9–12 for cerebral involvement [35].

Mycobacteria: TM and Non-tuberculous Mycobacterium (NTM)

The incidence of active TB in renal transplants in Western countries is between 0.3 and 1 % which is 20–70× higher than the general population, and in Asia rates of 5–15 % have been reported. Apart from country of origin, diabetes, chronic liver disease and the burden of immunosuppression (e.g. the use of depleting antibodies) are significant risk factors [36, 37]. Screening pre-transplant is difficult as tuberculin skin tests, e.g. Mantoux test, while helpful if positive, often result in false negatives in patients with ESRD, and patients with previous BCG may have false positives. CXR with signs of previous TB are clearly helpful, and interferon gamma release assays may be helpful but do not distinguish between previous exposure and active disease, but again can be negative in patients with ESRD or post-transplant [38].

Clinical presentation occurs at an average of about 10–12 months post-transplant with the majority of infections thought to be reactivation with roughly 10 % due to primary infection (a very small percentage of which are donor derived). Fever appears to be a prominent feature occurring in 70 % with weight loss and asthenia. Strikingly, two-thirds of patients present with extra-pulmonary disease (compared to 15 % in the general population) (Fig. 71.9) [39], and consequently tissue biopsy and ensuring procedurists send a sample for culture are important in making the diagnosis. In immunocompromised patients, mycobacterial burden is often high and mycobacterial blood cultures may be helpful, especially in the setting of disseminated atypical mycobacterial infections (e.g. *Mycobacterium avium-intracellulare* complex infections – see below).

Management for MTB in SOT is the standard anti-TB treatment but presents issues in terms of drug interactions, the main one being the induction of cytochrome p450 by rifampicin resulting in marked reduction in CNI levels. It is usual to have to triple the dose of CNI within the first 2 weeks of rifampicin-based therapy. Importantly, the converse is true when rifampicin is stopped with the need for significant dose reduction. It is critical therefore to have close liaison between the infectious disease team and the nephrologist. Treatment is often accompanied by ISR, but this needs to be done with
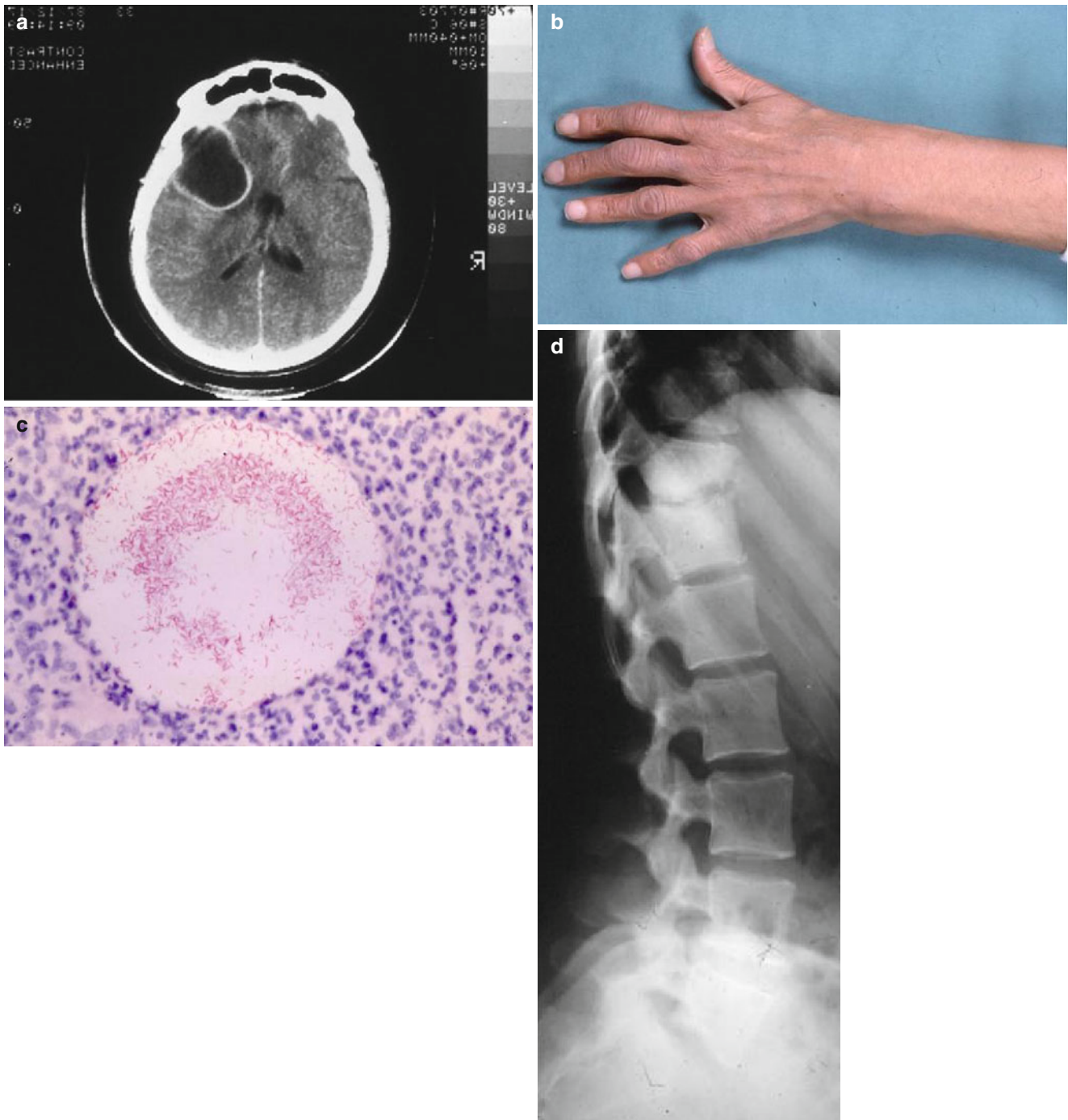
Fig. 71.9 (**a**) Frontotemporal tuberculoma in a transplant recipient presenting with erratic behaviour. (**b**) Metacarpophalangeal and wrist swelling secondary to atypical mycobacterium. (**c**) Skin biopsy showing copious acid-fast bacilli. (**d**) Lumbar spine X-ray showing destruction of disc and lumbar vertebral secondary to mycobacterium infection

caution if the TB is in a neurological site as IRIS may result in deterioration. The result from a recent retrospective analysis in France suggests a good outcome with a mortality much improved on historical data, of 6 % with little or no impact on graft survival except for those who develop haemophagocytic syndrome which augurs poorly [39, 40].

NTM are ubiquitous environmental pathogens that can become opportunistic infection in SOT. Donor-derived NTM has been documented but is rare. The overall incidence of NTM is not clear, but there are case reports of infection in renal transplants by many NTM species, but the most common appears to be Mycobacterium avium complex (MAC),

M. kansasii and *M. xenopi* with an average presentation of 2 years post-transplant [41]. In SOT (excluding lung transplants), the majority of disease is extra-pulmonary (CXR normal). Presentation is usually cutaneous with erythematous nodules, but tenosynovitis and arthritis are also common often at more than one site. Constitutional symptoms are often absent. MAC is more common in recipients with chronic lung disease where colonisation is facilitated. Therefore, making the diagnosis of NTB infection in this setting can be difficult, and the American Thoracic Society has issued guidelines involving a combination of consistent clinical and radiological findings, exclusion of other diseases and culture of BAL or biopsy specimen [42]. Debridement may be necessary for cutaneous involvement, and first-line agents often involve azithromycin, ethambutol and rifabutin, but treatment is a specialist area and requires liaison with the infectious disease team.

Fungi

Pneumocystis jirovecii (*PJ*) is an important opportunistic fungal infection, acquired asymptomatically (mostly in childhood), causing disease, mostly in the form of a severe pneumonia (PCP) in the immunocompromised through reactivation as well as primary or reinfection. In the absence of prophylaxis, the rates of 5–15 % occur in SOT and known risk factors include (1) use of steroids, (2) burden of immunosuppression and/or CD4+ count <200, (3) rejection episodes (especially repeated) and (4) CMV viraemia. There are now several reports of outbreaks, and respiratory transmission among transplant patients is clearly possible.

The incubation is thought to be about 7–8 weeks and cases are rare in the first month, but can also occur many years post-transplant. Clinically, onset is often insidious with slowly progressive dyspnoea and fever (may be suppressed), cough if present is unproductive, commonly there are no chest signs or fine basal inspiratory crackles, a moderate fever is common, and CRP tends not to be raised, whereas LDH is often raised. An invaluable early sign is desaturation on exertion and should be assessed in anyone with apparently mild dyspnoea. CXRs are often apparently normal in early disease, and CT scan has a much higher sensitivity showing classical ground-glass shadowing (see Fig. 71.10) and should be requested if there is any desaturation. The diagnosis is often made clinically, but there is a wide differential and high-dose septrin is not without its side effects, so if at all possible, the diagnosis should be confirmed. Bronchoalveolar lavage should be pressed for early if a positive-induced sputum is not available. Diagnosis is usually established by the presence of pneumocystis cysts

Fig. 71.10 CT scan showing ground-glass shadowing of *Pneumocystis jirovecii* infection in a patient who had steroid treatment for late rejection but no PCP prophylaxis. The chest X-ray was normal

with silver stains. Immunofluorescence staining of cell wall glycoproteins using monocloncal antibodies increases sensitivity. DNA-PCR-based assays of blood, saliva and sputum are under evaluation. Cysts may be present for 7 days after starting treatment and in some cases even after 3 weeks of treatment. Therefore, empirical treatment should not be withheld while awaiting diagnostic tests. Rarely, a biopsy (transbronchial or open-lung biopsy) may be required if there is severe disease, no diagnosis or no improvement with empirical treatment.

Prophylaxis against PCP is covered in Table 71.3 and is highly effective at reducing rates of PJ. Various guidelines recommend prophylaxis from 4 months up to 12 months. It is common practice to give at least 6 months prophylaxis following T-cell-depleting antibody, and most units using Campath-H1 continue until CD4+ count is >200; similarly we check the CD4+ count at the time of stopping prophylaxis on all our patients. In addition, it is important to have a system that considers every patient treated for rejection as returning to time zero and restarting transplant prophylaxis. Septrin is usually prescribed at 480 mg daily or 960 mg three times a week which has the considerable advantage of offering co-prophylaxis against Toxoplasma, nocardia and listeria and some protection against UTI (alternatives that do not offer the same co-prophylaxis are shown in Table 71.3). Recent evidence of outbreaks has resulted in the sensible recommendation that patients exposed to the sentinel case should be offered prophylaxis, and patients with PCP should be isolated until they completed 7 days of treatment [43].

First-line treatment for PCP is septrin at 120 mg/kg/day in divided doses [44]; this requires a large volume of IV fluid and can be problematic in patients with poor function. Septrin has good oral bioavailability, and mild to moderate disease can be treated orally. Alternatives include IV pentamidine which may be associated with numerous complications including infusion-induced hypoglycaemia, renal impairment and acute pancreatitis; primaquine and clindamycin; or (for milder disease) dapsone and atovaquone. Extrapolating from HIV literature, high-dose oral steroids are also recommended and should be started early (intravenous or oral prednisolone 40 mg b.i.d., tapered over 10 days). It is common practice to reduce overall immunosuppression simultaneously and to restart prophylaxis following successful treatment.

Treatment is for a minimum of 3 weeks; less than this is associated with treatment failure.

Invasive Fungi

A variety of other fungal infections occur in RTR, with the burden of immunosuppression (esp. the use of depleting antibodies), multiple rejection episodes, high-dose steroids (compromising the innate immune system), CMV viraemia and diabetes mellitus being significant risk factors. Consequently the majority of serious fungal infections occur within the first 12 months, cryptococcal infection being an important exception. Compared to other SOTs, RTRs are relatively spared from fungal infections but rates of 2–14 % have been reported, with rates in pancreas recipients much higher [45]. In a review of nearly 100 RTRs with invasive fungal infection, candida, cryptococcus and aspergillus are the three most common [46]. Fungal infections may be trivial colonisations, but all of the fungi discussed below can cause invasive disease with high mortality and early diagnosis is critical. Azoles used to treat several fungal infections have a profound inhibitory effect on cytochrome p450; consequently in the absence of close monitoring, starting an azole is highly likely to render a fungaemic patient CNI toxic.

Candida

Candida infection is the most common fungal infection in RTR usually presenting with orogenital involvement (see Fig. 71.11) especially in the setting of steroid exposure (and or diabetes mellitus) but also accounting for 60 % of invasive fungal infections. Beyond mucocutaneous infection, candida can involve the gut, severe oesophagitis being particularly common, urinary tract, lungs (focal cavity or pneumonitis), central nervous system and heart valves.

Prophylaxis with nystatin 1 ml q.d.s. is pretty effective at preventing oral candidiasis as long as patients take it (we discontinue prophylaxis when steroids stopped or down to

5 mg) as is clotrimazole or oral fluconazole 50 mg o.d. Distinguishing colonisation from UTI or respiratory tract infection can be very difficult, and a judgement call must be made but biopsy-proven tissue involvement or positive blood cultures need rapid treatment. *Candida albicans* is sensitive to azoles, but *C. glabrata* and *C. krusei* are often resistant. Treatment for oesophageal or systemic involvement is with fluconazole or caspofungin, voriconazole, posaconazole or amphotericin

Aspergillosis

Aspergillus niger is common as a harmless tongue infection, whereas *A. fumigatus* and *A. flavus* are responsible for 12 % of invasive fungal infections (0.7 % of RTR). As with other fungal infections, risk factors are total burden of immunosuppression, diabetes mellitus, chronic liver disease and CMV viraemia, but exposure to building works and smoking marijuana have also been implicated. The most common presentation is with pneumonia, but rhinocerebral (see Fig. 71.12), sinus, gut and skin involvement can also occur. Dyspnoea, unproductive cough and fever are usual, and haemoptysis, which may be torrential, can occur. While the classical appearance on CT scan of pulmonary nodules with a 'halo' sign is suggestive of angioinvasive aspergillosis, patients may often present with infiltrates or consolidation. Where there is a high index of suspicion for invasive aspergillosis (e.g. nonresponse to broad-spectrum antibiotics), a bronchoalveolar lavage or transbronchial biopsy may be required. Serum galactomannans, though useful, may have low sensitivity and specificity in SOT recipients. BAL galactomannans may have better specificity in this setting. Culture and cytology/histopathological findings are more specific.

Treatment for invasive disease is with IV voriconazole which is more effective than liposomal amphotericin – an alternative is caspofungin or a combination with immunosuppression reduction. In the context of an aspergilloma with invasion into pre-existing cavitary lung disease, pulmonary artery embolisation or surgical resection may be required. Surgical debridement may also be required in patients with invasive aspergillosis where there is impending massive haemorrhage or in the case of rhinosinusitis. Mortality is high and the emphasis should be on early diagnosis and aggressive treatment. Duration of therapy will depend on clinical response.

Cryptococcus neoformans (CN)

CN is an opportunistic environmental pathogen with highest risk of exposure related to birds and bird guano. Historical data suggests infection rates of 2–3.5 % in RTR, and this
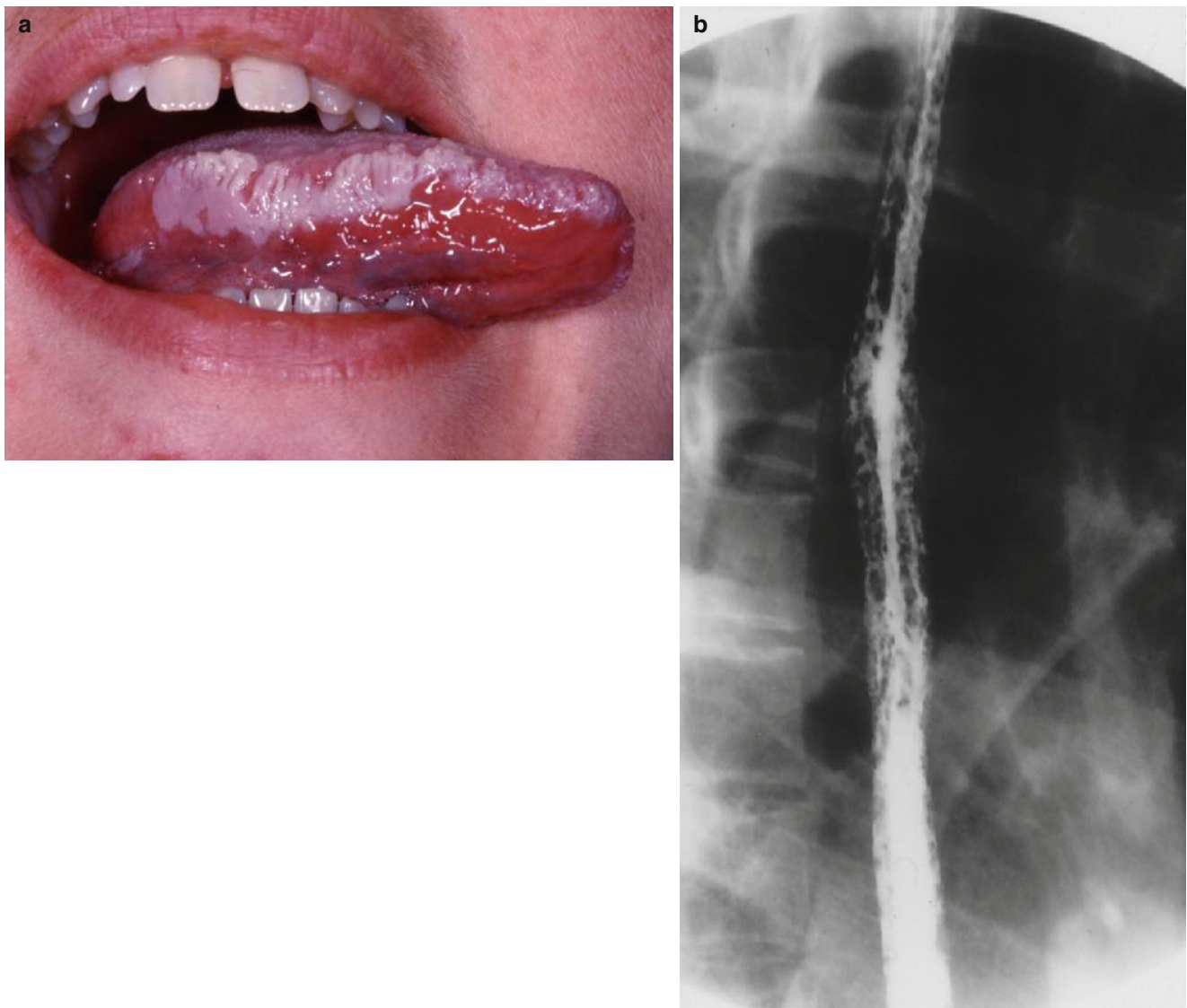
Fig. 71.11 (**a**) Oral candid adherent to the tongue. (**b**) Barium swallow showing extensive oral candidiasis. The patient who was on large doses of steroids presented with severe retrosternal chest pain with oral candidiasis

appears to be higher than in other SOT and accounts for 19 % of invasive fungal infections, although this may reflect previously higher use of steroids, and clinical experience suggests much lower rates in RTR than this currently. Patients may show signs of neurological, pulmonary and cutaneous involvement. Pneumonia has no characteristic features but dyspnoea and cough are common; X-rays may show either nodule(s) or lobar consolidation. Cutaneous involvement occurs in 10–20 % and is a very useful diagnostic focus [47]. Meningoencephalitis often has an indolent and non-specific presentation resulting in delayed diagnosis with headaches (over weeks), irritability and confusion in the absence of classical signs of meningism but ultimately progressing to a reduction in consciousness and or focal cranial nerve palsies. It is an important diagnosis not to miss and a high index of suspicion is required: at lumber puncture, high opening pres-

sure, moderate elevation of CSF protein and low white cell counts (predominantly lymphocytes) with low CSF serum glucose ratio are characteristic but not specific findings. An Indian-ink stain and cryptococcal antigen test must always be requested in this setting.

Treatment of cryptococcus infection in RTR is associated with a high rate of IRIS (5–11 %) presenting roughly 5 weeks after reduction in immunosuppression, and clinicians must be aware of the risk of associated hydrocephalus with a low threshold for reimaging.

Initial treatment is with liposomal amphotericin and flucytosine for the first 2 weeks, followed by high-dose fluconazole (400 mg/day) for 8 weeks. This should be followed by secondary prophylaxis with fluconazole 200 mg/day for at least 12 months (or lifelong if peripheral blood CD4 cells remain <200).

Fig. 71.12 Aspergillus infection. (**a**) Invasive nasopalatal aspergillus infection. (**b**) *Aspergillus niger* infection of the tongue

Morbidity and mortality in cryptococcal meningitis is mainly associated with raised intracranial pressure (as a result of CSF absorption blockade), and repeated lumber punctures to remove CSF are required in the first 2 weeks of therapy.

Mucormycosis

Mucormycosis is a rare opportunistic fungal infection most commonly documented in debilitated and poorly controlled diabetics but also documented in renal transplants (1 % of invasive fungal infections). Risk factors include prolonged neutropenia, diabetes and iron-chelation therapy as well as immunosuppression. Mucocutaneous, particularly orofacial, rhinocerebral and pulmonary involvement are the most common, and because of the propensity to invade vessel, a fatal outcome from pulmonary haemorrhage and dissemination is common (Fig. 71.13). Treatment is with IV liposomal amphotericin (with posaconazole as an alternative or dual therapy), and surgical resection of pulmonary and extra-pulmonary tissue is important. The mortality from

mucormycosis in RTR remains the highest of any fungal infection at over 50 %.

Histoplasmosis capsulatum and *Coccidioidomycosis immitis*

These are endemic fungi that are responsive for <4 % of invasive fungal infections in SOT but with a very high mortality. Both fungi occur in SW USA, Central and South America, but histoplasma is also reported in Europe, Asia and Africa. Outbreaks of both conditions have been described in RTRs, and rare cases of donor-derived infection have also been reported; however, the majority of infections appear to be reactivation (occurring within 6 months) or primary infections (occurring at any stage).

The main exposure risk for histoplasma is bird or bat guano. Histoplasmosis in RTR may present with fever, cellulitis, mouth ulcers and oronasopharynx, pulmonary or meningeal involvement [48]. Fungal cultures may take weeks, and as with other fungal infections biopsies can be
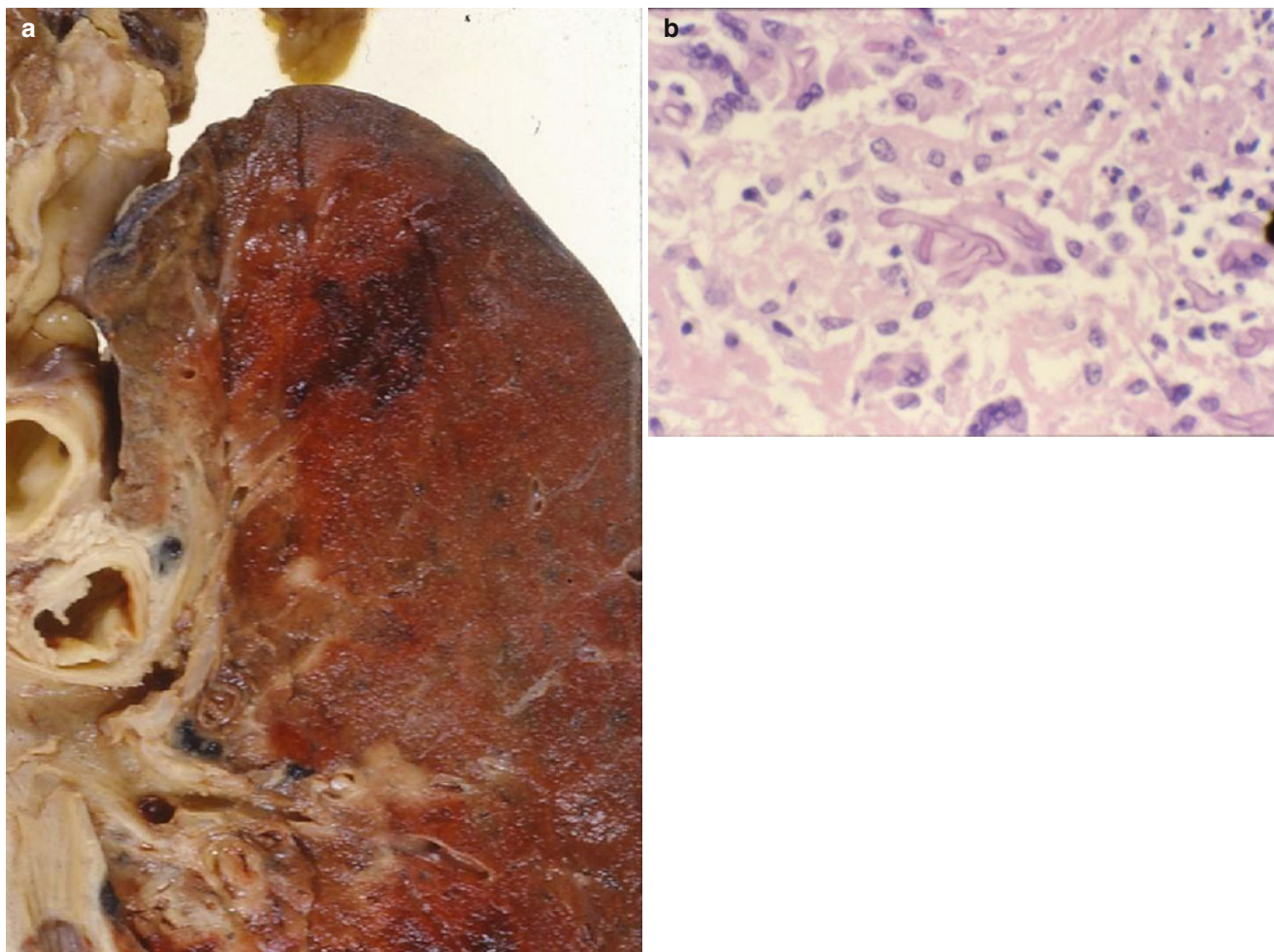
Fig. 71.13 (**a**) Post-mortem specimen showing the lung with haemorrhage secondary to vessel involvement of a transplant patient with mucormycosis. (**b**) Biopsy showing invasive mycelium

very helpful. Urine antigen screening has a high (>90 %) sensitivity but is not widely available. Histopathological examination may show characteristic intracellular organisms.

In immunocompetent individuals coccidioidomycosis almost exclusively causes pulmonary involvement, but in SOT 75 % is extra-pulmonary, commonly involving liver, bone marrow and meninges [49]. Guidelines do not recommend serological screening, but some authors advocate this for donor and recipient in endemic regions.

First-line treatment for both fungi is with liposomal amphotericin, with itraconazole as second line for histoplasmosis, fluconazole or caspofungin for coccidioidomycosis and accompanied by ISR. As fatal relapses can occur, it is usual to treat with an azole for at least a year, and after meningeal involvement, usually for life.

Cryptosporidiosis

Cryptosporidium parvum (associated with drinking water, swimming pools and livestock) can cause a chronic disabling diarrhoea in RTR which is watery/mucoid and associated with abdominal pain. In most individuals it is a self-limiting illness patients are not normally screened but in one study of SOTs with diarrhoea 20 % of cases were attributed to cryptosporidium, so it is probably underdiagnosed in most practice [50]. Cryptosporidium Ag testing by ELISA is highly sensitive with a good specificity and worth considering in any RTR with culture-negative diarrhoea not responsive to replacement of the usual suspect medications. There is no specific treatment, spiramycin, nitazoxanide and paromomycin have been tried with some success but relapses can occur.

Parasites

Toxoplasmosis

Toxoplasma gondii is an opportunistic parasite which can cause disease in RTR through reactivation, primary infection and occasionally through donor transmission. Risk fac-

tors include seronegative status of recipient, seropositive donor, burden of immunosuppression (CD4 counts below 200), lack of septrin prophylaxis and exposure to cats. Reactivation and donor-derived infection tend to present within the first 3 months of a transplant with pneumonitis (two-thirds) or neurological involvement (two-thirds) (90 % at post-mortem), and cardiac involvement is also common. Fever is common but neurological symptoms are non-specific with headache, confusion and ultimately coma [51]. Serology is only really helpful in diagnosing risk as seroconversion is often slow and rarely helpful in making the diagnosis. The diagnosis may be made by contrast CT or MRI scanning showing multiple ring-enhancing lesions and an appropriate radiological response after 2–3 weeks of treatment. CNS ring-enhancing lesions in SOT recipients may be due to a number of causes, and if an appropriate response to treatment is not seen, a stereotactic brain biopsy may be required. When safe to do so, a CSF examination with CSF Toxoplasma DNA detection by PCR is highly sensitive and specific for CNS toxoplasmosis.

Septrin prophylaxis for PCP is very effective at preventing toxoplasmosis, but reactivation can occur on stopping. Treatment is with pyrimethamine 200 mg loading dose followed by 50–75 mg daily and folinic acid plus sulphadiazine 4–6 weeks or septrin 5 mg/kg for 30 days. The mortality remains high at 50–65 %, those with primary infection being particularly at risk [52].

Strongyloides stercoralis

Strongyloidiasis in the setting of SOT is a very rare but serious condition with mortality of around 50 %. Strongyloides is endemic in large areas of the tropics and subtropics. Initial infection is via larval penetration of the skin and is usually asymptomatic. Larvae migrate to the pulmonary vessels and then via swallowed sputum to the duodenum and jejunum where mature female larvae shed eggs. Importantly infection can remain quiescent for over 30 years so a history of living in an endemic area is as important as being transplanted in an endemic area.

Reactivation and hyper-infestation can occur in those with previous exposure once significantly immunocompromised, usually within 6 months, sometimes within the first month, but occasionally years after a transplant. Presentation tends to be predominantly respiratory and gastrointestinal with abdominal pain, diarrhoea, nausea, vomiting and abdominal distension and may lead to ileus. Respiratory involvement is with tachypnoea, dyspnoea, fever and cough and ARDS occurs in about two-thirds of cases. The CXR is usually abnormal with diffuse or patchy infiltrates. Eosinophilia, although a very helpful clue, is often not present [53] although may well have been present but missed on pre-transplant bloods.

The diagnosis may be made by visualising larvae in sputum or stool, but there is a high false-negative rate and multiple stool samples may be necessary. Duodenal aspiration, bronchoalveolar lavage and the Enterotest (a piece of string taped to the nose passing into the duodenum then withdrawn for microscopy) all have their supporters and are all worth considering if there is clinical suspicion.

Treatment is with ivermectin (200 mcg/kg often for 5–7 days in hyper-infestation or 2 days in others) along with broad-spectrum antibiotics and repeat treatment if there is evidence of gut translocation. Patients can deteriorate very rapidly with hyper-infestation either via ARDS or recurrent gram-negative septicaemia as the larvae burrow into the gut. Early identification is therefore critical, and a sensible approach is to check strongyloides serology of all patients from endemic areas pre-listing. If positive, or with unexplained eosinophilia, stool should be screened for ova cysts and parasites and an ID opinion should be sought with regard to blind eradication.

Trypanosomiasis

Chagas disease (*Trypanosoma cruzi*) endemic in Central and South America can cause disease in RTR by reactivation (20 % of seropositive patients) or donor-derived infection (20 % of seropositive donors) [54]. Infection results in fever, myocarditis, meningoencephalitis or cutaneous involvement such as panniculitis typically within a year of transplant [55]. Pre-transplant serology or treatment is not currently recommended in part because of the toxicity of treatment but close surveillance post-transplant for D+ or R+. The diagnosis, management and treatment of trypanosomiasis should be undertaken with the infectious diseases team. Benzinidazole is the treatment of choice (with nifurtimox as an alternative) for 8 weeks in the context of parasitaemia.

Scabies

This can result in hyper-infestation and severe secondary bacterial infection (Fig. 71.14), but the pruritis may be subdued and source of the cellulitis not immediately apparent.

Syndromes

There are a variety of clinical scenarios in the immunocompromised with a wide differential diagnosis. Tables 71.8, 71.9, 71.10, 71.11 and 71.12 show the differential diagnosis for diarrhoea, chest infiltration, nodules, CNS space occupying lesions and meningoencephalitis.

Fig. 71.14 Hyper-infestation with Norwegian scabies

Table 71.8 Differential diagnosis of diarrhoea in SOT recipients

Medication:

Immunosuppression	Mycophenolic acid (may develop overtime), tacrolimus (NB: diarrhoea increases tacrolimus levels), mTORi
Antibiotics	
Miscellaneous	Laxatives, colchicine, metformin

Infectious opportunistic:

Viral:

CMV[a]	Usually but not always, associated with CMV viraemia, diarrhoea often bloody
Norovirus	Seasonal, nausea and vomiting prominent
Rotavirus	
Coxsackie[a]	
HSV[a]	
Adenovirus[a]	

Bacterial:

Clostridium difficile

Listeria[a]

MAI[a]

Table 71.8 (continued)

Salmonella[a]

Yersinia[a]

E. coli[a]

Campylobacter

Parasitic:

Cryptosporidium

Microsporidium[a]

Isospora belli

Giardia lamblia

Strongyloides[a]

Entamoeba histolytica[a]

[a]Can result in disseminated disease

Table 71.9 Differential diagnosis of pulmonary infiltrates in SOT recipient

Infection:

Bacteria	Conventional bacteria, mycobacteria, nocardia
Viruses	CMV, community respiratory viruses (influenza, parainfluenza, RSV)
Fungi	Aspergillus, pneumocystis, cryptococcus

Fluid:

ARDS	Sepsis, allergic reaction to anti-CD25mAb, ATG, OKT-3, Campath-H1
Fluid retention/cardiac failure	Left ventricular failure, diastolic dysfunction, transplant renal artery stenosis (flash pulmonary oedema)
Pulmonary haemorrhage	

Medication:

mTOR inhibitor	mTORi-induced pneumonitis; opportunistic infection less likely if CD4+ count >200 (if in doubt stop mTOR and treat with steroids)
Others	Azathioprine, cyclophosphamide, nitrofurantoin

Table 71.10 Differential diagnosis of pulmonary nodule in SOT recipient

Infective:

Bacterial abscess	Nocardia, legionella, gram positive (*Staph. aureus*, *Rhodococcus equi*), gram negative (Enterobacteriaceae, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*), anaerobes and septic emboli
Mycobacteria	Mycobacterium tuberculosis and non-TB mycobacteria
Fungal	Aspergillus, cryptococcus, histoplasmosis, coccidioidomycosis and paracoccidioidomycosis, PCP

Malignancy:

PTLD	May or may not be associated with EBV viraemia
KS	Usually multiple, may be associated with chylous effusion HHV-8 PCR positive
Donor-derived malignancy	

Table 71.11 Differential diagnosis of focal CNS lesion in SOT

Viral:	
PML	JC polyoma virus solitary or multiple white matter changes (no mass effect)
EBV	Usually part of PTLD
Bacterial:	
Typical bacterial abscess	*Staph. aureus*, *Strep. viridans*, *Strep. milleri*
Listeria	Usually brainstem meningoencephalitis but can form focal lesions
Nocardia	Focal lesions (often associated with abnormal CXR)
Mycobacteria:	
TB	>6 months, usually reactivation of latent TB. Single or multiple SOL may or may not enhance
Fungal:	
Aspergillus	Multiple lesions common
Candida	Usually meningitis but can cause microabscesses
Coccidioides	
Mucormycoses	
Histoplasma	
Parasitic:	
Toxoplasmosis	Primary infection or reactivation, single or multiple ring-enhancing lesions
Malignancy:	
PTLD	
Donor-derived tumour	Fortunately rare but important to consider in recipients of deceased donor kidneys
CNI toxicity	
	White matter changes can mimic SOL

Table 71.12 Differential diagnosis of meningoencephalitis in SOT: infective

Viral:	
HSV	Important comments, in particular clinical characteristics and diagnostic tests
VZV	Systemic infection usually apparent with cutaneous or pulmonary involvement
CMV	Usually accompanied by viraemia and other systemic evidence of infection
EBV	Can present as meningoencephalitis or SOL as part of PTLD
HHV-6	
Bacterial:	
Listeria monocytogenes	May have chest involvement
Others	Typical bacterial infections including *Strep. pneumoniae*, *Neisseria meningitidis*, group B Strep, *Haemophilus influenzae* and gram negatives
Mycobacteria:	
Fungal:	
Cryptococcus	
Coccidioides	

Table 71.12 (continued)

Parasitic:	
Toxoplasmosis	
Trypanosoma cruzi	
Differential diagnosis of meningoencephalitis in SOT: noninfective	
Medication:	
CNI neurotoxicity	Best seen on MRI with white matter changes consistent with PRES
Antivirals	Acyclovir-induced neurotoxicity more likely in renal impairment due to renal excretion

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Tips and Tricks for the Management of Post-transplant Infection

1. There is considerable merit in a robust system for properly screening patients on the waiting list (and live donors) with appropriate vaccination, treatment and plans for prophylaxis.
2. Ethnicity, travel and country of origin history of recipient and, if possible, donor should be obtained especially if investigating a fever post-transplant.
3. Culture of perfusion fluid and retention of donor serum, for serology screening if necessary, are cheap strategies that may help identify donor infections.
4. Robust strategies need to be in place to ensure appropriate chemoprophylaxis, dose and duration with extension for those receiving depleting anti-bodies, those with low Igs or CD4+ counts or those receiving treatment for late rejection.
5. A close relationship with virology and microbiology departments is vital, and rapid alert systems (such as e-mail alerts for viraemia or positive MSUs) are invaluable.
6. Many opportunistic infections have atypical presentations, and in the absence of diagnosis or improvement with empirical therapy, biopsy (for histology and culture) may be critical.

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