Prevention of opportunistic infections in immunosuppressed patients in the tropical Top End of the Northern Territory

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Abstract

The population of the Top End of the Northern Territory has a high incidence of several infections of particular significance in the immunosuppressed. The following protocol for evaluation and treatment of patients prior to immunosuppression was developed in order to reduce the incidence of serious opportunistic infections. The infections discussed are *Strongyloides stercoralis*, tuberculosis, scabies, chronic hepatitis B, melioidosis and other bacterial infections. We recommend that all patients planned to receive more than 0.5mg/kg/day of prednisolone for >14 days, or any more potent immunosuppressive drug, be evaluated and treated according to this protocol. Details of the rationale, evidence base, and proposed investigations and therapy for such patients are discussed. *Commun Dis Intell* 2003;27:526–532.

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Introduction

The Top End is unique, both in the infectious agents that are endemic there and in its population. This guideline has been developed with the people, geography and microbial ecology of the Top End in mind. It may also be useful for other parts of tropical Australia. It aims to supplement existing protocols and practices for defined patient groups, such as organ transplant recipients and chemotherapy patients. It also aims to draw attention to patients who are being immunosuppressed, but for whom no protocol exists regarding prevention of opportunistic infections.

This article focuses on recommendations for the prevention of disseminated strongyloidiasis (DS), tuberculosis, melioidosis and other bacterial sepsis, scabies hyperinfestation and activation of hepatitis B virus infection, which anecdotally have each presented as opportunistic complications in immunosuppressed patients in the Northern Territory over recent years. These conditions are generally more common in the Top End than elsewhere in Australia. The recommendations are justified by varying levels of evidence and represent a consensus guideline developed by local infectious diseases, renal, oncology and public health physicians.

This guideline is only intended to apply to people receiving significant immunosuppression. This is defined in Box 1.[1,2,3]

It does not include the following patients: inhaled corticosteroids, hydroxychloroquine, sulfasalazine, colchicine, gold, weekly methotrexate and oral courses of prednisone less than 14 days regardless of dose

Box 1. Eligible patients for the opportunistic infection prevention protocol

1. Anyone receiving ≥0.5mg/kg per day of prednisolone or the equivalent for >14 days.
2. Anyone currently receiving cyclosporin, cyclophosphamide, azathioprine, mycophenolate, tacrolimus or cancer chemotherapy.

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and where the frequency is less than six courses per year. Patients having ≥6 courses of prednisolone per year may also benefit from the protocol.

With systemically administered steroids, the risk of infection is related to the dose of steroid and the duration of therapy as demonstrated in a meta-analysis of 71 controlled trials.[3] The overall rate of infectious complications was 12.7 per cent in steroid-treated patients compared to 8.0 per cent in the control group (relative risk 1.6). The rate of infection was not increased in patients receiving less than 10 mg per day or a cumulative dose of less than 700 mg of prednisone (which is roughly equivalent to 0.5mg/kg for 20 days). Therefore a cut-off of prednisolone ≥0.5mg/kg/day for >14 days for this protocol is practical. This is supported by there having been to date no confirmed cases of disseminated strongyloidiasis in the Top End in patients on intermittent prednisolone therapy for respiratory and other conditions.

Each infection will be addressed in turn.

Strongyloides stercoralis

Strongyloides infestation is endemic in most remote communities of the Top End of the Northern Territory, particularly in the East Arnhem region. A stool microscopy prevalence study in 1997 at Galawin`ku (Elcho Island, Arnhem Land) showed strongyloides larvae in the stool in 15 per cent of 300 people.[4] In 1991/1992, at least 3.4 per cent (68/2000) of all admissions to Royal Darwin Hospital (RDH) had strongyloides larvae detected in stool.[5] During this 12-month period, another 98 cases of strongyloidiasis were detected in other Top End laboratories. Reliable prevalence data for other Top End communities is not available, but the incidence of symptomatic infection and stool positivity seems significantly lower outside East Arnhem. We encourage collection and analysis of stool prevalence data from Northern Territory communities outside East Arnhem to confirm this impression.

The authors are aware of six cases of disseminated strongyloidiasis (including 1 death) in immunosuppressed patients from the Top End over the last 10 years, with a range of 0–2 cases per year.[6] There may also be undiagnosed cases occurring, as overwhelming sepsis in the absence of a microbiological diagnosis is relatively common at RDH. The reported mortality of DS is up to 87 per cent.[7] Thus, detection and treatment of infestation prior to immunosuppression could avoid potentially fatal DS. However, in immunocompetent individuals with chronic asymptomatic infestation, even the best diagnostic methods may miss the presence of strongyloides. Eosinophilia is usually absent in immunosuppressed people with strongyloides hyperinfestation, although it is often present before immunosuppression begins. In a 1993 RDH survey, peripheral eosinophilia was only present in 57 per cent of immunocompetent patients with asymptomatic infection.[5]

Direct stool examination for strongyloides larvae has a sensitivity of approximately 30 per cent if one stool is examined[8] and 50 per cent for three stools.[9] One study claimed sensitivity of close to 100 per cent if seven stools are examined.[10] This is clearly impractical in our setting.

Culture of stool (as opposed to direct microscopic examination) improves sensitivity, but is labour intensive, and poses a small risk of laboratory-acquired infection. Agar-plate culture of a single stool specimen was approximately 90 per cent sensitive in one study.[8] This takes 2–3 days and may not be practical for screening large numbers of specimens.

The utility of serology varies widely depending on the exact nature of the test used.[7] Using an ELISA method, with crude extract of filariform larvae, improves sensitivity. Performance can be enhanced by pre-incubating the patient's serum with *Onchocerca* antigens to eliminate non-specific cross-reactions before testing. Under the above conditions, the assay was 88 per cent sensitive and >90 per cent specific for the detection of strongyloides infection in a non-endemic setting.[11] Serology may remain positive for months to years after a successfully treated infection, and may cross-react with other helminth infestations, notably *Ascaris lumbricoides*. The titre does not reliably fall with successful eradication.[12] RDH is using an ELISA with *Strongyloides rattii* as the antigen. We do not have good data about the sensitivity and specificity of this technique in our setting, and therefore the above-quoted published rates may not apply.

In summary the sensitivity of current diagnostic methods is not sufficiently high to be able to confidently exclude chronic asymptomatic infestation in a patient who is about to begin immunosuppression.

Disseminated strongyloidiasis can occasionally occur with mild levels of immunosuppression e.g. a 65-year-old man receiving 20 mg per day of prednisolone for severe chronic obstructive pulmonary disease (COPD) for 6 weeks.[1] However, most case reports relating to DS in patients on prednisolone, were with doses around 1 mg/kg/day.[2] There are also multiple case reports suggesting a strong association of disseminated strongyloidiasis with HTLV-I infection, and less so with HIV infection. However, this association has to date not been borne out in Central Australia where HTLV-I infection is endemic.

A recent review recommends empiric treatment (including those with negative serology and stool examinations) before organ transplantation in 'high-risk patients from endemic areas'.[13]

Ivermectin is very well tolerated. Repeated dosing has been used in the Northern Territory for crusted scabies for at least the last five years without any significant toxicity.[14] Large-scale studies with regular six-monthly dosing have been conducted in West Africa, also without significant drug toxicity detected.[15]

For the treatment of simple strongyloides infestation (in immunocompetent patients), a single dose of ivermectin seems equivalent to 2 doses of ivermectin, but is superior to three days of albendazole.[16,17,18] Disseminated strongyloidiasis, where the worm burden is massive, requires multiple doses of ivermectin, and suspected cases of DS should be discussed urgently with an infectious diseases specialist.

The concern for DS applies primarily to patients with solid organ transplants, chemotherapy for malignancy, immunosuppression for SLE and other autoimmune disorders, and patients with severe, steroid dependant COPD/asthma requiring multiple courses of higher dose prednisolone.

The recommended management procedures to prevent disseminated strongyloidiasis are shown in Box 2.

Tuberculosis

A significant proportion of the population of the Top End has latent infection with *Mycobacterium tuberculosis* (LTBI). Immunosuppressive medication greatly increases the chance of reactivation. In patients with HIV co-infection, the chance of developing active TB is approximately 10 per cent per year (compared with 10 per cent over 10–20 years for immunocompetent people).

This risk is similarly increased in patients taking immunosuppressive medications, although this risk is less well defined. Early treatment of LTBI with nine months of isoniazid greatly decreases the chance of reactivation (by around 90%) and should be strongly considered in a person with LTBI who is to begin immunosuppression. A short course alternative is the combination of rifampicin and pyrazinamide for two months, however there may be an unacceptably increased risk of adverse reactions to the medication with this latter regime.

Box 2. Management recommendations to prevent disseminated strongyloidiasis in eligible patients

1. Encourage the wearing of shoes to prevent infection or decrease worm burden through reduced exposure to soil-borne larvae.

2. Before immunosuppression (or at initial evaluation):

– test all eligible patients with serology, eosinophil count and stool microscopy and culture. Treat all patients from highly endemic areas (East Arnhem), regardless of the above results, with a single dose of oral ivermectin 200 mcg/kg. Pregnancy test is first required for all reproductive age women.

  For patients with a positive stool microscopy or culture, give a second dose of ivermectin 7 days after the first dose. Repeat stool culture 7 days after the second dose. If still positive, discuss with the Infectious Diseases Unit.

– Outside of East Arnhem, only treat those with evidence of strongyloides infection.

3. With ongoing immunosuppression:

– In East Arnhem, repeat ivermectin every 3 months without investigation. Elsewhere, undertake serology, stool microscopy and culture for strongyloides and eosinophil count every 3 months and treat if positive.

4. Treat any immunosuppressed patient with unexplained pulmonary infiltrates, fever, abdominal pain or septic shock with ivermectin on a day 0,1 and 7,8 regimen.

Box 3 shows the management recommendations to prevent tuberculosis.

Box 3. Management recommendations to prevent tuberculosis in eligible patients

1. Ascertain past history of tuberculosis or latent tuberculosis infection.

– The relevant communicable diseases clinic or chest clinic should be contacted to ascertain if the patient already has a diagnosis of LTBI or partially treated TB. If there is no record of a Mantoux, one should be performed, before starting immunosuppression if possible, as immunosuppression (particularly corticosteroids) will significantly decrease response to the test. If immunosuppression must be commenced immediately, do a Mantoux on day one.

2. Baseline two-step Mantoux testing.

– The cutoff for a positive Mantoux prior to immunosuppression is 10 mm. If immunosuppression already exists, the cutoff is 5 mm.

– If the initial Mantoux result is negative (<10 mm or <5 mm as appropriate), a second Mantoux should be performed 1 to 3 weeks after the first in order to boost a false-negative first result to a true positive value (when a person has LTBI, but has acquired infection many years before, or has anergy to tuberculin).

– A positive Mantoux result on the initial or second test in the absence of active TB (on CXR and at clinical review) will require treatment of LTBI with a 9-month course of isoniazid (plus pyridoxine to decrease neurotoxicity) or a 2-month course of rifampicin and pyrazinamide.

3. Ongoing screening if baseline two-step Mantoux is negative.

– If the baseline two-step Mantoux test is negative, annual Mantoux screening for newly acquired LTBI should occur in those with continuing immunosuppression.

4. If LTBI or past partially treated TB is identified, treat for this as above.

Scabies

Scabies infestation is very common in many Top End communities, and poses a risk of secondary bacterial sepsis. Infected immunosuppressed patients may develop a severe form of scabies, crusted (Norwegian) scabies,[14] therefore it should be treated before immunosuppression. The mortality of crusted scabies in the Top End was up to 50 per cent within five years of diagnosis until recent improvements in scabies treatment and prevention and treatment of secondary sepsis.[19] Scabies infestation can be reliably detected by clinical examination.

Management recommendations to prevent scabies are shown in Box 4.

Box 4. Management recommendations to prevent scabies in eligible patients

1. Treat pyoderma with a single dose of intramuscular benzathine penicillin (Bicillin), 1.2 million units (900 mg).

2. Treat scabies with 5 per cent topical permethrin at days 0 and 7. All household contacts should also be treated.

3. If crusted scabies is present or suspected, hospital admission for eradication of infection should be organised prior to or coincident with the initiation of immunosuppression.

Hepatitis B virus

Chronic hepatitis B virus (HBV) infection is endemic in Top End communities with over 40 per cent of individuals in some communities having evidence of hepatitis B exposure. Endemicity, clinical impact and recommendations for follow up in immunocompetent patients from remote communities has been published. A guideline for follow up and management of these non-immunosuppressed patients from remote communities is in use[20] and should be used for patients on steroids alone, but not for those on more potent immunosuppression (Box 5). In a study at the RDH renal unit of patients undergoing renal replacement therapy, 73 of 122 Indigenous patients (59.8%) had evidence of hepatitis B virus exposure while 10 (8.2%) were HBsAg positive (Dr Nick Gray, Registrar in Renal Medicine, Royal Darwin Hospital, 2001, unpublished).

Box 5. Management recommendations to prevent reactivation of hepatitis B in eligible patients

- Any HBsAg positive patient in whom chemotherapy for cancer or potent immunosuppression is planned should be referred to the liver clinic for assessment, preferably prior to therapy.
- Non-immune patients should be vaccinated against hepatitis B prior to planned immunosuppression.

Rapidly progressive chronic active hepatitis may occur in chronically HBV-infected people who become immunosuppressed.[21] HBsAg positive patients undergoing renal transplantation almost invariably develop significant liver dysfunction with deaths from fulminant hepatic failure documented.[22] Antiviral therapy is of proven benefit in the renal transplantation setting, and it is now standard practice that antiviral therapy be used pre-emptively for patients who are HBsAg positive, irrespective of other markers of hepatitis B viraemia or liver enzyme levels.[23,24] Reactivation of hepatitis B in patients undergoing chemotherapy or potent immunosuppressive therapy has a mortality of 37 to 60 per cent.[25] Pre-emptive antiviral use is also now standard practice in liver transplant recipients, since studies in recent years have provided evidence of its efficacy and safety.[26,27]

For the prevention of reactivation of hepatitis B recommendations in this protocol, potent immunosuppression refers to chemotherapy for malignancy, organ transplantation, or potent therapy for autoimmune disease. This would include cyclophosphamide, azathioprine, cyclosporin, mycophenolate and leflunomide but **not** corticosteroids alone. Assessment will usually include a liver biopsy and initiation of lamivudine and possibly regular hepatitis B immunoglobulin. The other and most newly available antiviral treatment is adefovir dipivoxyl. At this stage, adefovir remains reserved for use in those developing the YMDD (lamivudine resistant) mutation of the reverse transcriptase gene, which occurs commonly e.g. up to 27 per cent of liver transplant recipients on lamivudine at 52 weeks.[26] The use of antiviral medications for hepatitis B is generally restricted to approved liver clinics.

Bacterial sepsis/melioidosis

Melioidosis is more common, more severe and more likely to cause death in people who are relatively immunosuppressed.[28] These data mainly apply to those with diabetes, heavy alcohol intake or chronic renal impairment, all of whom have subtle immune defects including poor neutrophil function. There have been cases of both acute melioidosis and relapsed melioidosis in people on therapeutic immunosuppression,[29] and thus it is probable that all significant therapeutic immunosuppression increases the probability of melioidosis occurring, and of it being more severe if it does occur.

Nocardia infection is uncommon, but well described in immunosuppressed people. Pulmonary and cerebral infections are likely to occur if an immunosuppressed person is infected, and are difficult to treat and have a high mortality.

Skin and systemic sepsis with *Staphylococcus aureus*, Group A streptococcus and *Streptococcus pneumoniae* (among others) are very common in the Top End. Opportunistic infections have been a significant cause of morbidity and mortality in renal transplant patients, with a reported odds ratio for all infectious complications of 30 compared with non-transplant patients.[30] The majority of these infections are with one of the three bacteria mentioned above. Bacterial sepsis with *S. aureus* and *Escherichia coli* were the commonest causes of death in Top End patients with SLE from 1984–90.[6] In these patients, staphylococcal and *E. coli* sepsis were particularly common in the setting of disease exacerbation and a significant increase in steroid dosage with or without other immunosuppressive agents.

A recent review reported, 'The use of low-dose trimethoprim-sulfamethoxazole in organ transplantation markedly reduces the risk of developing *Listeria* infection, *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, nocardiosis, and urinary tract infections'.[13] It is usual after solid organ transplantation to give prophylactic trimethoprim-sulfamethoxazole for the first 6–12 months post-transplant. Its efficacy has been confirmed in renal transplant patients in a randomised controlled trial which found a highly significant decrease in all bacterial infections, but not in PCP.[31] In our setting, we recommend continuing the prophylactic trimethoprim-sulfamethoxazole as long as potent immunosuppression continues, provided no attributable significant and unavoidable adverse medication reactions occur.

Prophylactic antibiotics are usually not needed with steroids alone. The exception to this rule is patients on particularly high doses (100 mg per day or more of prednisolone or equivalent). In the study on SLE in the Top End quoted previously, when steroid dose was intensified, the incidence of serious opportunistic infections increased significantly, so trimethoprim-sulfamethoxazole prophylaxis may be justified in this subgroup. This is for PCP prophylaxis, and also will decrease bacterial infections (including those from *Nocardia*, staphylococci, streptococci and gram negatives, including *Burkholderia pseudomallei*). The recommended dose is trimethoprim-sulfamethoxazole one double strength tablet daily (160 mg/800 mg).

Varicella zoster virus (VZV) vaccination prior to heavy immunosuppression[13] should be given prior to organ transplantation if the patient is not already immune, as recommended by the Infectious Diseases Society of America.[13] As it is a live vaccine, it should NOT be given to those who are already immunosuppressed.

Management recommendations to prevent melioidosis and bacterial sepsis are shown in Box 6.

Box 6. Management recommendations to prevent melioidosis and bacterial sepsis in eligible patients

Pneumococcal vaccination (23-valent pneumococcal polysaccharide) should be given, and other adult vaccinations made up to date, **before** planned immunosuppression (VZV, MMR, ADT, polio). Pneumococcal vaccination should be repeated every 5 years with ongoing immunosuppression.

– Prophylactic trimethoprim/sulfamethoxazole one double strength tablet (160 mg/800 mg) daily should be given to all patients receiving potent immunosuppression (as defined in Box 5 above) plus those on 100 mg per day or more of prednisolone or equivalent.

– In the wet season, patients should be encouraged to wear gardening gloves and footwear when coming into contact with mud or soil.

– Melioidosis serology should be performed on all patients in the Top End prior to immunosuppression. If positive (an indirect haemagglutination titre of ≥1:40), swabs for melioidosis culture should be taken from throat, rectum and any wounds. Urine and sputum (if any) should also be collected for melioidosis culture. If cultures are positive, full treatment is required (refer to Infectious Diseases Unit).

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