Review

Infectious diseases in patients receiving monoclonal antibodies

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SUMMARY. Monoclonal antibodies (MA) act against specific antigens and are indicated for the treatment of inflammatory and neoplastic diseases as well as in the control of immune responses in transplant patients. More than 30 MA are currently in use in clinical practice, including rituximab, targeting the CD-20 antigen of B lymphocytes, bevacizumab against vascular endothelial growth factor (VEGF), infliximab and adalimubab against tumour necrosis factor alpha (TNF-α) and omalizumab, which neutralizes circulating IgE. The use of MA has been associated with infective complications due to their immunomodulatory action. The prevalence of herpes virus infections, Pneumocystis jirovecii pneumonia and Mycoplasma tuberculosis infection is increased in patients receiving MA. Prevention of these infective complications is based on the clinical evaluation of patients before treatment with MA and close monitoring of the parameters associated with infections during treatment. ***Pneumon 2012, 25(4):402-409.***

INTRODUCTION

Monoclonal antibodies (MA) are molecules derived from living cells. They act against specific antigens and are aimed at cellular elements in the cascade of the immune response/inflammation reaction. They are responsible for the inhibition or reduction of function of specific cells, such as B and T lymphocytes, and for the suppression of certain cytokines.[1] MA have been used since the 1980s in transplant patients to cope with acute graft rejection, in the treatment of lymphoma and leukaemia, and in the management of rheumatoid arthritis and recently other inflammatory diseases (Table 1).[1,2] The MA that has been used the most frequently is rituximab, which is used mainly for CD20+ lymphomas [chronic lymphocytic leukaemia/small lymphocytic cell lymphoma (CLL), follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmatocytic lymphoma (LPL)]. Over the past decade more than 30 MA molecules have been approved by the US Food and Drug Administration (FDA) and are in current use, while the bioactivity of hundreds of new MA has been proved and their production is pending.[2]

TABLE 1. Biological agents used for treatment of non-rheumatic, non-haematological diseases

Disease	Biological agent	Mechanism of action
Psoriasis	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
	Etanercept	TNF neutralizer
	Ustekinumab	Anti-IL12/IL23 (p40 subunit)
	Briakinumab (under development)	Anti-IL12/IL23 (p40 subunit)
Inflammatory bowel disease	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
Uveitis	Infliximab	Anti-TNF
	Adalimumab	Anti-TNF
Bronchial asthma	Omalizumab	Anti-IgE
	Mepolizumab (under development)	Anti-IL5
Diabetes mellitus type I	Teplizumab (under development)	Non activated anti-CD3
	Otelixizumab (under development)	Non activated anti-CD3
Diabetes mellitus type II	Anakinra (under development)	Recombinant IL1 receptor antagonist
Multiple sclerosis	Interferon β	Immunomodulation
	Natalizumab	Anti-α4 integrin
	Rituximab	B cell suppression (anti-CD20)
	Alemtuzumab (under development)	Lymphocyte suppression (anti-CD52)

TNF: tumour necrosis factor, IL: interleukin

MA are aimed at various different targets depending on the disease, including soluble contacts- receptors, membrane binding proteins and cytokines, but without limiting their action to a specific target, since they also activate immune mechanisms other than that of primary therapeutic interest, which modulate the recognition and defense against endogenous and exogenous insults.[3] This "side effect" has led to an increased prevalence of infective complications, especially in HIV(+) patients with CD4 <50 cells /ml, including viral infections such as cytomegalovirus (CMV), JC virus (JCV) which causes multifocal leukoencephalopathy (PML) and hepatitis B reactivation, and also tuberculosis, Pneumocystis jirovecii infection and common bacterial infections.[3]

This is a review of the most common infections presenting in the setting of treatment with MA and their appropriate treatment for the best outcome.

MA IN CURRENT THERAPEUTICS

MA in oncology

Rituximab (antibody against CD20)

CD20 antigen is expressed in normal B cells, promoting their growth and activity, and in neoplastic B cells (>90% in non-Hodgkin lymphoma, 10% in chronic lymphocytic leukaemia).[4] Rituximab is an anti-CD20 MA, an antibody with chimerical properties that is derived from ape and human epitopes (anti-CD20 MoAb IDEC-2B8 of ape and human IgG1). It binds to a CD20 epitope promoting apoptosis and cell lysis through a cytotoxic dependent complement action.[5] Rituximab is administered intravenously (iv) in a dosage of 375 mg/m^2 once weekly for 4 weeks, which results in intense B cell suppression of 3 to 6 months duration. Rituximab is also indicated for treatment of rheumatoid arthritis.

Trastuzumab [antibody against human epidermal growth factor receptor 2 (HER2)]

The anti-HER2 MA is a transmembrane receptor of 185-kDa, a member of the tyrosine kinase (TK) family of receptors. It binds to an epitope of HER2 and directly inhibits cell growth. It also induces apoptosis and inhibits angiogenesis in breast cancer. Trastuzumab is administered iv in a loading dose of 4 mg/kg followed by a single dose of 2 mg/kg.[6]

Gemtuzumab ozogamicin (antibody against CD33)

CD33 is a type I transmembrane glycoprotein, expressed on the surface of myeloid cells and blasts in acute myeloid leukaemia. Gemtuzumab ozogamicin binds to the cell surface of CD33 (+) leukaemia cells, promoting endocytosis and release of calicheamicin, which, through the action of glutathione, composes an active compound (intermediate complex) that binds DNA and promotes apoptosis.[7] Gemtuzumab ozogamicin has been removed from the market by FDA, because of its high toxicity.

Bevacizumab [antibody against vascular endothelial growth factor (VEGF)]

VEGF is an angiogenetic factor the action of which depends on the activation of VEGF 2 receptor [VEGFR-2 (Flk-1/KDR)], which has a high affinity to tyrosine kinase. VEGF can also bind to other sites on the cellular surface, such as receptor VEGF1 and neuropilin-1 and 2, receptors located in vascular and lymphatic endothelial cells.[8] VEGF action on cells through VEGFR-2 is mitotic and angiogenetic and results in inhibition of cell death. Bevacizumab neutralizes VEGF activity in cases of rhabdomyosarcoma and breast, colon and lung cancer, and inhibits tumour growth by reducing the blood supply and microvascular density and permeability of the tumour.[9]

MA in autoimmune/inflammatory and infectious diseases

Infliximab, Adalimumab, Golimumab [antibodies against tumour necrosis factor alpha (TNF-α)]

TNF-α is a pro-inflammatory cytokine associated with chronic inflammation and cachexia. Infliximab (anti-TNF-α MA) is indicated for the treatment of various autoimmune diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and ankylosing spondylitis. Infliximab inhibits adhesion of TNF-α to its receptors and neutralizes all forms, while a TNF-α antagonist neutralizes the soluble TNF-α and β receptors only.[10] Adalimumab also acts against TNF-α and leads to a marked reduction in the levels of cytokine and inflammatory indices, specifically C-reactive protein (CRP) and fibrinogen, in patients with rheumatoid arthritis. Recently a new MA active against TNF-α, golimumab, with a mode of action similar to infliximab, has been introduced. It is administered subcutaneously (sc) once a month, alone or in combination with methotrexate for the treatment of rheumatoid arthritis, psoriatic arthritis and active ankylosing spondylitis. [11, 12]

Palivizumab [a respiratory syncytial virus (RSV)-neutralizing MA]

The RSV belongs to the genus Pneumovirus and the family of Paramyxoviridae. RSV is the cause of severe infections in children and adults. Palivizumab binds RSV F protein and is the first MA to be used for prophylaxis against RSV.[13]

Eculizumab (against CD5)

Eculizumab, which acts against terminal complement protein C5, has been recently used to treat haemolytic-uraemic syndrome (HUS) due to infection with Escherichia coli producing Shigatoxin (STEC-HUS), characterized by thrombotic microangiopathy.[14]

MA for the treatment of severe asthma

Omalizumab, mepolizumab, pitrakinra, daclizumab

Omalizumab is a humanized monoclonal antibody that binds circulating IgE, thus preventing it from binding to its specific high-affinity receptor on mast cells and basophils. Omalizumab treatment in patients with allergic asthma improves symptoms and reduces the number of exacerbations.[15] Mepolizumab is an anti-interleukin-5 (IL5) monoclonal antibody, pitrakinra is a recombinant protein that binds IL-4Ra and daclizumab binds to CD25 inhibiting binding to IL-2 and subsequent activation of T lymphocytes.[16-18] Daclizumab is indicated for transplant patients as part of the treatment against graft rejection, it has been used for the treatment of multiple sclerosis (MS), and although bronchial asthma is not among its primary indications, it is currently also being used for asthma control.

MA under development

MA (against CD26)

CD26 is a surface glycoprotein acting as a dipeptidyl peptidase IV involved in T-lymphocyte activation and is implicated in the development of malignancies in humans (mesothelioma, kidney cancer). The MA against CD26 is under development and it causes cell lysis in malignant mesothelioma by inhibiting TNF-α and transposing CD26 from the cell surface to the nucleus, acting as an inhibitor of the growth of malignant cells. [19]

Infections in patients treated with MA

The attributable risk of infection after treatment with MA is hard to estimate, because it is impossible to know whether the infection develops because of the main disease (malignancy or autoimmunity) or the co-administration of immunosupressants and MA, or both. [20] Infective complications after MA treatment include infections caused by common bacteria, viruses (including hepatitis), invasive fungal disease, tuberculosis and opportunistic infections, due mainly to Pneumocystis jirovecii.

Herpes virus infections

Cytomegalovirus infection (CMV)

CMV infection may be manifested as pneumonia, enteritis, encephalitis, retinitis, hepatitis or bone marrow depression, and it has been associated with various MA, including anti-TNF-α derivatives (TNF-α controls CMV replication), infliximab, alemtuzumab and rituximab. [21]

Bone marrow transplant recipients, patients with lymphoproliferative disease and those with chronic lymphocytic leukaemia are at greatest risk. Effective monitoring and management of these patients require:

Weekly PCR testing of the CMV viral load or pp65 testing for CMV antigenaemia (the 4th week of treatment is considered critical due to the peak of lymphopenia)

Antiviral prophylaxis (valgaciclovir, acyclovir in high doses, valacyclovir) during MA treatment and for at least 2 months after the end of treatment

Treatment of symptomatic patients with CMV antigenaemia or positive PCR with valacyclovir and valgaciclovir, as along with interruption of MA treatment (MA treatment can be reinstituted after the successful completion of anti-CMV treatment). [22]

In the case that the viral load increases while the patient remains asymptomatic, pre-emptive treatment without predetermined duration should be considered (usually administered for 14-21 days and until the viral load is zeroed).

Epstein - Barr virus (EBV) and Infectious Mononucleosis

EBV belongs to the family of herpes viruses and causes infectious mononucleosis in young people and malignant diseases (nasopharyngeal carcinoma, Burkitt's lymphoma and Hodgkin's disease) in immunocompromised patients by infecting B- and T-lymphocytes. EBV infection of transplant patients who are treated with MA (mainly with alemtuzumab and anti-TNF-a agents) may lead to the development of post-transplant lymphoproliferative disease (PTLD).[23] If the organ transplant recipients are EBV seronegative and the organ donors are EBV seropositive, monitoring of the recipients with a quantitative molecular method for detection of EBV DNA is mandatory every month for one year after start of treatment with MA. [23] In the event that EBV DNA is detected in a seronegative transplant recipient, immunosuppressive therapy should be reduced and frequent monitoring of EBV DNA levels is required, but it is not yet clear whether MA treatment should be stopped.[24] When PTLD develops, the MA rituximab may be used as treatment, with a 50% response rate, although side effects are common (suppression of CD20 antigen on malignant B-lymphocytes, etc.).[24]

Varicella-Zoster (VZV) infection

Treatment with infliximab, adalimumab and etanercept is associated mostly with new VZV infection or VZV reactivation. [21] Patients developing VZV should be treated with acyclovir or valaciclovir and MA should be stopped, but can be re-administered once the blisters are gone.[25] Vaccination is contraindicated, as because the vaccine contains live viruses its use in patients on immunosuppressive treatment or anti-TNF-α agents is not safe.[21,25]

Herpes simplex virus (HSV) and human herpes virus 8 (HHV-8) infections

HSV and HHV-8 (HHV-8/KSHV) have been implicated in sporadic cases of infections after treatment with infliximab, adalimumab and rituximab.[21,26]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections

HBV reactivation is very common in patients treated with rituximab, infliximab, etanercept and adalimumab. Patients who are candidates for MA treatment should be tested for HBV surface antigen (HBsAg) and when this is detected they should receive prophylaxis with nucleotide analogues, starting one week before MA treatment. For HBV prophylaxis the following agents may be administered: (a) lamivudine 100mg PO once daily when HBV DNA levels are low (duration of treatment may be up to one year) and (b) tenofovir 300 mg/day PO, or entecavir (0.5-1.0 mg/day PO, if HBV DNA are above 2000 IU/mL, and the duration of treatment should be more than one year.[27] This strategy is proposed in order to avoid drug resistance, which could emerge through mutations of

HBV DNA polymerase. In patients whose serum shows HBsAg (-) and HbcAg (+) (i.e., anti-hepatitis B core antigen), indicative of a previous infection, close monitoring of serum HBV DNA by quantitative methods is mandatory, along with prophylaxis, even if DNA levels are low (<100 copies/mL).[27] MA treatment in these patients should be stopped, while the outcome depends on the viral load detected on diagnosis. Anti-TNF-α agents (infliximab, etanercept) and rituximab appear to be fairly safe for HCV positive patients.[28]

Tuberculosis (TB)

The risk of active TB is high in patients with inflammatory arthritis, mainly rheumatoid, and is further increased up to 25fold during treatment with MA. The progression from latent TB to active disease is the principal mechanism for TB development on treatment with MA. TB activation has been associated mostly with the use of TNF-α blockers (the risk is higher with infliximab and adalimumab than with etanercept), as TNF-α comprises an important mediator for immune response against M. tuberculosis and other intracellular bacteria.[29] The mechanisms responsible for TB reactivation are complicated because they involve many different pathogenetic pathways and immune cells, with the attenuation of T-cell memory and the inhibition of the protective action of complement being the principle mechanisms.[30]

The tuberculin skin test (PPD), which detects cell immunity response and the IGRA tests, which detect the in vitro IFN-γ production from circulating macrophages, are useful for the diagnosis of TB in these patients.[31] These tests, however, have limitations: the PPD test has a low specificity for active TB disease in patients with previous BCG vaccination and the IGRA tests often show "indeterminate results" in patients with autoimmune inflammatory diseases.[31]

Patients treated with MA should undergo screening testing for latent TB and posteroanterior and lateral chest X-rays.[32] Screening tests, in association with the results of PPD and IGRAs, should guide the decision as to whether to start treatment for latent infection or active TB disease. Treatment of latent TB includes various therapeutic combinations (depending on the country): isoniazid 300 mg daily for 6-12 months, isoniazid plus rifampicin for 3 months or rifampicin for 4 months.[32] The 9 months regimen of isoniazid 300 mg daily is the most popular treatment of latent TB and it must be started 4 weeks before MA administration (Table 2).

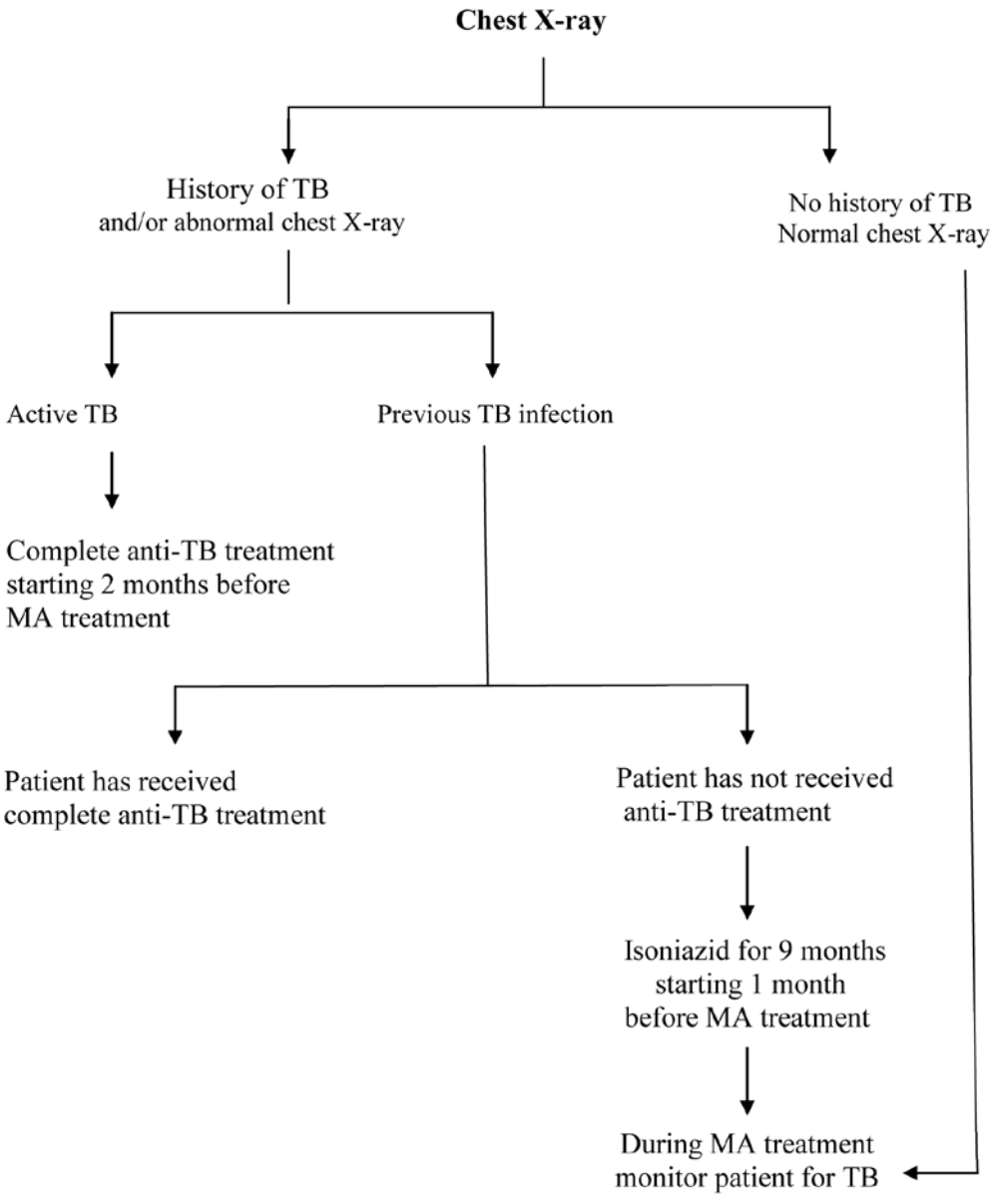
Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia is a serious complication in patients treated with chemotherapy or immunosuppressants (fludarabine, alemtuzumab, rituximab etc.)[33]. Until recently it was considered an infrequent complication, but its incidence appears to be increasing due to the use of more aggressive chemotherapeutic protocols and new immunosuppressive drugs (e.g., dose-dense chemotherapy, where treatment is administered at shorter intervals than usual).[34] In particular, in case series of patients treated with CHOP or R-CHOP 14 schemes (cyclophosphamide, adriamycin, vincristine and prednisone, with or without rituximab every 2 weeks instead of 3 weeks) a high incidence (up to 11%) of microbiologically confirmed Pneumocystis jirovecii pneumonia has been reported. Possible reasons for this include: a) frequent use of high dose steroids and immunosuppressants (B-cell suppression), and b) the pharmacokinetics of the agents used (i.e., macrophages and monocytes absorb more drug, alter their immune response and the tumour cells are exposed to a larger quantity of drug resulting in a more effective treatment).[35-38] Although the available data are limited, prophylaxis for Pneumocystis jirovecii pneumonia in patients treated with dose-dense chemotherapy is standard (trimethoprim–sulfamethoxazole, 3 times weekly), unless chemotherapy is administered in 3 week cycles, in which case Pneumocystis prophylaxis is not necessary.

Fungal Infections

MA treatment is strongly associated with fungal infections, although clinical documentation is limited and the relevant data concern mainly the anti-TNF-a agents (etanercept, infliximab, adalimumab and rituximab)[39]. Inhibition of IFN-γ production, reduced transcription of receptors and a reduction in the rate of white blood cell apoptotis are considered to be possible mechanisms of fungal infection in patients under treatment with etanercept, infliximab and adalimumab. The possible mechanisms of action for rituximab are hypogammaglobulinaemia, neutropenia, attenuated B-cell activity (i.e., poor antibody response to new antigens) and possible T-cell interaction[40,41]. Risk factors for fungal infections are graft versus host disease, a previous history of invasive aspergillosis or other invasive fungal infection, fungal colonization, environmental exposure, travelling to high risk areas for endemic mycoses (e.g. histoplasmosis, coccidiomycosis) and high risk activities (construction work,

TABLE 2. Follow up for detection of tuberculosis (TB) infection of patients receiving monoclonal antibodies (MA).



etc.)[42]. Filamentous fungal infections (specifically 64 cases of aspergillosis) have usually been reported in patients suffering from haematological malignancies and after bone marrow transplantation (75%). Yeast infections and Cryptococcus spp. infections have been reported in 64 and 28 cases respectively. Four cases of zygomycates and a small case series of endemic mycosis complicating MA treatment have also been reported (coccidiomycosis 29 cases, histoplasmosis 84 cases, blastomycosis 2 cases and sporotrichosis 1 case)[42-50].

In conclusion, treatment with MA constitutes a promising modern approach to the management of human malignancies and inflammatory diseases. The increasing use of MA during the past few years,however, has been associated with the development of infections, considered to be the result of an altered immune response. Prevention of these infective complications is based on careful clinical evaluation of patients before treatment and close monitoring of the parameters associated with infections during their treatment.

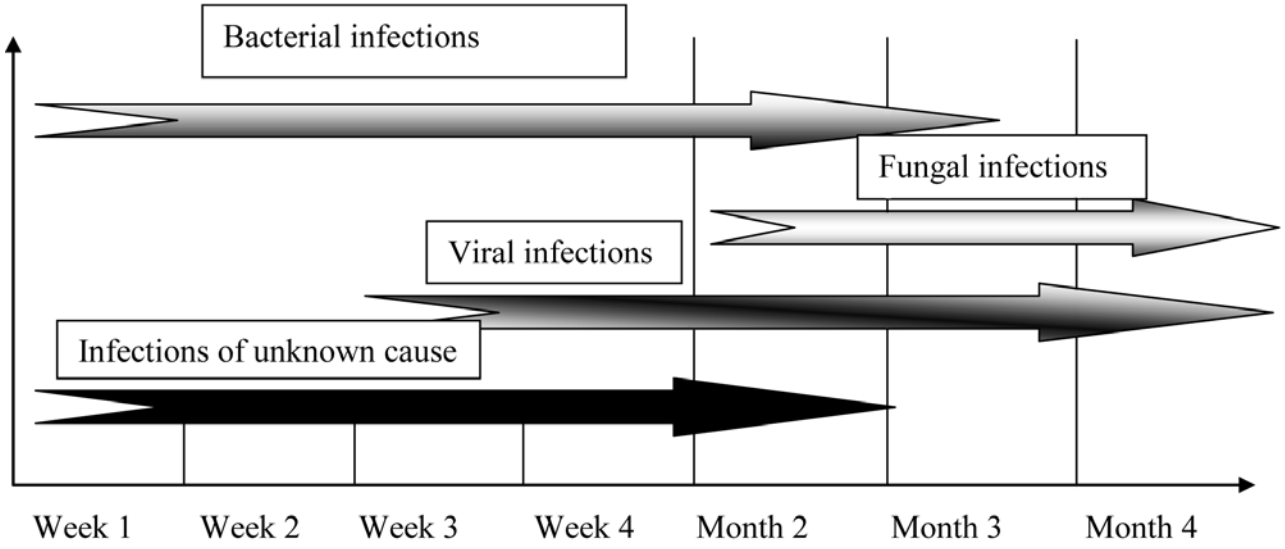


FIGURE 1. Infections in patients receiving monoclonal antibodies with respect to time and immune response. In the first 4 weeks from the start of treatment bacterial, viral and infections of unknown cause are common, while during the 2nd month fungal infections develop.

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