Attachment

Table 3: Associations between certain immunosuppressive/antineoplastic active substances and their target structures and a selection of infectious complications [474], [475], [476], [477], [478]

Target molecule (active substances*)	Specific infectious complications
TNF-α (infliximab, adalimumab, golimumab, certolizumab pegol, etanercept)	• Reactivation of latent tuberculosis • Reactivation of other granulomatous infections • Reactivation of chronic hepatitis B • Increased risk of severe and potentially fatal fungal infections
IL-1α, IL-1β (anakinra, canakinumab, gevokizumab, rilonacept)	• General increase in the risk of infection • Theoretically increased risk of reactivating latent tuberculosis
IL-5 (mepolizumab, reslizumab)	• No association with specific infections reported to date
IL-6 (tocilizumab, siltuximab)	• General increase in the risk of infection • Reactivation of VZV • Reactivation of chronic hepatitis B • Reactivation of latent tuberculosis
IL-12, IL-23 (common p40 subunit, ustekinumab, risankizumab, guselkumab)	• Slightly increased risk of reactivating VZV • Slightly increased risk of reactivating chronic hepatitis B • Theoretically increased risk of reactivating latent tuberculosis • Tinea infections (tinea pedis, tinea cruris, tinea corporis, pityriasis versicolor, tinea manuum, onychomycosis) with risankizumab
IL-17 (secukinumab, ixekizumab, brodalumab)	• Slightly increased risk of mucocutaneous candidiasis
IgE (omalizumab)	• Possibly increased risk of parasitic infections (geohelminths, case reports)
Complement component C5 (eculizumab, ravulizumab)	• Infections with o *Neisseria meningitidis* o *Neisseria gonorrhoeae* • Other bacterial infections, including *Streptococcus pneumoniae* and *Haemophilus influenzae B*
VEGF-A, VEGF-B, PIGF (bevacizumab, panitumumab, aflibercept)	• General increase in the risk of infection, most likely due to neutropenia • Increased risk of gastrointestinal perforation with secondary peritonitis and bacteraemia
VEGFR-2, tyrosine kinase domain of VEGFR (ramucirumab, sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib)	• Only ramucirumab; like VEGF-A and VEGF-B
EGFR/HER1 (cetuximab, panitumumab)	• General increase in the risk of infection, most likely due to neutropenia • Superinfection of the papulopustular rash
ErbB2/HER2 (trastuzumab, trastuzumab emtansine, pertuzumab)	• No association with specific infections reported to date
Tyrosine kinase domains of EGFR/HER1, ErbB2/HER2 and other members of the ErbB family (erlotinib, gefitinib, afatinib, neratinib, lapatinib, osimertinib)	• No association with specific infections reported to date
BCR-ABL, c-KIT, others (imatinib, dasatinib, nilotinib, bosutinib, ponatinib)	• Invasive fungal infections • Reactivation of VZV • Reactivation of latent tuberculosis • CMV reactivation/infection (particularly dasatinib)
Ras/Raf/MEK/ERK (vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, selumetinib)	• No association with specific infections reported to date

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Target molecule (active substances*)	Specific infectious complications
Bruton's tyrosine kinase (ibrutinib, acalabrutinib)	• *Pneumocystis jirovecii* pneumonia • Invasive fungal infections • Progressive multifocal leukoencephalopathy (ibrutinib)
Ras/PI 3-kinase/Akt/mTOR (idelalisib, buparlisib, rigosertib, duvelisib)	• *Pneumocystis jirovecii* pneumonia • Invasive fungal infections • CMV reactivation/infection
BCL2 (venetoclax)	• No association with specific infections reported to date
JAK/STAT (ruxolitinib, tofacitinib, baricitinib)	• *Pneumocystis jirovecii* pneumonia • Reactivation of VZV • Reactivation of latent tuberculosis • CMV reactivation/infection • EBV reactivation/infection • Progressive multifocal leukoencephalopathy
Ras/PI 3-kinase/Akt/mTOR (sirolimus, everolimus, temsirolimus)	• Reactivation of VZV • Reactivation of latent tuberculosis
Histone deacetylase inhibitors (vorinostat, panobinostat, romidepsin)	• No association with specific infections reported to date
CD19 (blinatumomab)	• Reactivation of HSV • Reactivation of VZV • *Pneumocystis jirovecii* pneumonia • Reactivation of chronic hepatitis B
CD20 (rituximab, obinutuzumab, ofatumumab, veltuzumab, ocrelizumab)	• Neutropenia risk • Possibly *Pneumocystis jirovecii* pneumonia • Reactivation of chronic hepatitis B • Reactivation of hepatitis C • Enteroviral infections • Progressive multifocal leukoencephalopathy
CD52 (alemtuzumab)	• Reactivation of HSV • Reactivation of VZV • Reactivation of Epstein-Barr virus • Reactivation of chronic hepatitis B • At higher doses for indications other than multiple sclerosis also *Pneumocystis jirovecii* pneumonia, invasive fungal infections, reactivation of JC and BK polyomavirus, neutropenia • At lower doses for multiple sclerosis also human papillomavirus, reactivation of latent tuberculosis, listeriosis and candidiasis
CD22 (epratuzumab, inotuzumab ozogamicin)	• No association with specific infections reported to date
CD30 (brentuximab vedotin)	• Neutropenia • Reactivation of chronic hepatitis B • CMV reactivation/infection • Progressive multifocal leukoencephalopathy
CD33 (gemtuzumab ozogamicin)	• No association with specific infections reported to date
CD38 (daratumumab)	• Neutropenia • Reactivation of VZV
CD40 (dacetuzumab)	• Neutropenia • Possibly infections comparable with those occurring in hyper IgM syndrome (*Pneumocystis jirovecii* pneumonia, CMV reactivation/infection, invasive fungal infections, protozoa)
CD319 (elotuzumab)	• Reactivation of VZV

Target molecule (active substances*)	Specific infectious complications
CCR4 (mogamulizumab)	• Possibly neutropenia • Reactivation of chronic hepatitis B • CMV reactivation/infection
CTLA-4 (ipilimumab, abatacept)	• Reactivation of latent tuberculosis • Listeriosis • Secondary infections caused by supportive treatment with corticosteroids: *Pneumocystis jirovecii* pneumonia, invasive aspergillosis
PD-1, PDL-1 (nivolumab, pembrolizumab, atezolizumab)	• Reactivation of latent tuberculosis • Listeriosis • Secondary infections caused by supportive treatment with corticosteroids: *Pneumocystis jirovecii* pneumonia, invasive aspergillosis
LFA-3/ CD2 (alefacept)	• No association with specific infections reported to date
Integrins (natalizumab, vedolizumab)	• Progressive multifocal leukoencephalopathy (natalizumab) • *Clostridioides difficile* (vedolizumab)
Sphingosine-1-phosphate receptor (fingolimod, siponimod, ozanimod)	• Reactivation of VZV • Cryptococcal meningitis • Progressive multifocal leukoencephalopathy • Human papillomavirus (ozanimod)
Proteasome inhibitor (bortezomib, carfilzomib, ixazomib)	• Reactivation of VZV • Respiratory illnesses • Complications after influenza

*Active substances are grouped together for methodological reasons. There may be significant differences in the risk of specific infectious complications between individual active substances in these groups.

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Table 4: Pathogens causing invasive infections in immunocompromised patients

Neutropenia	• Coagulase-negative staphylococci (CoNS, e.g. *Staphylococcus epidermidis*) • *Staphylococcus aureus* • α-haemolytic (viridans) streptococci (e.g. *Streptococcus mitis*) • *Enterococcus faecium* • Enterobacteriaceae (*Escherichia coli, Enterobacter* spp.*, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus* spp.*, Serratia marcescens)* • Non-fermenters (*Achromobacter xylosoxidans, Acinetobacter baumannii, Burkholderia cepacia, Pseudomonas aeruginosa, Ralstonia pickettii, Stenotrophomonas maltophilia)* • *Legionella* spp. • Fungi (*Aspergillus* and *Candida* spp., Mucoraceae)
T-cell defect	• Mycobacteria (particularly *Mycobacterium tuberculosis* but also nontuberculous mycobacteria (NTM) such as *Mycobacterium avium, Mycobacterium fortuitum, Mycobacterium marinum, Mycobacterium septicum,* etc.) • *Listeria monocytogenes* and *Nocardia* spp. • Viruses (CMV, HSV, VZV, HHV-6, RSV, HMPV, ADV, polyomaviruses, e.g. BK virus) • Fungi (and *Cryptococcus* spp., *Pneumocystis jirovecii*) [479], [480] • Parasites (e.g. *Toxoplasma gondii* or *Cryptosporidium parvum / Cryptosporidium hominis*) [481], [482].
Antibody deficiency	• Mainly encapsulated bacteria, e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae* • Viruses (CMV, HSV, norovirus, rotavirus, adenovirus) • Fungi (*Candida* spp.)
Splenectomy/ functional asplenia	• Capsule-forming bacteria (e.g. pneumococci*, Haemophilus influenzae, Neisseria meningitidis*) • *Salmonella enteritidis*, *Salmonella typhimurium*
Others	
Mucositis of the gastrointestinal tract	• α-haemolytic (viridans) streptococci (e.g. *Streptococcus mitis*) • *Clostridioides difficile* (and very rarely: *Clostridium septicum)* • *Enterococcus faecium* and *Enterococcus faecalis* • *Leuconostoc* spp.*, Rothia mucilaginosa* • *Campylobacter jejuni*
Skin lesion/ venous catheter infection	• Coagulase-negative staphylococci (CoNS, e.g. *Staphylococcus epidermidis*) • *Staphylococcus aureus* • *Corynebacterium* spp. • *Pseudomonas aeruginosa* (Ecthyma gangrenosum), *Stenotrophomonas maltophilia* • Very rarely: Nontuberculous mycobacteria • Fungi (*Aspergillus* spp.)

Table 5: General information on the prevention of food-related infections (and for food preparation by patients in all risk groups and their companions) [5], [58], [59], [60], [163]

Food	High risk	Low risk
Meat including poultry, fish	Raw or insufficiently cooked (e.g. sashimi, insufficiently cooked seafood such as mussels or prawns) • Raw minced pork, tartar and similar foods made of raw minced meat • Raw sliced meat such as carpaccio • Spreadable short-aged raw sausage (e.g. made from raw minced pork and/or beef, Braunschweiger smoked sausage) • Hard salami	Sufficiently cooked[a] (meat that is white or brown in the middle after cooking, clear juices)
Eggs and egg products	Raw or insufficiently cooked	Eggs: hard-boiled egg white and yolk (at least 8 min); if the recipe calls for raw eggs, use pasteurised egg products (e.g. liquid egg)
Dairy products like quark and cheese	Products made from unpasteurised (raw) milk, surface-ripened[b] cheese, whether it is pasteurised or not (e.g. sour milk cheese, Harzer, Mainzer, yellow cheese, Olomouc, Limburger, Münster, Tilsit, etc.)	Products that have at least been pasteurised
Salad	Buffet-style salad bar Raw sprouts	Salad that has been carefully washed and freshly prepared
Water/ice	Tap water that has not been filtered or boiled, still mineral water	Drinking water monitored by infection control specialists (for *Pseudomonas aeruginosa*, etc.); drinking water that has been boiled or filtered with a 0.2 µm filter, tea made with sufficiently boiled water (rapid boil for 1 min)
Fruit and vegetables	Not cleaned or washed	Well washed (perhaps cleaned with a soft brush or peeled)
Nuts		Only vacuum-packed, roasted, shelled nuts; consume within 24 hours
Muesli	Large pack	• Small patient-specific pack consumed within a week • In risk groups 2 and 3, autoclaved individual portions
A selection of basic hygiene rules for food handling		
• Pay attention to best-before dates and do not use damaged packs. • Wash hands with soap before preparing food (disinfect hands after touching potentially contaminated meat or fish products). • Use fresh meat and fish within 2 days. • Have separate "unclean" (raw meat, unwashed vegetables, etc.) and clean areas; different areas (and kitchen utensils) for preparing raw meat/poultry/fish, vegetables and other foods. • Store food in a refrigerator with adequate refrigeration (4-8°C). • Store leftover food (including opened fruit juices) in a refrigerator and only for short periods (no more than 24 hours) or freeze and cook thoroughly before eating. • Crockery is best cleaned in a dishwasher (at least 65°C). • Do not use a sponge to wash up, clean kitchen surfaces with disposable wipes, wash kitchen textiles at a minimum of 60°C and iron after drying.		

[a] Core temperature at least 75˚C.

[b] *Brevibacterium* spp., micrococci and yeasts are used to ripen soft cheese and sour milk cheese. During ripening, these cheeses develop a yellowish or reddish-orange surface smear.

Table 6: Selection of infectious agents isolated in zoonotic diseases [61], [62], [63], [310], [311], [312], [313], [314], [315], [316]

Animal species	Zoonotic disease/pathogen
Dog	• *Capnocytophaga canimorsus*, *Pasteurella multocida* (bite wound, wound infection, sepsis; also transmitted though kissing animals, face/wound licking) • Methicillin-resistant *Staphylococcus aureus* • Parasites: intestinal parasites (*Cryptosporidium parvum, Cryptosporidium hominis*), microsporidiosis (*Microsporidium canis*) • Fungi (*Trichophyton mentagrophytes*)
Cat	• Cat scratch disease, peliosis hepatis, bacillary angiomatosis (*Bartonella henselae,* other *Bartonella* spp.), leptospirosis (*Leptospira interrogans, Leptospira icterohaemorrhagiae*), *Pasteurella multocida* • Parasites: toxoplasmosis (*Toxoplasma gondii*) • Fungi: *Malassezia pachydermatis* [483, 484], microsporidiosis (*Microsporidium canis), Trichophyton mentagrophytes,* Sporotrichosis (*Sporothrix schenckii*)
Reptiles (tortoise, snake, gecko)	• Salmonellosis (rare serovars) Caution: chronic shedding!
Hens/poultry	• *Campylobacter* infections • Salmonellosis
Calves, pigs, animal feed	• *Staphylococcus aureus* • *Campylobacter* infections • Yersiniosis, salmonellosis • Enterohaemorrhagic *Escherichia coli* (haemolytic-uraemic syndrome)
Calves, lambs	• Giardiasis (*Giardia lamblia*)
Lambs, flocks of sheep	• Q fever (*Coxiella burnetii*)
Fish tanks	• Atypical mycobacteria (*Mycobacterium marinum*) • *Pseudomonas aeruginosa* and other opportunistic pathogens associated with water
Wild mice	• *Streptobacillus moniliformis* • Hantaviruses
Rats, dogs, mice, hedgehogs	• Leptospirosis (*Leptospira icterohaemorrhagiae*)
Doves	• Cryptococcosis *(Cryptococcus neoformans)*
Budgerigars, parrots	• Psittacosis, parrot fever (*Chlamydia psittaci)*
Horses	• *Rhodococcus equi* (atypical pneumonia) • Aspergillus and other moulds
Mice, guinea pigs, hamsters	• Lymphocytic choriomeningitis (LCM virus)

Compilation 1:

A selection of measures for preventing zoonotic diseases when handling pets [61], [63], [316], [485], [486]

- Hand hygiene (wash with water and soap solution or disinfect the hands) after touching the animal or objects contaminated by the animal (caution: dry food can also be heavily contaminated with pathogens).
- Do not leave small children alone with the pet (supervise contact).
- Do not feed the animal raw meat where possible.
- Do not feed the animal in the kitchen.
- Do not let the pet in the bedroom (or sleep in the same bed).
- Do not kiss the animal and do not get licked (especially wounds). Clean and disinfect scratches and cover with a sterile plaster.
- Do not let immunosuppressed patients clean cat litter trays – clean daily – (bird cages or fish tanks) or wear protective clothing (gloves, FFP2 mask).
- Wash dog blankets and similar textiles at a minimum of 60°C.
- Keep cats in the house where possible.
- Do not let dogs off the lead outside the home.
- Do not acquire any new animals (particularly animals under 6 months old) during immunosuppressive therapy.
- Have the pet checked by a vet and take it to the vet at the first signs of an infection. Inform the vet that a member of the household is immunosuppressed.
- Do not linger in a stable (groom the horse, etc.) for as long as there is an increased risk of invasive fungal infections.

Compilation 2

Possible (a selection of) starting points for antibiotic/antifungal stewardship programmes in immunosuppressed patients

Interdisciplinary development, implementation and evaluation (plan-do-check-act cycles) of internal guidelines on the following subjects

- medication to prevent infection (bacteria, fungi), including in patients with asplenia,
- diagnostic testing and treatment of fever without a focus during neutropenia,
- diagnostic testing and treatment of sepsis during neutropenia or immunosuppressive therapy,
- prevention (in general: prevention bundles for NI [see relevant KRINKO recommendations]), diagnostic testing and treatment of intravascular catheter-related infections,
- empirical (or pre-emptive) treatment with antifungals,
- diagnostic testing, treatment and prevention of CDI,
- diagnostic testing and treatment of bloodstream infections caused by *S. aureus* (including MRSA),
- diagnostic testing and treatment of bloodstream infections caused by *Candida* spp.,
- perioperative antibiotic prophylaxis in patients undergoing chemotherapy and surgical interventions,
- restriction of the use of carbapenems and glycopeptides.

Establishing an ongoing surveillance and reporting system for

- selected nosocomial infections,
- pathogen and resistance statistics (invasive isolates),
- pathogen and resistance statistics (from screening materials),
- the use of anti-infectives, and specifying how the results of this surveillance will be handled by the interdisciplinary team and used to identify any action that needs to be taken.

Preparing an in-house list of anti-infectives with specific information on

- dosage and administration (example: prolonged or continuous administration of certain beta-lactam antibiotics) and the most important adverse reactions and interactions,
- particular anti-infectives which usage should be restricted (where appropriate, only after approval or with a compulsory follow-up review in the form of an infectious diseases consultation),
- drug monitoring, where use of a particular anti-infective requires this.

Strategies for adapting antibiotic treatment
(selecting the most suitable anti-infectives, methods of administration, dosage details, duration of treatment)

- to the patient's risk profile
  (e.g. oral outpatient vs intravenous inpatient treatment),
- to a pre-existing colonisation (or known previous infections) with certain multidrug-resistant pathogens (MRSA, MRGN, VRE),
- because of possible drug interactions (co-medication) or organ dysfunction (e.g. kidney failure, inner ear hearing loss, neuropathy),
- to confirmed pathogens and known antibiotic susceptibility (de-escalation).

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