Complications of Immunosuppression in Pediatric Surgery

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Contents

Introduction ............................................................................................................. 2
Impact of the Underlying Disorder on Immunosuppression-Related Complications During and After Surgery ......................................................... 4
Immunodeficiency Syndromes ........................................................................ 4
Malignoma ........................................................................................................ 5
Impact of Therapeutic Immunosuppression ....................................................... 6
Chemotherapy ..................................................................................................... 6
Radiotherapy ........................................................................................................ 8
Immunosuppressive Therapy .............................................................................. 8
Case Reports ......................................................................................................... 9
A 13-Year-Old Boy with Relapsing Liver Abscesses ......................................... 9
12-Year-Old Girl with a Big Lump in the Proximal Thigh .................................... 9
Conclusions and Future Directions ................................................................. 10
Cross-References ................................................................................................. 10
References ......................................................................................................... 10

Abstract

An intact immune system is required to distinguish between self and nonself, as well as between dangerous and non-dangerous signals to maintain a homeostasis of regenerating tissues and to avoid invasion of pathogens into an organism. Any immunodeficiency disorder, whether primary (inborn) or secondary immunodeficiency, due to immunosuppressive or cytotoxic treatment, may therefore increase the risk of perioperative complications in pediatric surgery.

This chapter defines underlying conditions such as leukemias, solid tumors, autoimmune diseases, and inborn errors of immunity such as immunodeficiency syndromes as well as treatment modalities, e.g., cytotoxic chemotherapy, radiotherapy, hematopoietic stem cell transplantation, and pharmacological immunosuppression, that represent potential reasons for an increased risk of local, endoprosthetic,
and systemic infections and wound healing complications in pediatric patients. The mechanism of action of most commonly used therapeutic agents in pediatric oncology and patients with autoimmune diseases like corticosteroids, chemotherapy, biologicals, small compounds, etc. and their potential adverse effects (e.g., immunosuppression, impairment of collagen synthesis, antiproliferative effects) on the perioperative course of children are described.

In conclusion, planning and scheduling of any surgical treatment in immunocompromised children and adolescents should include the analysis of absolute neutrophil counts; the concentration of immunoglobulin G, platelet counts, and plasmatic coagulation; and an assessment of the functional impairment of inflammation regulation and immunity conferred by pharmacological treatment. These facts then need to be put in the context of current scientific evidence and allow for a risk-minimizing multidisciplinary planning of surgery and supportive care.

Keywords
Immunodeficiency · Immunosuppression · Chemotherapy · Complication · Tumor surgery · Pediatric surgery · Radiotherapy · Hematopoietic stem cell transplantation · Wound dehiscence · Wound infection · Wound healing

Introduction
Immunosuppression of children or adolescents undergoing surgery may impose an increased risk of postoperative complications like infections (including endoprosthetic infections) and impaired wound healing. Thus, similar to the assessment of the hematocrit, coagulation parameters, and platelet counts, it is relevant for the surgeon to be aware of potential factors that could compromise the patient’s immunity, before performing pediatric surgery.

Immunosuppression relevant to a pediatric surgery procedure may stem from (i) an underlying disorder that involves the immune system (e.g., an inborn error leading to primary immunodeficiency or an acquired immunodeficiency syndrome) or (ii) from pharmacological immunosuppressive treatment (e.g., in the context of oncological therapy or of autoimmunity-directed drugs). Figure 1 provides a sketch of the potential surgical complications, together with their underlying reasons and imposed risks, of immunocompromised children or adolescents.

Surgery is a key part of the treatment for many solid tumors. With exception of many brain tumors (see “Brain Tumors”), preoperative chemotherapy, sometimes also radiation, immune therapy, or hormone treatment, is recommended to reduce the tumor size, the tumor cell viability, and the reaction of the surrounding healthy tissue. The main aim of the conservative pretreatment is facilitation of the surgical procedure to follow and a reduction of the need to mutilate while enhancing the chance of radical tumor extirpation (see also “Neuroblastoma”, “Rhabdomyosarcoma”, “Osteosarcoma and Ewing Sarcoma”, “Renal Tumors”, “Rare Malignant Tumors”, and “Teratomas”). The period of this so-called neoadjuvant preparative treatment may last between weeks and months according to international treatment protocols, and it may be accompanied by various degrees of immunosuppression. Additionally, other (not tumor-targeted) surgical interventions may be necessary in immunocompromised oncologic or immunodeficient patients, like in the case of invasive organ infections (e.g., aspergilloma), gastrointestinal complications (e.g., appendicitis, ileus, pancreatitis, herniae), soft tissue infections (e.g., pseudomonas abscess), or other underlying anatomical problems that need to be tackled surgically in order to reduce the risk of long-term complications in future (e.g., vesicoureteral reflux, gastroesophageal reflux). While in the first scenario of neoadjuvant therapy, the immunologic “fitness” may be controlled to some extent by the timing of surgery, this may not be possible in the latter situation of an emergency procedure. Ideally, surgery in a cancer patient should be performed at a time point after hematologic recovery from the last
immunosuppressing treatment measure. Likewise, the following postoperative continuation of chemotherapy or radiation therapy should take place only when internal and external wounds are safely healing, inflammation parameters falling, and the clinical condition visibly recovering.

In addition to disease- and treatment-specific factors, more general risk factors apply to tumor-related pediatric surgery. A study on complications of tumor endoprosthesis surgery showed that the operation time, a high body mass index, the need of blood transfusions, intensive care, and postoperative hematoma were independent risk factors for endoprosthetic infections (Peel et al. 2014). Similarly, the body location of tumor surgery and a risk of seroma development have been shown to impose risks of infectious wound complications, which are, for example, higher in the proximal lower extremity adductor compartment than in other regions (Moore et al. 2014). Moreover, the notion that tissue oxygenation, trophic level, and thus wound healing may be impaired by smoking, diabetes, and obesity was confirmed in the same study (Moore et al. 2014).

Although the chapter title and key words like “immunosuppression AND surgery” may elicit expectations of an article on pharmacological rejection prophylaxis in organ transplantation and its complications, these rather transplantation-specific topics are tackled in other sections of this book (▶ “Principles of Transplantation”, ▶ “Renal Transplantation”, ▶ “Liver Transplantation”, ▶ “Lung Transplantation”, ▶ “Heart Transplantation”). Likewise, the unspecific immunosuppression due to surgery- and anesthesia-related stress will not be discussed in this article (▶ “Anesthesia and Pain Management”). Lastly, the potentially increased risk of thrombosis in cancer patients undergoing surgery or receiving surgically implanted central
venous lines should be considered another specific problem that is not directly related to immunosuppression and is thus not covered here. From the view of a pediatric hematologist-oncologist and immunologist, this chapter covers relevant aspects of primary or secondary immunodeficiency and its impact on perioperative care.

Consequences of an immunosuppressive pre-treatment or underlying conditions could involve adjustment of a surgical technique, modified supportive care, or eventually only rescheduling of the procedure. In many instances, however, there may not be a direct effect on the pre- and perioperative management, but only on the timing (or an interruption) of immunosuppressive treatment before and the continuation of treatment after surgery. Neutrophil counts may be raised therapeutically in immunocompromised patients under certain circumstances. Additionally, immunoglobulin G may be substituted prophylactically in case of hypogammaglobulinemia, which may otherwise constitute a risk of bacterial infections. The following section will define underlying risks and mechanisms of immunosuppression that could interfere with an optimal outcome in pediatric surgery.

Impact of the Underlying Disorder on Immunosuppression-Related Complications During and After Surgery

Immunodeficiency Syndromes

Primary Immunodeficiencies
Essentially all components of the immune system, such as T and B lymphocytes, NK cells, granulocytes, monocytes/macrophages, immunoglobulins, cytokines, or other signaling molecules and their corresponding receptors, and complement factors may be defective in certain inborn conditions and thus lead to a loss of the precise function, i.e., a specific primary immunodeficiency (PID). These diseases are classified according to the predominant immune phenotypical abnormality, and the list of PIDs is regularly updated (Tangye et al. 2020). While most patients with PID suffer from severe and recurring infections until they are diagnosed, some PIDs mainly lead to an increased risk of autoimmunity or to a hyperinflammatory state. Because the underlying disorder may be fully corrected by substitution therapy and thus be rendered irrelevant for any required future surgery, the most important thing to know for pediatric surgery of PID patients is the state and mode of treatment and the degree of correction of the PID. Thus, communication with the physician in charge of the pediatric immunology department prior to the procedure is highly recommended.

In case the underlying diagnosis of a patient with a history of infections or immune dysregulation, who fulfils the criteria of a probable PID (Farmand et al. 2011), is unclear, or if the disorder is not being treated or not treatable, at least two simple steps may help to estimate the peri-surgical risk: first, the medical history with a special focus on infections requiring intravenous antibiotic treatment, wound healing, umbilical cord detachment, family history, physical development and thriving, and previous surgical procedures should be taken. Second, the most relevant laboratory parameters in this context are the absolute neutrophil count and the serum immunoglobulin G concentrations. Functional tests include the neutrophil function (oxidative burst and phagocytosis) and concentrations of specific IgG antibodies directed against earlier infections or vaccinations. Determination of these lab values does not substitute for a consultation with a specialist for pediatric immunology, infectiology, or hematology-oncology and cannot replace a comprehensive immunologic workup. Lymphocyte subsets and functions will also be needed to estimate the degree and type of defect but might be of minor relevance for surgery. Additionally, the interpretation of the lab results may not be trivial. Nonetheless, if the predominant compartments of the immune system that are required for wound healing and fighting bacterial infections, namely, phagocytes and B cells/antibodies, work normally, the most frequent PIDs that potentially imply an increased risk for surgery may be considered excluded with high likelihood.
Secondary and Acquired Immunodeficiency

Barriers of the body, like the skin, mucous membranes, secretions, gastric acid, or anatomical structures like the lymph system, anterograde laminar flow of air and liquids in the body, and the blood-brain barrier, are examples of protective measures of our organism against infections. Many of these may be disturbed in case of certain diseases or pathologic conditions, ultimately leading to an increased risk of infections. Anatomical malformations of the airways, the gastrointestinal or urinary tract, cilial dysfunction, etc. may reduce the effect of an intact immune system similar to a disturbed glucose metabolism in diabetes mellitus or impaired nutrition and oxygenation of tissues. Similarly, loss of lymph and proteins, e.g., in exsudative enteropathy, in intestinal lymphangiectasia, or in patients after Fontan surgery, may lead to a secondary immunodeficiency. In these patients, a careful evaluation of the immunologic risk factors and specific laboratory tests need to be undertaken on an individual basis.

The human immunodeficiency virus (HIV) causes progressive loss of T cell immunity if inefficiently or untreated, which ultimately leads to a highly increased risk of opportunistic infections and lymphoma. Of note, taking the considerable spectrum of side effects of antiviral treatment into account, a controlled HIV infection should not have a negative effect on peri-surgical risks or care.

Asplenia/Splenectomy

Patients without spleen function, e.g., patients with sickle cell disease, patients after spleen irradiation for Hodgkin’s lymphoma, or people with congenital asplenia, have a permanently increased risk of severe infections with encapsulated bacteria such as pneumococci, Haemophilus influenzae, or Neisseria species like meningococci. These risks should be taken into account when planning surgery. In case of an elective splenectomy, vaccination against these bacteria with conjugated polysaccharide-protein vaccines at least two, better 4–6 weeks prior to surgery is highly recommended. For pneumococci, a 13-valent conjugate vaccine should be preferred for the first dose and, according to current recommendations, ideally boosted with the 23-valent polysaccharide vaccine 2 months later (Lazarus et al. 2011) (ideally, still before surgery). Splenectomized people should carry an “asplenia-emergency card” and be treated with prophylactic antibiotics for many years after surgery. Given the lifelong risk of overwhelming post-splenectomy infection (OPSI), it is difficult to judge and has been studied with inconclusive results, at which time point, whether a certain number of years after surgery, or at a defined age of the patient, the antibiotic prophylaxis may be omitted.

Malignoma

The risk of malignancies is higher in patients with genetically determined inborn errors of immunity than in the general population (Hauck et al. 2018). The degree of tumor predisposition and the underlying cellular and molecular mechanisms vary through the categories of inborn errors of immunity (Kindler 2018).

Leukemias

Leukemia is the most common malignancy in children and adolescents. Because it is a disease of white blood cells, the manifestation of leukemia implies a certain degree of immunodeficiency even before initiation of steroid and/or cytostatic treatment. In acute lymphoblastic leukemia (ALL), there may be a relevant reduction of neutrophils due to replacement of normal hematopoiesis with leukemic blasts, which ultimately leads to (i) severe neutropenia and an increased risk of bacterial and fungal infections and (ii) to a reduction of all other blood cell compartments (i.e., erythrocytes, platelets, healthy lymphocytes, etc.) with corresponding clinical consequences. Thus, to estimate the degree of immunosuppression in ALL, it is highly recommended to assess absolute neutrophil counts. In the less frequent acute myeloblastic leukemias (AML), there is an additional concern that even in the presence of normal or increased numbers of white blood cells, the “remaining” leukocytes are dysfunctional. Therefore, the degree of impairment of antibacterial and antifungal complications...
immunocompetence is generally higher in patients with AML than in ALL.

**Lymphoma and Solid Tumors**

In contrast to malignoma of blood cell progenitors (and thus a primarily disturbed immune system), solid tumors rarely cause an immediate immunosuppression. With the exception of bone marrow infiltrating metastases yielding secondary myelosuppression, a direct effect of a solid tumor on the immune system is unlikely. Nevertheless, metastasizing tumors like neuroblastoma may present as systemic disease, and one of the first symptoms may be a severe infection, pallor, and bleeding tendency on the basis of pancytopenia due to bone marrow infiltration. In that scenario, neuroblastoma may resemble leukemia in its clinical symptoms and degree of immunosuppression.

Depending on the tissue type and the tumor location, an activation of hemostasis may occur and lead to the consumption of clotting and fibrinolysis factors, which are relevant risks to be assessed before surgery. While many types of lymphoma are treated with a cocktail of cytotoxic drugs and corticosteroids similar to that of lymphoblastic leukemias, the oncologic therapy of solid tumors varies widely with respect to the drugs, surgery, and radiotherapy used.

**Impact of Therapeutic Immunosuppression**

Table 1 provides an overview of the immunosuppressive and antiproliferative effects as well as the potential disturbance of protein synthesis required for wound healing of the most relevant drugs used in pediatric oncology and in children with autoimmune diseases (Table 1). In summary, physiological processes of “reparative” inflammation, hemostasis, and platelet function are necessary for wound healing, as well as fibroblast function, collagen and mucopolysaccharide synthesis, growth factors, proliferation, and migration of phagocytes. To avoid bacterial wound, endoprosthetic, deep organ, or systemic infections, immune functions such as those of the innate immune system (phagocytes, natural killer cells, dendritic cells) are needed. Secondly, the natural barriers of the body (epithelial surfaces, protective secretions, longitudinal flow of fluids and air) should be left as intact or restored during surgery as far as possible. Thirdly, the main component of the adaptive immune system that is required to fend off bacterial infections in the context of surgery is immunoglobulin G (IgG), the serum concentration of which can be easily checked before surgery in routine laboratories.

**Chemotherapy**

**Dose, Type, and Duration of Chemotherapy**

Although studies of surgery in bone and soft tissue tumors showed that neither chemotherapy, radiotherapy, nor episodes of febrile neutropenia were linked to an increased incidence of endoprosthesiis infections (Jeyes et al. 2005; Morii et al. 2010; Peel et al. 2014), it is recommendable that elective surgery including the tissue recovery and healing period thereafter should be planned to fall in a phase of a largely recovered hematopoietic system after chemotherapy. The nadir of blood cell counts may be estimated to occur usually 7–10 days after beginning of an intense dose chemotherapy regimen (e.g., a 1–5-day treatment element). Thus, very roughly, surgery may be planned 14–21 days after the first day of the latest chemotherapy, and, conversely, an interval of a maximum of 3–5 days before sufficient wound healing should be taken into account before continuation with postoperative chemotherapy. Some conditions, for instance, the need to destroy tumor cells that were potentially spread during surgery, may require an immediate administration of chemotherapy after surgery. In this situation, the postoperative care needs to be intensified. During planning and scheduling of surgery, the ideal time point may be determined when the pediatric oncologist communicates estimated phases of hematopoietic depression and immunosuppression and, conversely, the pediatric surgeon informs the oncologists of the time needed for wound healing and tissue recovery.
Hematopoietic Stem Cell and Organ Transplantation

There is an array of issues relevant for pediatric surgeons when hematopoietic stem cell transplantation recipients are concerned. However, most “surgical complications” such as gastrointestinal, catheter-related, ear, nose, and throat, and perianal complications may not require operative surgical intervention, as shown by a recent study (Anabtawi et al. 2011). The specific immunosuppression of hematopoietic stem cell transplantation may be simplified as a two-step process. Firstly, a more or less intensive (“myeloablative or “reduced intensity”) chemotherapy, also called conditioning treatment, is given to create space for donor cells to arrive in the recipient’s bone marrow, yielding a similar albeit typically more pronounced phase of pancytopenia as in many chemotherapy regimens described above. In this phase, similar precautions apply as in other patients with chemotherapy. Second, to reduce the risk of incompatibility reactions and graft-versus-host disease, a rather specific T cell-directed immunosuppression is administered from shortly before until many weeks or months after transplantation. There are various means to achieve T cell immunosuppression, the details of which go beyond the scope of this chapter. However, although strongly immunosuppressive in the strict sense (impairing antigen recognition, defense against viruses, fungi, and other opportunistic germs, reactivation of previous virus infections, induction of new antibody formation by B cells, etc.), the adverse effect on wound healing and reparative tissue proliferation of pharmacological immunosuppression typically used in hematopoietic stem cell transplantation is low. Nevertheless, given the underlying disease that indicated stem cell transplantation plus, most often, a history of vast polychemotherapy and antimicrobial therapies with potential irritation of various organ systems, patients within their first 6–12 months after hematopoietic stem cell transplantation have to be considered multi-morbid and thus as high-risk patients in the setting of pediatric surgery.

Organ transplantation, the long-term posttransplant immunosuppressive treatment aims to prevent rejection and may include other substances, such as mTOR inhibitors (see below), which may have a stronger impact on wound healing than the calcineurin inhibitor-based graft-versus-host disease prophylaxis of hematopoietic stem cell transplantation.

Table 1

| Immunosuppression | Corticosteroids (especially prolonged glucocorticoid treatment above Cushing threshold) | Chemotherapy (alkylating agents, antimetabolites, spindle toxins, topoisomerase inhibitors, cytotoxic antibiotics, etc.) | Radiotherapy | Small compounds* (kinase inhibitors, mTOR inhibitors, proteasome inhibitors, etc.) | Biologicals† (antibodies against cytokines or cell surface antigens, cytokine receptor antagonists, depleting enzymes) | Immune modulators*, immunosuppressants (calcineurin inhibitors, mycophenolate mofetil, anti-thymocyte globulin, etc.) |
|-------------------|---------------------------------|-------------------------------------------------|-------------|---------------------------------|---------------------------------|------------------------------------------------|
| Impairment of protein synthesis (collagen, clotting factors, etc.) | † | † | † | † | † | Not generally observed |
| Antiproliferative effect | † | † | † | † | † | Not generally observed |
| Recommended measure and/or caveat | Consider (slow) dose reduction below Cushing threshold or discontinuation (if possible without bout of disease) | Check absolute neutrophil count and trend before surgery; consider interval for healing after surgery | Effect depends on location and dose; be aware of prolonged impact | Effect depends on specific pathway of action; limited experience with novel substances; consider pause | Effect depends on specific pathway of action; consider interval from surgery | Lymphocyte-directed treatment alone may have limited impact on surgery, but consider comorbidity of patients who receive these drugs; check immunoglobulin concentrations |

*Except stimulating immunomodulators such as interferons, interleukins, and growth factors that are sometimes used in tumor therapy to enhance anti-tumor immunity; except bevacizumab and other inhibitors of angiogenesis that are not directly immunosuppressive but may strongly affect wound healing.
†Other factors such as nutritional status, protein loss, normal vitamin and trace element supply, smoking habits, and body mass index should be considered as accompanying independent risk factors.
| Generally, checking the absolute neutrophil count, the immunoglobulin G concentration, and the plasmatic hemostasis tests are recommended.
| For example, anti-TNF-a.
| For example, asparaginase.

Table 1 Pharmacological immunosuppression and standard oncological therapy as risk factors for immunological complications of pediatric surgery
Radiotherapy

Similar to chemotherapy, it is indicated in Table 1 that the effects of radiotherapy on the risks of surgical complications vary with dose, location, and time interval between it and surgery. Of note, preoperative radiotherapy, which is typically used in addition to chemotherapy to reduce tumor size and improve operability, and postoperative radiotherapy were shown to represent some of the biggest risks of wound complications in sarcoma surgery (Moore et al. 2014). The effect on general immunosuppression may be compared to chemotherapy, although it is usually lower, either because the irradiated tumor region does not contain major sites of blood production or immune function or because of dose fractionation. One factor that is more difficult to calculate in the individual subject may be the duration of the effect of radiation on the regenerative capacity of the tumor bed and other irradiated regions. Involvement of hematopoietic bone marrow in irradiated regions may lead to prolonged cytopenias of varying degree and thus a reduced tolerability of further chemotherapy and surgery. Consequences of functional asplenia after spleen irradiation are described above. Additionally, late effects of radiotherapy including the increased risk of secondary malignoma and myelodysplastic syndrome are remarkable, but not topic of this chapter.

Immunosuppressive Therapy

Glucocorticoids

Steroidal anti-inflammatory drugs such as prednisolone and dexamethasone are widely used in the treatment of cancers, of leukemias, and of autoimmune diseases. Glucocorticoid hormones are vital during situations of stress, because they usurp a central role in providing a fast supply of energy (gluconeogenesis, protein catabolism, enhanced lipolysis) and they influence the electrolyte balance, sensitize the cardiovascular system to catecholamines, and increase the alertness of the central nervous system. One of their main actions that are exploited pharmacologically is the inhibition of both early and late inflammatory processes (dilatation of capillaries, edema, leukocyte migration, fibrin deposits, and fibroblast proliferation, collagen synthesis, etc., respectively). Neutrophil counts in the peripheral blood are increased both through a different distribution and reduced decay, while lymphocyte counts and functions are decreased by glucocorticoids, again by distribution but also by apoptosis induction. Cellular functions of lymphocytes such as cytotoxicity as well as cytokine production are reduced. There are even direct antiproliferative effects, especially on thymocytes and fibroblasts, however, not as pronounced as those of other cytostatic drugs used in oncology. Together, these largely dose-dependent effects of glucocorticoids represent paramount reasons for an increased risk of complications after pediatric surgery (Table 1).

Biologicals, Monoclonal Antibodies

Antibodies directed against cytokines or their receptors, e.g., against tumor necrosis factor alpha (TNF-a) or interleukin (IL)-1, IL-6, as well as TNF-receptor or IL-receptor antagonists, are used to treat autoimmune diseases and hyper-inflammatory states of various origins such as in rheumatology, dermatology, gastroenterology, or stem cell transplantation. These agents, like monoclonal autoantibodies directed against various cell surface antigens that inhibit cell-cell interactions or directed against various mediators of inflammation including complement factors, have striking effects in blocking certain specific pathways of immune reactions in the context of disease but may physiologically be needed for the fine-tuning of immunity in the defense of microorganisms as well as in wound healing and tissue homeostasis. Therefore, possible side effects and the duration of action of these drugs need to be kept in mind when planning surgery in patients who receive one or more of these drugs. The list of adverse reactions of biologicals and monoclonal antibodies includes sepsis, opportunistic infections, disturbed wound healing, and even malignoma. Although TNF-a is known to promote collagen synthesis and is involved in wound healing, and recommendations to discontinue anti-TNF-a treatment at least four half-lives
before major surgery exist (Smith et al. 2009), a retrospective study showed no direct unfavorable effect of anti-TNF-a in patients with psoriasis who underwent surgery (Fabiano et al. 2014). The risk of provoking a relapse of the underlying autoimmune disease by stopping a working treatment regimen, which might further delay surgery, also needs to be weighed against the risk of potential side effects of the drug on the postoperative course (den Broeder et al. 2007).

**Small Compounds, Immune Modulators, and Immunosuppressants**

Tyrosine kinase inhibitors, such as imatinib or sunitinib and similar derivatives, and inhibitors of mammalian target of rapamycin (mTOR) have very specific points of action in the signaling pathway that leads to tumor cell proliferation, leukemias, or graft rejection. It is no surprise that these effects may also affect wound healing. Table 1 aims to provide an estimation of the relative effects of these compounds as compared to steroids, cytotoxic chemotherapy, radiotherapy, etc. However, it is beyond the scope of this chapter to go into detailed mechanisms of actions of all these compounds or to deduct any general recommendation for precautions in the context of pediatric surgery. Classical specific lymphocyte-directed immunosuppressants like calcineurin inhibitors that blunt IL-2 signaling, T-lymphocyte function and proliferation, or anti-thymocyte globulin, alemtuzumab, rituximab, etc. to eliminate subsets of lymphocytes are almost exclusively used in transplantation medicine and refractory autoimmune diseases. Most of these drugs and, to a lesser extent, also mycophenolate mofetil, which inhibits guanine nucleotide synthesis and thereby predominantly T and B cell proliferation, are highly immunosuppressive but have little if any antiproliferative effect on other tissues or on wound healing (Table 1). As mentioned above, the mechanism and duration of action need to be considered before planning surgery and weighed against the risks of discontinuation of this treatment.

**Case Reports**

**A 13-Year-Old Boy with Relapsing Liver Abscesses**

A boy of a non-consanguineous Egyptian family living in Austria underwent surgery for a solitary liver abscess; no pathogen could be isolated. One year later, another liver abscess appeared at a different site, again, without conclusive underlying cause. The diagnostic workup included, like at the first occurrence, a vast microbiological and parasitical analysis, but was negative. Histology was inconclusive and showed granulomatous inflammation and abscess formation. It was unclear whether the recurrence was due to intraoperative seeding of any infectious agent, representing a complication appearing as relapse, or to a new manifestation of an underlying condition. Ultimately, the pediatric surgeon thought of the possible differential diagnoses of recurring granulomata and ordered a neutrophil function test (oxidative burst and phagocytosis assays), which were clearly pathologic. Genetic analyses confirmed the presence of autosomal-recessive chronic granulomatous disease, an inherited immunodeficiency.

**12-Year-Old Girl with a Big Lump in the Proximal Thigh**

A Caucasian, moderately obese girl presented to the family care practitioner with a pomelo-sized hard lump in her thigh, located in the adductor region. Given the size and location, it may have developed slowly over a prolonged time and remained uncovered. The girl admitted she was too ashamed to consult someone at an earlier point during the last few months when she felt something develop because of the delicate location. She was diagnosed with a synovial sarcoma and underwent an array of chemotherapy cycles and neoadjuvant radiotherapy. The tumor shrank only unsatisfyingly, but the consequent surgery could be performed with complete tumor resection, primary endoprosthesis implantation, and a
plastic tissue flap reconstruction. Nevertheless, seroma developed, and because the supplying connective tissue beneath the tissue flap was missing, a long phase of inflammation and wound dehiscence followed. No exclusively responsible pathogenic germ could be isolated. She was treated with various antibiotics and numerous attempts of local debridement, negative pressure systems, etc. with limited success. The overall prognosis of this patient who initially presented with a large tumor size in the adductor compartment of the proximal lower extremity and multiple lung metastases that hardly responded to neoadjuvant oncological therapy is very poor.

Conclusions and Future Directions

Little scientific evidence of functional analyses of the immune system and tissue reparative capacity and their consequences for surgery exists for pediatric patients under cytotoxic chemotherapy or pharmacological immunosuppression. Empirical data and retrospective surveys of surgical complications of patients under immunosuppressive therapy predominate. Surgical risks of children with primary immunodeficiencies are even less thoroughly investigated. Hence, larger studies of homogenous patient cohorts are needed to assess the risks of immunocompromised children undergoing surgery. Until then, it is safest to deduce from the specific underlying disease or the mechanisms of the drugs used, which kind and degree of adverse effects on the course of surgery are to be expected. It is important to be aware that a certain degree of inflammation is similarly required for tissue regeneration as are the basic mechanisms of endogenous debridement and antibacterial immunity. Absolute neutrophil counts, immunoglobulin G levels, and the prerequisites for a balanced inflammatory response (without high-dose glucocorticoid or other pharmacological inhibition) should be included in the basic preoperative assessment just like plasmatic coagulation tests and platelet counts. Ideally, a multidisciplinary tumor board conference in cancer patients or a corresponding platform for surgery planning in patients with inborn errors of immunity or autoimmune diseases who have to undergo elective surgery should provide the setting for both an evidence- and an experience-based assessment of individual risk factors and allow for an accordingly planned surgery with minimized complications from immunosuppression during the postoperative course.

Cross-References

- Brain Tumors
- Heart Transplantation
- Hodgkin and Non-Hodgkin Lymphoma
- Intestinal Transplantation
- Liver Transplantation
- Liver Tumors
- Lung Transplantation
- Musculoskeletal Tumors excluding Rhabdomyosarcoma (Osteosarcoma & Ewing Sarcoma)
- Neuroblastoma
- Principles of Transplantation
- Rare Malignant Tumors
- Renal Tumors
- Rhabdomyosarcoma
- Splenic Disorders
- Teratomas (All Locations)

References

Anabtawi I, Abdel-Rahman F, Al Masri M. Surgical complications related to hematopoietic stem cell transplantation. Eur J Surg Oncol. 2011;37(7):576–82.
den Broeder AA, Creemers MC, Fransen J, de Jong E, de Rooij DJ, Wymenga A, de Waal-Malefijt M, van den Hoogen FH. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007;34(4):689–95.
Fabiano A, De Simone C, Gisondi P, Piaserico S, Lasagni C, Pellacani G, Conti A. Management of patients with psoriasis treated with biological drugs needing a surgical treatment. Drug Dev Res. 2014;75(Suppl 1):S24–6.
Farmand S, Baumann U, von Bernuth H, Borte M, Foerster-Walldl E, Franke K, Habermehl P, Kapau P, Klock G, Liese J, Marks R, Muller R, Nebe T, Niehues T, Schuster V, Warnatz K, Witte T, Ehl S, Schulze I. Interdisciplinary AWMF guideline for the diagnostics
of primary immunodeficiency. Klin Padiatr. 2011;223 (6):378–85.
Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. J Allergy Clin Immunol. 2018 Jan;141(1):59–68.e4. https://doi.org/10.1016/j.jaci.2017.06.009. Epub 2017 Jun 29. Review. PMID: 28669558
Jeys LM, Grimer RJ, Carter SR, Tillman RM. Peri-prosthetic infection in patients treated for an orthopaedic oncological condition. J Bone Joint Surg Am. 2005;87(4):842–9.
Kindler O, Quehenberger F, Benesch M, Seidel MG. The Iceberg Map of germline mutations in childhood cancer: focus on primary immunodeficiencies. Curr Opin Pediatr. 2018 Dec;30(6):855-863. https://doi.org/10.1097/MOP.0000000000000680. Review. PMID: 30124581
Lazarus R, Clutterbuck E, Yu LM, Bowman J, Bateman EA, Diggle L, Angus B, Peto TE, Beverley PC, Mant D, Pollard AJ. A randomized study comparing combined pneumococcal conjugate and polysaccharide vaccination schedules in adults. Clin Infect Dis. 2011;52(6):736–42.
Moore J, Isler M, Barry J, Mottard S. Major wound complication risk factors following soft tissue sarcoma resection. Eur J Surg Oncol. 2014;40(12):1671–6.
Morii T, Yabe H, Morioka H, Beppu Y, Chuman H, Kawai A, Takeda K, Kikuta K, Hosaka S, Yazawa Y, Takeuchi K, Anazawa U, Mochizuki K, Satomi K. Postoperative deep infection in tumor endoprosthesis reconstruction around the knee. J Orthop Sci. 2010;15(3):331–9.
Peel T, May D, Buisling K, Thursky K, Slavin M, Choong P. Infective complications following tumour endoprosthesis surgery for bone and soft tissue tumours. Eur J Surg Oncol. 2014;40(9):1087–94.
Smith CH, Anstey AV, Barker JN, Burden AD, Chalmers RJ, Chandler DA, Finlay AY, Griffiths CE, Jackson K, McHugh NJ, McKenna KE, Reynolds NJ, Ormerod AD. British Association of Dermatologists’ guidelines for biologic interventions for psoriasis 2009. Br J Dermatol. 2009;161(5):987–1019.
Tangye SG, Al-Herz W, Bousilha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Picard C, Puck J, Torgerson TR, Casanova JL, Sullivan KE. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2020 Jan 17. https://doi.org/10.1007/s10875-019-00737-x. [Epub ahead of print]