SPECIAL COMMENTARY

# Regional anesthetic procedures in immunosuppressed patients: risk of infection

Carsten Gronwald[a], Thorsten Vowinkel[b] and Klaus Hahnenkamp[a]

[a]Department of Anesthesiology and Intensive Care and [b]Department of General and Visceral Surgery, University Hospital, Münster, Germany

Correspondence to Klaus Hahnenkamp, MD, Department of Anesthesiology and Intensive Care, University Hospital, Albert-Schweitzer-Campus 1, Building A1, 48149 Münster, Germany
Tel: +49 251 83 47252; fax: +49 251 1627374; e-mail: Klaus.hahnenkamp@ukmuenster.de

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**Purpose of review**

Due to demographic developments anesthesiologists encounter an increasing number of older and multimorbid patients in their daily routine. Consequently the proportion of immunosuppressed patients (e.g. those with cancer, diabetes mellitus, and those receiving immunosuppressive treatment and/or chemotherapy – e.g. for inflammatory bowel diseases, autoimmune diseases, and after transplantation) will also rise. Regional anesthesia (peripheral nerve blocks and neuraxial blockade) may be beneficial in these patients and will have to be considered in order to provide adequate pain management and minimize risks for the patients.

**Recent findings**

There is only little available research and data on regional anesthesia procedures in specific immunosuppressed patient population. However, recent analyses from great databases dealing with general postoperative pain management have been published.

**Summary**

So far, there are no guidelines available dealing with indications and limitations of regional anesthetic procedures in these patients. The complication rate is rare but potentially disastrous. However, the technique itself cannot be regarded as absolute contraindication for immunosuppressed patients if precautions are taken. An interdisciplinary approach regarding the indication of regional anesthesia techniques in immunosuppressed patients is recommended. Efforts must therefore be made to achieve an interdisciplinary consensus with relevant risk–benefit considerations.

**Keywords**

immunosuppression, infection, regional anesthesia

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## Introduction

Regional anesthetic procedures such as neuraxial and peripheral nerve blockade have become a fundamental element of modern anesthesia. Demographic developments are important in connection with establishing the indications for regional anesthesia and conducting the procedure. With increasing age and increasing grades in the American Society of Anesthesiologists (ASA) classification, the incidence of anesthesia-related mortality also increases [1]. The proportions of older patients and patients with multimorbid conditions will also rise, and consequently the proportion of immunosuppressed patients (e.g. those with cancer, diabetes mellitus, and those receiving immunosuppressive treatment and/or chemotherapy – e.g. for inflammatory bowel diseases, autoimmune diseases, and after transplantation). For these patients, regional anesthesia (peripheral nerve blocks and neuraxial blockade) may be beneficial and will have to be considered in order to provide adequate pain management and minimize risks for the patients. So far, there are no guidelines available dealing with indications and limitations of regional anesthetic procedures in these patients. The following review is therefore intended to provide an up-to-date picture of the current state of knowledge in the field of infectious complications accompanying regional anesthesia procedures in various settings of immunosuppressed patients.

## Infectious complications following regional anesthesia

Severe complications and persistent symptoms are very rare following regional anesthesia [2••]. However, they may have serious consequences for the patient, for example paralysis.

### Peripheral blockades

Neuburger *et al.* [3] investigated the complication rates in relation to infections and neurological injury in peripheral

catheter regional anesthesia, in a study including 2491 catheter procedures. The rates were 4.2% for mild infections, 2.4% for moderate infections, and 0.8% for severe infections. Mild infection was defined as the presence of at least two characteristics (rubor, swelling, and pressure pain at the catheter puncture site). Moderate infection was defined as the presence of at least two of the following characteristics: raised C-reactive protein (CRP), pyorrhea at the puncture site, fever, leukocytosis, and a need for antibiotic therapy. Severe infection was considered to be present when a surgical procedure was indicated. Patients with severe infection frequently had severe comorbid conditions such as diabetes mellitus or coronary heart disease. The indwelling catheters had been in place for an average of 4.69 days before the infection developed. Mild or severe nerve injury occurred in 0.3 and 0.2% of cases, respectively [3]. A prospective study of 1065 peripheral nerve blocks conducted in Australia reported a 0.22% rate of neurological complications. The study did not provide any explicit information about risk factors or comorbid conditions in the affected patients [4].

### Neuraxial blockades

The location for an infection following neuraxial blockade [epidural anesthesia (PDA) and spinal anesthesia (SPA)] is dangerous *per se* as neurological damage might lead to persistent paraplegia.

### Spinal epidural abscesses (meningitis)

The clinical picture of spontaneous spinal epidural abscess currently has an incidence of approximately 1 per 10 000 hospital admissions annually, although the rate has doubled during the past 20 years [5,6]. A meta-analysis including 915 patients with spinal epidural abscesses identified the following characteristics or risk factors for the condition: most often in the age group 30–70, male : female sex ratio 1.0 : 0.56, diabetes mellitus ($n = 128$), intravenous drug abuse ($n = 75$), alcohol abuse ($n = 41$), infections ($n = 377$), trauma ($n = 85$), comorbid conditions ($n = 83$), and invasive procedures ($n = 188$, including 42 PDAs and nine SPAs). Widely differing types and sites of infection were included in the category 'infection'; in declining order of frequency, the four most frequent were skin abscess, furuncle, paronychia ($n = 128$); vertebral osteomyelitis/diskitis ($n = 59$); pulmonary/mediastinal infection ($n = 41$); and sepsis ($n = 39$) [7].

Although there have been several publications in recent years on the risk of spinal/epidural abscesses in connection with neuraxial blockades, it is not possible to quantify the risk precisely. A prospective study conducted in Denmark over a 12-month period assessed the course of 17 372 PDA catheterizations. Spinal epidural abscesses developed in a total of nine patients, among whom eight were classified as being immunocompromised (malignancies, diabetes mellitus, multiple trauma). The overall incidence was given as 1 in 1930, with a further distinction being made between university hospitals (1 in 5661) and general hospitals (1 in 796). The median catheterization period was 6 days, and the latency period up to the diagnosis of infection was a median of 5 days [8]. In a study in Sweden, a total of 450 000 PDAs (including 200 000 obstetric procedures) and 1 260 000 SPAs in the period 1990–1999 were investigated [9]. Thirteen cases of spinal epidural abscess occurred (12 with PDA, one with SPA), giving an incidence of 1 in 37 500 for PDA and 1 in 1 260 000 for SPA. At least one risk factor for infection was present in 75% of the patients with PDA: diabetes mellitus ($n = 4$), malignancy ($n = 3$), chronic alcohol abuse ($n = 1$), and long-term glucocorticoid treatment ($n = 1$). The indication for PDA was adequate pain therapy following trauma in six patients. The median latency period between catheter insertion and initial symptoms was 5 days in the Danish study. The study also noted cases of purulent meningitis. These occurred after four PDA procedures and 20 SPAs. In the PDA group, one patient had chest trauma and two others were known to have diabetes mellitus. No prior disease was present in the SPA group, with the exception of one patient with diabetes mellitus and another receiving glucocorticoid therapy for Addison's disease [9]. Incidence of an epidural abscess was studied prospectively in three recent studies [2••,10,11]. Out of 30 500 cumulative prospective patients 29 patients were diagnosed with epidural abscess or meningitis, resulting in an overall incidence of 1 : 3127. Immunocompromising risk factors were present in 12 patients. Five patients suffered from cancer, two patients were on chronic glucocorticoid therapy, three patients had diabetes and one patient was undernourished. In 17 patients no risk factors were reported [2••,10,11].

**Key points**

- Patients with immunosuppressive conditions of various causes are at higher risk for contracting infectious complications; the complication rate seems to be rare but any complication is potentially disastrous.
- Immunosuppression is not only restricted to active immunosuppressive treatment but also includes diseases such as diabetes mellitus, malignancies, HIV infection, malnutrition, drug or alcohol abuse or chronic inflammatory bowel diseases.
- Immunosuppression in patients is not an absolute contraindication for the techniques of regional anesthesia if precautions are taken.
- The routine use of regional anesthesia techniques in immunosuppressed patients, for example in organ transplantation asks for an interdisciplinary consensus on the indication for such techniques.

Llewellyn and Moriarty [12] studied the complication rate in 10 633 epidural anesthesia procedures in children over a 5-year period in the UK. Two cases of spinal epidural abscess (1 in 5316; catheterization periods 22 and 115 h) and one case of meningitis (1 in 10 633; catheterization period 96 h) were found. Neural injuries were described in a total of six cases (1 in 1772).

Obstetric regional anesthesia procedures are of major importance, as 60% of women opted for PDA in more than 4 million births in the USA in 2003, for example. Ruppen *et al.* [13] carried out a meta-analysis of more than 1.2 million PDAs administered for labor. The risk of epidural infection was 1 in 145 000 and the risk of persistent neurological damage was 1 in 237 000 [13].

## Immunodeficiency/immunosuppression

In immunosuppressed patients there is *per se* an increased risk for infections, which can be aggravated after medical procedures. Immunodeficiencies are divided into primary or secondary forms, depending on their cause. Congenital and thus primary forms include, for example, Bruton–Gitlin syndrome (a T-cell defect), DiGeorge syndrome (a B-cell defect), and Louis-Bar syndrome (combined T-cell and B-cell defect). Acquired and thus secondary forms of immunodeficiency can be caused by various diseases such as diabetes mellitus, malignancies, HIV infection, malnutrition, drug or alcohol abuse, chemotherapy, glucocorticoid therapy and immunosuppressive treatment following organ transplantation, autoimmune diseases, vasculitis, rheumatoid diseases, or chronic inflammatory bowel diseases [14•]. The extent and duration of granulocytopenia (less than 500 granulocytes per milliliter) are the best-characterized risk factors for general infection [15]. When granulocytopenia lasts for up to 5 days, there is only a minor risk; with a period of 6–10 days there is a higher risk (risk of infection 30% with leukopenia $<1000/\mu l$ or 50% with granulocytes $<100/\mu l$); when granulocytopenia lasts for more than 10 days, patients are classified as being at high risk (risk of bacterial infections 70%) [16–18].

## Infectious complications in distinct immunocompromising settings and diseases

Several clinical settings and diseases are accompanied with immunosuppression. Information about the risk of infection in this distinct disease and setting is relevant for the indication of regional anesthesia techniques.

### Chronic glucocorticoid therapy

Around 1–3% of the world's population receive long-term glucocorticoid therapy, with the risk of potential side-effects such as truncal obesity, hypertonia, osteoporosis, glaucoma, muscular atrophy, psychosis, and infections. There are many different indications for chronic glucocorticoid therapy, for example asthma, rheumatoid arthritis (RA), lupus erythematosus, chronic inflammatory bowel diseases or organ transplantation. A dosage of 7.5 mg prednisone (or equivalent) per day is described as being the 'threshold dose' for inducing Cushing's syndrome [19•]. The level of hypercorticoidism correlates with the risk of bacterial or opportunistic infection [20]. This predisposition is caused by multifactorial influences on the immune system. Even after a single administration of glucocorticoids, lymphocytopenia, monocytopenia, and eosinopenia follow 4–6 h later. Not only are cell counts reduced, but cell functions such as phagocytosis, bactericidal activity, migration, and cytokine production are also impaired [21,22]. Typical opportunistic pathogens include invasive aspergillosis, invasive candidiasis, *Pneumocystis carinii*, herpes simplex virus, atypical mycobacteria, and cytomegalovirus [23].

The risk of general infection in chronic glucocorticoid therapy depends on the type, method of administration, dosage, and duration of treatment [19•]. This was shown in a meta-analysis of 71 controlled studies including 4198 patients. The rate of infectious (fatal and nonfatal) complications in the 'steroid group' was 12.7%, in comparison with 8.0% in the 'control group'. Unfortunately, no details are given to allow further differentiation of the infectious complications. Stuck *et al.* [24] concluded that there was no evidence of an increase in the risk of infection at less than 10 mg/day. In a recently published study by Wolfe *et al.* [25], a dose-dependent relationship between prednisone and the risk of pneumonia in patients with RA was noted. There was already a significant increase in the risk at a dosage of less than 5 mg/day prednisone [25]. In another study on RA, it was shown that the risk of severe bacterial infection is doubled when glucocorticoids are used in comparison with methotrexate and that there is a dose–effect relationship for dosages above 5 mg/day: relative risk (RR) at 5 mg/day or less, 1.34; at 6–9 mg/day, RR 1.53; 10–19 mg/day, RR 2.97; at least 20 mg/day, RR 5.48 [26]. Prednisone also has been shown to be a risk factor for severe infections in patients receiving treatment for Crohn's disease [27]. Several case reports on spinal epidural abscesses due to the tendency for fistulas to develop in Crohn's disease are worth mentioning but the abscesses developed spontaneously and had no causal connection with regional anesthesia [28–31]. Apart from the above-mentioned analyses of great pain management databases no further retrospective studies are available. The risk of epidural abscess in chronic glucocorticoid treatment varies from 1 : 15 250 to 1 : 450 000 [2••,9].

### Chemotherapeutic agents

Many different chemotherapeutic agents, with sometimes substantial side-effects, are used to treat malignant

tumors. Major side-effect of chemotherapeutic agents is their influence on hematopoiesis, resulting in anemia, leukopenia/neutropenia, and thrombocytopenia. Neutropenia is the most frequent of these, and its extent and duration correlate directly with the incidence of severe infections [15]. However, specific studies other than the Swedish study reporting 3 out of 450 000 PDA abscesses and the three prospective studies with 5 out of 30 500 PDA in patients with malignancies are lacking [2••,9–11]. A case report on peripheral regional anesthesia has described diffuse neurological but not infection-related damage to the brachial plexus following an interscalene block in a 14-year-old girl with a sarcoma in the area of the proximal humerus who had undergone polychemotherapy [32]. Compared to chronic glucocorticoid therapy the risk of epidural abscess in malignancies seems to be higher and amounts of 1 : 6 100 to 1 : 150 000 [2••,9–11].

### Immunosuppression following organ transplantation

Patients undergoing organ transplantation have a substantial increase in the risk of infectious complications due to their immunosuppression treatment [33]. Numerous immunosuppressive agents have various levels of hematological toxicity as a side-effect. It is possible for thrombocytopenia to be induced by antilymphocyte globulins/antithymocyte globulins (ALG/ATG), muromonab CD3 (OKT3), and mycophenolate mofetil (MMF) [34]. Anemia can be caused by azathioprine (AZA), and leukopenia by ALG/ATG, OKT3, AZA, steroids, tacrolimus (FK-506), sirolimus, everolimus, and MMF [34].

Intraoperative and postoperative neuraxial blocks are increasingly preferred by organ transplantation centers, to ensure adequate perfusion during the transplantation of solid organs. There have been only a few studies so far on the potential risk of complications in patients who have undergone transplantation with PDA. A retrospective analysis from a pediatric transplantation center in Australia reported no severe complications such as spinal epidural hematoma or abscess in 39 children following kidney transplants. However, it should be noted that the study provided no data about the immunosuppression administered and that the mean duration of epidural catheterization was 1.7 days. In 20 patients, patient controlled intravenous analgesia also had to be supplemented with systemic administration of opioids when the quality of the analgesia was inadequate [35]. Combined spinal and epidural anesthesia was compared with general anesthesia ($n = 50$) in adult patients undergoing kidney transplantation, and the authors stated that there was no increase in the complication rate. However, no data are given about immunosuppression or the period of epidural catheterization [36]. Trzebicki *et al.* [37•] report about their experience with thoracic epidural anesthesia in patients undergoing liver transplantation. Epidural anesthesia was applied to 67 patients out of 279 patients undergoing liver transplantation since 2000. Patients had a mean MELD (Model of Endstage Liver Disease) Score of 13 and exclusion criteria were an international normalized ratio greater than 1.5, an activated partial thromboplastin time above 45 s and thrombocytes below 70 000. Epidural catheters were removed after 5 days and the authors report about no complications associated with thoracic epidural anesthesia in their patients [37•]. In addition, there have been a few case reports describing successful and complication-free caudal or epidural anesthesia in children with liver transplants [38,39]. There are, however, two case reports describing spinal epidural abscess during immunosuppressive treatment, which developed spontaneously without regional anesthesia [40,41].

### HIV infection

Estimates suggest that 20–25% of HIV-positive patients may require surgery during the period of their disease [42]. Therefore HIV infection might be present when a regional anesthetic procedure is being planned. Pregnant patients who are HIV-positive and have a high viral load are recommended to undergo delivery with a primary Cesarean section in a contraction-free uterus, in order to reduce the transmission rate to the child [43]. Whether the complication rate associated with regional anesthesia is higher in this group of patients has been mainly investigated in smaller studies. In the study by Hughes *et al.* [44], regional anesthesia (PDA and SPA) was administered without any problems in 18 patients for delivery. In addition regional anesthesia itself had no influence on the state of the disease, preoperative and postoperative comparisons showed no changes in the immune functions examined. However, the authors themselves emphasize that these were 'relatively healthy' patients in CDC stages A2 or B2 (CDC stages: A, asymptomatic HIV infection; B, HIV-associated symptoms and diseases, but no AIDS-defining diseases; C, AIDS-defining diseases; 1 = CD4 cell count >350 cells/μl, 2 = CD4 cell count <350 cells/μl, 3 = CD4 cell count <200 cells/μl) [44]. Avidan *et al.* [45] examined 44 HIV-positive pregnant patients in whom SPA was carried out for delivery. No anesthesia-relevant complications occurred in any of the patients. The $CD4^+$ T-lymphocyte count was a median of 396/μl at the time of the operation; the reference range is 400–2200/μl [45]. In another study, 54 patients were examined in the context of SPA. No direct anesthesia-related complications occurred, but postoperative complications such as bronchitis, pneumonia, and wound healing disturbances developed in 17% of the patients. There was a significant association between a low $CD4^+$ T-lymphocyte count and the risk of complications. The authors concluded that immune reconstruction aiming for a $CD4^+$ T-lymphocyte count above 400/μl should therefore be attempted at the time of a Cesarean section [46]. Du Pen *et al.* [47] reported an

infection rate of 82% in 11 AIDS patients examined, during long-term therapy with special epidural catheters and long subcutaneous tunneling.

A study with case reports on the use of an autologous epidural blood patch in six HIV-positive men identified no neurological or infectious complications during a follow-up period of 2 years [48–50].

## Hygienic considerations

Careful and meticulous observance of hygiene measures when invasive procedures are being carried out is an elementary factor in prophylaxis against infections [49,50]. Also, in regional anesthetic procedures, particularly with catheter techniques, sterile precautions are absolutely necessary and must be observed. The validity of this is demonstrated by numerous case reports on infectious complications. For example, necrotizing fasciitis with a fatal outcome developed in a female patient following an axillary plexus blockade (single-shot technique) for carpal tunnel decompression. The pathogen isolated was group A streptococci, potentially originating from the anesthetist's skin flora or oral cavity [51]. Baer [52] reported the case of a 28-year-old patient with *Streptococcus viridans* meningitis. The first symptoms developed 8 h after accidental perforation of the dura in obstetric PDA, with a fatal outcome 2 days after delivery [52]. Schneeberger *et al.* [53] identified the same pathogen in a throat swab from the anesthetist and in four patients with postpuncture meningitis.

## Practical recommendations

A limited catheterization period – 72 h with an epidural catheter, for example – generally appears to be a relatively well tolerated procedure for the patient. In patients receiving immunosuppressive therapy, it may be useful to measure the absolute leukocyte count not just once preoperatively, but instead to also carry out a differential blood count to allow quantification of the various cell types and assessment of the course. The goal would be a normal leukocyte count and a $CD4^+$ T-lymphocyte count greater than 400/μl. Patients receiving glucocorticoid therapy at less than 10 mg/day or with a cumulative dosage of less than 700 mg prednisone do not appear to have an increased risk of infection [24]. If possible, bacterial filters in pump systems should not be exchanged without a compelling reason, and disconnected catheter systems should be reconnected only within a time window of up to 6 h [54,55]. To avoid contamination with skin bacteria, the catheter tip should not be touched during insertion [56]. Subcutaneous tunneling of the catheter can reduce bacterial colonization [57]. Changes of the dressing at the catheter puncture site should be minimized and should be carried out with sterile precautions [58]. A general microbiological examination of the catheter tip following removal is not useful [59]. In addition, daily rounds to visit patients with catheter procedures and the constant presence of a competent contact person are indispensable to ensure that complications are recognized as early as possible. In addition, diagnosis and therapy must be instigated immediately – for example, when there is any suspicion of a spinal epidural hematoma [60]. Any time delay must be absolutely avoided in this type of case in order to achieve a complete return to health for the patient, without any neurological deficits.

## Conclusion

Patients with immunosuppressive conditions of various causes are at higher risk for contracting infectious complications. Both typical pathogens and also opportunistic agents can be relevant. There is only little available research and data on regional anesthesia procedures in immunosuppressed patients. The complication rate is rare but potentially disastrous. Therefore an interdisciplinary approach regarding the indication of regional anesthesia techniques in immunosuppressed patients is recommended. Efforts must therefore be made to achieve an interdisciplinary consensus with relevant risk–benefit considerations. The technique itself cannot be regarded as absolute contraindication for immunosuppressed patients if precautions are taken. The catheterization period should therefore be as short as possible, hygienic measures must be respected and most importantly a close supervision following the procedure is mandatory.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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