Incidence and Outcome of Renal Failure in Liver Transplantation

With improvements of surgical techniques and peri-operative care, survival of liver transplant patients has continuously improved over the last decades. Unfortunately, this trend is accompanied by a growing incidence of chronic renal failure. Also, due to the introduction of the MELD system, a large proportion of patients present with some degree of renal dysfunction prior to transplantation, which increases the risk of acute renal failure postoperatively.

Depending on the criteria applied, reported incidences for acute and chronic renal failure in liver transplant recipients vary between 4% and 95%. Whereas acute renal failure most often is a reversible state that can be controlled, early detection and prevention of chronic renal failure remains a difficult task. Since currently used clinical markers to monitor nephrotoxicity, like serum creatinine, can not successfully discriminate patients at risk, the focus should shift to new diagnostic tools which could identify at-risk patients earlier and allow for kidney rescue therapies to commence before structural damage occurs. The new strategies could facilitate an individualization of immunosuppressive therapy.

A review of current literature shows that calcineurin inhibitor toxicity represents the most significant factor for the development of acute and chronic renal dysfunction beside factors like preexisting renal dysfunction or hepatorenal syndrome, liver allograft dysfunction, diabetes or hepatitis C that have been reported to be associated with the incidence of renal failure following transplantation. Despite their shortcomings, calcineurin inhibitors (CNI’s) remain the best alternative for preventing allograft rejection. No alternative drugs seem either potent or safe enough to entirely replace CNI’s. Thus, active strategies should concentrate on optimizing CNI treatment protocols with early detection markers for toxicity, paired with the conversion to alternative drugs such as MMF and sirolimus.

Key words: heptorenal syndrome, calcineurin inhibitors, liver transplantation, renal failure

Inzidenz und Verlauf von Nierenfunktionsstörungen nach Lebertransplantation

Durch kontinuierliche Optimierung der chirurgischen Techniken und der perioperativen Versorgung konnte das Überleben von Patienten nach Lebertransplantation in den letzten Jahrzehnten kontinuierlich verbessert werden. Leider ist es damit auch zu einer
steigenden Inzidenz von chronischem Nierenversagen gekommen. Die Einführung des MELD Systems hat zusätzlich dazu geführt, dass viele Patienten bereits vor dem Zeitpunkt der Transplantation zeichen einer Nierenfunktionsstörung zeigen, was wiederum das Risiko eines akuten postoperativen Nierenversagens erhöht. Je nachdem welche Definitionskriterien Anwendung finden, wird die Inzidenz einer akuten oder chronischen Niereninsuffizienz zwischen 4% und 95% beschrieben. Stellt das akute Nierenversagen meist eine reversible und damit kontrollierbare Situation dar, stellt das rechtzeitige Erkennen und Vermeiden des chronischen Nierenversagens eine weit größere Herausforderung dar.

Eine Analyse der aktuellen Literatur zeigt, dass neben Faktoren wie eine präoperative Nierendysfunktion z.B. als hepatorenales Syndrom, eine Dysfunktion des Leberallografts, Diabetes oder Hepatitis C, die Behandlung mit Calcineurin-Inhibitoren (CNI’s) offensichtlich der stärkste Faktor für die Entwicklung einer akuten und chronischen Nephrotoxizität ist.

Da sich aber bisher keine der neueren weniger nephrotoxischen Immunsuppressiva in ihrer Wirkung als so potent und sicher gezeigt haben, dass man auf den Einsatz von CNI’s ganz verzichten könnte, stellen diese nach wie vor die beste Alternative zur erfolgreichen Vermeidung einer Abstoßung dar. Bis zur Einführung verträglichere und equipotenter Immunsuppressiva sollten daher CNI-Behandlungsprotokolle durch eine bessere Erkennung von Nephrotoxizität weiter optimiert, und der Einsatz weniger nephrotoxischer Substanzen wie Sirolimus und MMF zugunsten einer CNI-Reduktion vorangetrieben werden.

Da sich die zurzeit benutzten klinischen Marker wie z. B. Serumkreatinin nur bedingt als geeignet erwiesen haben, Risikopatienten einer Nierenfunktionsstörung rechtzeitig zu erkennen, sollte sich die Zielsetzung heutiger Forschung auch auf die Entwicklung neuer diagnostischer Parameter konzentrieren, um so diese Patienten früher zu identifizieren, um sie dann einer nierenprotectiven, individuellen Abstimmung der Immunsuppression unterziehen zu können, bevor es zu einer irreversiblen strukturellen Nierenschädigung kommt.

Schlüsselwörter: hepatorenales Syndrom, Calcineurin-Inhibitoren, Lebertransplantation, Nierenversagen

Risk Factors for Renal Dysfunction

Over the last decades, continuous progress in postoperative care and surgical techniques has significantly improved patient survival following orthotopic liver transplantation. However, with the benefit of a better survival, co-morbidities from organs other than the transplant have become a growing problem. Since a number of patients already present with varying degrees of renal dysfunction, including hepatorenal syndrome (HRS), prior to liver transplantation, and standard immunosuppression protocols are based on calcineurin inhibitors (CNI) with known nephrotoxic side effects, a majority of liver recipients will eventually develop some degree of renal insufficiency. Thus, not only acute but especially chronic renal dysfunction after transplantation of a non-renal organ has become a major complication that significantly compromises patients’ outcome (1-3). Despite the fact that reported incidences for renal insufficiency following liver transplantation may vary from 17 to 95% for acute and 4 to 80% for chronic postoperative renal insufficiency depending on the criteria used for definition (1-6), most authors agree that the incidence of renal function impairment increases over time (5-7).

In the largest multi-center trial to date identifying the incidence of chronic renal dysfunction following transplantation of a non-renal organ (defined as a creatinine clearance equal to or below 29ml/min per 1.73 m² of body surface area), 18% of liver transplant recipients (n=36,849) had associated chronic renal dysfunction, a number only exceeded by small bowel transplantation (21%, n=228) (6). This clearly emphasizes the need to better identify at-risk patients and to develop new strategies to prevent or minimize renal damage after liver transplantation.

In the reports of possible risk factors for renal dysfunction, there is no consensus on how to define that impairment. Some authors include mild degrees of damage where others use advanced renal failure and end stage renal disease (ESRD) requiring hemodialysis as their benchmark for study. Also, risk factors and especially prognosis are differently defined for acute and chronic renal failure.

Commonly suggested etiologies for acute postoperative renal function impairment include tubular necrosis caused by toxic or ischemic insults, pre-existing hepatorenal syndrome (HRS) (8), or drug-induced interstitial nephritis (9). Preoperative renal dysfunction, delayed or primary non-function of the liver graft as well as elevated bilirubin levels have been connected to acute renal failure in the early postoperative course (2, 10).

In a retrospective analysis of 1189 transplantations performed in our department, we found an incidence of acute renal failure (ARF) (defined as a serum creatinine above 1.6 mg/dL) in 41% of the transplant recipients (489 cases). The majority of these patients (322/ 27%) presented with creatinine elevations below 3mg/dL and did not
require hemodialysis. However, a significant number (131/11%) required replacement therapy (RRT), and in these patients preoperative renal dysfunction (Table 1) and increased immunosuppressant serum levels (Figure 1) were statistically indicative of possible risk. Other factors such as intra-operative hypotension, number of blood units given, graft cold ischemic time, age or gender showed no difference compared to patients with normal postoperative renal function. Although there was a great chance for recovery of renal function in all patients with ARF (95% of patients initially requiring renal replacement therapy had no symptoms of ARF at the end of the observation period of 100 days), in patients who required postoperative RRT long-term survival was significantly reduced (Figure 2).

For chronic renal dysfunction similar risk factors have been discussed, and age at time of transplantation, preoperative diabetes, dialysis prior to transplantation and hepatitis C have been variably shown to be associated with an increased risk of chronic renal insufficiency (6, 7, 11). All studies conducted so far agree on calcineurin inhibitor toxicity as the major source and predominant factor for chronic renal dysfunction in non-renal transplantation. Interestingly, in a meta-analysis by Ojo et al. (6) the excess risk of chronic failure after liver transplantation was only increased in cases with cyclosporine in the initial immunosuppressive protocol (relative risk 1.25; compared to tacrolimus relative risk 1.0), a result confirmed by a recently conducted retrospective analysis of our own patients, where we found cyclosporine but not tacrolimus in the initial immunosuppression protocol as the only independent risk factor for the development of chronic renal dysfunction (defined as creatinine ≥ 1.8mg/dL, observation period starting 3 months after transplantation, median follow-up 5.2 years). Chronic renal dysfunction in long-term survivors may progress into end-stage renal disease (ESRD). In a retrospective analysis by Fisher et al. (1), an incidence of chronic renal failure of 4% beyond 1 year after transplantation was found, and nearly half of these patients eventually developed ESRD. A similar result was reported by Gonwa et al. (4), in a ten year follow-up of 834 patients, where the incidence of chronic renal

### Tab. 1: Incidence and risk factors of acute renal dysfunction within 100 days following transplantation, overall 489 (41%) of 1189 primary liver transplantation had elevated serum creatinine levels (*significant versus I/II, p<0.05)

<table>
<thead>
<tr>
<th></th>
<th>I crea 1.6-3mg/dL</th>
<th>II crea&gt; 3mg/dL</th>
<th>III crea&gt; 3mg/dL + dialysis</th>
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<tr>
<td>Group</td>
<td>number patients</td>
<td>Age</td>
<td>Creatinine preoperatively</td>
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<tr>
<td></td>
<td>322 (27%)</td>
<td>49 (19-68)</td>
<td>1.09±0.49</td>
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<tr>
<td></td>
<td>36 (3%)</td>
<td>42 (20-62)</td>
<td>1.08±0.57</td>
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<tr>
<td></td>
<td>131 (11%)</td>
<td>52 (16-67)</td>
<td>1.51±1.15*</td>
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**Fig. 1:** Peak trough levels of calcineurin inhibitor (group I: crea 1.6 to 3mg/dL, group II: crea > 3mg/dL no dialysis, group III: crea > 3mg/dL + dialysis), (differences not significant)
dysfunction reached 14.4%, of which over 50% eventually developed ESRD (7.9%) defined as serum creatinine levels > 2.5mg/dl or requiring dialysis or kidney transplantation. Again, as a major risk factor calcineurin inhibitor toxicity was identified in 73.3% followed by hepatorenal syndrome and focal sclerosing glomerulonephritis (both 6.7%).

Influence of Renal Dysfunction on Patient Outcome

Similar to the large variation on reported incidences of renal failure post liver transplantation, studies on the impact of kidney dysfunction on patient and graft outcome also deliver variable and partially conflicting results. In a comparison to patients with normal kidney function, Ojo et al. found chronic renal failure associated with an elevated risk of death after transplantation (relative risk: 4.55, p<0.001). However, this increased risk could not be entirely attributed to patients with ESRD, since patients with chronic renal failure that had not yet progressed to ESRD had a risk of death nearly twice as high as patients with normal kidney function (6).

In a subset of our patients with chronic renal failure, we found a significantly reduced 5 or 10 year survival to 76 or 68%, respectively, in patients presenting with chronic renal dysfunction (CRD) (defined as creatinine ≥ 1.8mg/dl 3 months after transplantation) compared to patients with no or milder signs of CRD (5/10 year survival 84/76%). However, a further division of our CRD patients into an early (within the first) and late-onset (after the first year) group revealed a significant worsening in survival for the early-onset patient group (5/10 year survival: 66/46%).

For acute renal failure (ARF), in a series of 102 cases reported by Rimola et al. (12), there was a reported incidence of 48% (occurring within the first 6 days) in which renal dysfunction prior to transplantation appeared as a major contributing factor of death, and in a large retrospective analysis by Gonwa et al. (13) on 1535 liver transplantations, 1-year survival was significantly affected in patients with ARF requiring postoperative renal replacement therapy (RRT) compared to those who had already been on RRT preoperatively (41% vs. 73.6%, p=0.03). A more recent study by the same authors (14) not only confirms the impact of preoperative renal dysfunction on post-transplant outcome but also demonstrates the strong influence of the severity of preoperative renal dysfunction on the risk of death (preoperative serum creatinine of 0-0.99 mg/dl, 1-1.99 mg/dl, > 2.0 mg/dl or requiring RRT - relative risk of death following transplant: 1.11, 1.58, 1.77, and 1.44 respectively).

Fraley et al. (15), have previously reported that both pre- and post-operative acute renal failure are associated with an increased mortality, and a further stratification into subgroups who required postoperative intermittent hemodialysis, continuous renal replacement therapy (CRRT) or no dialysis showed the worst outcome for the CRRT group. In a consecutive analysis of 259 patients by Gainza et al. (16), mortality rate for patients requiring RRT was also increased tenfold (52.1 versus 6.8% in the total population studied, relative risk 24, p<0.001). These reports are partially reflected by a retrospective analysis of our department where only patients with acute renal failure who required RRT showed a significant reduction of survival (Figure 2).

Immunosuppression - Calcineurin Inhibitor Toxicity

Most immunosuppression protocols after organ transplantation are based on the calcineurin-inhibitors cyclosporine or tacrolimus. Although biochemically different, both drugs have similar mechanisms of action and help to protect the transplanted organ from rejection. However, they may also cause persistent renal vasoconstriction and endothelial lesions which will eventually lead into interstitial fibrosis and tubular atrophy in the kidney (17).

Thus, immunosuppressant nephrotoxicity is not only observed in kidney transplantation where the immunogenicity of the organ makes it more susceptible to drug toxicity (18, 19), it also affects a great proportion of patients with other non-renal solid organ transplantations where chronic nephrotoxicity can be found between 6.9% (combined heart and lung) and 21.3% (small intestine) and which significantly compromises survival in those patients (6).

The major problem of calcineurin inhibitors is their low therapeutic index. Their tolerability profile is characterized by a number of adverse effects that are related to exposure, including neurotoxicity, hypertension, hyperlipidemia and new-onset diabetes (20-23), but the most limiting side effect of the CNI’s cyclosporine and tacrolimus is acute or chronic nephrotoxicity (24, 25).
In contrast to the acute and dose-related reversible decrease of glomerular filtration rate, prolonged use of CNIs leads into an irreversible state of chronic kidney disease by interstitial fibrosis. Although the exact mechanisms are not yet solved, an angiotensin-dependent up-regulation of profibrotic factors such as transforming growth factor beta (TGF-β) and endothelin-1 has been discussed (26). Another contributing factor for the development of structural kidney damage evolves from the vasoconstrictive properties of CNI’s (27).

Regarding CNI toxicity, some studies including an early report from our department have found similar rates of nephrotoxicity using either cyclosporine or tacrolimus (3, 28), which seems logical since both drugs use similar pathways. However, other reports, including more recent data from our patients, have demonstrated a possible benefit of tacrolimus over cyclosporine on renal function in transplantation (6, 29, 30). However, validation of results comparing the risk of kidney failure through cyclosporine- or tacrolimus-based immunosuppression is often conflicting and of limited value due to inherent differences of study design. Also, many studies target on kidney transplant patients who lack their sympathetic renal innervation, which has been implicated as a possible contributing mechanism for calcineurin inhibitor toxicity (31), or on patients who were switched between two calcineurin inhibitors after chronic renal failure when irreversible structural changes within the kidney had already occurred (29, 30, 32-34). Although the nephrotoxic properties of calcineurin inhibitor treatment are well known (23, 28, 35, 36), the complexity of pathophysiologic changes leading to chronic renal function impairment after liver transplantation explains the variability of findings among different studies and so far inability to unambiguously identify patients at risk (3, 4, 6).

**Strategies to Reduce Renal Dysfunction after Liver Transplantation Immunossuppression**

Since most immunosuppressant drugs today are able to prevent acute rejection, the focus of interest has shifted from immunosuppressive potency to tolerability and long-term graft survival. In the management of liver transplant patients, the general idea remains that improvement of renal function can usually be achieved by reduction or change of immunosuppression in patients who develop chronic renal insufficiency but present with satisfactory liver graft function (37, 38). Problems occur in patients with co-existing acute liver transplant rejection and failure of renal function recovery after CNI reduction, as is likely in patients who have been on long-term CNI therapy (1, 39). Generally, in cases of liver transplant dysfunction with concomitant renal deterioration, the main emphasis is on preservation of the liver, with full dose calcineurin therapy, regardless of the impact on renal function, and since renal failure can be managed by hemodialysis but no replacement therapy exists for liver graft function, this approach has been justified.

One strategy to expand the therapeutic index of a calcineurin inhibitor-based immunosuppressive drug regimen is to combine immunosuppressive agents that interact in a synergistic fashion and allow for dose reduction of the combination partners, thus reducing toxicity while maintaining immunosuppressive potency (40, 41). With the mTOR inhibitor sirolimus, a promising combination partner for CNI’s has recently become available (42-44). As shown in clinical trials and in animal studies (45-47), an interaction between sirolimus and cyclosporine results in synergistic immunosuppressive activity. However, as a coincidental finding, although not nephrotoxic by itself, sirolimus enhances the negative effects of cyclosporine on kidney function, as demonstrated by a study of Kahan et al. (48) who found higher creatinine serum concentrations and reduced creatinine clearance in a cyclosporine/ sirolimus protocol compared to a cyclosporine/azathioprine control group after 6 and 12 months. It seems reasonable to expect that sirolimus would also enhance the negative effects of tacrolimus on kidney cell metabolism but preliminary clinical data suggests a better safety profile of this combination than cyclosporine/ sirolimus drug regimens (40, 41, 49).

Previous reports have demonstrated a possible recovery of renal function with the addition of MMF and dosage reduction of CNI for liver and heart transplantation (35, 50). In other studies, focusing on patients with more severe renal insufficiency, the decrease of CNI dosage was less successful (37, 51). Several clinical studies have tried to reduce the doses of CNI’s, to discontinue CNIs or to start de novo transplant patients on CNI-free immunosuppressive protocols (21, 36, 52-54), but success has been limited, and a proportion of patients remain in which progression of structural kidney damage has proceeded too far for successful rescue therapy. This factor probably explains a finding in a retrospective analysis of a subgroup of our patients with severe chronic renal failure (defined as an increase of serum creatinine ≥ 1.8mg/dL) where we were unable to demonstrate a clear benefit of immunosuppressive protocols adding MMF to calcineurin inhibitors. In an observation period of three years, elevated serum creatinine decreased in 55% of patients (76/137), remained unchanged in 18% (24/137) or increased in 27% (37/137), and this tendency did not differ significantly in those cases treated with additional MMF and CNI dose reduction (n=44) (48% decrease, 21% no change, 32% increase) compared to those receiving no MMF treatment (n=93) (59% decrease, 16% no change, 25% increase; p=0.821). Although patients receiving MMF therapy had higher creatinine levels at entry (2.4 ± 1.4mg/dL) compared to non-MMF treated cases (2.1 ± 0.5mg/dL), MMF treatment did not lead to a significant change of mean serum creatinine levels compared to non-MMF treatment either (Figure 3), which could be a result of the higher percentage of non-responders in the MMF group. A further split of MMF/no MMF groups in either FK or CyA treatment basically confirmed this result, showing no benefit for either CNI. Nevertheless, recent studies clearly demonstrate a benefit of MMF in patients with renal dysfunction after liver transplantation (51, 55). Studies without calcineurin inhibitors during the early post-transplant period using sirolimus/ azathioprine/ prednisone (45) or sirolimus/ mycophenolate mofetil/ prednisone (43) reported that up to 40% of the patients required treatment for acute rejection, and it seems like the use of calcineurin-based drug regimens during the early postoperative period is necessary to reduce the incidence of acute rejection. Even be-
several of which enhance toxicities of immunosuppressants and other drugs, today most patients receive multiple (28, 57, 58). This is not surprising since not a viable strategy to prevent toxicity in liver transplantation, it seems ing incidence of chronic renal dysfunc- tion (CRD) (n=137/1173; 11.7%), Immunosuppression: CNI+MMF/CNI+no MMF (n=44/93) (inclusion criteria for CRD: minimum creatinine of 1.8mg/dL for a minimum of 14 days). Higher variation of creatinine levels among patients treated with MMF compared to CNI mono-therapy. (0-3: years after transplantation). (One-way ANOVA: differences between groups not significant)

**Future Perspectives - Novel Strategies to Monitor Immunosuppressant Toxicity**

The key to reduce or avoid the negative effects of immunosuppressant nephrotoxicity is early detection. Whereas acute toxicity is most often induced by increased drug exposure and can usually be controlled by therapeutic drug monitoring, detection and avoidance of the multifactorial state of chronic nephrotoxicity is more challenging, and the assessment of serum creatinine and histology as the most common tools to monitor kidney function and nephrotoxicity are not sensitive enough and often only reflect irreversible structural damage of the kidney. The value of pharmacokinetic therapeutic drug monitoring to prevent chronic toxicity in itself is controversial, and with the growing incidence of chronic renal dysfunction in liver transplantation, it seems not a viable strategy to prevent toxicity (28, 57, 58). This is not surprising since today most patients receive multiple immunosuppressants and other drugs, several of which enhance toxicities when combined (59).

Pharmacodynamic assays to monitor immunosuppressive activity based on assessment of lymphocyte proliferation, expression of surface markers on T-cells, production of cytokines by T-cells and quantification of the interaction between the drug and its molecular targets as surrogate markers for pharmacodynamic response have been developed (57, 60), but either failed to successfully detect patients at risk at an early stage or were inapplicable in the clinical routine. This is partially because, in contrast to the immunosuppressive mechanisms, the biochemistry underlying calcineurin inhibitor and/or sirolimus toxicities is still poorly understood (61-64).

Thus, as a future perspective, modern screening technologies such as genetics (genomics), protein profiling (proteomics) and biochemical profiling (metabonomics) which is defined as “a quantitative measurement of multiparametric metabolic responses of multicellular systems to pathophysiological stimuli” (65), provide attractive new strategies to characterize the mechanisms leading to nephrotoxicity by the identification of certain biomarker patterns as molecular “signatures” that might allow for monitoring of immuno- suppressant toxicity (57). Major technologies for the detection of such subtle mechanistic changes are provided by the very sensitive diagnostic tools of magnetic resonance spectroscopy and mass spectrometry.

In general, specific biomarker patterns defined as “characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacological response to therapeutic intervention” will confer significantly more information than a single measurement and enable better specificity and sensitivity (66, 67). An ideal case scenario for diagnostic testing is the use of readily available body fluids such as plasma and urine for biomarker analysis, which is based on the concept that all cells either directly or indirectly (via extracel- lular fluid) communicate with body fluids and that cell metabolites, peptides and proteins will be released by the cells via normal excretion, trans-membrane diffusion and transport as well as after cell death (68). Thus changes in protein, peptide and metabolite patterns in body fluids would, to a certain extent, be reflective of intra-cellular changes.

**Conclusions**

With the introduction of the MELD score and further improvements in general care allowing for longer survival of liver transplant patients, acute and especially chronic renal dysfunction are a growing problem that influences patients’ outcome and increases the need of long-term renal replacement therapy and concomitant kidney transplantation. This not only compromises patients’ quality of life but also presents a major cost factor for our health system. It is therefore essential to implement preventive measures when possible. This includes a thorough assessment of preexisting renal dysfunction and a further improvement of perioperative care to minimize the risk of acute postoperative renal failure. Since calcineurin inhibitors have been identified as a key risk factor for acute and chronic nephrotoxicity, active strategies should concentrate on optimizing calcineurin inhibitor treatment protocols with the addition of alternative drugs such as MMF and sirolimus if possible, or even calcineurin inhibitor free maintenance protocols. Also, the employment of monoclonal antibodies and delayed introduction of CNI’s in the early phase
could reduce the risk of acute renal failure. Moreover, the development of new immunosuppressant drugs that are equally potent to prevent rejection but less nephrotoxic than cyclosporine are warranted. Until then, future strategies should focus on a better understanding of mechanisms behind nephrotoxicity, which would lead to better diagnostics, help to identify at-risk patients earlier and allow for kidney rescue therapies to commence before structural damage occurs and facilitate an individualization of immunosuppressive therapy.

References


\[ \text{Author: V. Schmitz, G. Puhl} \]

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Matthias Glanemann, Thomas Henneberg

Therapiestandards der chirurgischen Intensivstation

Das Buch beinhaltet neben intensivmedizinischen Grundlagen eine Ansammlung operationsspezifischer Behandlungspläne, die zu einem besseren Verständnis und zur Vereinheitlichung der postoperativen Therapie führen sollen. Es richtet sich vor allem an Neuanwärter auf der Intensivstation, um die ersten Tage und Wochen klarer und hoffentlich stressfreier zu erleben. So ist das Buch in drei Abschnitte gegliedert. Im ersten Teil soll grundlegendes intensivmedizinisches Verständnis vermittelt werden, wohingegen im zweiten Teil besonderes Augenmerk auf die chirurgischen Besonderheiten und postoperativen Implikationen der einzelnen Operationen gelegt wird. Im dritten Abschnitt werden die wichtigsten Notfälle beschrieben.

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Dr. Volker Schmitz
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Charité, Campus Virchow
Medizinische Fakultät der Humboldt Universität zu Berlin
Augustenburger Platz 1
13353 Berlin
E-Mail: volker.schmitz@charite.de