Published in final edited form as:
Biol Blood Marrow Transplant. 2011 November ; 17(11): 1573–1584. doi:10.1016/j.bbmt.2011.09.013.

NCI, NHLBI First International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: Long Term Organ Damage and Dysfunction Following Pediatric Hematopoietic Cell Transplantation

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Abstract

Long term complications following hematopoietic cell transplantation (HCT) have undergone comprehensive study. Although virtually every organ system can be adversely affected after HCT, the underlying pathophysiology of these late effects are incompletely understood. This manuscript describes current understanding of the pathophysiology of late effects involving the gastrointestinal, renal, cardiac, pulmonary systems along with a discussion of post-HCT metabolic syndrome studies. The patient's underlying disease, pretransplant exposures, transplant conditioning regimens, graft versus host disease (GVHD) and other therapies contribute to these problems. Because organ systems are interdependent, long term complications with similar pathophysiology often involve multiple organ systems. Current data suggest that post-HCT organ complications occur as a result of cellular damage that leads to a cascade of complex events. The interplay between inflammatory processes and dysregulated cellular repair likely contributes to end-organ fibrosis and dysfunction. Though many long term problems cannot be prevented, appropriate monitoring can lead to detection and organ-preserving medical management at earlier stages. Currently, management strategies are aimed at minimizing symptoms and optimizing function.

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There remain significant gaps in knowledge regarding pathophysiology of therapy-related organ toxicities disease following HCT. These gaps can be filled by closely examining disease biology and defining which patients are at highest risk of adverse outcomes. In addition, strategies should be developed for targeted disease prevention and health promotion efforts for individuals at high risk because of their genetic makeup or specific exposure profile.

Introduction

The incidence of and risk factors for long term complications following hematopoietic cell transplantation (HCT) have undergone comprehensive study. Virtually every organ system can be adversely affected in some way after HCT and although much is known about these potential toxicities, the underlying pathophysiology of most are incompletely understood.

In April 2011 an NCI/NHLBI sponsored consensus conference of international experts in clinical and biological research into late effects after HCT convened to review the state of the science of pediatric studies and identify key areas for future research. This manuscript will describe the conclusions shared at that conference relating to the pathophysiology of late effects involving the gastrointestinal, renal, cardiac, metabolic, and pulmonary systems. The patient's underlying disease, pretransplant exposures, transplant conditioning regimens, graft versus host disease (GVHD) and other therapies all contribute to these problems. Since no organ system functions independently, it is clear that long term complications are usually inter-related and rarely limited to one system.

Iron Overload

Secondary iron overload is a nearly universal complication of HCT; the most troublesome complications are not hepatic, but cardiac, pancreatic, pituitary and thyroid-related. It develops from repeated red blood cell transfusions and increased gastrointestinal iron absorption in the setting of ineffective erythropoiesis and inflammatory conditions, including GVHD.[1] The iron burden among patients presenting for transplantation for chronic anemias or protracted hematologic malignancy can be substantial.[2,3] Iron overload after transplantation for hematologic malignancy is very common, ranging from 1832–13120g/g dry weight (measured biochemically) before day 100 after HCT.[4] Except in patients transplanted for thalassemia[5], the effects of iron overload on morbidity in transplant survivors have not been fully investigated.

Recent studies using serum ferritin as a marker suggest that iron levels fall slowly over time after transplant, reaching normal levels years later.[6,7] Humans cannot excrete excess iron; iron mobilization and removal is needed to accelerate this process when prolonged iron excess could lead to excessive morbidity.[8] Phlebotomy can mobilize iron from overloaded tissues if patients have recovered normal erythropoiesis.[9] In heavily iron-overloaded patients, iron reduction therapy may improve transplantation outcomes[10] and cardiac function[5], but few data are available for transplant survivors from underlying diseases other than thalassemia. Table 1 provides a literature summary of the adverse health outcomes from excess body iron.

Application of iron-specific MRI to the study of transplant survivors is lacking. Risk factor analyses of survivors, with iron burden as a co-factor, have not been carried out with regard to cardiac events, growth and development, gonadal development, fertility, endocrine dysfunction, fibrotic liver disease, and secondary malignancy. The threshold of cardiac iron concentration for cardiac events is unknown. The most important recent development has been standardization of the T2* MRI method of quantifying tissue iron. This methodology will provide a foundation for future studies of transplant survivors. Using T2* MRI,

epidemiologic studies using several study designs (prospective, cross-sectional, and disease-specific) are urgently needed to better understand the role of iron overload on long-term transplant outcomes. Intervention studies should then follow.

Gastrointestinal, Hepatobiliary, and Pancreatic Dysfunction

Gut symptoms in the years following transplant are usually a continuation of problems during the first year (protracted acute GVHD, chronic GVHD, medication side effects, and infection related to immune suppression). The frequency and severity of these problems wanes with time—but new problems involving the gut and liver may arise decades later. Table 2 describes the symptoms and causes of gastrointestinal problems associated with transplantation.

The majority of GI late effects are GVHD-related. Unfortunately, the significant current knowledge gaps include the mystery of why some patients fail to develop graft tolerance and why others suffer from refractory chronic GVHD. Current research on GVHD biomarkers may help identify flares so that pre-emptive therapy can be given. In the future, focus areas should include acceleration of immune reconstitution, development of tolerance, and discovery of markers of incipient GVHD. New therapies for protracted acute and chronic GVHD are urgently needed.

Chronic Kidney Disease (CKD)

CKD is frequently diagnosed after transplant. There are multiple clinical forms of CKD but the most commonly described ones include thrombotic microangiopathy, nephrotic syndrome, calcineurin inhibitor toxicity, acute kidney injury and GVHD-related CKD. Various risk factors associated with the development of CKD have been described; however, outlined below are recent studies that suggest that GVHD may also be a proximal cause of renal injury.

In a systematic review of 9317 adults and children who underwent HCT from 28 study cohorts, approximately 16.6% (3.6% to 89%) of patients developed CKD defined as a decrease in estimated glomerular filtration rate (eGFR) of at least 24.5 mL/min/1.73 m^2 within the first year after transplant[55]. The cumulative incidence of CKD developing approximately 5 years after transplant ranges from 4.4%–44.3% depending on type of transplant and stage of CKD.[56,57] Mortality rates among patients with CKD in this setting are significantly higher than in transplant recipients who retain normal renal function, even when controlled for co-morbidities[58] Patients who develop CKD after HCT have a range of possible outcomes, including end-stage renal disease (ESRD) requiring chronic dialysis and renal transplant.

The mechanisms of HCT-related chronic renal dysfunction are still unknown. Although many clinical factors have been associated with the development of CKD, findings from the Seattle group and others have refuted previous traditional risk factors such as TBI. [59–61] These new data suggest that both acute and chronic graft vs. host disease (GVHD) are the primary pathogenic mechanisms. Early studies focused on patients receiving TBI as part of their conditioning regimen who later developed hemolytic uremic syndrome (HUS) [62–67] or on patients who developed nephrotic syndrome after HCT [68]. However, these are specific subtypes of renal disease and likely do not account for the majority of cases of CKD. Current thought regarding the pathophysiology of CKD implicates GVHD and/or the therapies used to manage GVHD. (Figure 1).

This new paradigm positing HCT-related CKD as a renal manifestation of GVHD could occur through two different mechanisms: the kidney could be a direct target of T-cell

mediated renal damage or the chronic systemic inflammatory state of GVHD could lead secondarily to cytokine-mediated nephropathy. A third potential explanation is that chronic exposure to calcineurin inhibitors, such as cyclosporine and tacrolimus used for GVHD prevention and/or treatment, causes CKD. These are not mutually exclusive hypotheses as T-cell mediated injury in GVHD is intertwined with cytokine effects,[69] and the effects of cyclosporine can be potentiated in the presence of a chronic inflammatory state. In an autopsy study of 26 autologous and allogeneic transplant patients, renal tubulitis identical to that seen in renal allograft rejection was present in 67% of patients. [70] In a report of minimal change nephrotic syndrome that developed after HCT, large numbers of CD8+ donor T-cells were found infiltrating the interstitium and periglomerular areas of the kidney.[71] A mouse model of GVHD kidney disease has shown that progressive venulitis, endothelialitis and tubulitis can begin within 2 weeks of transplant.[72]

Although albuminuria and other conventional risk factors for renal disease progression have been identified in other patient populations, little is known about risk factors for CKD progression or why CKD and proteinuria increase nonrelapse mortality in the HCT patient population. In a cohort of 142 patients (median age 47 years) undergoing their first HCT, albuminuria and proteinuria at day 100 were associated with an increased risk of CKD and non-relapse (HR=12.8; 95% CI 2.7–60.6) and overall mortality (HR=7.7; 95%CI 2.4–24.7) respectively 1 year after transplant (Figure 2 and 3)[73]. In a cohort of 376 patients with CKD at 1 year, (defined as a GFR <60 ml/min/1.73 m^2), 8% of the 109 patients for whom follow-up data was available (up to 8 years), progressed to ESRD.

Albuminuria and proteinuria may reflect GVHD-induced endothelial injury, inflammatory tubular and interstitial damage and progressive CKD; however, it is not known if albuminuria or proteinuria by themselves cause the increased morbidity and mortality of HCT, or merely reflect other processes. Recent research has focused on the direct role of albuminuria and proteinuria on progression of CKD [see review][74]. It is thought that albuminuria triggers the release of pro-inflammatory cytokines and chemokines that recruit macrophages and other inflammatory cells into the interstitium causing fibrosis and progression of CKD. It may be that in HCT patients, inflammatory damage to the tubules from GVHD leads to albuminuria and the latter is a manifestation of renal GVHD. Establishing such a mechanism would have important therapeutic implications. Thus, it is critical to determine if albuminuria and proteinuria are epiphenomenon or true independent risk factors for progression and mortality in the HCT population before changes in management can be proposed in a prospective clinical trial. Longer term follow-up is needed in these patients to determine whether patients progress from albuminuria to overt proteinuria and then to ESRD or if these conditions resolve when their GVHD and its associated inflammation are successfully treated.

Extrapolating from the studies in the diabetic population, we speculate that ACEI and ARB would be useful in patients with albuminuria and hypertension after HCT. In fact, Cohen and colleagues led a single institution trial in which patients were randomized to receive either captopril (n=28) or placebo (n=27) starting at Day + 35 after HCT.[75] Patients who received placebo had a 15% incidence at one year of developing hemolytic uremic syndrome, compared to a 4% incidence in treated patients. Five year survival was 20% in the placebo group and 45% in the captopril group.

Current evidence suggests a need to think differently about CKD in patients after HCT. Most post-HCT CKD is not secondary to TBI or cyclosporine use but rather can be a consequence of nephropathic processes such as GVHD and the chronic inflammatory state that accompanies it (Figure 1). It is clear that we first need to better define the scope of the problem of CKD in this patient population using accurate and sensitive measures of kidney

function. Identifying those patients at risk for the development of CKD will be important for early intervention and even prevention clinical trials in this patient population. In order to determine how to minimize and treat CKD, future studies will need to focus on the mechanisms by which GVHD leads to renal injury, determining if albuminuria is an indicator of disease or a target for therapy, optimizing prevention strategies and deciding how best to measure post-transplant renal function.

Cardiovascular Disease

Cardiovascular complications are a leading cause of therapy-related morbidity and mortality in long-term survivors of childhood malignancy.[76–79] In patients who do not undergo hematopoietic cell transplantation (HCT), it is well-recognized that there is a strong dose-dependent association between anthracycline exposure and risk of CHF; this risk is modified by younger age at exposure, female gender, and chest irradiation.[80–83] Less is known regarding the incidence and predictors of CHF following HCT in childhood. Potentially cardiotoxic exposures unique to HCT include conditioning with high-dose chemotherapy (especially cyclophosphamide) and total body irradiation (TBI).[83] In addition, HCT survivors are at increased risk of developing cardiovascular risk factors such as hypertension and diabetes due, in part, to exposure to TBI, prolonged immunosuppressive therapy following allogeneic HCT, or other health conditions such as hypothyroidism or growth hormone deficiency.[83,84] The modifying influence of these cardiovascular risk factors on risk of CHF following cardiotoxic therapy has also not been fully investigated.

The independent role of pre-HCT exposure to therapeutic agents, transplant-related conditioning and co-morbidities in the development of late CHF after HCT has been recently examined.[85] From a cohort of nearly 3,000 1+ year survivors who underwent HCT, patients with late CHF were identified. Pre-HCT exposure to anthracyclines and the presence of post-HCT co-morbidities were primarily responsible for the risk of late CHF after HCT. Conditioning-related exposures did not appear to contribute significantly to this risk. The cardiotoxic effect of anthracyclines was highest for autologous HCT recipients, with a cumulative dose of ≥250 mg/m^2 being associated with a 30-fold increased risk of late CHF. Overall survival was less than 50% at 2 years after CHF diagnosis. A subsequent study[86] evaluating long-term health-related outcomes in three cohorts - conventionally treated childhood cancer survivors, survivors of childhood HCT, and sibling controls – revealed that while survivors of HCT were at a 13-fold risk of severe or life-threatening cardiovascular complications when compared to healthy controls, the risk was equivalent to that seen in conventionally treated patients. One possible explanation for this finding is that, as seen in previous studies,[87,88] the risk for late-occurring cardiovascular complications following HCT may be largely due to pre-HCT therapeutic exposures, with little additional risk from conditioning-related exposures or GvHD.

It is becoming increasingly recognized that risks for many diseases result from an interaction between inherited gene variants and environmental factors, including chemical, physical, and behavioral factors. However, there continue to be large gaps in knowledge with regards to the pathogenesis of therapy-related adverse events. There is emerging evidence to suggest that individual genetic susceptibility could be a determinant of therapy-related CHF.[89,90] Significant cardiotoxicity has been reported at cumulative doses of less than 250 mg/m^2,[9] while doses that exceed 1000 mg/m^2 have been tolerated without long-term sequelae by a few individuals.[91] Among long-term HCT survivors, 40% of cases with clinical CHF had received a cumulative dose of less than 250 mg/m^2.[11] This heterogeneity could be explained, in part, by the presence of genetic polymorphisms that alter the metabolism of anthracyclines, the myocardial response to the drug, as well as other factors thought to play a role in susceptibility to *de novo* disease.[89,90,92]

Using a nested case-control study design the role of functional SNPs in genes involved in free radical metabolism (NAD[P]H oxidase: subunits *NCF4*, *RAC2*, *CYBA*) as well as those impacting synthesis of cardiotoxic anthracycline alcohol metabolites (carbonyl reductase: *CBR1* and *CBR3*) in modifying of risk of CHF following HCT was recently examined.[93] Patients with CHF and controls (without CHF) were matched by: age at HCT, type of HCT, ethnicity, anthracycline dose, and length of follow-up. Multivariate conditional logistic regression revealed that a polymorphism in the NAD(P)H oxidase subunit *RAC2* (rs13058338, 7508T→A) conferred a 3.2-fold risk of A-CHF (Odds Ratio [OR]: 3.2; p=0.05), and there was a 10.8-fold risk (OR: 10.8, p=0.04) for those with the GG genotype of rs9024 (1096G→A) in *CBR1*. These preliminary findings support the "unifying hypothesis"[94] that A-CHF could develop as a result of oxidative stress or metabolic derangements induced by cardiotoxic alcohol metabolites, and that the high-risk variants of *RAC2* and *CBR1* play a critical role in modifying this risk. If these findings are replicated and confirmed by others in independent study samples, they could set the stage for identifying a subgroup of patients up front who could perhaps receive alternative treatment for management of their cancer; while for those who have already received the anthracyclines, identification of high-risk alleles would warrant closer surveillance for cardiotoxicity and use of medications that modulate cardiac function.

Insulin Resistance and Abnormal Body Composition

Survivors after allogeneic HCT have a risk of premature cardiovascular (CV) related death that is increased 2.3-fold compared to the general population.[96,97] The exact etiology of CV risk and subsequent death is largely unknown, although development of "metabolic syndrome" (the constellation of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension, that is associated with a substantially increased risk for type 2 diabetes mellitus and atherosclerotic CV disease; see Table 3) and more specifically, insulin resistance as a consequence of HCT has been suggested.[98–100] In studies of conventionally treated leukemia survivors compared to those who underwent HCT, transplant survivors are significantly more likely to manifest metabolic syndrome or multiple adverse cardiac risk factors including central adiposity, hypertension (HTN), insulin resistance and dyslipidemia.[102,103] The concern over time is that survivors who develop metabolic syndrome after HCT will be at higher risk for developing significant CV related events and/or premature death from CV related causes. The Bone Marrow Transplant Survivor Study examined diabetes, hypertension, and cardiovascular events in 1089 patients who were two or more year survivors after HCT.[103] At a mean age of 39 years and with a mean follow-up after HCT of nearly 9 years, survivors of allogeneic HCT were 3.6 times more likely to report diabetes than siblings and 2 times more likely to report hypertension. TBI exposure was also associated with an increased risk of diabetes (OR=3.42; 95% CI, 1.55– 7.52). Rates of CV outcomes also have been examined among nearly 1,500 >2 year transplant survivors treated in Seattle from 1985–2006 relative to an age, year, and sex matched population-based comparison group.[104] Using state hospital and death registry data defining key CV outcomes, survivors experienced increased rates of cardiovascular death and had an increased cumulative incidence of ischemic heart disease, cardiomyopathy/heart failure, stroke, vascular diseases, and rhythm disorders. Survivors also had an increased cumulative incidence of related conditions that predispose towards more serious cardiovascular disease: hypertension, renal disease, dyslipidemia, and diabetes.

Many gaps exist in our current knowledge of why HCT survivors have a higher risk of adverse CV outcomes. While descriptive and epidemiologic based studies have at least made us aware of the problem, they have thus far provided little information into the underlying pathophysiology of CV disease in HCT survivors or why these events are happening in HCT survivors at greater frequency than in the general population. We also know little if anything

about whether there are preventative strategies or other interventions that may modify this risk.

The association of obesity with diabetes and CV disease risk in the general population is well established, but obesity as determined by body mass index (BMI) is uncommon in long term survivors after HCT.[103] However, despite having a normal BMI, HCT survivors develop significantly altered body composition that results in both an increase in total percent fat mass (PFM) as well as a reduction in lean body mass (LBM). This finding is termed “sarcopenic obesity” and results in a loss of myocyte insulin receptors and an increase in adipocyte insulin receptors, the latter of which are less efficient in binding insulin and clearing glucose ultimately contributing to insulin resistance.[104–106] Preliminary data from 119 children and young adults (current mean age 26.1(±0.8) yr, 61.3% male) who had received HCT at a mean age of 12.2 yr, ±0.6) and 81 healthy sibling controls (current mean age 22.8(±0.9)yr, 49.4% male) found that compared to siblings, HCT survivors had significantly lower weight but no differences in BMI or waist circumference.[107] HCT survivors had significantly higher PFM and lower LBM. Insulin resistance was measured by means of euglycemic hyperinslulinemic clamp studies and results were adjusted for PFM. HCT survivors were significantly more insulin resistant than controls and they also had other CV risk factors (significantly higher levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides). Interestingly, these differences were only found in patients who had received TBI as part of their transplant conditioning regimen. These preliminary data are thus revealing that even at a relatively young age HCT survivors have increased CV risk factors which are independent of obesity, but may be related to alterations in body composition (↓LBM and ↑PFM), insulin resistance and exposure to TBI.

While it is becoming more evident that HCT survivors are at risk for developing insulin resistance, the mechanistic pathways and risk factors leading to this are still undefined and thus determining more specifically what these are at a cellular and genetic level will be critical. Additionally, further definition of the role that alteration in body composition plays in insulin resistance and CV risk in HCT survivors is needed. Whether CV risk and abnormal body composition is related primarily to TBI exposure, corticosteroid exposure, a chronic inflammatory state (mediated or related to graft vs. host disease), or some other mechanism needs to be carefully examined. Finally, the post-HCT time course of development of adverse CV risk factors and changes in body composition begins will be important to determine and will guide us in devising preventative strategies and interventions.

Chronic Pulmonary Dysfunction

Decline in lung function is a significant complication in the months and years following successful allogeneic-HCT. Two forms of chronic pulmonary dysfunction are commonly observed: obstructive lung disease (OLD) and restrictive lung disease (RLD).[113–117] The incidence of both forms of lung toxicity can range from 10% to 40% depending upon donor source, the time interval after HCT, definition applied and presence of chronic GVHD.[113] In each scenario, collagen deposition and the development of fibrosis either in the interstitial (RLD) or peri-bronchiolar (OLD) space are believed to contribute to the patterns of lung dysfunction displayed on pulmonary function tests (PFTs).[118]

The most common form of OLD following allogeneic-HSCT is bronchiolitis obliterans (BO).[115,119,120] First reported in the 1980’s, BO is a serious and potentially life-threatening late effect that is characterized by an inflammatory process resulting in bronchiolar obliteration, fibrosis and progressive obstructive lung disease.[113] Historically, the term BO has been used to describe “chronic GVHD of the lung” and begins 6–20 months after HSCT.

Patients with BO may be initially asymptomatic, but typically present with a cough, wheezing or dyspnea on exertion.[118] PFTs show OLD with general preservation of forced vital capacity (FVC), reductions in forced expiratory volume in one second (FEV1) and associated decreases in the FEV1/FVC ratio with or with out significant declines in the DLCO.[121] The diagnosis of OLD without histologic confirmation is commonly referred to as bronchiolitis obliterans syndrome or BOS. More recently, “air flow obstruction” has been defined as a more than 5% per year decline in percent predicted FEV_1 with the lowest post-transplant FEV_1/FVC ratio less than 0.8.[122] Risk factors for BO include lower pre-transplant FEV_1/FVC values, concomitant pulmonary infections, chronic aspiration, acute and chronic GVHD, older recipient age, the use of mismatched donors and high dose (vs. reduced intensity) conditioning.[113,119] The clinical course of BO is variable, but patients frequently develop progressive and debilitating respiratory failure despite the initiation of enhanced immunosuppression.[113]

RLD is defined by reductions in FVC, total lung capacity (TLC) and diffusion capacity of the lung for carbon monoxide (DLCO). In contrast to OLD, the FEV_1/FVC ratio is maintained near 100%. RLD is common after HSCT and has been reported in as many as 25% to 45% of patients by day 100.[113] Importantly, declines in TLC or FVC occurring at 100 days and one year after HCT are associated with an increase in non-relapse mortality. Early reports suggested that the incidence of RLD increases with advancing recipient age, but more recent studies have revealed significant RLD in children receiving HCT.[123] The most recognizable form of RLD is bronchiolitis obliterans organizing pneumonia (BOOP). Clinical features include dry cough, shortness of breath and fever. Radiographic findings show diffuse, peripheral, fluffy infiltrates consistent with airspace consolidation. Although reported in less than 10% of HSCT recipients, the development of BOOP is strongly associated with prior acute and chronic GVHD.[124]

The complex pathophysiology of chronic lung injury after HCT is poorly understood and represents the most significant gap in current knowledge for this spectrum of late effects. This limitation stems from the paucity of 1) correlative data obtained from afflicted HCT recipients, 2) controlled clinical trials and 3) suitable animal models for either RLD or OLD. RLD and OLD after HCT likely involve an initial insult to pulmonary vascular endothelium and leukocyte recruitment into the lung parenchyma followed by a dysregulated reparative response characterized by the interplay between recruited donor-derived leukocytes, bronchiolar and interstitial epithelial cells and lung fibroblasts and the ultimate deposition of collagen.[113] The possible role of innate immunity in the development of OLD was recently highlighted by two clinical studies. Investigators have found that genetic variations in the bactericidal/permeability-increasing (BPI) protein and nucleotide-binding oligomerization domain containing 2 / caspase recruitment domain family member 15 (NOD2/CARD15) influence the risk of airflow obstruction and BO after allogeneic-HCT.[125,126]

A tri-phasic model of RLD and OLD after HCT has been proposed wherein alloantigen recognition is the inciting stimulus for pulmonary inflammation.[113] In phase I, an acute pneumonitis develops as a consequence of an allo-immune response, resulting in the sequential influx of lymphocytes, macrophages and neutrophils into an inflamed lung parenchyma. In phase II, the persistence of an inflammatory signal in the setting of exuberant repair mechanisms promotes the transition from acute to chronic injury. If the inciting injurious stimuli predominantly involves bronchiolar epithelial cells, phase II is associated with the concentric infiltration of lymphocytes and collagen deposition in the peri-bronchiolar areas resulting in the development of chronic bronchiolitis. If, by contrast, the principal target of early damage is the alveolar epithelium, leukocyte recruitment and matrix deposition during phase II are confined primarily to the interstitial space. Activated lymphocytes then migrate into the airway mucosa and contribute to epithelial injury. As

chronic inflammation proceeds to phase III, lung fibroblasts increase in number and contribute to the enhanced deposition of collagen and granulation tissue in and around bronchial structures, ultimately resulting in complete obliteration of small airways and fixed obstructive defects. Similarly, fibroblast proliferation and intra-septal collagen deposition during phase III ultimately results in interstitial thickening, septal fibrosis, significant volume loss and severe restrictive lung disease.

Clinical and experimental data suggest that the progression to a chronic, pro-fibrotic form of pulmonary toxicity involves the secretion of immunomodulatory proteins, and in this context, TNFα may be a central factor in the tri-phasic model outlined above. Strong evidence for a role of TNFα in the transition from acute to chronic lung injury comes from a study using transgenic mice with targeted over-expression of TNFα in the lungs. Early lung histopathology includes a robust leukocytic infiltrate whereas prolonged exposure to TNFα results in chronic inflammation and fibrosis[127].

Patients with more severe disease at the time of diagnosis tend to have a poor prognosis; early recognition and treatment may be important to successful outcomes. Hence, increased surveillance for lung dysfunction by serial PFTs (including an assessment of lung volumes, spirometry and diffusion capacity) for the first two years following HCT should be considered whenever feasible. Given the significant morbidity and mortality associated with advanced OLD and RLD, a careful, comprehensive evaluation is recommended once persistent signs or symptoms of pulmonary dysfunction are detected.[119,120] Testing should include a high-resolution, computer-assisted tomography (CT) scan of the chest and broncho-alveolar lavage to exclude opportunistic infections. Lung biopsy can also be quite helpful in making a definitive diagnosis.

The “standard” therapy for OLD combines enhanced immunosuppression in conjunction with supportive care including antimicrobial prophylaxis, bronchodilator therapy and supplemental oxygen when indicated. While the approach to RLD is less well defined, increasing evidence suggests that this form of pulmonary dysfunction may also be immunologically mediated.[124] Unfortunately, the response to multiple agents including corticosteroids, cyclosporine, tacrolimus and azathioprine is limited and tends to occur only early in the course of treatment.[113] The potential role for TNFα in the pathogenesis of both OLD and RLD suggests that neutralizing agents such as etanercept (Enbrel ®, Amgen Inc) may have promise.[128] The combination of azithromycin, montelukast (FAM) and inhaled fluticasone is currently being investigated to prevent progression of newly-diagnosed BOS.[129]

Non-infectious lung injury remains a significant problem following allogeneic-HSCT. It is extremely important to determine if the lung is a target of GVHD. Similarities between the histopathologic features of BO seen in association with OLD after allogeneic-HSCT and during lung allograft rejection, together with reports of improvement in lung function with immunosuppression, strongly suggest that pathways of allo-immune activation are operative. Further research into mechanisms of chronic lung injury after HSCT is paramount for improving our understanding of this debilitating spectrum of late effects and the development of novel therapeutic strategies for treatment and prevention. Studying a tri-phasic model of chronic, non-infectious lung injury after HCT that involves T cell activation, leukocyte recruitment, the deposition of collagen and the development of fibrosis may lead to improvements in therapy. Finally, discovering what determines the anatomic specificity (peribronchiolar vs. interstitial) of chronic lung injury and understanding the role of acute inflammation in the initial damage to the alveolar or bronchiolar epithelium will enhance our understanding of post transplant pulmonary dysfunction.

CONCLUSION

Current data suggest that post-HCT organ complications occur as a result of cellular damage that leads to a cascade of complex events. The degree of cellular damage that occurs is related to the overall health status, presence of other co-morbidities and baseline organ function of the pre-HCT recipient, with additional impact related to the intensity of the conditioning regimen, infections, drug exposures, and delayed immune tolerance. The interplay inflammatory processes and dysregulated cellular repair likely contributes to end-organ fibrosis and dysfunction (Figure 4).

HCT survivors have a high burden of morbidity; especially as it relates to development of organ specific late effects after HCT. However, there remain significant gaps in knowledge regarding pathophysiology of therapy-related organ toxicities disease following HCT. These gaps can be filled by closely examining disease biology and defining which patients are at highest risk of these adverse outcomes. In addition, strategies should be developed for targeted disease prevention and health promotion efforts for individuals at high risk because of their genetic makeup or specific exposure profile.

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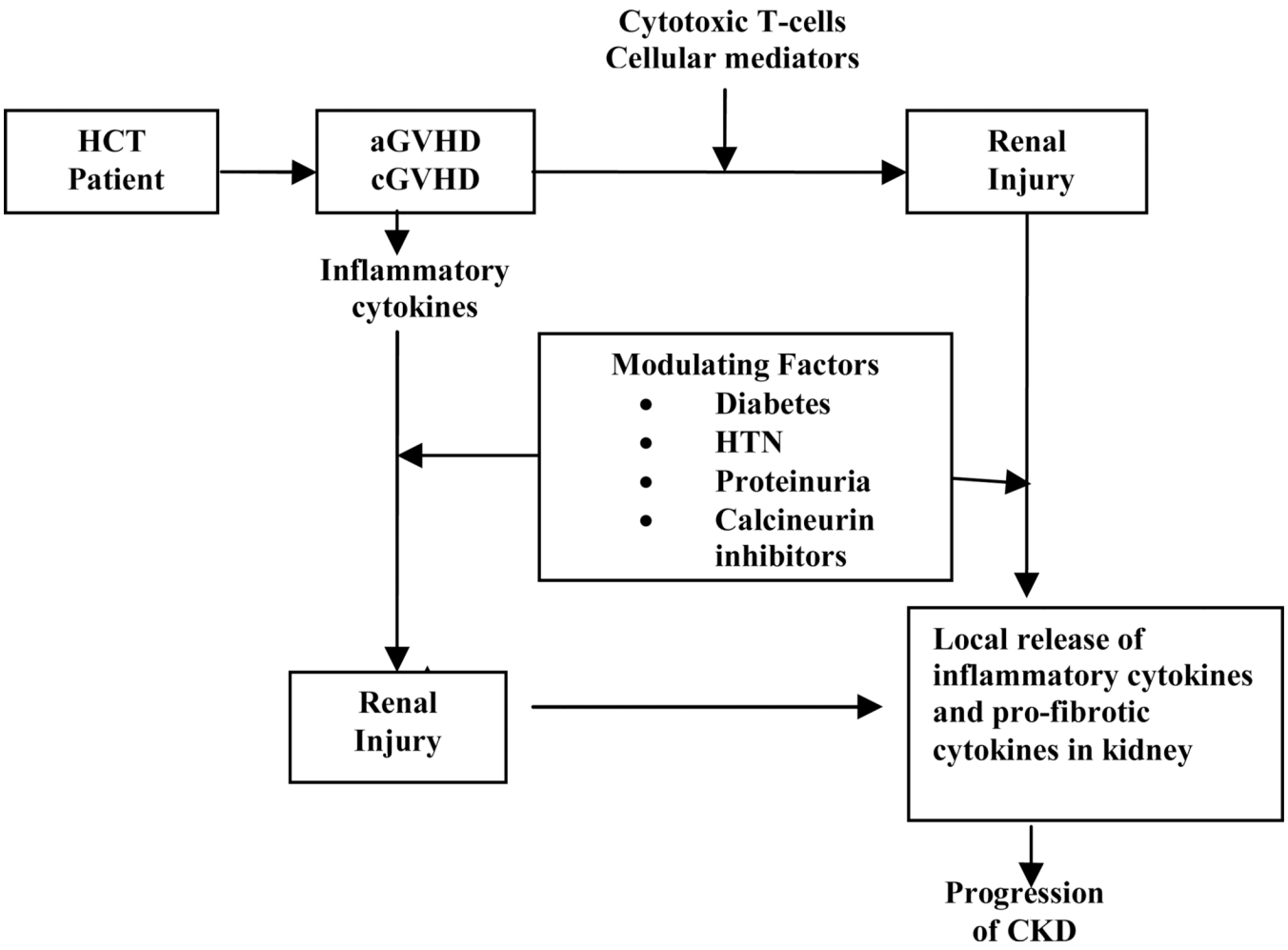

Figure 1.

Proposed conceptual representation of pathogenesis of CKD in HCT recipients (aGVHD: acute GVHD, cGVHD: chronic GVHD, HTN: hypertension)

From: Hingorani, S., *Chapter 97: Kidney and Bladder Complications of Hematopoietic Cell Transplantation*. Thomas ED, Appelbaum FR, Forman,SG, Negrin, RS, Blume, KG, editors. Hematopoietic Cell Transplantation. Fourth ed. Wiley Blackwell Science; 2009. p. 1473.

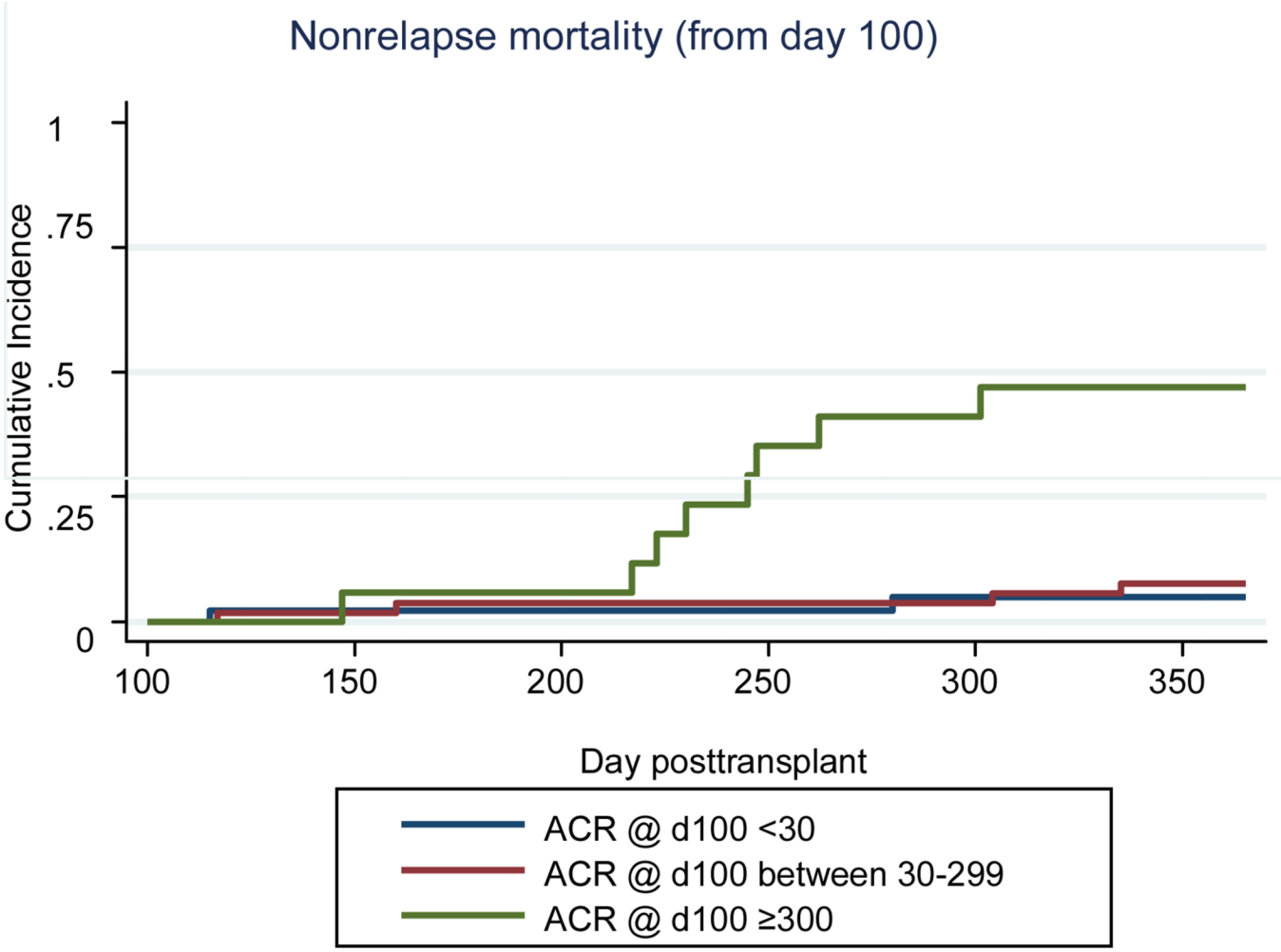

Figure 2.
Cumulative incidence curves of albuminuria and non-relapse mortality from day 100 to 1 year post-transplant. N=43 for ACR <30 N=54 for ACR 30–299; N=17 for ACR≥300. From: Hingorani, S., et al., *Albuminuria in Hematopoietic Cell Transplant (HCT) Patients: Prevalence and Risk Factors*. Journal of the American Society of Nephrology, 2006. **17**: p. 405A.

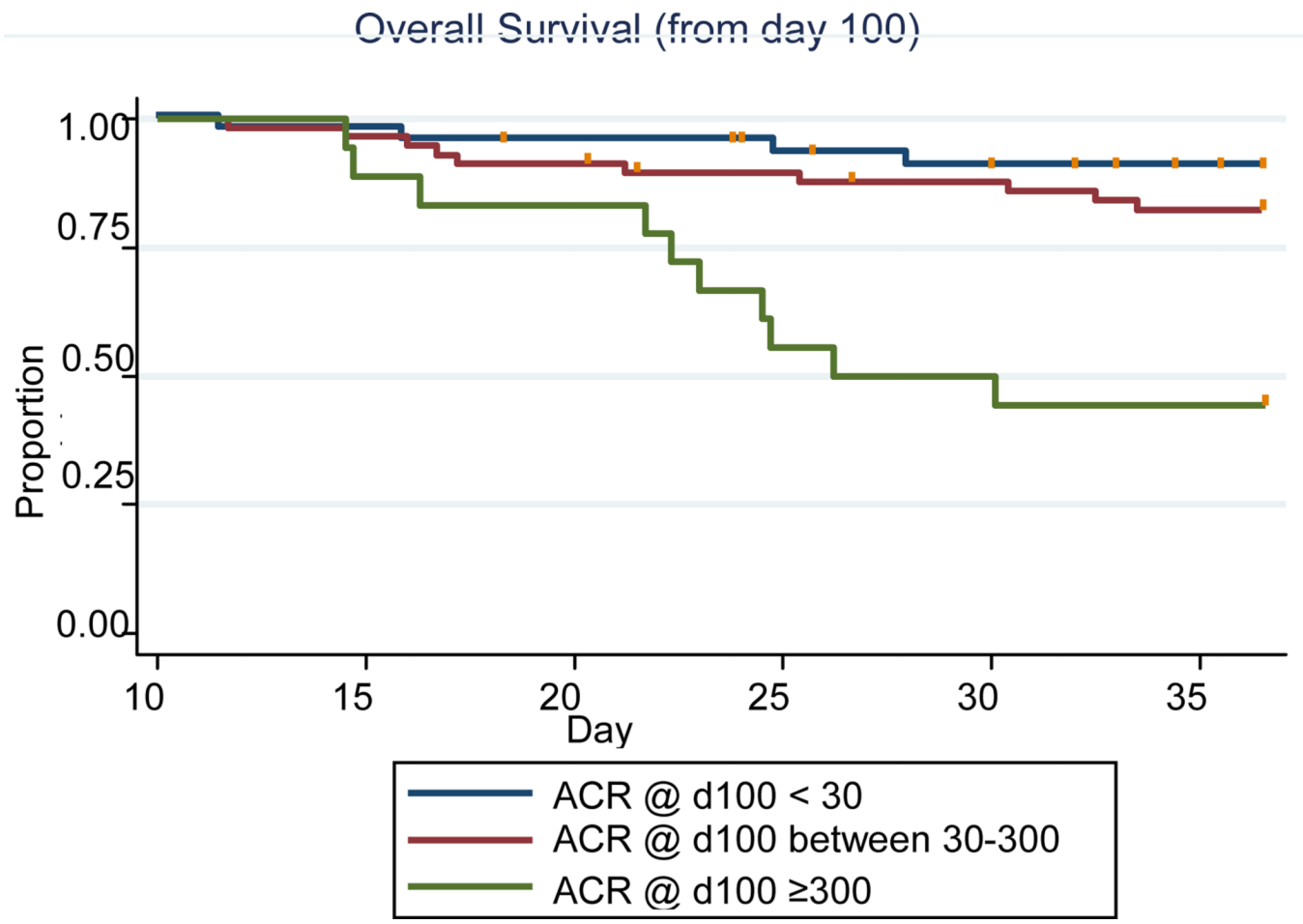

Figure 3.
Kaplan-Meier curves of albuminuria and overall survival from day 100 to 1 year post-HCT. N=44 for ACR<30; N=58 for ACR 30–299; N=18 for ACR≥300.
From: Hingorani, S., et al., *Albuminuria in Hematopoietic Cell Transplant (HCT) Patients: Prevalence and Risk Factors*. Journal of the American Society of Nephrology, 2006. **17**: p. 405A.

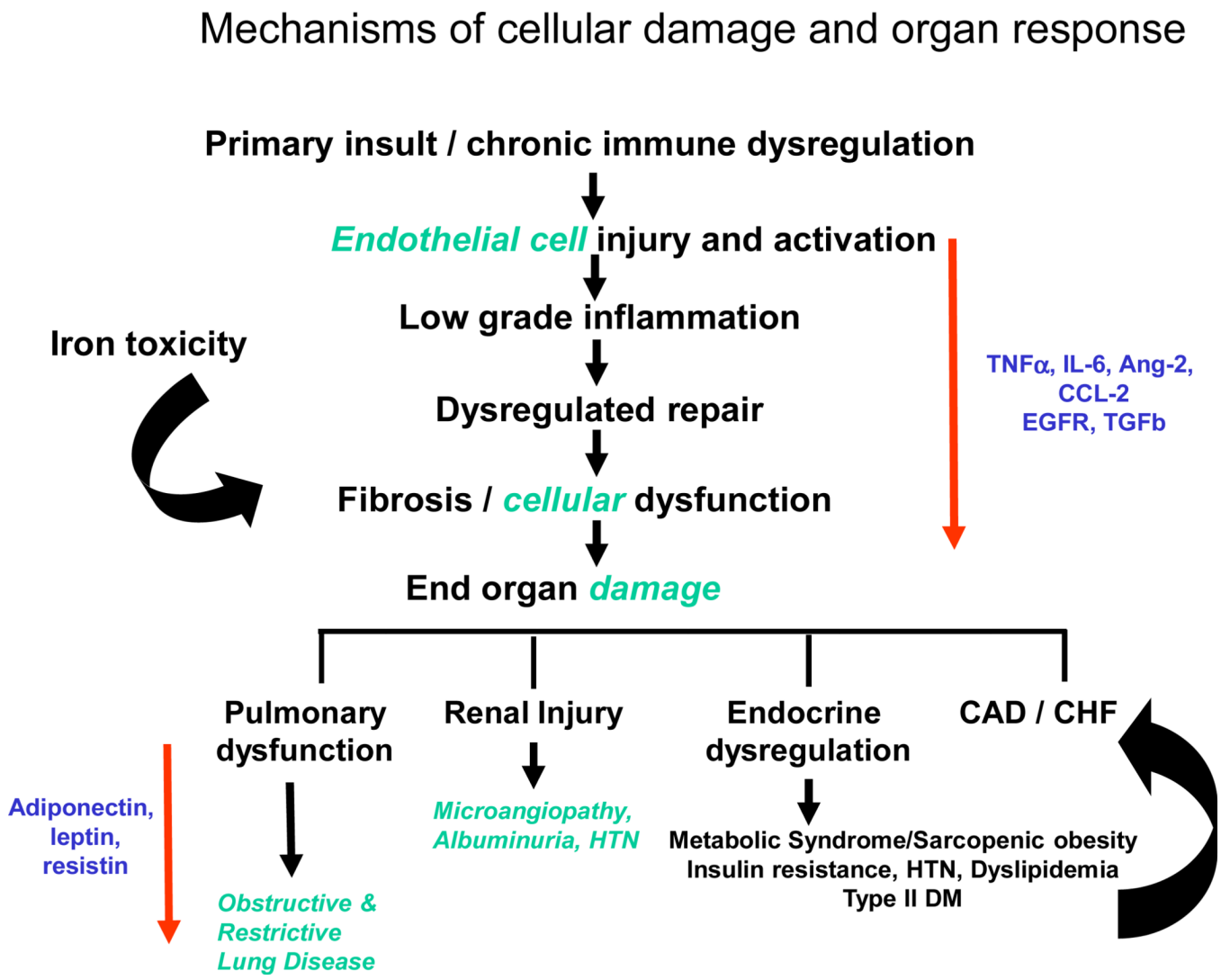

Figure 4.
Mechanisms of cellular damage and organ response

Table 1

Potential clinical consequences of iron overload in transplant survivors, based on data from studies of iron burdens in non-transplant populations.

Organ involved	Potential consequences	References
Heart	Cardiac failure, arrhythmias, death	11–13
Pituitary	Hypogonadism, delayed puberty, growth hormone deficiency	14–16
Thyroid	Hypothyroidism	14,15
Pancreas	Insulin-dependent diabetes mellitus	14,17 –20
Brain	Neurocognitive defects	21,22
Secondary malignancy	Solid tumor development	23–26

Table 2

Causes of gastrointestinal, hepatobiliary, and pancreatic problems in long-term transplant survivors.

Problem areas	Common causes	Less common causes
Esophageal symptoms: [27–32] • Heartburn • Dysphagia • Painful swallowing	• Oral cGVHD (mucosal changes, poor dentition, xerostomia) • Reflux of gastric fluid	• cGVHD of the esophagus (webs, rings, submucosal fibrosis & strictures, aperistalsis) • Hypopharnngeal dysmotility (myasthenia gravis, cricopharyngeal incoordination) • Squamous > adenocarcinoma • Pill esophagitis • Infection (fungal, viral)
Upper gut symptoms[33–37] **Anorexia, nausea, vomiting**	• Protracted acute gastrointestinal GVHD • Activation of latent infection (CMV, HSV, VZV) • Medication adverse effects	• Secondary adrenal insufficiency • Acquisition of infection (enteric viruses, giardia, cryptosporidia, H. pylori) • Aut dysmotility
Mid-gut and colonic symptoms: Diarrhea and abdominal pain[38,39]	• protracted acute GI GVHD • activation of latent CMV, VZV • drugs (MMF, Mg++, antibiotics, etc.)	• Acquisition of infection (enteric viruses, bacteria, parasites) • Pancreatic insufficiency • Clostridium difficile colitis • Collagen-encased bowel (GVHD) • Rare – IBD, sprue[39] – Bile salt malabsorption – Disaccharide malabsorption
Liver problems[40–50]	• cholestatic GVHD • chronic viral hepatitis (HCV, HBV) • Cirrhosis • Focal Nodular Hyperplasia (FNH) • Non-specific elevation of liver enzymes in serum (AP, ALT, GGT)	• Hepatitic GVHD • VZV, HSV hepatitis • fungal abscess • Nodular Regenerative Hyperplasia (NRH) • Biliary obstruction • Drug Induced Liver Injury (DILI)
Biliary and pancreatic problems[51–54]	• Cholecystitis • Common duct stones / sludge • Gall Bladder sludge (calcium bilirubinate) • gallstones	• Pancreatic atrophy / insufficiency • Pancreatitis/edema—stone or sludge-related • Pancreatitis—tacrolimus-related

Table 3

ATP III criteria for metabolic syndrome – indicated by 3 or more positive findings:

Criterion	Adults	Adolescents*
High Triglyceride Level, mg/dL	≥150	≥110
Low HDL-C level, mg/dL		
Males	<40	≤40
Females	<50	≤40
Abdominal obesity, waist circumference, cm		
Males	>102	≥90th Percentile
Females	>88	≥90th Percentile
High fasting glucose level, mg/dL	≥100**	≥100**
High blood pressure, mm Hg	≥ 130/85	≥90th Percentile

*ATP III criteria modification for adolescents (age 12–19 years) as described by Cook et al, 2003[110]

**American Diabetes Association 2003 definition lowers abnormal fasting glucose level to 100mg/dL[111] and this change has been incorporated into the current definition of metabolic syndrome[112]