International Guideline Harmonization Group
for Late Effects of Childhood Cancer

**IGHG Hepatic toxicity surveillance recommendations 2021**

Late liver injury

| **General recommendation** |
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| Childhood, adolescent and young adult cancer survivors and their healthcare providers should be aware of the risk of late liver injury[1] after (treatment with):<br>• radiotherapy potentially exposing the liver, including total body irradiation (moderate- to high-quality evidence)<br>• busulfan (low-quality evidence)<br>• thioguanine (low-quality evidence)<br>• mercaptopurine (expert opinion)[2]<br>• methotrexate (expert opinion)[2]<br>• dactinomycin (expert opinion)[2]<br>• hematopoietic stem cell transplantation (irrespective of GVHD) (expert opinion)<br>• hepatic surgery (low-quality evidence)<br>• chronic viral hepatitis (low-quality evidence)<br>• sinusoidal obstruction syndrome (expert opinion)[2]<br>(strong recommendation) |
| **Who needs surveillance for late liver injury?** |
| Surveillance for liver injury is recommended for childhood, adolescent and young adult cancer survivors treated with radiotherapy potentially exposing the liver, including total body irradiation (moderate- to high-quality evidence, strong recommendation). |
| Surveillance for liver injury is reasonable for childhood, adolescent and young adult cancer survivors treated with or with a history of:<br>• busulfan (low-quality evidence)<br>• thioguanine (low-quality evidence)<br>• mercaptopurine (expert opinion)[2]<br>• methotrexate (expert opinion)[2]<br>• dactinomycin (expert opinion)[2]<br>• hematopoietic stem cell transplantation (irrespective of GVHD) (expert opinion)<br>• hepatic surgery (low-quality evidence)<br>• chronic viral hepatitis (low-quality evidence)<br>• sinusoidal obstruction syndrome (expert opinion)[2]<br>(moderate recommendation). |
| **What surveillance modality should be used, when should surveillance be initiated and at what frequency should surveillance be performed?** |
| Physical examination[3] and measurement of serum liver enzyme concentrations (ALT, AST, gGT, ALP) is recommended once at entry into long-term follow-up, with further surveillance as clinically indicated (expert opinion/existing guidelines, strong recommendation) |
| **What should be done when abnormalities are identified?** |
| In case of increased liver enzyme values between 1 and 2 x ULN, the test should be repeated within 1 year in survivors (expert opinion/existing guidelines, strong recommendation). |
| In case of increased liver enzyme values between 2 and 5 x ULN, the test should be repeated within 3-6 months in survivors (expert opinion/existing guidelines, strong recommendation). |
| In case of increased liver enzyme values >5 x ULN, the test should be repeated within 2 weeks in survivors (expert opinion/existing guidelines, strong recommendation). |
| If persistent liver abnormalities (> ULN) or signs of advanced liver disease are identified in survivors, it is recommended to:<br>• discuss with or refer to a hepatologist or gastroenterologist for further evaluation if there is no obvious explanation (alcohol, medication, obesity)<br>• use potentially hepatotoxic medications[4] and supplements judiciously |

- evaluate body mass index and discuss healthy weight goals, especially in those with evidence of metabolic syndrome
- consider immunization against hepatitis A and B, if not already immune
- counsel about importance of measures to maintain liver health:
    - cautious use or avoidance of alcohol intake
    - maintenance of a healthy weight and lifestyle

(expert opinion/existing guidelines, strong recommendation).

For survivors with chronic HBV/HCV infection it is recommended to counsel about precautions to reduce viral transmission to household and sexual contacts and continue follow-up by a hepatitis specialist according to the hepatitis clinical practice guidelines in each country (expert opinion/existing guidelines, strong recommendation).

Note: No surveillance recommendations for FNH and NRH were formulated, because these are rare entities that are typically detected incidentally.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, gGT, gamma-glutamyltransferase; ULN, upper limit of normal.

[1] Clinical outcomes: hepatocellular liver injury confirmed by liver histology; liver fibrosis or cirrhosis (compensated or decompensated) confirmed by liver ultrasound, elastography or liver histology; Subclinical outcomes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for cellular liver injury; gamma-glutamyltransferase (gGT), alkaline phosphatase (ALP) and bilirubin for hepatobiliary dysfunction and biliary tract injury; prothrombin time and albumin for liver synthetic function.

[2] Late liver injury is typically only seen in the context of previous acute liver injury.

[3] Physical examination to evaluate height, weight, and body mass index and check for signs of liver disease or bile duct injury, i.e. hepatosplenomegaly, jaundice/icterus, spider nevi, pruritus.

[4] Potentially hepatotoxic medications are defined as those associated with elevated liver enzymes described in >1% of the general population using the drug.

Green representing a strong recommendation to do with a low degree of uncertainty; Yellow representing a moderate recommendation to do with a higher degree of uncertainty.

Iron overload

| **General recommendation** |
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| Childhood, adolescent and young adult cancer survivors who have undergone hematopoietic stem cell transplantation or received multiple red blood cell transfusions and their healthcare providers should be aware of the risk of iron overload (expert opinion, strong recommendation). |
| **Who needs surveillance for iron overload?** |
| Surveillance for iron overload is recommended for childhood, adolescent and young adult cancer survivors who have undergone hematopoietic stem cell transplantation and/or received multiple red blood cell transfusions (very-low quality evidence/expert opinion, strong recommendation). |
| **What surveillance modality should be used, when should surveillance be initiated and at what frequency should surveillance be performed?** |
| Measurement of serum ferritin is recommended once at entry into long-term follow-up, with further surveillance as clinically indicated. It is important to be aware of the diagnostic limitations of serum ferritin measurement that may represent inflammation and not iron overload (expert opinion/existing guidelines, strong recommendation). |
| **What should be done when abnormalities are identified?** |
| In case of increased serum ferritin >500 ng/ml the test should be repeated within 6 months in survivors (expert opinion/existing guidelines, strong recommendation). |
| If persistently elevated serum ferritin levels (>500 ng/ml) are identified, it is recommended to perform a T2* magnetic resonance imaging (MRI) to quantify the liver iron content (expert opinion/existing guidelines, strong recommendation). |
| For survivors with confirmed elevated liver iron content it is recommended to refer to a hematologist or other specialist to start treatment, such as phlebotomy or chelation therapy (expert opinion/existing guidelines, strong recommendation). |

Green representing a strong recommendation to do with a low degree of uncertainty.