Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-021 Avatrombopag

Stand: März 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Avatrombopag
für die Behandlung einer schweren Thrombozytopenie bei erwachsenen Patienten mit chronischer Lebererkrankung

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	siehe Übersicht II: Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Avatrombopag B02BX08 Doptelet®	Anwendungsgebiet laut Zulassung (vom 20.06.2019): Doptelet wird angewendet zur Behandlung einer schweren Thrombozytopenie bei erwachsenen Patienten mit chronischer Lebererkrankung, bei denen ein invasiver Eingriff geplant ist.
Humanes Thrombozyten-konzentrat	Die Gabe von Thrombozytenkonzentraten ist indiziert zur Behandlung einer Blutungsneigung, bedingt durch eine schwere Thrombozytopenie infolge thrombozytärer Bildungsstörungen, im Notfall auch bei Umsatzstörungen, jedoch nicht bei einer niedrigen Thrombozytenzahl allein. Damit durch die Zufuhr von Plättchen eine Besserung der thrombozytär bedingten Blutungsneigung zu erwarten ist, sollte vor der Behandlung zunächst deren Ursache abgeklärt werden. (FI Stand September 2013)
Lusutrombopag B02BX07 Mulpleo®	Mulpleo is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

Quellen: AMIS-Datenbank, Fachinformationen. Stand März 2020.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-021 (Avatrombopag)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. März 2020

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Abkürzungsverzeichnis

AVH	Acute variceal haemorrhage
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDP	Clinical practice guideline
CPB	Cardiopulmonary bypass
CVC	Central venous catheter
EASL	European Association for the Study of the Liver
ECRI	ECRI Guidelines Trust
FFP	Fresh frozen plasma
G-BA	Gemeinsamer Bundesausschuss
GDG	Guideline development droup
GI	Gastrointestinal
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
Hb	Haemoglobin
HR	Hazard Ratio
ICU	Intensive Care Unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LP	Lumbar puncture
LVP	large-volume paracentesis
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PDT	Percutaneous dilational tracheotomy
PPCD	post-paracentesis circulatory dysfunction
PT	Prothrombin time
RR	Relatives Risiko

SIGN	Scottish Intercollegiate Guidelines Network
TPO	Thrombopoietin
TRALI	Transfusion-related acute lung injury
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung einer schweren Thrombozytopenie bei erwachsenen Patienten mit chronischer Lebererkrankung, bei denen ein invasiver Eingriff geplant ist

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Thrombozytopenie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.02.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 780 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse / IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Estcourt LJ et al., 2018 [1].

Prophylactic platelet transfusions prior to surgery for people with a low platelet count

Fragestellung

To determine the clinical effectiveness and safety of prophylactic platelet transfusions prior to surgery for people with a low platelet count.

Methodik

Population:

- People of all ages with a low platelet count who were due to have surgery including invasive procedures.

Intervention/Komparator:

- Comparison 1: prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery (placebo or no treatment).
- Comparison 2: prophylactic platelet transfusion prior to surgery versus alternative treatments (cryosupernatant, antifibrinolytics, TPO mimetics).
- Comparison 3: different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery.

Endpunkte:

Primary outcomes

- Mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery.
- Number of participants with major procedure-related bleeding within seven days of surgery, defined as:
  - surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing;
  - bleeding of sufficient size to cause delayed wound healing, or wound infection or surgical site bleeding that was unexpected and prolonged or caused haemodynamic instability (as defined by the study) that was associated with a 20 g/L drop in haemoglobin (Hb);
  - bleeding that required two or more units of wholeblood/red cells within 24 hours of the bleeding;
  - bleeding defined by the study with no further details.

Secondary outcomes

- Number of participants with minor procedure-related bleeding within seven days of surgery (e.g. haematoma, prolonged bleeding at surgical site that did not fulfil the definition for major bleeding).

- Number of platelet transfusions per participant and number of platelet components per participant.
- Number of red cell transfusions per participant and number of red cell components per participant.
- Proportion of participants requiring additional interventions to stop bleeding (surgical; medical, e.g. tranexamic acid; other blood products, e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen) within seven days of surgery.
- Quality of life assessment.
- Serious adverse events due to:
  - transfusion (transfusion reactions, TRALI, transfusion-related infection, transfusion-associated circulatory overload, transfusion-related dyspnoea) within 24 hours of the transfusion;
  - surgery (e.g. delayed wound healing, infection) within 30 days after the operation.
- Length of hospital stay and length of ICU stay.
- Venous and arterial thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction).

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, 2017, Issue 12), MEDLINE (OvidSP, Epub Ahead of Print, In-Process and other Non-Indexed Citations, and 1946 to 11 December 2017), PubMed (for e-publications ahead or print only) (www.ncbi.nlm.nih.gov/pubmed), Embase (OvidSP, 1974 to 11 December 2017), CINAHL (EBSCOHost, 1937 to 11 December 2017), Transfusion Evidence Library (www.transfusionevidencelibrary.com; 1950 to 11 December 2017 – this included a search of grey literature), LILACS (1982 to present) (lilacs.bvsalud.org/en/), Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 11 December 2017)

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs

Charakteristika der Population:

Trials comparing platelet transfusions with no transfusion before the surgical procedure

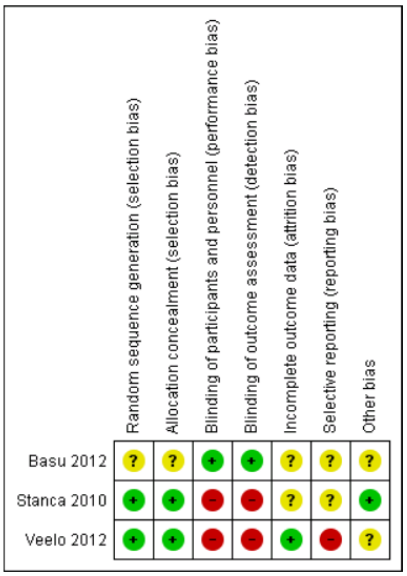
- One trial (72 participants) compared platelet transfusion to no platelet transfusion before a surgical procedure (Veelo 2012). It included people requiring mechanical ventilation who had mild coagulation disorders (defined as prothrombin time (PT) 14.7 seconds to 20.0 seconds, or platelet count 40 × 10^9/L to 100 × 10^9/L, or active treatment with aspirin (acetylsalicylic acid), or any combination) who required a percutaneous dilational tracheotomy (PDT).

Trials comparing platelet transfusion to alternative treatments before the surgical procedure

- Two trials (108 participants) compared platelet transfusions to different alternative treatments (Basu 2012; Stanca 2010). Both included adults with liver disease, and excluded people with bleeding disorders, hepatocellular carcinoma and treatment with antiplatelet medications. Participants in Basu 2012 had severe thrombocytopenia (no further details). Stanca 2010 included people with moderate coagulopathy (defined as platelet count of 30 × 10^9/L to 50 × 10^9/L) (22 participants), or an international normalised ratio (INR) of 2.0 to 3.0, or both. In Basu 2012, the procedure was percutaneous liver biopsy, and in Stanca 2010, the procedure was dental extractions.

Qualität der Studien:

- All three included trials in this review were RCTs; however, none of the trials were free from methodological bias. See the visual summary of the risk of bias assessment on each domain. Two trials were at risk of performance and detection bias, this was due to the nature of the intervention “platelet transfusion” (Stanca 2010; Veelo 2012). Most ’Risk of bias’ tool domains of one of the included trial were at unclear risk of bias as the trial was only available as an abstract (Basu 2012).



Studienergebnisse:

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: no platelet transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no platelet transfusion	Risk with platelet transfusion				
All-cause mortality within 30 days of surgery	Study population 405 per 1000	316 per 1000 (166 to 588)	**RR 0.78** (0.41 to 1.45)	72 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,b]	—
Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery (surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing)	Study population 61 per 1000	97 per 1000 (18 to 541)	**RR 1.60** (0.29 to 8.92)	64 (1 RCT)	⊕⊝⊝⊝ **Very low**[b,c]	—
The number of participants with minor procedure-related bleeding within 7 days of surgery	Study population 576 per 1000	743 per 1000 (518 to 1000)	**RR 1.29** (0.90 to 1.85)	64 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,c,d]	—
Serious adverse events (surgery-related adverse effects within 30 days)	No events occurred in either study arm			64 (1 RCT)	⊕⊝⊝⊝ **Very low**[a,c,d]	—

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Only adults in the intensive care unit were included in this trial (downgraded one level for indirectness).
[b]The confidence intervals included a serious risk of harm or benefit (downgraded two levels for imprecision).
[c]This is a subjective outcome and the trial was unblinded (downgraded one level for risk of bias).
[d]The confidence intervals included a risk of harm or benefit (downgraded one level for imprecision).

Summary of findings 2. Prophylactic platelet transfusion prior to surgery versus alternative treatments

Prophylactic platelet transfusion prior to surgery versus alternative treatments

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: desmopressin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with desmopressin	Risk with platelet transfusion				
All-cause mortality within 30 days of surgery – not reported	—	—	—	—	—	—

Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery (bleeding that required ≥ 2 units of whole blood/red blood cells within 24 hours of the bleeding)	No events in either study arm			36 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	—
Number of participants with minor procedure-related bleeding within 7 days of surgery	Study population 59 per 1000	52 per 1000 (4 to 778)	**RR 0.89** (0.06 to 13.23)	36 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	—
Serious adverse events (transfusion-related adverse effects within 24 hours of the transfusion)	Study population 0 per 1000	0 per 1000 (0 to 0)	**RR 2.70** (0.12 to 62.17)	36 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b,c]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Open-label trial (downgraded one level for risk of bias).
[b]Study only included adults with chronic liver disease (downgraded one level for indirectness).
[c]Confidence intervals included a serious risk or benefit or treatment (downgraded one level for imprecision, as already downgraded one level for indirectness and risk of bias).

Summary of findings 3. Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: TPO mimetic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TPO mimetic	Risk with platelet transfusion				
All-cause mortality within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery	No bleeding in any of the study arms			65 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Number of participants with minor procedure-related bleeding within 7 days of surgery	No bleeding occurred in any of the study arms			65 (1 RCT)	⊕⊖⊖⊖ **Very low**[a,b]	—
Serious adverse events – not reported	—	—	—	—	—	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **TPO:** thrombopoietin.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Study only included adults with chronic liver disease (downgraded one level for indirectness).
[b]No events occurred (downgraded two levels for imprecision).

- Quality of the evidence
  - Overall, the quality of evidence was rated according to the GRADE methodology as very low across different outcomes due to high risk of bias (unblinded studies), imprecision of the estimates, and indirectness (only adults with liver disease or adults in the ICU were included in the studies).

  We assessed the GRADE quality of evidence as very low for:

  - all-cause mortality;
  - number of participants with major procedure-related
  - bleeding within seven days of surgery
  - number of participants with minor procedure-related bleeding within seven days of surgery
  - serious adverse events

  We could not assess the quality of the evidence for: mortality secondary to bleeding, mortality secondary to thromboembolism and mortality secondary to infection because none of the trials reported these outcomes.

Anmerkung/Fazit der Autoren

Findings of this review were based on three small trials involving minor surgery in adults with thrombocytopenia. We found insufficient evidence to recommend the administration of preprocedure prophylactic platelet transfusions in this situation with a lack of evidence that transfusion resulted in a reduction in postoperative bleeding or all-cause mortality. The small number of trials meeting the inclusion criteria and the limitation in reported outcomes across the trials precluded meta-analysis for most outcomes. Further adequately powered trials, in people of all ages, of prophylactic platelet transfusions compared with no transfusion, other alternative treatments, and considering different platelet thresholds prior to planned and emergency surgical procedures are required. Future trials should include major surgery and report on bleeding, adverse effects, mortality (as a long-term outcome) after surgery, duration of hospital stay and quality of life measures.

3.3 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.4 Leitlinien

National Clinical Guideline Centre, 2015 [4].

National Institute for Health and Care Excellence (NICE)

Blood transfusion

Leitlinienorganisation/Fragestellung

This guideline covers the assessment for and management of blood transfusions in adults, young people and children over 1 year old. It covers the general principles of blood transfusion, but does not make recommendations relating to specific conditions.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensusprozesse (unklar, ob formal) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- MEDLINE, Embase, and The Cochrane Library till 29 January 2015

LoE/GoR

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Table 2: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Sonstige Hinweise

- Die Empfehlungen beziehen sich nicht spezifisch auf Personen mit chronischer Lebererkrankung.

Empfehlungen

Platelet: Thresholds and Targets

Empfehlung 1: Patients with thrombocytopenia who are bleeding

- 19. Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below 30×10^9 per litre. 20.
- 20. Use higher platelet thresholds (up to a maximum of 100×10^9 per litre) for patients with thrombocytopenia and either of the following:
  - severe bleeding (WHO grades 3 and 4)

- bleeding in critical sites, such as the central nervous system (including eyes).

Quality of evidence

- No studies were identified which met the review protocol criteria.
- The recommendations for platelet transfusion for patients who were bleeding and were thrombocytopenic were based on the consensus expert opinion of the GDG members.
- There was no specific evidence available for the use of platelets in the paediatric population.

Empfehlung 2: Patients who are not bleeding or having invasive procedures or surgery

- 21. Offer prophylactic platelet transfusions to patients with a platelet count below 10×10^9 per litre who are not bleeding or having invasive procedures or surgery, and who do not have any of the following conditions:
  - chronic bone marrow failure
  - autoimmune thrombocytopenia
  - heparin - induced thrombocytopenia
  - thrombotic thrombocytopenic purpura

Quality of evidence

- The quality of evidence for most of the outcomes was low or very low by GRADE criteria. This was largely due to risk of bias arising from a lack of allocation concealment, inadequate blinding, serious or very serious imprecision and indirectness of population and outcomes.
- The recommendation was based on this evidence and the consensus expert opinion of the GDG members.
- There was no specific evidence available for the use of platelets in the paediatric population.

Empfehlung 3: Patients who are having invasive procedures or surgery

- 22. Consider prophylactic platelet transfusions to raise the platelet count above $50x10^9$ per litre in patients who are having invasive procedures or surgery.
- 23. Consider a higher threshold (for example $50 – 75\times10^9$ per litre) for patients with a high risk of bleeding who are having invasive procedures or surgery, after taking into account:
  - the specific procedure the patient is having
  - the cause of the thrombocytopenia
  - whether the patient's platelet count is falling
  - any coexisting causes of abnormal haemostasis.
- 24. Consider prophylactic platelet transfusions to raise the platelet count above 100×10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes).

Quality of evidence

- The recommendations for prophylactic platelet transfusions in patients who were undergoing invasive procedures or surgery were based on indirect evidence and the consensus expert opinion of the GDG members.
- The quality of the indirect evidence for most of the outcomes was low or very low by GRADE criteria. This was largely due to risk of bias arising from a lack of allocation concealment, inadequate blinding, serious or very serious imprecision and indirectness of population and outcomes.

Empfehlung 4: When prophylactic platelet transfusions are not indicated

- 25. Do not routinely offer prophylactic platelet transfusions to patients with any of the following:
  - chronic bone marrow failure
  - autoimmune thrombocytopenia
  - heparin - induced thrombocytopenia
  - thrombotic thrombocytopenic purpura.
- 26. Do not offer prophylactic platelet transfusions to patients having procedures with a low risk of bleeding, such as adults having central venous cannulation or any patients having bone marrow aspiration and trephine biopsy.

Quality of evidence

- No studies were identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the GDG members.

Kaufmann RM, 2015 [3].

AABB (formerly, American Association of Blood Banks)

Platelet transfusion: a clinical practice guideline from the AABB

Leitlinienorganisation/Fragestellung

These guidelines were designed to provide pragmatic recommendations, based on the best available published evidence, about when platelet transfusion may be appropriate in adult patients. For several common clinical situations, we attempted to identify a platelet count threshold below which platelet transfusion may improve hemostasis and above which platelet transfusion is unlikely to benefit the patient. We did not attempt to address all clinical situations in which platelets may be transfused, and these guidelines are not intended to serve as standards. Clinical judgment, and not a specific platelet count threshold, is paramount in deciding whether to transfuse platelets.

These guidelines provide advice for adult patients who are candidates for platelet transfusion.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu (keine Patientenbeteiligung);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

PubMed from 1946 to the first week of April 2013, and the Cochrane Central Register of Controlled Trials and Web of Science from 1900 to the first week of April 2013; an updated search of these databases was done from the first week of April 2013 to the first week of September 2014.

LoE/GoR

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Sonstige Hinweise

- Die Empfehlungen beziehen sich nicht spezifisch auf Personen mit chronischer Lebererkrankung.

Empfehlungen

Clinical Setting 2: Adult Patients Having Minor Invasive Procedures

Recommendation 2:

The AABB suggests prophylactic platelet transfusion for patients having elective central venous catheter placement with a platelet count less than 20×10^9 cells/L.

Quality of evidence: low; strength of recommendation: weak.

Recommendation 3:

The AABB suggests prophylactic platelet transfusion for patients having elective diagnostic lumbar puncture with a platelet count less than 50×10^9 cells/L.

Quality of evidence: very low; strength of recommendation: weak.

Rationale for Recommendations

Serious bleeding complications after CVC placement are rare, and when they occur, they are often unrelated to the platelet count (such as accidental arterial puncture). In aggregate, the existing data support the use of a 20×10^9– cells/L platelet count threshold for CVC placement. The reported studies included patients with a wide range of primary diagnoses; this recommendation is intended to be broadly applicable to adult patients with hypoproliferative thrombocytopenia.

Bleeding complications are rare with LPs, but hemorrhage anywhere in the central nervous system has the potential to cause devastating neurologic sequelae. In the absence of better published data supporting the safety of a lower threshold in adult patients, a fairly liberal

platelet count threshold for LPs (that is, 50×10^9 cells/L) seems prudent. The 50×10^9– cells/L threshold is intended for simple diagnostic or therapeutic LPs only. Despite a lack of supportive data, a greater platelet count is often recommended for other procedures, such as epidural anesthesia (50, 51).

Clinical Setting 3: Adult Patients Having Major Elective Nonneuraxial Surgery

Recommendation 4:

The AABB suggests prophylactic platelet transfusion for patients having major elective nonneuraxial surgery with a platelet count less than 50×10^9 cells/L.

Quality of evidence: very low; strength of recommendation: weak.

Recommendation 5:

The AABB recommends against routine prophylactic platelet transfusion for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass (CPB). The AABB suggests platelet transfusion for patients having CPB who exhibit perioperative bleeding with thrombocytopenia and/or with evidence of platelet dysfunction.

Quality of evidence: very low; strength of recommendation: weak.

Rationale for Recommendations

The consensus opinion of the panel is that platelet counts of 50×10^9 cells/L and greater are safe for major nonneuraxial surgery. There is no evidence of increased perioperative bleeding risk in thrombocytopenic patients with platelet counts greater than 50×10^9 cells/L. We recommend that platelet transfusion be withheld in nonbleeding surgical patients when the platelet count is greater than 50×10^9 cells/L and there is no evidence of coagulopathy. In contrast, we suggest that platelet transfusion should be considered in cardiac surgical patients with perioperative bleeding and thrombocytopenia and/or suspected qualitative platelet abnormalities, which often result from exposure of platelets to the CPB circuit (54). Platelet transfusions are often administered to nonbleeding cardiac surgical patients (55). There are no data supporting this practice, and it should be discouraged.

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European Association for the Study of the Liver, 2018 [2].

EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis

Leitlinienorganisation/Fragestellung

The following Clinical Practice Guidelines (CPGs) represent the first CPGs on the management of decompensated cirrhosis.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft nicht zu (ausschließlich aus der Hepatologie);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche teilweise dargelegt (keine Suchbegriffe); Auswahl und Bewertung der Evidenz: unklar;
- Konsensusprozesse (unklar, ob formal) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- PubMed and Cochrane database searches before 27 March 2018

LoE/GoR

Table 1. Level of Evidence and Grade of Recommendations.

Level of evidence	
I	Randomised, controlled trials
II-1	Controlled trials without randomisation
II-2	Cohort and case-control analytical studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology
Grade of recommendations	
1	**Strong recommendation:** Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
2	**Weaker recommendation:** Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: higher cost or resource consumption

Sonstige Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz für Personen mit chronischer Lebererkrankung wird die LL jedoch ergänzend dargestellt.

Empfehlungen

Management of uncomplicated ascites

Grade 3 or large ascites

Empfehlungen

- LVP is the first-line therapy in patients with large ascites (grade 3 ascites), which should be completely removed in a single session (I;1).
- LVP should be followed with plasma volume expansion to prevent PPCD (I;1).

Hintergrundtext

Grade 3 or large ascites. The treatment of choice for the management of patients with grade 3 ascites is represented by LVP. Paracentesis should be performed under strict sterile conditions

using disposable sterile materials. The procedure is associated with a very low risk of local complications, particularly bleeding[61,62] even in patients with international normalized ratio (INR)>1.5 and platelet count <50,000/ll, minor bleeding from puncture site occurred in two out of 142 paracentesis.[61] Thus, there are no data supporting the prophylactic use of fresh frozen plasma of pooled platelets, even though these are employed in many centres when prothrombin activity is below 40% and platelet count <40,000/ll. LVP should be avoided in the presence of disseminated intravascular coagulation.

Gastrointestinal bleeding

Prevention and treatment of variceal haemorrhage - Variceal haemorrhage

Empfehlungen

- Acute GI bleeding, both due to gastro-oesophageal varices or to non-variceal lesions, carries a high incidence of complications and mortality in decompensated cirrhosis and therefore requires close monitoring (II-2;1).
- Volume replacement should be initiated promptly to restore and maintain haemodynamic stability (III;1). Either colloids and/or crystalloids should be used (III;1). Starch should not be used for volume replacement (I;1).
- A restrictive transfusion strategy is recommended in most patients with a haemoglobin threshold for transfusion of 7 g/dl and a target range of 7–9 g/dl (I;1).

Hintergrundtext

Acute GI bleeding in cirrhosis, either because of gastro-oesophageal varices or non-variceal lesions, is a medical emergency with a high incidence of complications and high mortality and therefore requires intensive care. Acute variceal haemorrhage (AVH) must be suspected in any cirrhotic patient presenting with upper acute GI bleeding and treatment should be started as soon as bleeding is clinically confirmed, regardless the lack of confirmation by upper endoscopy.[195] Initial therapy should be directed at restoring volaemia.[196] Vasoactive drug therapy[197,198] and antibiotic prophylaxis[195,196] should be initiated as soon as AVH is suspected. Goals of therapy in AVH include the control of bleeding, as well as the prevention of early recurrence and the prevention of six-week mortality, which is considered the main treatment outcome by consensus.[168,199] Blood volume restitution should be initiated promptly to restore and maintain haemodynamic stability to ensure tissue perfusion and oxygen delivery. To facilitate resuscitation at least two catheters should be placed, large enough to allow rapid volume expansion, which can usually be done with crystalloids.[196] No benefit has been demonstrated with the use of colloids compared to crystalloids.[200] Red blood cells are used to improve oxygen delivery to tissues in case of severe anaemia. A restrictive transfusion strategy is adequate in most patients with acute GI bleeding, with a haemoglobin threshold for transfusion of 7 g/dl and a target range after transfusion of 7 to 9 g/dl.[201] The threshold for transfusion may be higher in patients with massive haemorrhage or in those with underlying conditions that preclude an adequate physiological response to acute anaemia. Recommendations regarding management of coagulopathy and thrombocytopenia cannot be made based on currently available data.[168,169,199]

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, February 2020) am 11.02.2020

#	Suchfrage
1	MeSH descriptor: [Thrombocytopenia] explode all trees
2	(thrombocytopeni* OR thrombocytopaeni* OR thrombopeni*):ti,ab,kw
3	#1 OR #2
4	#3 with Cochrane Library publication date from Feb 2015 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 12.02.2020

#	Suchfrage
1	thrombocytopenia[mh]
2	((thrombocytopeni*[tiab]) OR thrombocytopaeni*[tiab]) OR thrombopeni*[tiab]
3	#1 OR #2
4	(#3) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
5	(#4) AND ("2015/02/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 11.02.2020

#	Suchfrage
1	thrombocytopenia[mh]
2	((thrombocytopeni*[tiab]) OR thrombocytopaeni*[tiab]) OR thrombopeni*[tiab]
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	(#4) AND ("2015/02/01"[PDAT] : "3000"[PDAT])

Referenzen

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