Konsensusempfehlungen Bethesda 2006 – Umsetzung in der Praxis?

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International Consensus Recommendations on the Flow Cytometric Immunophenotypic Analysis of Hematolymphoid Neoplasia

Bethesda Conference 2006
Cytometry Part B (Clinical Cytometry) 72B:S14–S22 (2007)

Bethesda 2006
International Consensus recommendations

- Treffen „internationaler Experten“

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Bethesda 2006
International Consensus Recommendations

- Medizinische Indikationen zur Durchflußzytometrie
- Antikörper und Reagenzien
- Form und Inhalt des Befundberichts
- Training und Weiterbildung

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Bethesda 2006
International Consensus Recommendations

Medizinische Indikationen zu Durchflußzytometrie: Symptome

- Lymphknotenschwellungen, Splenomegalie, Hepatomegalie
- Zytopenien
- Leukozytose
- Atypische Zellen (Blasten im pB, etc.)
- Positive Immunfixation i.S oder i.U.

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International Consensus Recommendations

Medizinische Indikationen zur Durchflußzytometrie: Patientenmonitoring

- Staging bei hämatologischen Neoplasien (KM oder Liquorbeteiligung?)
- Detektion von therapeutischen Zielen (CD20, CD52, CD33, CD123)
- MRD Nachweis
- Diagnose sekundärer Erkrankungen (tMDS, PTLD)

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Bethesda 2006
International Consensus Recommendations

Medizinische Indikationen zur Durchflußzytometrie: Patientenmonitoring

- Blastenquantifizierung (nach Leukämietherapie, bei MDS)
- Detektion Prognose-assoziierter Marker (z.B. ZAP 70)

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International Consensus Recommendations

Keine Indikation bei

- Thrombose
- Neutrophilen-Leukozytose
- Polyklonale Hypergammaglobulinämie
- Polyglobulie
- Thrombozytose
- Basophilie

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Cell Lineages to be Evaluated for Each Medical Indication

Medical indication	Lineage to be evaluated
Anemia	B, T, M, P
Leukopenia	B, T, M, P
Thrombocytopenia	B, T, M, P
Pancytopenia	B, T, M, P
Neutrophilia	M (limited)
Monocytosis	M
Lymphocytosis	B, T
Eosinophilia	T, M
Erythrocytosis	M (limited)
Thrombocytosis	M (limited)
Blasts in blood or marrow	B, T, M
Lymphadenopathy	B, T
Extranodal masses	B, T
Splenomegaly	B, T, M (limited)
Transformation of chronic leukemia—B cell	B
Transformation of chronic leukemia—T or NK cell	T
Staging for non-Hodgkin lymphoma—B cell	B
Staging for non-Hodgkin lymphoma—T/NK cell	T
Skin rash	B, T
Atypical cells in body fluids (CSF, serous, ocular, etc.)	B, T, M (limited)
Monoclonal gammopathy	B, P
Unexplained Plasmacytosis of bone marrow	B, P
Monitoring of Rx response (unknown diagnostic immunophenotype)	
Mature B cell neoplasm	B
Mature T or NK cell neoplasm	T
Acute lymphoid leukemia—B cell	B
Acute lymphoid leukemia—T cell	T
Acute myeloid leukemia	M
MDS/MPD/Overlap Syndrome	M
Plasma cell neoplasm	P

B, B cell; T, T cell; M, myeloid; P, plasma cell.

Symptom / Erkrankung und empfohlene immunologische Linienevaluation

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Antikörperpanel

Bethesda 2006: Antigen consensus

- Die Konferenz konnte sich nicht auf fixierte Antikörperkombinationen oder Panels einigen
- Es wurde eine Übersicht „empfohlener Marker“ zur Untersuchung einzelner Indikationen erstellt
- Keine klare Empfehlung zum Gating
- Erwartete Sensitivität bei der Detektion einzelner Zellreihen:
  B 0,1%, T 0,1%, M 0,5%, P 0,1%

Antikörperpanel

Bethesda 2006: Antigen consensus

	B cell							T cell								Myelomonocytic														Plasma cell				
	Kappa	Lambda	CD5	CD10	CD19	CD20	CD45	CD2	CD3	CD4	CD5	CD7	CD8	CD45	CD56	CD5	CD7	CD11b	CD13	CD14	CD15	CD16	CD33	CD34	CD38	CD45	CD56	CD64	CD117	HLA-DR	CD19	CD38	CD45	CD56	CD138
Anemia	91	91	80	69	100	69	100	57	97	89	80	86	89	97	89	37	63	74	91	74	69	71	94	94	51	94	69	54	83	80	60	80	74	66	23
Leukopenia	89	89	77	69	100	74	100	57	100	94	80	89	94	100	89	37	63	74	91	74	69	69	94	94	51	94	69	54	83	80	51	69	66	54	11
Thrombocytopenia	91	91	74	69	100	69	100	57	97	89	77	83	89	97	86	34	60	74	89	71	69	69	94	94	51	94	69	54	83	80	54	74	69	57	17
Pancytopenia	91	91	77	69	97	71	100	57	97	89	80	86	89	97	89	40	66	77	91	77	71	74	97	94	54	94	71	60	83	83	57	74	71	63	17
Neutrophilia	37	37	26	29	57	23	54	26	49	43	31	34	43	51	40	31	49	69	77	57	60	71	74	71	40	80	49	60	57	60	23	34	31	23	3
Monocytosis	43	43	34	37	69	37	63	29	54	46	34	40	46	54	51	37	63	80	89	94	83	80	91	89	51	94	71	83	77	89	26	37	34	23	6
Lymphocytosis	97	97	94	83	100	86	100	66	100	97	83	91	97	100	91	23	29	37	46	29	23	31	46	46	20	63	29	20	29	40	34	46	43	29	3
Eosinophilia	43	43	34	37	66	43	66	43	71	66	57	66	66	74	63	37	57	71	83	60	69	74	83	86	43	86	63	51	69	71	23	34	31	20	3
Erythrocytosis	40	40	26	26	57	29	57	20	46	40	29	31	40	51	37	29	40	54	69	46	51	57	71	74	31	74	46	40	57	63	17	29	26	14	3
Thrombocytosis	37	37	29	29	57	29	57	29	51	46	37	40	46	57	49	34	49	63	77	54	60	66	80	86	37	83	57	46	66	71	20	31	29	17	3
Blasts in blood or marrow	74	74	60	94	100	89	100	69	97	86	83	91	86	94	83	40	74	71	97	77	80	66	97	97	66	97	74	66	94	91	26	46	37	26	6
Lymphadenopathy	97	97	91	86	100	94	100	60	100	100	80	89	100	97	91	9	14	29	46	34	23	26	49	40	17	60	17	17	26	34	29	43	40	26	3
Extranodal masses	97	97	94	91	100	97	100	60	100	100	80	89	100	97	91	6	11	26	49	34	17	23	51	43	14	54	17	14	23	34	37	54	46	34	14
Splenomegaly	97	97	91	89	100	97	100	57	94	94	77	83	94	91	89	14	23	46	66	49	37	49	63	54	29	69	37	29	43	54	29	43	40	26	3
Transformation of chronic leukemia - B cell	97	97	97	83	97	94	91	26	49	43	31	34	40	43	43	6	9	20	34	26	11	20	37	31	14	49	11	9	14	31	20	29	29	14	3
Transformation of chronic leukemia - T or NK cell	34	34	29	37	51	26	40	86	97	97	94	94	97	94	97	6	9	20	31	26	11	23	34	34	14	46	14	9	14	31	17	23	23	11	3
Staging for non-Hodgkin lymphoma - B cell	100	100	94	97	100	97	94	23	54	46	26	31	46	43	34	6	9	23	34	17	11	20	34	29	11	49	11	9	14	26	26	34	34	20	3
Staging for non-Hodgkin lymphoma - T/NK cell	43	43	34	34	57	31	49	94	100	100	97	97	100	97	100	6	9	26	37	20	11	23	37	31	11	51	14	9	14	31	14	20	20	11	3
Skin rash	71	71	54	54	74	60	71	83	94	94	89	91	94	94	91	9	23	37	57	40	23	34	51	40	17	60	31	20	31	43	14	23	23	11	3
Atypical cells in body fluids (CSF, serous, ocular, etc.)	100	100	83	83	97	80	97	54	91	89	69	69	89	80	77	14	23	43	66	40	29	37	66	63	26	71	29	23	40	43	34	51	46	37	20
Monoclonal gammopathy	86	86	66	49	89	74	83	23	43	37	29	29	37	34	34	9	11	23	31	17	11	20	31	26	11	49	17	11	17	29	80	89	86	80	54
Unexplained Plasmacytosis of bone marrow	69	69	37	34	71	60	74	26	46	40	29	31	40	34	37	9	11	23	31	17	11	20	34	29	14	51	17	11	17	31	89	97	94	89	57
Monitoring of Rx response																																			
Mature B cell neoplasm	100	100	94	94	100	100	97	17	46	37	23	26	37	43	31	11	11	20	31	14	9	20	37	29	14	51	17	9	11	26	29	40	37	23	9
Mature T or NK cell neoplasm	23	23	17	14	46	20	40	94	100	97	97	97	97	97	97	9	14	23	34	14	9	20	40	31	11	54	14	9	11	29	9	17	20	9	0
Acute lymphoid leukemia - B cell	77	77	49	97	97	94	94	17	46	34	20	20	29	40	29	9	14	20	40	17	9	20	49	43	20	51	14	9	29	34	14	23	26	11	9
Acute lymphoid leukemia - T cell	26	26	20	34	49	23	46	91	97	94	97	97	94	97	77	14	17	20	46	20	9	17	49	40	14	49	14	11	26	31	9	14	20	9	3
Acute myeloid leukemia	29	29	20	29	51	26	49	23	49	40	20	23	34	40	29	40	80	74	97	89	80	77	97	94	54	97	80	77	89	91	9	17	23	9	3
MDS / MPD / Overlap Syndrome	31	31	23	29	49	29	49	29	49	37	26	26	40	43	34	46	71	74	86	80	77	80	86	83	60	83	74	71	83	83	14	29	26	14	0
Plasma cell neoplasm	54	54	23	29	57	49	54	17	43	34	20	20	31	40	34	9	11	20	31	11	9	20	34	31	17	46	23	9	20	23	97	100	97	94	60

Consensus cutoff is 66% (red) with other potential cutoffs at 60% (blue) and 50% (green) for comparison.

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Basis Antikörperpanel

Bethesda 2006: Antigen consensus

Consensus Reagents for Initial Evaluation for Hematopoietic Neoplasia

Lineage	Primary reagents
B cells	CD5, CD10, CD19, CD20, CD45, Kappa, Lambda
T cells and NK cells	CD2, CD3, CD4, CD5, CD7, CD8, CD45, CD56
Myelomonocytic cells	CD7, CD11b, CD13, CD14, CD15, CD16, CD33, CD34, CD45, CD56, CD117, HLA-DR
Myelomonocytic cells (limited)	CD13, CD33, CD34, CD45
Plasma cells	CD19, CD38, CD45, CD56

„core“ Panel mit 23 Antikörpern

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Erweitertes Antikörperpanel

Bethesda 2006: Antigen consensus

Reagents for Secondary Evaluation of Specific Hematopoetic Cell Lineages

Lineage	Secondary reagents
B cells	CD9, CD11c, CD15, CD22, cCD22, CD23, CD25, CD13, CD33, CD34, CD38, CD43, CD58, cCD79a, CD79b, CD103, FMC7, Bcl-2, cKappa, cLambda, TdT, Zap-70, cIgM
T cells and NK cells	CD1a, cCD3, CD10, CD16, CD25, CD26, CD30, CD34, CD45RA, CD45RO, CD57, αβ-TCR, γδ-TCR, cTIA-1, T-beta chain isoforms, TdT
Myelomonocytic cells	CD2, CD4, CD25, CD36, CD38, CD41, CD61, cCD61, CD64, CD71, cMPO, CD123, CD163, CD235a
Plasma cells	CD10, CD117, CD138, cKappa, cLambda

Antikörperanzahl je Panel:

Linie	*Basis*	*Zusatz*	*Gesamt*
B	7	23	30
T	8	15(+)	23(+)
M	12	14	26
P	4	5	9

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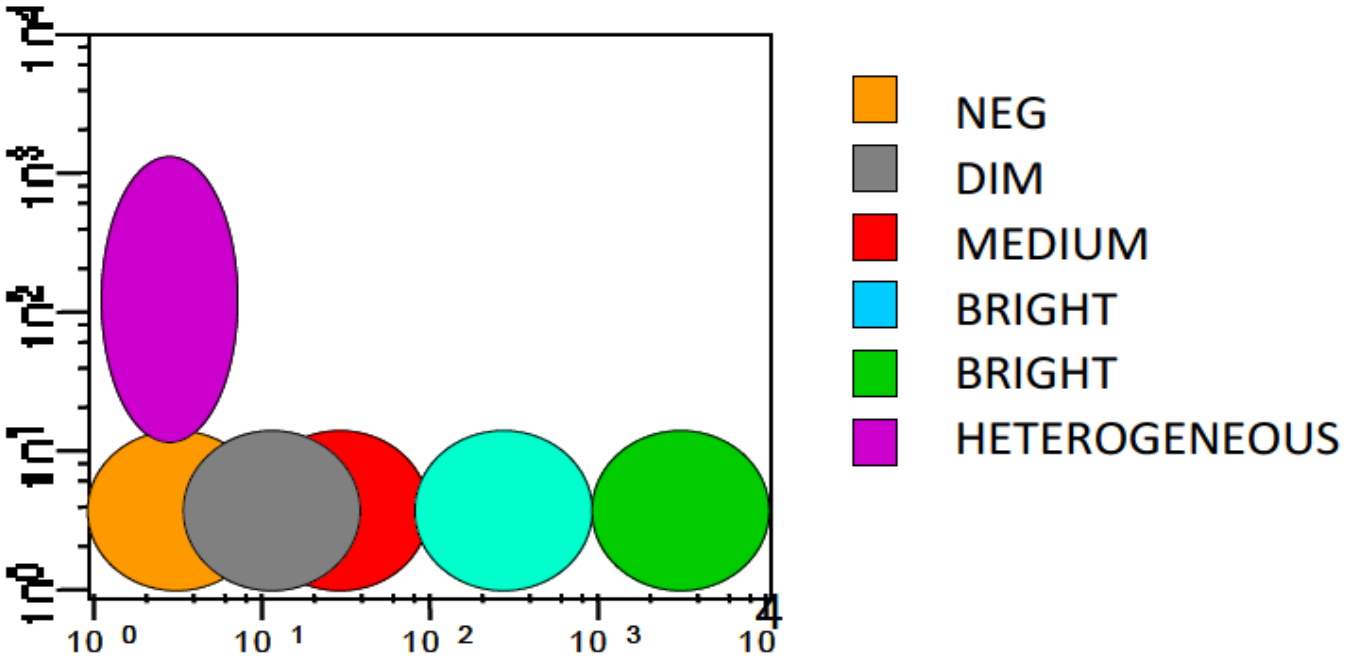
Antigenexpression und -positiviät

Bethesda 2006: Criteria for antigen expression

Bethesda criteria (Wood et al., Clin Cytometry 72B, 2007):

- description of **antibody distribution**: *negative, positive, partially positive* – relative to an *appropriate* negative population
- description of antibody **fluorescence intensity**: *dim, bright, heterogeneous* – relative to **an *appropriate* negative population**



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Empfehlungen zur „Panelkonstruktion“

Bethesda 2006

- Stark exprimierte Antigene sollten mit Antikörpern mit schwach leuchtenden Fluorochromen nachgewiesen werden (und vice versa)
- Mitführen *eines* Antikörpes in allen „Tubes“ (z.B. CD45, CD34, CD19, CD3)
- Kombination von Pan-Linienmarkern mit Markern, die Subgruppen beschreiben (z.B. CD3 und CD4)
- Kombination von Ausreifungsmarkern (z.B. CD34, CD38, CD117)
- Mitführen von differenzierenden Markern

Qualitätssicherung

Bethesda 2006

- Stets Morphologie vor Immunphänotypisierung
  Mikroskopisches Bild stimmig zum Analysematerial der Durchflußzytometrie?

- Vorbefunde?

- Feedback des Klinikers über den klinischen Verlauf oder das Ergebnis komplementärer Untersuchungen?

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Befundbericht:

notwendige und empfohlene Angaben

	REQUIRED	OPTIONAL
Patient Information		
Name / ID#	1997	
SSN / Hosp ID		2006
Age / Date of birth	1997	
Gender	1997	
Referring / attending physician name(s)	1997	
Referring / attending physician phone / fax / email		2006
Referring institution		2006
Referring Institution address / phone / fax / email		2006
Requesting physician / pathologist name(s)	2006	
Requesting physician address / phone / fax / email		2006
History / relevant clinical information, diagnoses, ICD-9 code	1997	
Reason for FCM request / Symptoms	1997	
Previous / Current relevant therapy	1997	
Previous FCM studies (documented)		1997
Other lab results (WBC, differential count)		1997
Sample Information		
Requesting Lab Specimen ID	1997	
Reporting Lab Specimen ID / accession number [if different from requesting lab]	2006	
Sample source / location (axillary, inguinal, etc)	1997	
Sample type (BM, PB, core, L/N, FNA, etc)	1997	
Sample description [anticoagulant, volume / dimensions, color, firmness)		1997
Sample date/time collected from the patient	1997	
Sample date/time received in the lab	1997	
Other materials received (BM-EDTA, PB-EDTA, core bx, etc)		1997
Other procedures on original sample (imprints, smears, freezing, genetics, fixation, etc.)		1997
Sample saved / stored		1997

Befundbericht:
notwendige und empfohlene Angaben

	REQUIRED	OPTIONAL
Sample preparation / staining data		
Cell suspension preparation method (RBC lysis, Ficoll-Hypaque)		1997
Cell suspension preparation date/time		1997
Cell yield / specimen cellularity		1997
Cell viability		1997
Microscopic control (cytospins)		1997
Other tests on cell suspension (DNA content, cytochemistry, genetics, other)		1997
Sample date/time stained		1997
Nonviable cell staining		1997
Cells saved/stored		1997
Antibodies used (CDs) / Tests Performed	1997	
Antibodies used (trade name)		1997
Fluorochrome combination used (surface and/or cytoplasmic)		1997
Cell analysis information		
Date/time FCM analysis		1997
Technologist / Data Analyst		2006
Data analysis		
Qualitative description of light scatter and/or immunophenotypic features of cells of interest (eg. Large B cells)	1997	
% of abnormal cells relative to a defined population	2006	1997
Fluorescence distribution on the cells of interest (The marker is negative, positive, or partially expressed)	2006	
Fluorescence intensity for relevant, positive markers (dim, bright, heterogeneous)	1997	
(Brightness noted is relative to the brightness of normal, similar hematolymphoid cells)		
Relative counts in PB in special circumstances		1997
Normal cells present (eg. Polyclonal B, Polytypic T, NK, Monos, Grans, Plasma Cells, Erythroid)		2006
Kappa: Lambda ratio		1997
CD4:CD8 ratio		1997
Morphologic description of cell suspension (quality control of cells flowed)		1997
Pertinent test results on sample: microscopy, cytochemistry, immunohistochemistry, DNA content, genetics, etc.		1997

Befundbericht:
notwendige und empfohlene Angaben

	REQUIRED	OPTIONAL
Interpretation		
If no abnormal population is identified, a description of the normal populations present is provided.	1997	
If an abnormal population is detected, its phenotype and differential diagnosis is provided.	1997	
Include W.H.O. defined interpretation (include FAB interpretation if requested)	2006	
If additional relevant clinical and/or laboratory data are available, a more definite diagnosis is included.	1997	
Include comments, disclaimers, and limitations of the interpretation.	2006	
Include sign-out pathologist name and contact information (phone / fax / email)	2006	
Flow Cytometry Laboratory Information		
Report Name (eg. Flow Cytometry Leukemia / Lymphoma Report)		2006
Laboratory Name		2006
Laboratory Address		2006
Laboratory Phone (eg. Pathology secretary or client services)		2006
Laboratory Licenses (CAP, CLIA, MEDICARE, etc)		2006
Additional elements		
Representative histograms/plots		1997
Recommendations for additional studies		1997
Co signature by professional with proper expertise		1997
Documentation of discussion with referring physician(s) or verbal reporting (date/time)		1997
Selected references		1997
Consultations		1997
Date/time of final report	1997	
CPT Codes: 88182, 88184, 88185, 88187, 88188, 88189 [USA only]	2006	
FDA statement on the use of ASR reagents for "home brew" clinical diagnostic applications [USA only]	2006	

Zusammenfassung

- Die Bethesda Konsensusempfehlungen sind weitgehend identisch mit den Empfehlungen anderer Expertengruppen:

- Der Umfang der empfohlenen Antikörperpanel überschreitet das in der Routine mögliche (und nötige)
- Die Indikationsausweitung der Immunphänotypisierung zur Abklärung unklarer Symptome und Befunde stagniert (z.B. „Abklärung Splenomegalie“)
- Trotz mittlerweile etablierter Methodik werden einige hämatologische Erkrankungen weiterhin selten der Immunphänotypisierung zugeführt (z.B. das Multiple Myelom, MDS)

Zusammenfassung: Bessere Kooperation

- Die Kliniker müssen über die Möglichkeiten und Grenzen der Immunphänotypisierung informiert werden
- Die Qualität der Untersuchung ist abhängig von den Angaben des Klinikers (!)
- Vollständigere Angaben über die Situation des Patienten wären wünschenswert (z.B. Vortherapien, Lymphknotenvergrößerung)
- Rückmeldungen über den Krankheitsverlauf oder das Ergebnis anderer ergänzender Untersuchungen sind für das Labor lehrreich