



UZ
LEUVEN



Automatische celtellingen in lichaamsvochten

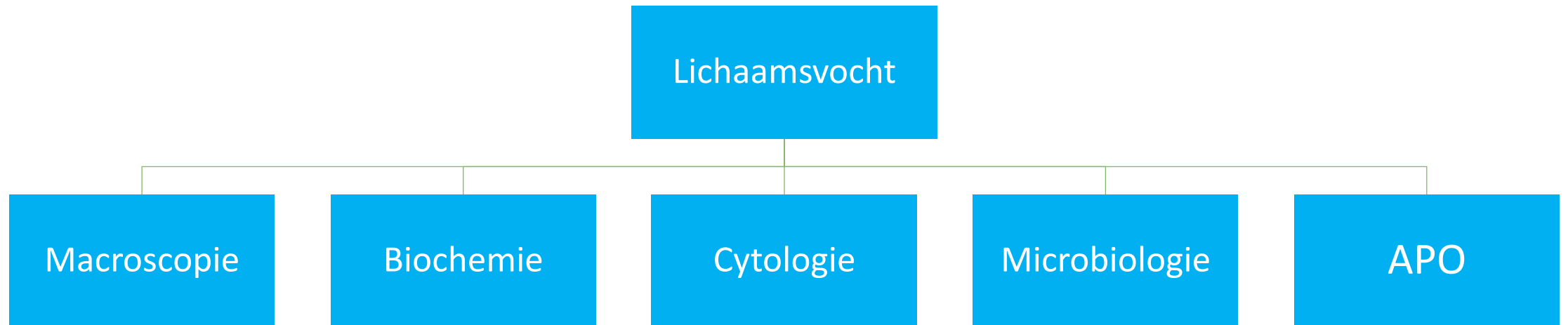
C. Van Laer – 4/10/2022

OVERZICHT LICHAAMSVOCHTEN

Lichaamsvochten

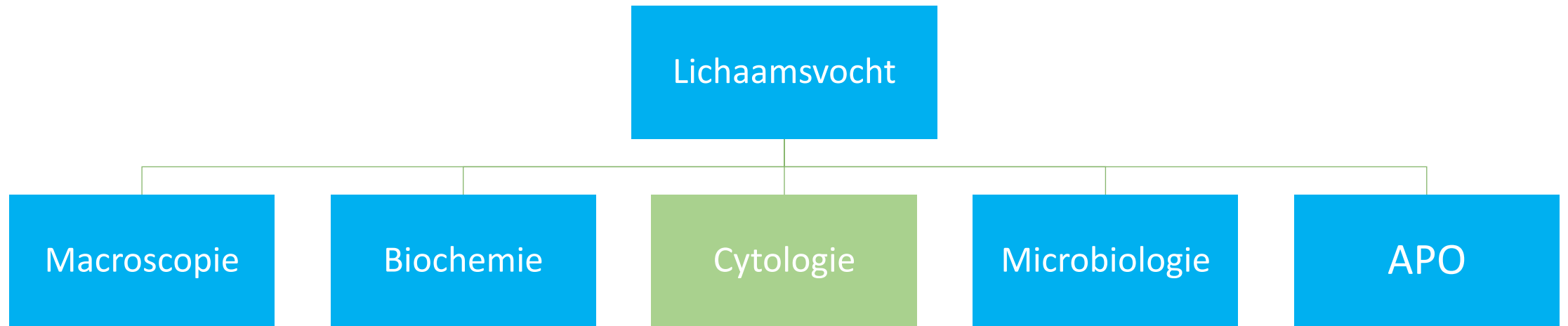
- Ultrafiltraat van bloed
 - Aan- en afvoer nutriënten
 - Bevat biomerkers
 - Aanwezig in gezonde personen en pathologische situaties
- Pathogene processen geven aanleiding tot accumulatie lichaamsvochten
- Vochtcollectie heeft diagnostische en/of therapeutische doeleinden

Onderzoek lichaamsvchten



https://w1.uzleuven.be/labo/Leermodule/SEMINARS/pdf/LES_190206_Lichaamsvchten.pdf

Onderzoek lichaamsvchten



Aantal en identificatie type cellen: RBC / WBC / weefselcellen / maligne cellen

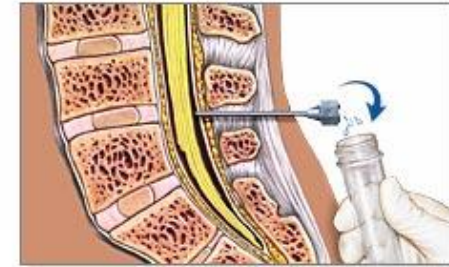
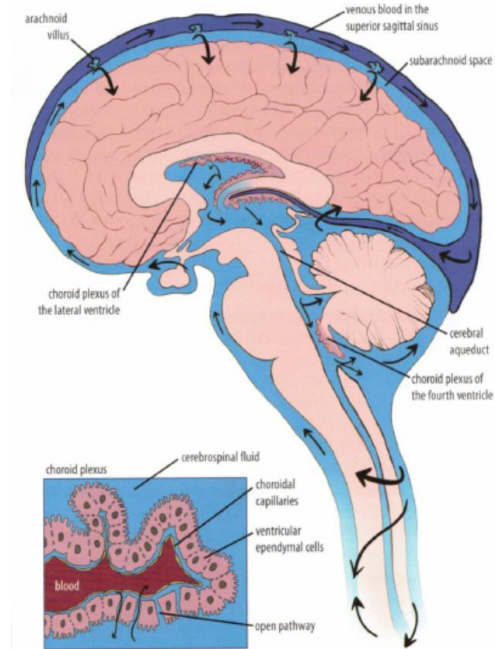
→ infectie? inflammatie? bloeding? maligniteit?

Types lichaamsvochten

- Cerebrospinaal vocht
- Sereus lichaamsvocht
 - Pleura
 - Ascites - peritoneaal
 - Pericard
- Synoviaal vocht

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CNS pathologie

Pathologie	CSV bevindingen
Subarachnoidale bloeding	Bloeding
Meningeale infectie	Inflammatie - Leukocyten - Micro-organismen
Maligniteit	Maligne cellen in CSF - Lymfoom - Acute Leukemie - Niet-hematologische maligniteit
Demyeliserende pathologie	Leukocyten in CSF, oligoclonale Ig

H56-A

Body Fluid Analysis for Cellular Composition; Approved Guideline

This guideline provides users with recommendations for collection and transport of body fluids, numeration and identification of cellular components, and guidance for qualitative and quantitative assessment of body fluid.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

Staalafname CSV

Table 1. Specimen Requirements for Cerebrospinal Fluid*			
<u>Test</u>	<u>Anticoagulant</u>	<u>Volume (mL)</u>	<u>Comments</u>
(e.g., protein, glucose, other special tests)	None	3-5	Tube #1 If traumatic tap is suspected, cell count should also be performed on Tube 1.
Gram stain and culture	None	3-5	Tube #2
Cell count and differential	None	3-5	Tube #3 or 4
Other tests as required (e.g., cytology)	None	3-5	Tube #4
* Suggested specimen requirements. Usually in an adult, 10 to 20 mL are collected.			

↓ perifeer bloeds contaminatie

Cytose

WBC

Leeftijd (jaar)	WBC (/μL)
< 1	0 - 30
1 - 4	0 - 20
5 - 18	0 - 10
> 18	0 - 5

Bacteriële meningitis	Virale meningitis
> 1000 /μL	< 250 /μL

RBC

RBC (x10 ¹² /L)
<0.002

Correctie WBC aantal bij bloederige punctie

$$WBC_{\text{corr}} = WBC_{\text{obs}} - WBC_{\text{added}}$$

$$WBC_{\text{added}} = WBC_B \times RBC_{\text{CSF}}/RBC_B$$

of

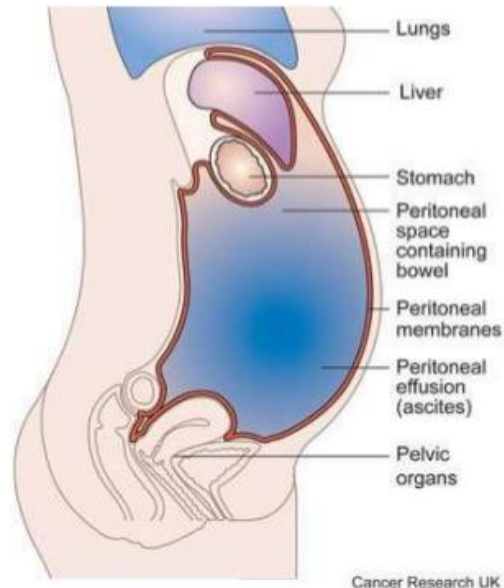
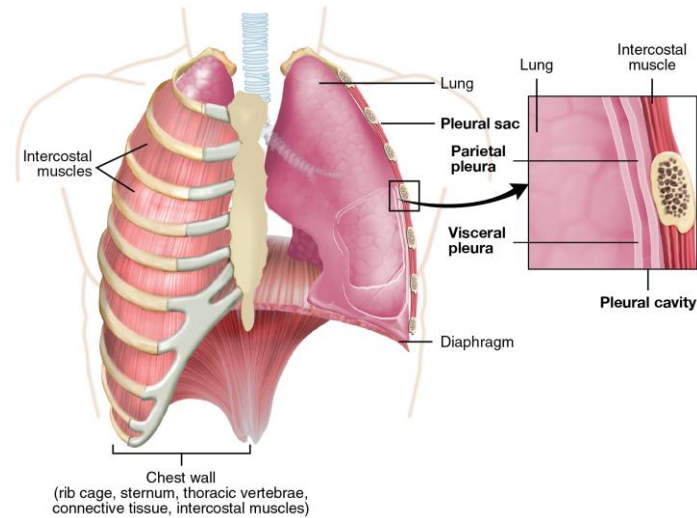
Algemene regel: **+/- 1 WBC per 500 – 1000 RBCs**

Differentiatie in CSV

Celtype	Normaalwaarden (%)		Klinische betekenis bij <u>toename</u>
	volwassenen	neonati	
lymfocyten	40 - 80	5 - 35	virale, tuberculaire en fungale meningitis, bacteriële meningitis (zeldzaam), Multiple sclerose
monocyten	15 - 45	50 - 90	verhoogd aantal monocyten wijst op een niet specifieke meningale irritatie - samen met <u>neutrofielen, lymfocyten en plasmacellen</u> : tuberculose en fungale meningitis, chronische bacteriële meningitis, ... - samen met <u>voornamelijk lymfocyten en plasmacellen</u> : virale meningoencephalitis, syphilis meningitis, listeriosis, ...
neutrofielen	0 - 6	0 - 8	bacteriële meningitis, vroege (<2-3d) virale, tuberculaire en fungale meningitis, intracraniële bloeding, intrathecale injecties, meningeale maligniteit
eosinofielen	zeldzaam	zeldzaam	parasitaire infectie (>10%)

Types lichaamsvochten

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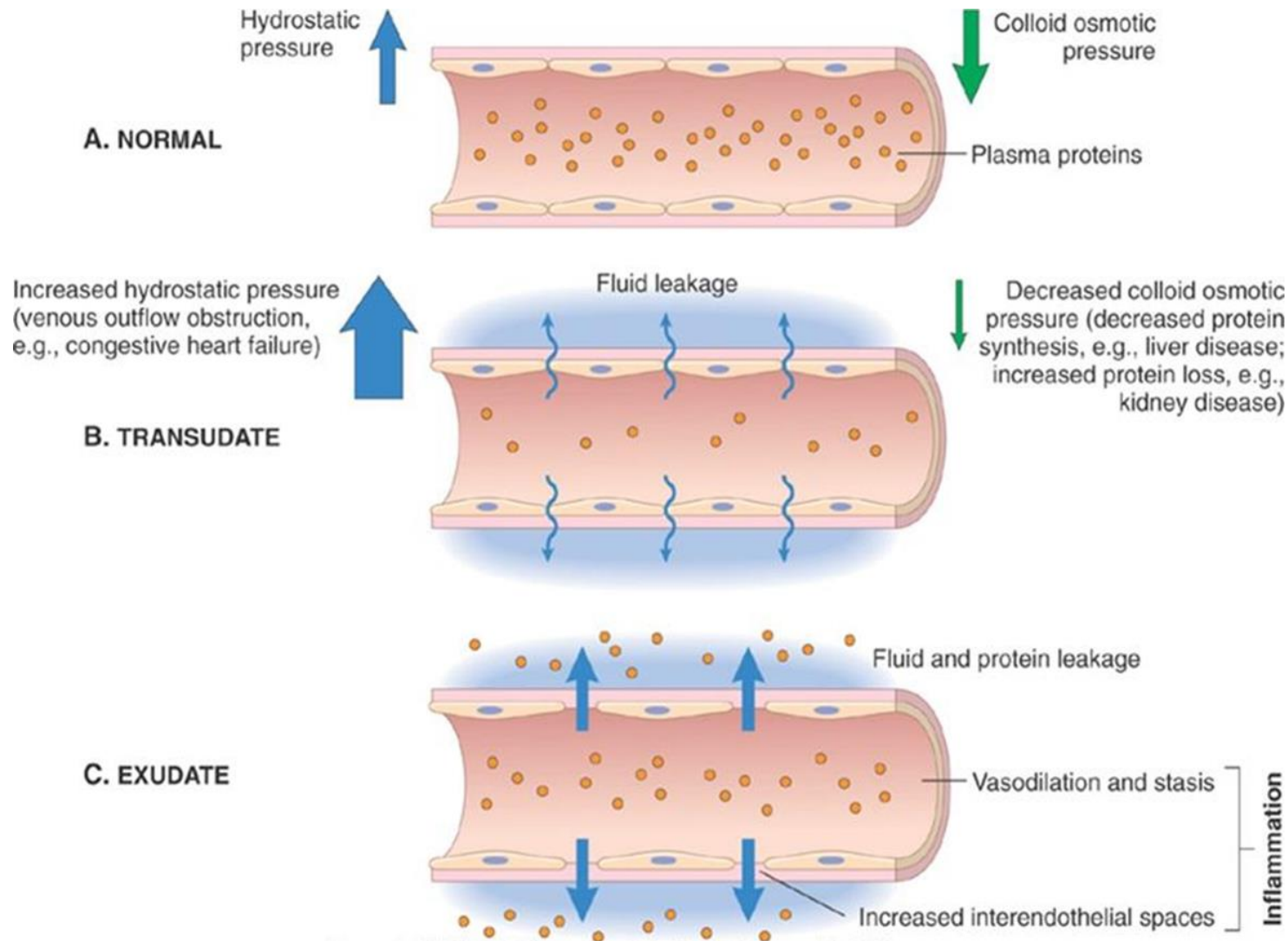
Causes of ascites

Cirrhosis	81 percent
Cancer	10 percent
Heart failure	3 percent
Tuberculosis	2 percent
Dialysis	1 percent
Pancreatic disease	1 percent
Other	2 percent

Staalafname sereus vocht

Table 2. Specimen Requirements for Serous Fluids**		
<u>Tests</u>	<u>Anticoagulant</u>	<u>Volume (mL)</u>
Cell count and differential cell counts	EDTA <i>Geen anticoagulant vereist</i>	5-8
Total protein, LD, glucose amylase	Heparin, none	8-10
Gram stain, bacterial culture	SPS*, none, or anticoagulant without bactericidal or bacteriostatic effect	8-10
AFB culture	SPS, none, or anticoagulant without bactericidal or bacteriostatic effect	15-50
PAP stain, cell block	None, heparin, EDTA	5-50
*SPS = Sodium polyanetholsulfonate		
** Suggested specimen requirements		

Transsudaat vs. exsudaat



WBC < 1.0 x10⁹/L

WBC > 1.0 x10⁹/L

- < 5: TBC, maligniteit
- > 10: bacteriële pneumonie, acute pancreatitis, ...
- > 50: gecompliceerde parapneumonische effusie (bv. empyeem)

Differentiatie pleuravocht

TABLE 1
RESULTS OF TOTAL AND DIFFERENTIAL CELL COUNTS IN PLEURAL LAVAGE FLUID
OF NONSMOKERS, SMOKERS, AND AGGREGATE STUDY POPULATION

	M/F Ratio	RBC ($\times 10^3/\text{ml}$)	WBC ($\times 10^3/\text{ml}$)	N (%)	EO (%)	L (%)	MC (%)	M ϕ (%)	CD4 ⁺ /CD8 ⁺
Nonsmokers (n = 21)	9/12								
Median		36	91	0	0	23	1	75	0.75
Minimum		6	38	0	0	15	0	58	0.18
Maximum		1,070	297	3	1	38	7	92	2.7
Geometric mean		41	115	—	—	24	—	73	0.77
Interquartile range		20–47	74–198	0–1	0–0	18–36	0–2	64–80	0.6–1
Smokers (n = 13)	5/8								
Median		78	147	1	0	20	1	75	0.72
Minimum		1	53	0	0	11	0	60	0.4
Maximum		481	443	14	1	40	10	86	1.5
Geometric mean		58	161	—	—	19	—	73	0.76
Interquartile range		19–180	117–224	1–3	0–0	12–28	0–2	69–81	0.4–1.4
Difference (p value)	0.6	0.37	0.1	0.015	0.52	0.18	0.8	0.87	0.81
Aggregate sample (n = 34)	14/20								
Median		38.5	125	1	0	23	1	75	0.74
Minimum		1	38	0	0	11	0	58	0.18
Maximum		1,070	443	14	1	40	10	92	2.7
Geometric mean		46.5	130.6	—	—	22	—	73	0.77
Interquartile range		19–121	83–214	0–2	0–0	16–31	0–2	64–81	0.47–1.36

Definition of abbreviations: EO = eosinophils; L = lymphocytes; MC = mesothelial cells; M/F = male/female; M ϕ = macrophages; N = neutrophils; RBC = total red blood cell count; WBC = total white blood cell count.

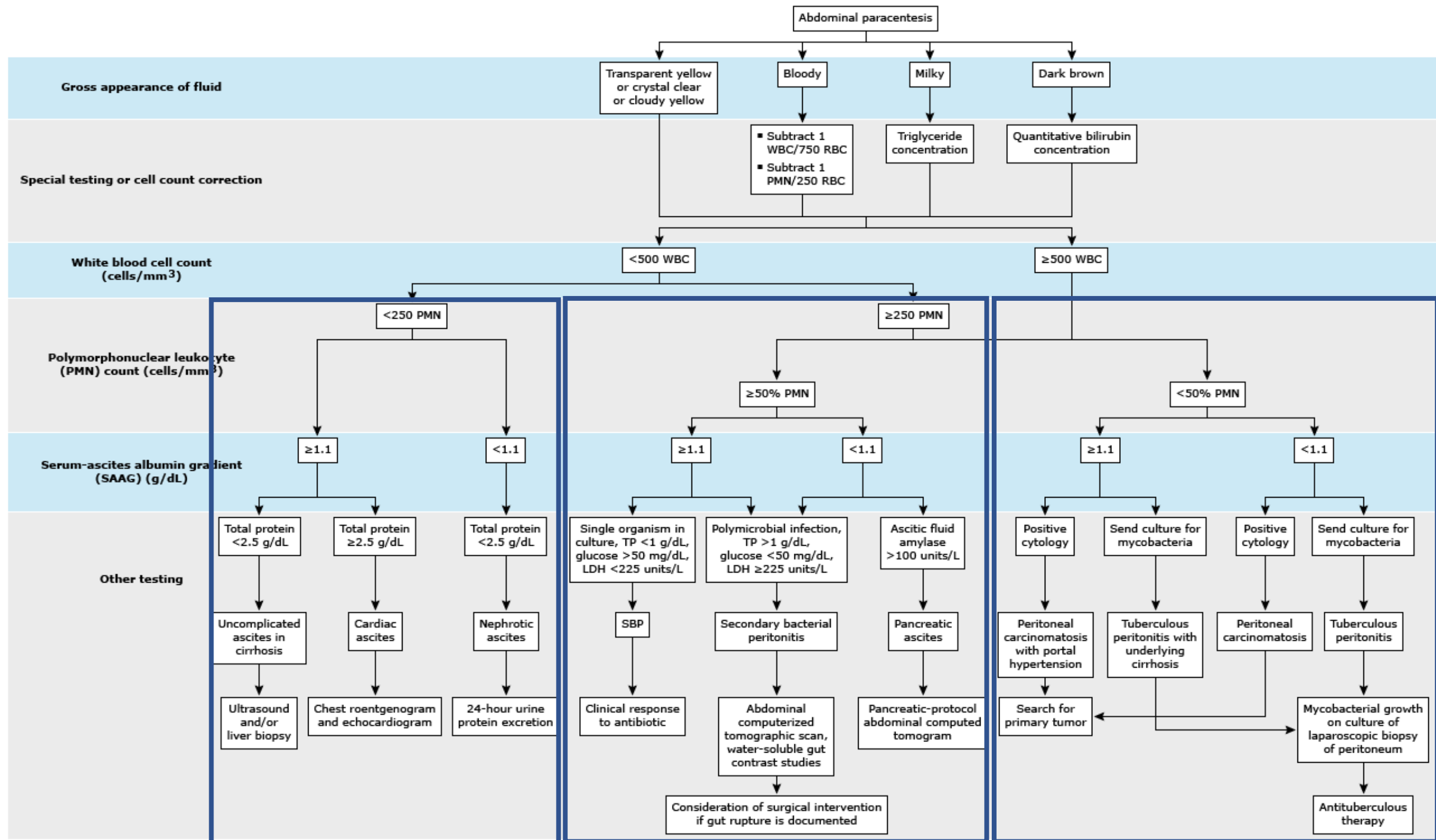
Celtelling en differentiatie **peritoneaal vocht**

WBC

- onderscheid transsudaat (cirrose), 20 – 100 WBC/ μ L, vs exsudaat (spontane bacteriële peritonitis)

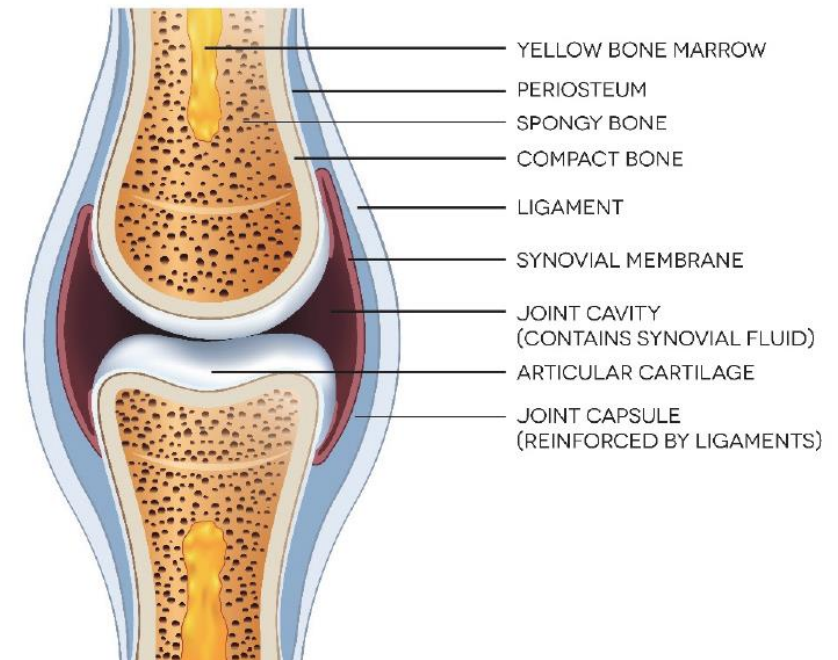
Differentiatie

- Normaal
 - Mesotheel en macrofagen >70%
 - Lymfocyten <18%
 - Neutrofielen <7%
- Neutrofielen $\geq 250/\mu$ L bacteriële peritonitis
- Lymfocyttaire formule CHF, cirrose, nefrotisch syndroom, chyleuze effusies, tuberculeuze peritonitis en maligniteit
- Eosinofilie >10% CAPD, hartfalen, vasculitis, lymfoom, allergie, parasitair, maligniteit



Types lichaamsvchten

- Cerebrospinaal vocht
- Sereuze lichaamsvchten
 - Pleuravocht
 - Ascitesvocht
 - Pericardvocht
- Synoviaal vocht



Synoviaal vocht

= ultrafiltraat plasma vanuit subsynoviale capillairen in subsynoviale ruimte met hyaluronzuur

Indicatie arthrocentese bij gewrichtseffusie

- Infectie (septische artritis)
- Kristalartritis
- Degeneratieve artritis
- Inflammatoire aandoeningen
- Bloedingen
- *Maligniteiten*

Synoviaal vocht

Parameter	Referentiewaarden (volw.)
RBC	$< 0.002 \times 10^9/L$
WBC	$< 0.15 \times 10^9/L$
neutrofielen (PMN)	± 10 (0 - 25%)
lymfocyten	± 30 (0 - 75%)
monocyten/macrofagen	± 60 (0 - 70%)

	Groep I Niet-inflammatoir	Groep II Inflammatoir	Groep III Infectieus	Groep IV Kristal geïnduc.	Groep V Hemorrhagisch
WBC ($\times 10^9/L$)	0 - 3	3 - 75	50 - 200	0.5 - 200	0.05 - 10
PMN (%)	< 30	> 50	> 90	< 90	25 - 50

Staalafname synoviaal vocht

Table 3. Specimen Requirements for Synovial Fluid*			
<u>Test</u>	<u>Anticoagulant</u>	<u>Volume (mL)</u>	<u>Comments</u>
Cell count, differential, crystals, inclusions	Heparin, EDTA <i>None: steriele tube</i>	3-5	Can be done on a few drops of fluid. Mix thoroughly.
Glucose	Fluoride or none	3-5	8-hr. fast preferred
Protein	None		
CH50	None		Freeze if not tested immediately.**
C3, C4	None or EDTA		Requires 1 mL
Culture	SPS, none, or anticoagulant without bactericidal or bacteriostatic effect	3-5	Sterile tube required
* Requirements may change with advances in technology. ** Specimen should be frozen as recommended in the assay protocol.			

+ hyaluronzuur

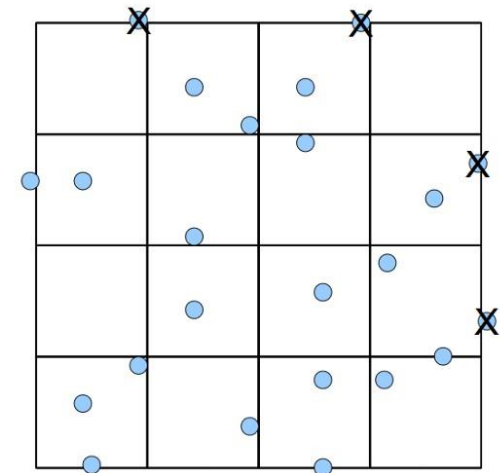
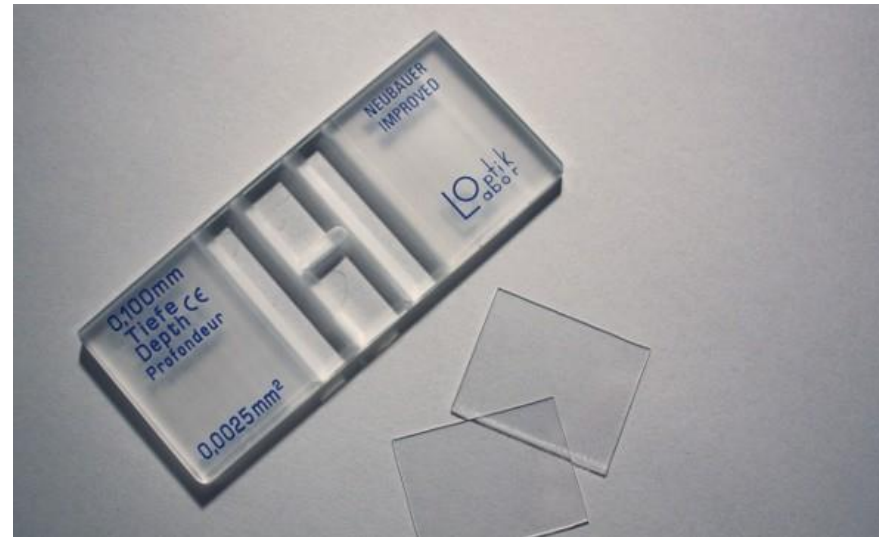
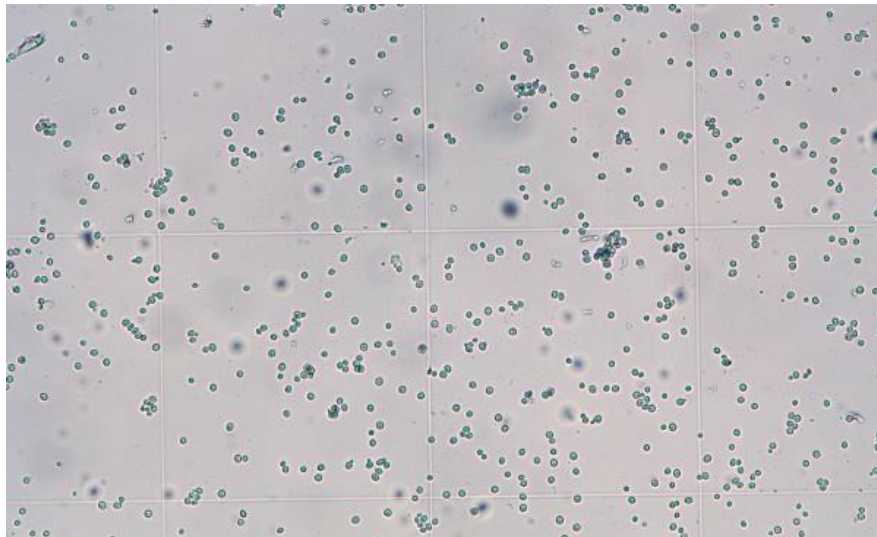
AUTOMATISCHE CELTELLINGEN

Manuele vs. automatische celtellingen

Gouden standaard

= manuele celtelling mbv **Fuchs-Rosenthal telkamer**

= **microscopische** evaluatie van **cytocentrifugatie** preparaat

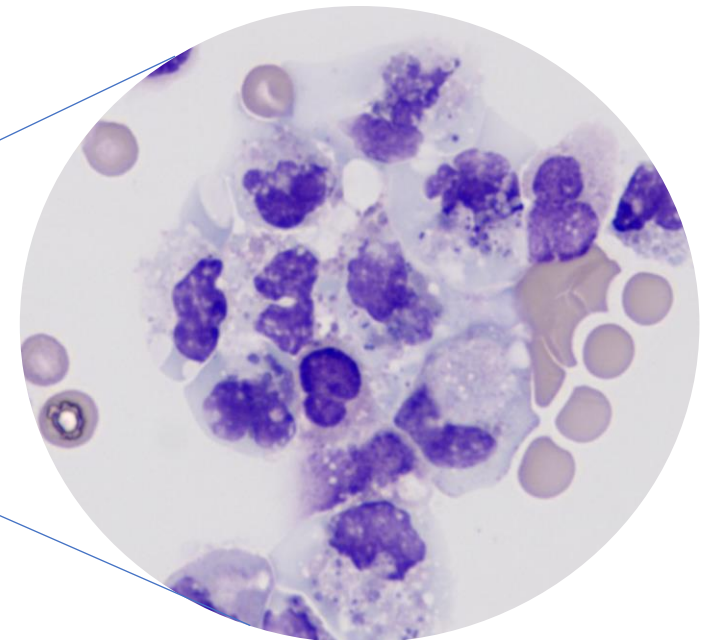
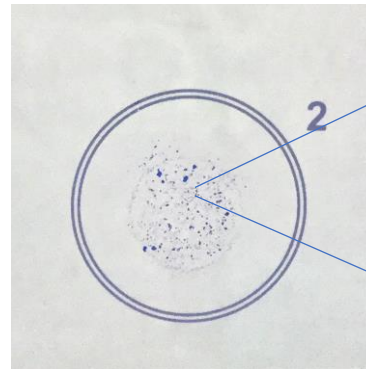
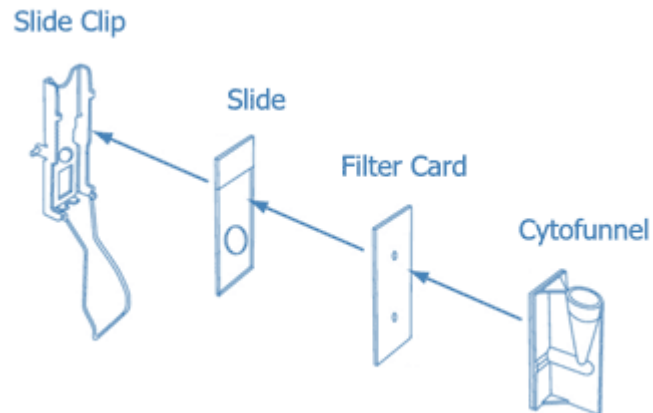


Manuele vs. automatische celtellingen

Gouden standaard

= manuele celtelling mbv **Fuchs-Rosenthal telkamer**

= **microscopische** evaluatie van **cytocentrifugatie** preparaat



Manuele vs. automatische celtellingen

Gouden standaard

= manuele celtelling mbv **telkamer (hemocytometer)**

= **microscopische** evaluatie van **cytocentrifugatie** preparaat

MAAR

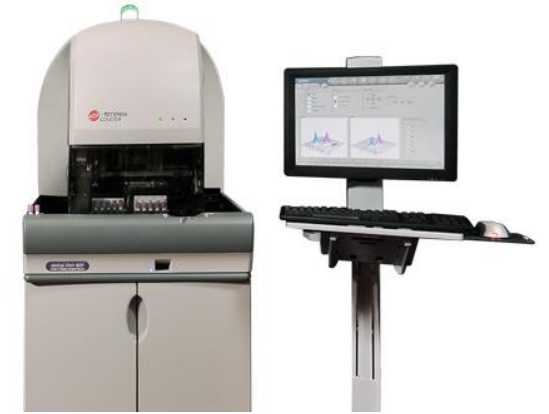
- Tijdrovend en **arbeidsintensief**
- **Lage reproduceerbaarheid en precisie** owv hoge inter- en intraobserver variabiliteit
- Cytocentrifugatie kan leiden tot celverlies en morfologische veranderingen

Lichaamsvochten modules

Sysmex: XN-BF mode



Beckman Coulter: UniCel DxH



Sien Automatische celtellingen blijven beperkingen hebben → microscopische beoordeling kan noodzakelijk blijven



Abbott Diagnostics: CELL-DYN

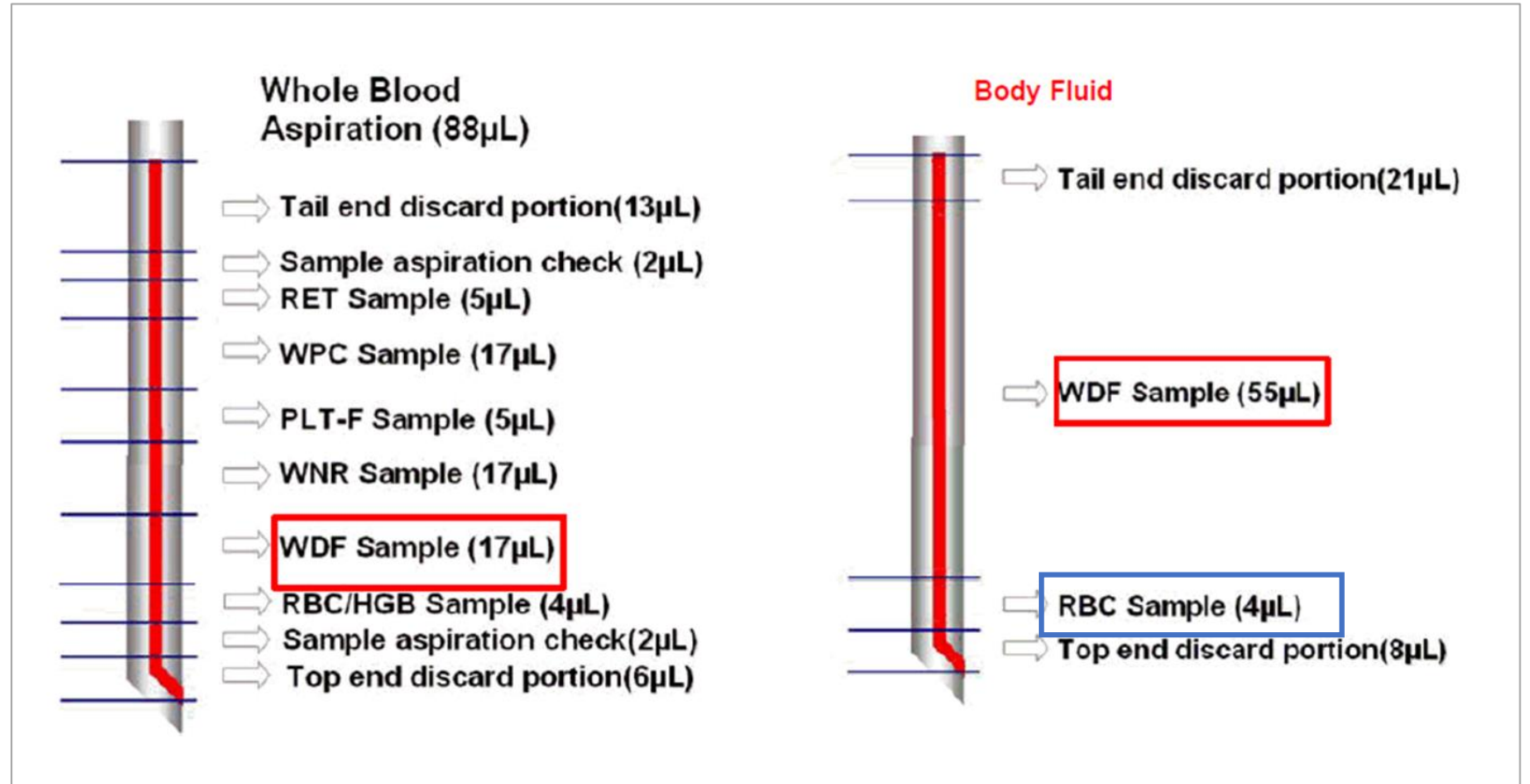


Aandachtspunten celtelling en differentiatie !

- Cellulaire degradatie: zo snel mogelijk analyseren
- Transport op kamertemperatuur
- Opmengen stalen
 - Automatische menger: maximum 2-5 min
 - Manuele opmenging: 10-15x
 - **Uitz.** Synoviaal vocht: langer opmengen
- Verdunningen afhankelijk van cytose
 - 1:10 – 1:200
 - ! Diluent
- Zeer laag – zeer hoog meetbereik

☒	Rerun	Order	Run	Test	Result	C	Unit
☒				Body Fluid Count			
☒		R	1	DILUTION_FACTOR	1/1		
☒		I	1	RBC-BF	Value		*1
☒		I	1	WBC-BF	1/1		*9
☒		R	1	WBC-BF2	1/5		
☒		I	1	TC-BF#	1/10		*9
☒				Body Fluid Differential	1/20		
☒		I	1	MN#	1/50		*9
☒		I	1	MN%	1/100		
☒		I	1	PMN#			*9

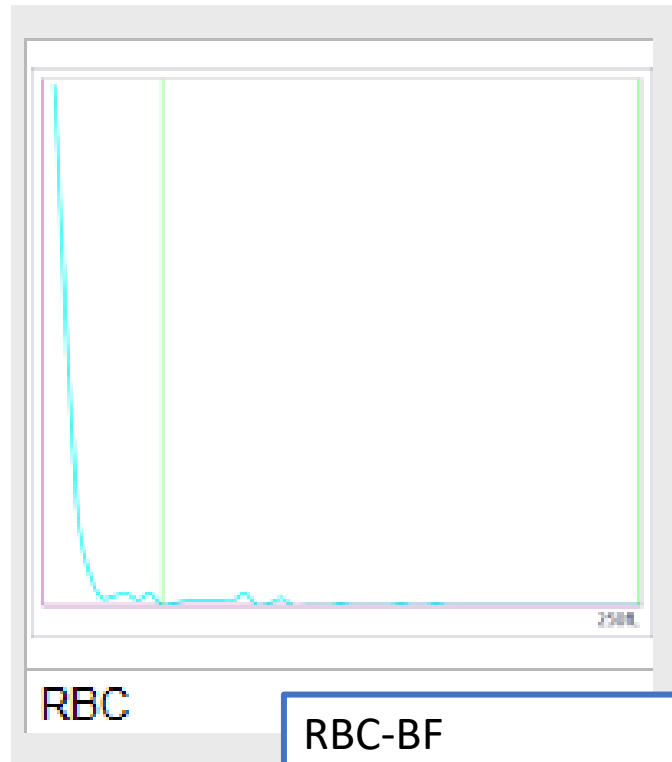
Sysmex XN Body fluid mode



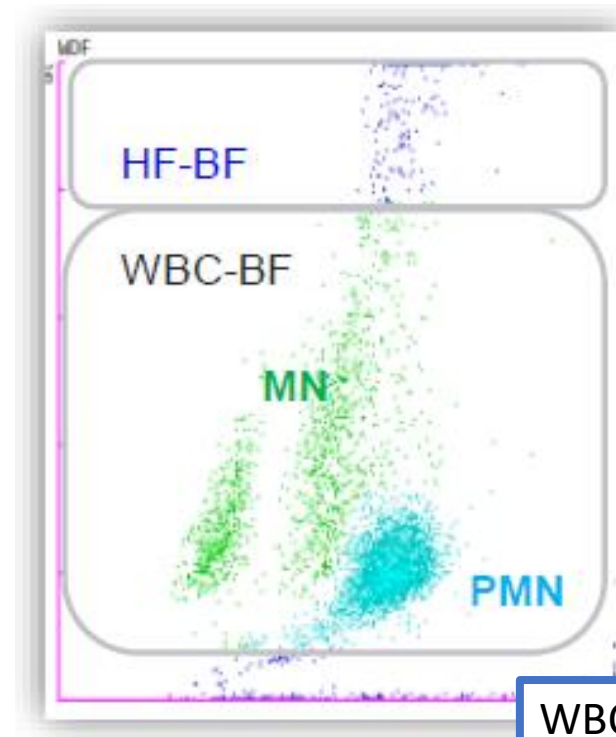
XN BF-module

added value
XN-BF

Impedantie methode



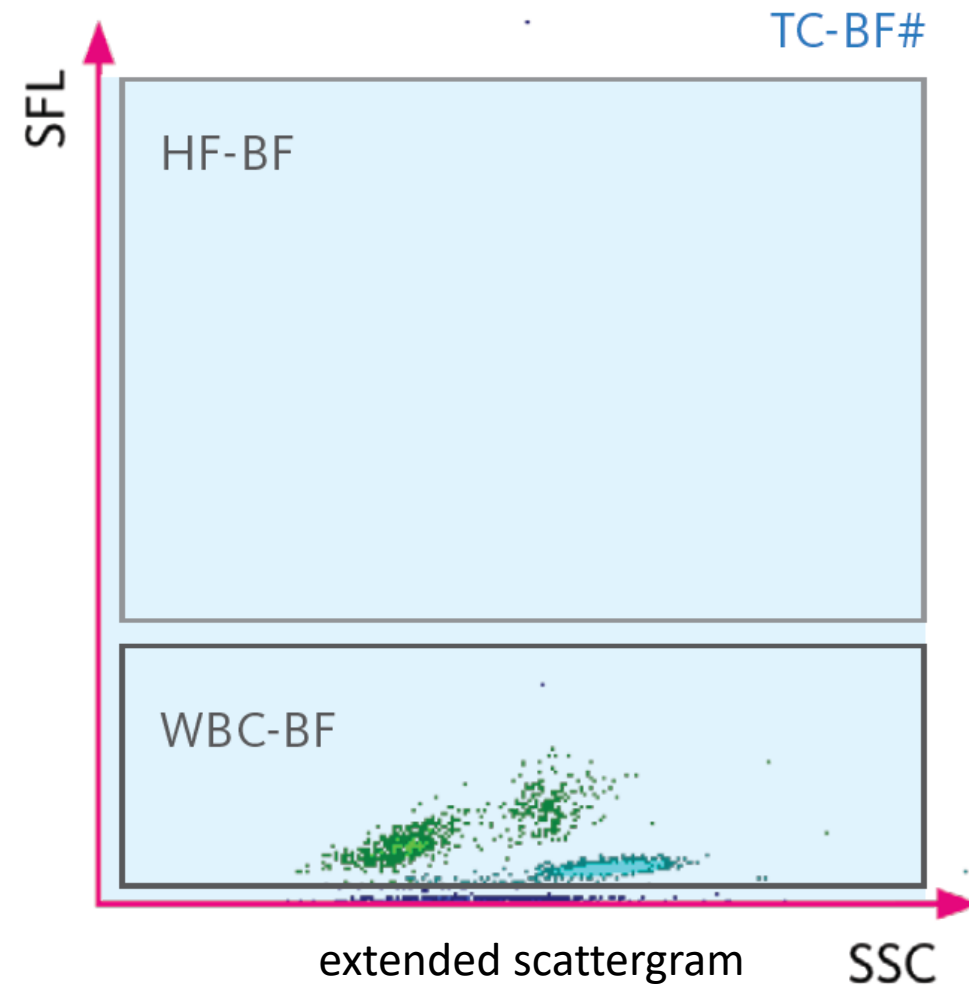
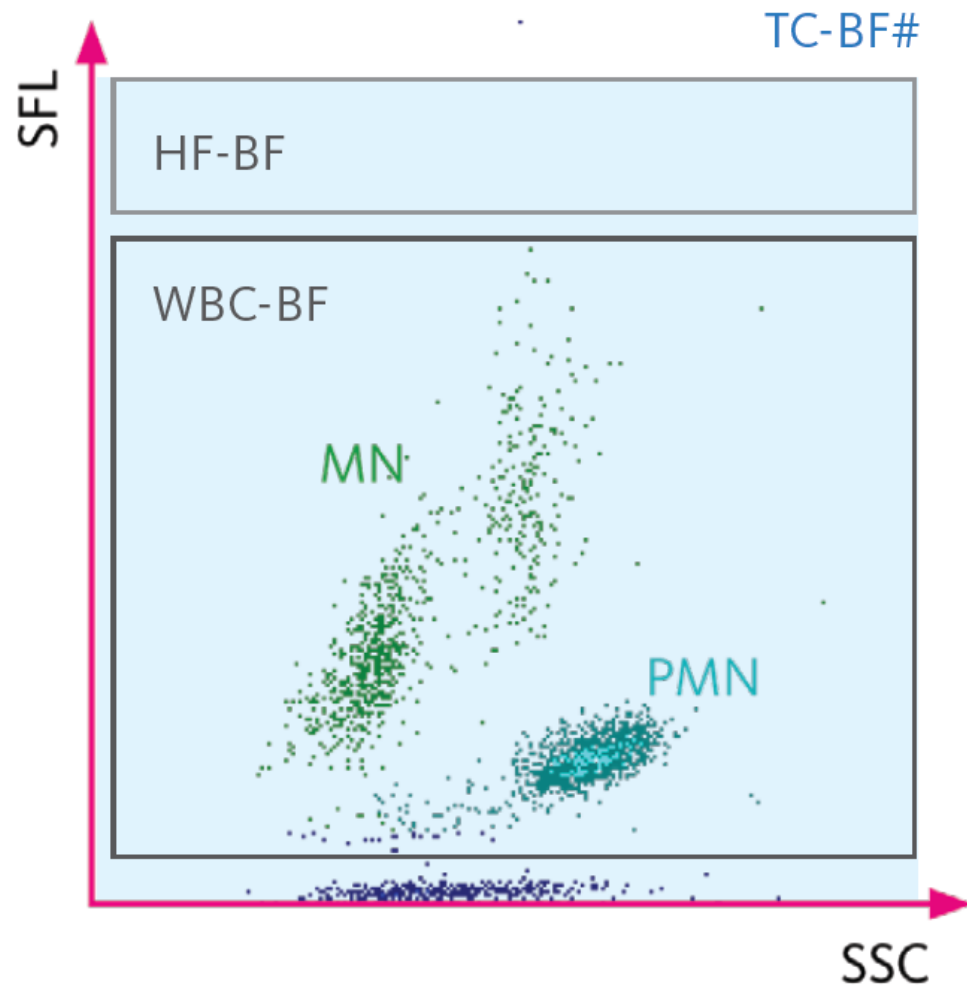
Fluorescentie flow cytometrie



WBC-BF
TNC-BF
PMN % en #
MN % en #

Research: NE-BF, LY-BF, MO-BF, EO-BF, HF

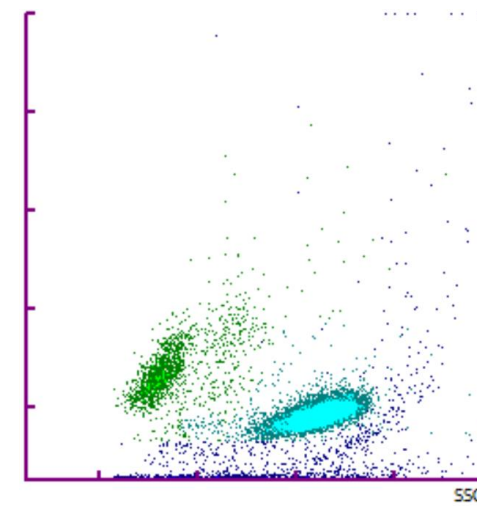
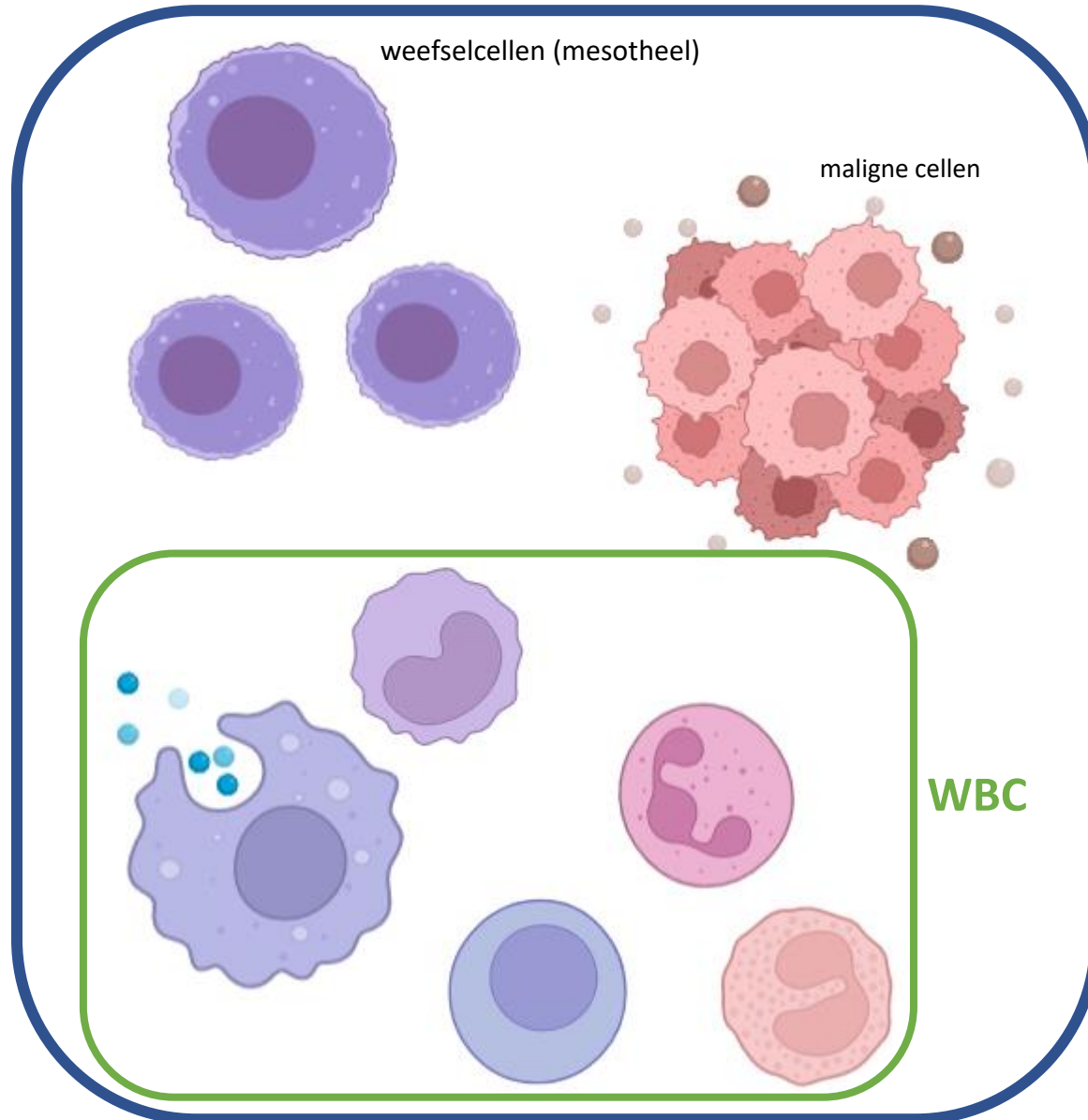
WDF scattergram



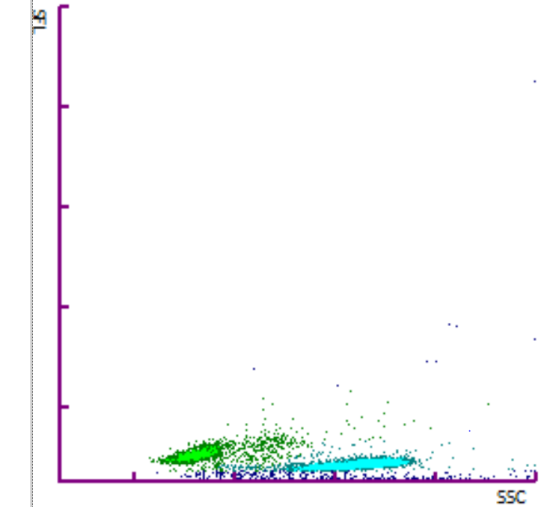
↔ perifer blood: WBC in WNR scattergram

WBC telling

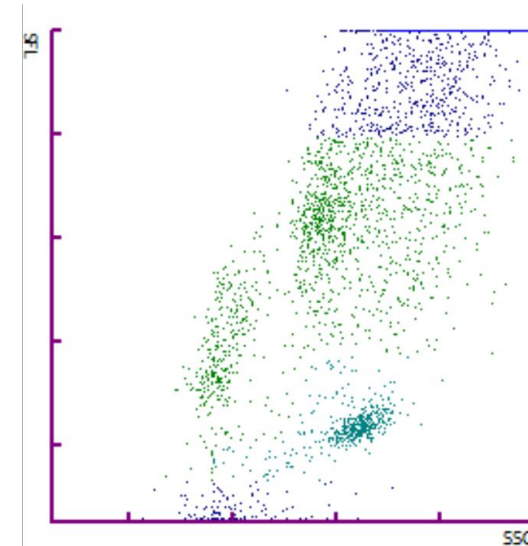
Total nucleated cell (TNC)



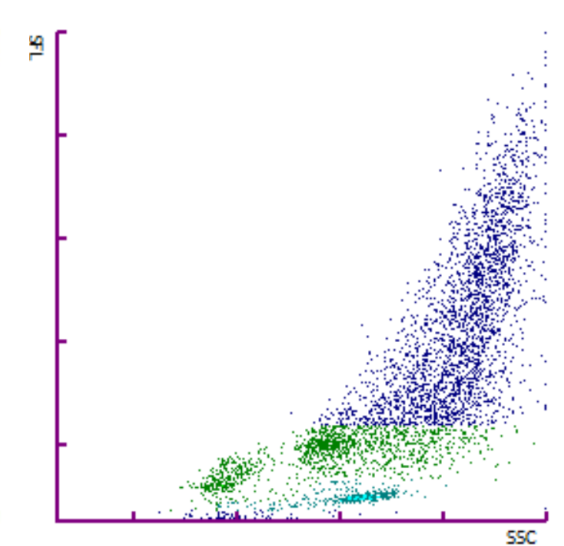
WBC $1,140 \times 10^9/\text{L}$



TNC $1,141 \times 10^9/\text{L}$

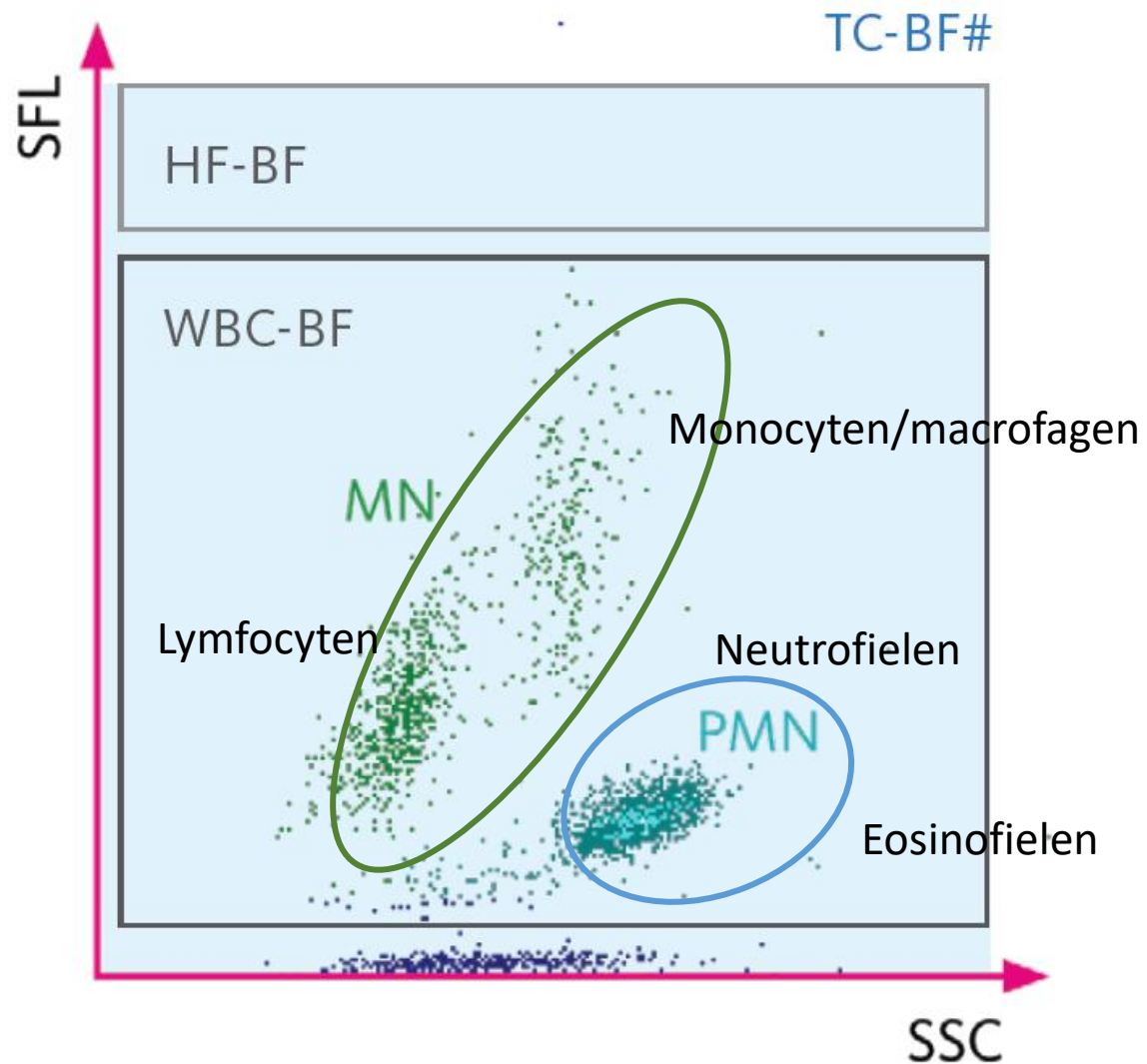


WBC $2,430 \times 10^9/\text{L}$



TNC $4,311 \times 10^9/\text{L}$

WBC differentiatie



PMN
polymorphonuclear leukocytes

MN
mononuclear leukocytes

vs.

4 (5)- differentiatie

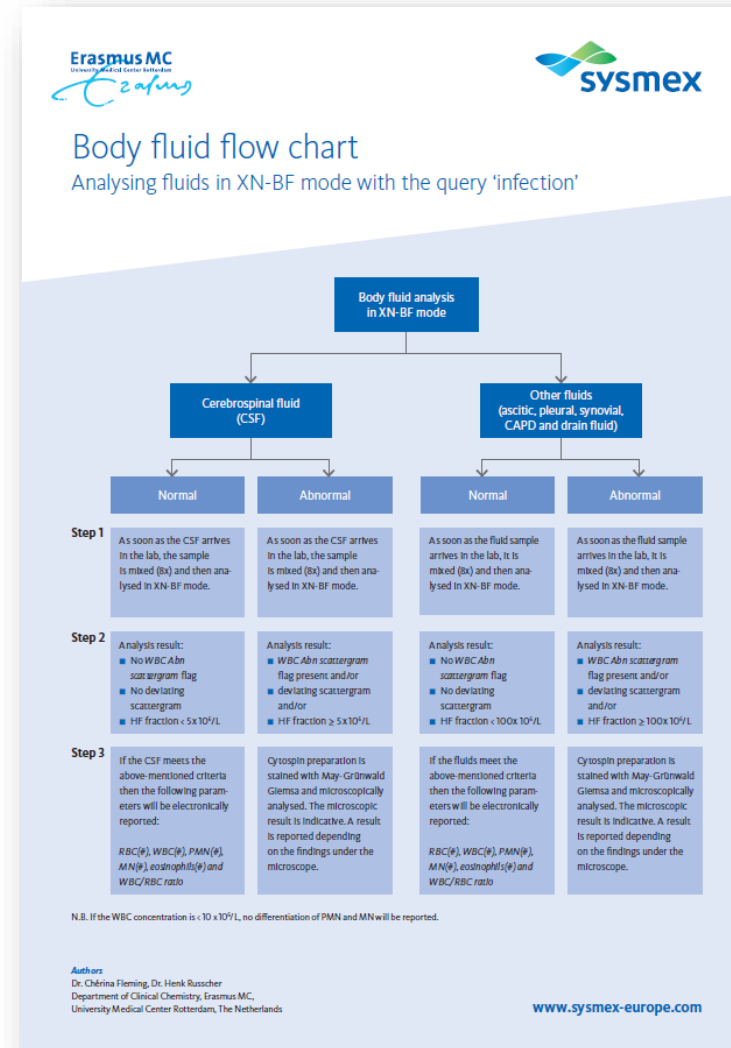
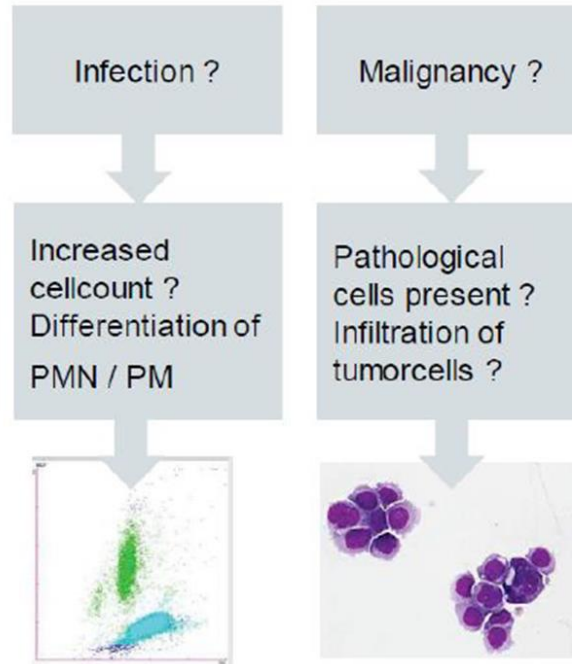
Plaats van manuele telling?

Beperkingen automatische celtellingen

- ✓ niet alle toestellen hebben **adequate analytische sensitiviteit**
- ✓ meeste toestellen werden gevalideerd voor **PMN en MN**
- ✓ geen identificatie van **niet-hematologische cellen** (zoals mesotheel en maligne cellen)
- ✓ geen identificatie van **hematologische maligniteiten** (blasten, lymfoomcellen).
- ✓ **HF parameter** als criterium voor microscopische review

Algoritme voor bepaling nood aan microscopisch nazicht

1/ Klinische vraagstelling?

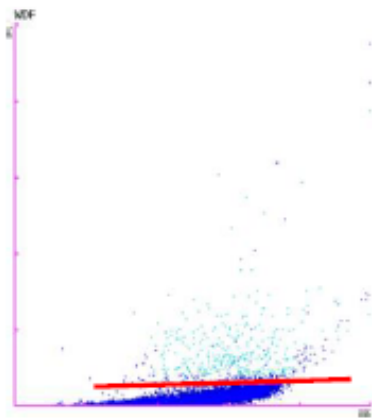


2/ Sysmex EPU Body Fluid rule set

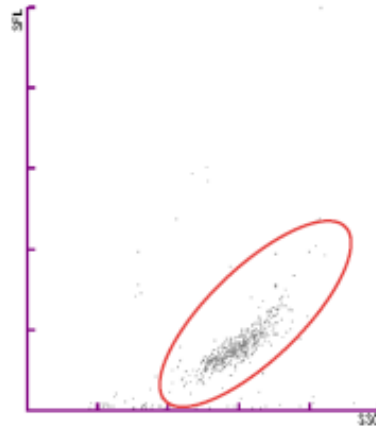
1. WBC Abn Scattergram
2. HF-BF cells
3. EO-BF for CAPD
4. Possible RBC interferences

2.1 EPU: WBC Abn Scattergram

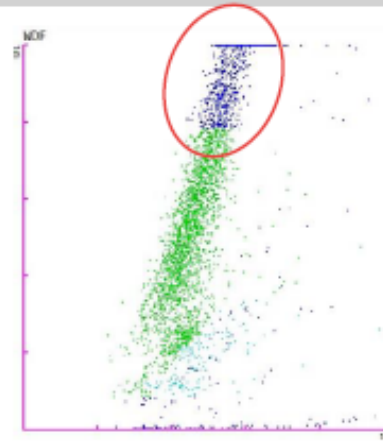
WBC Abn Scattergram



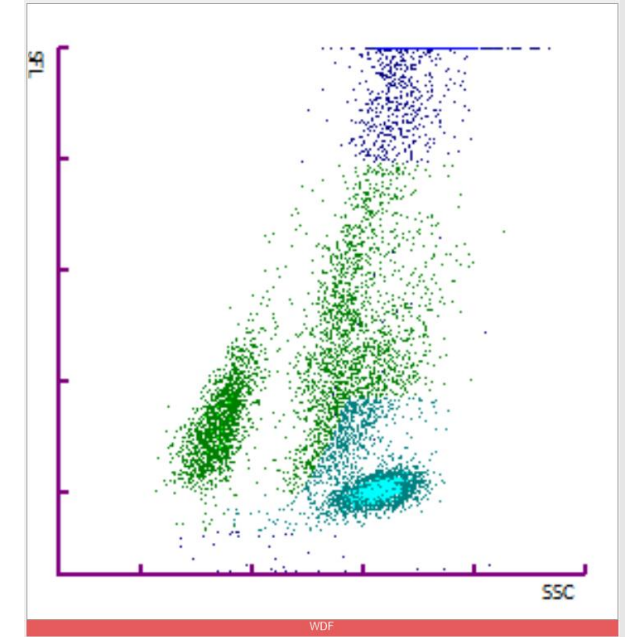
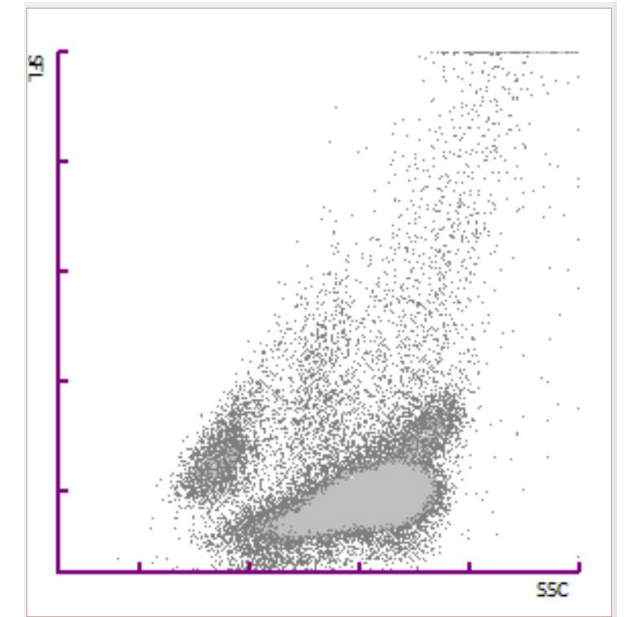
Debris region cannot be separated from WBC



Algorithm detects the presence of liposome interference



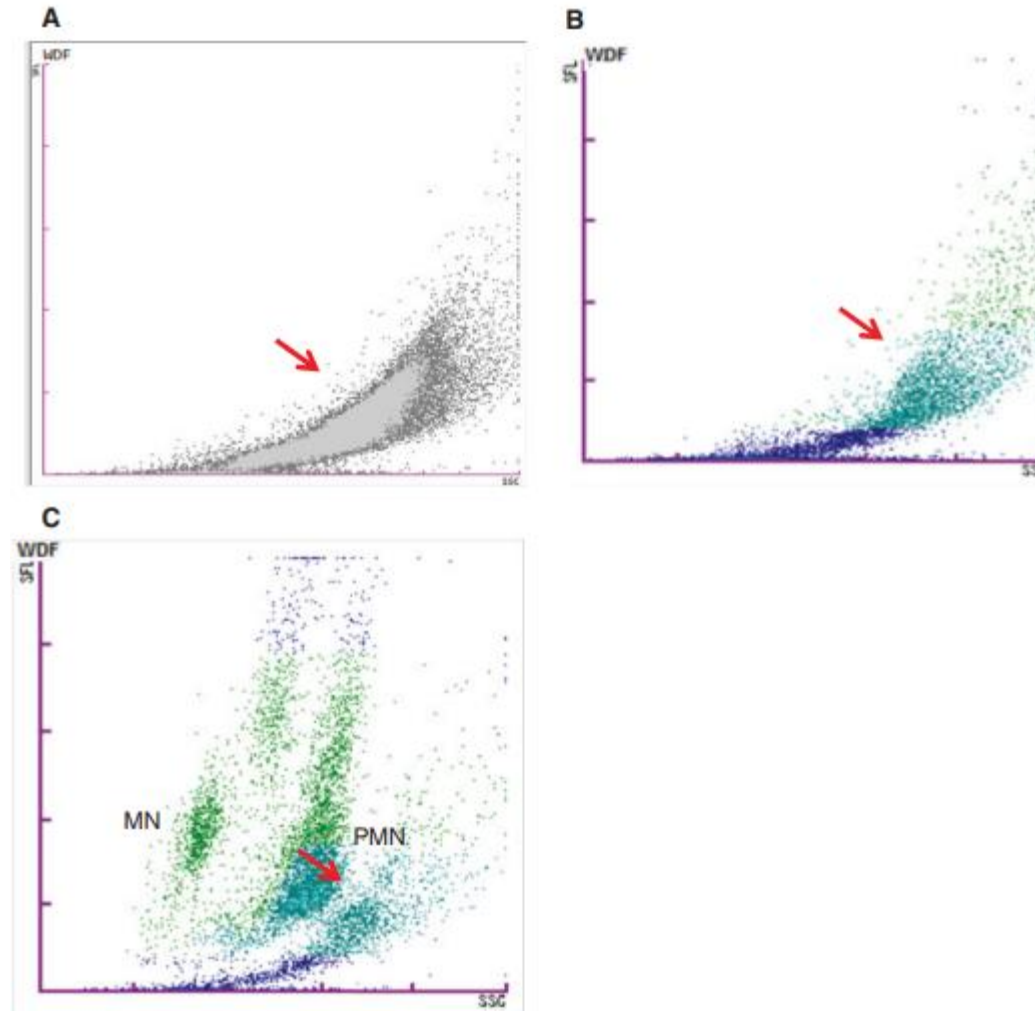
HF-BF cells – is managed in EPU



Potentiële interfererende niet-cellulaire elementen

Fleming et al. (2016)

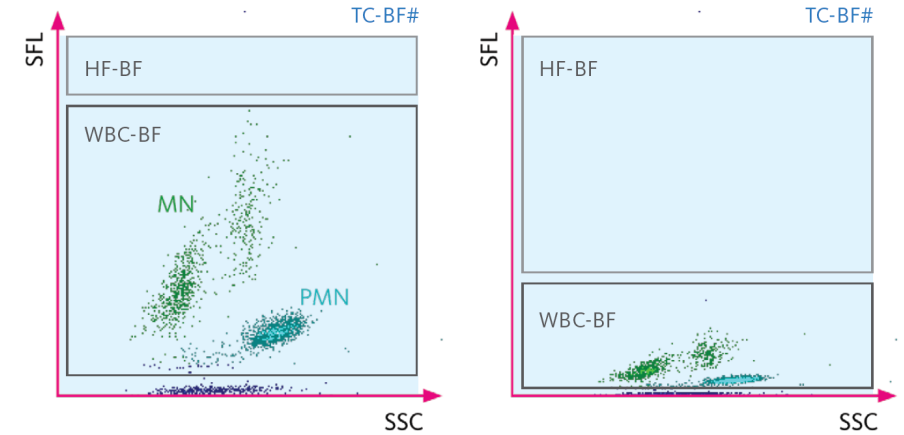
- CSV: intrathecale therapie
- **Liposomale interferenties**
- *'banana' shape*



HF-cells

= *High-fluorescent cells*

- Hoge nucleus/cytoplasma ratio en hoog nucleïnezuurgehalte
- Mesotheel / macrofagen / maligne cellen
 - specificiteit voor maligniteit: 55-87%
- ! % of absolute waarden
- Nog geen standaardisatie



HF-BF# 

CSV
 $\geq 5/\mu\text{L}$

Niet-CSV
 $\geq 100/\mu\text{L}$ of $0.1 \times 10^9/\text{L}$

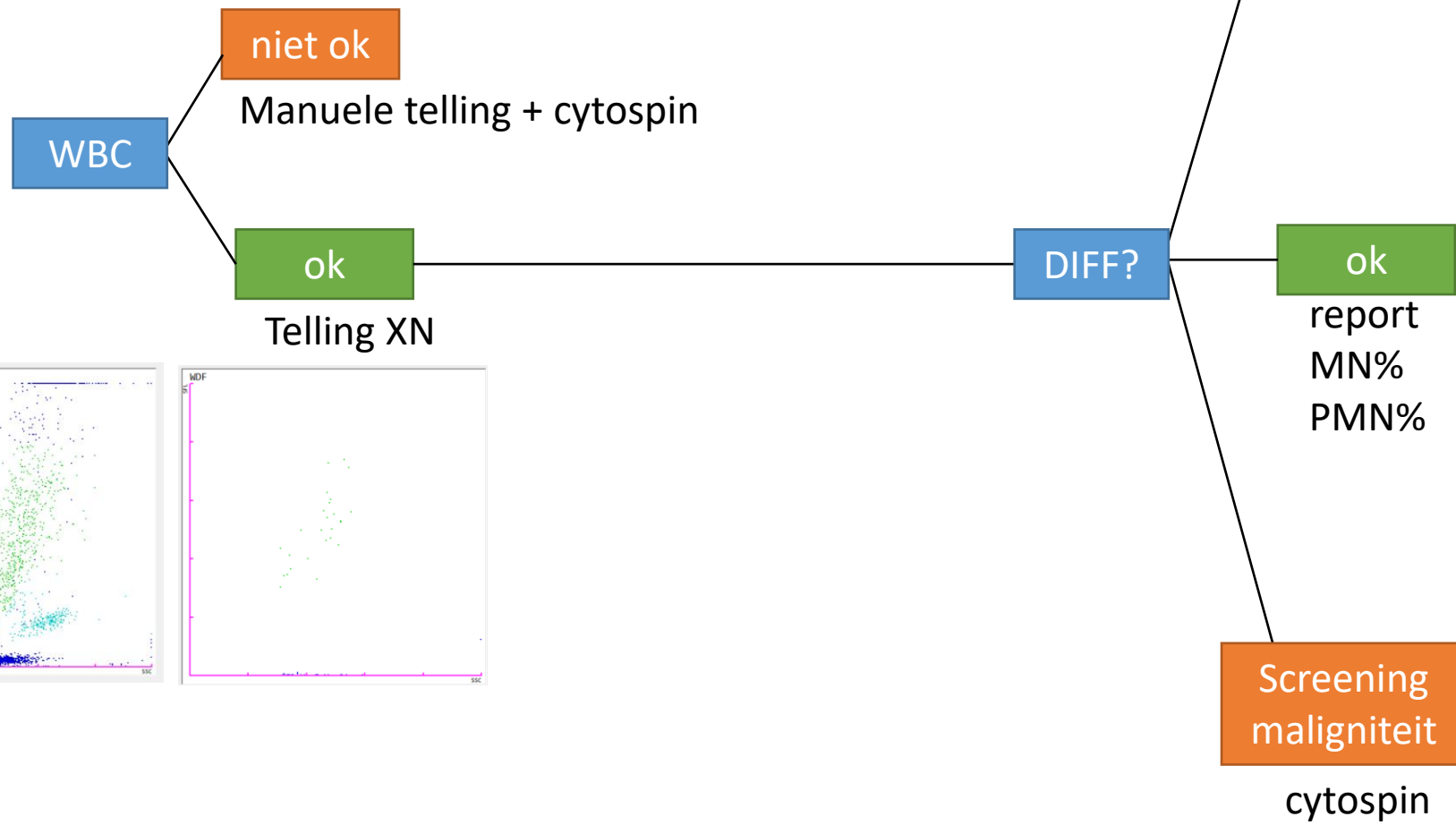
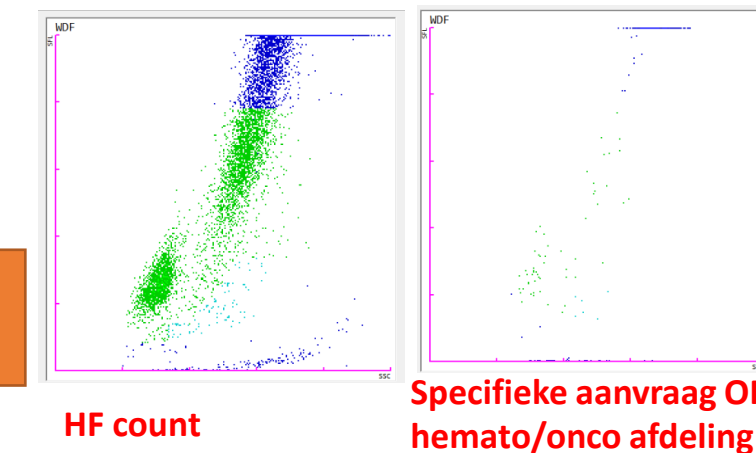
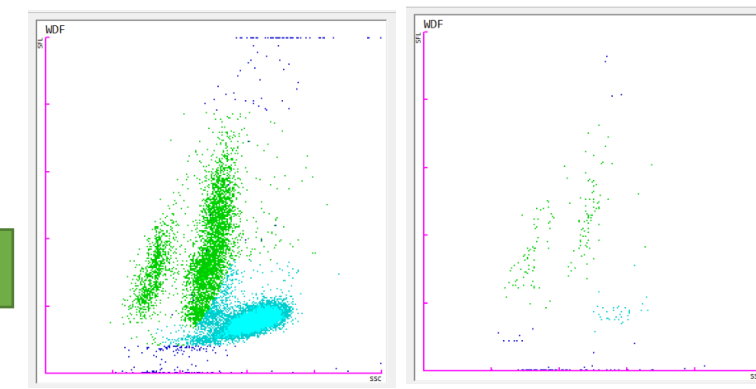
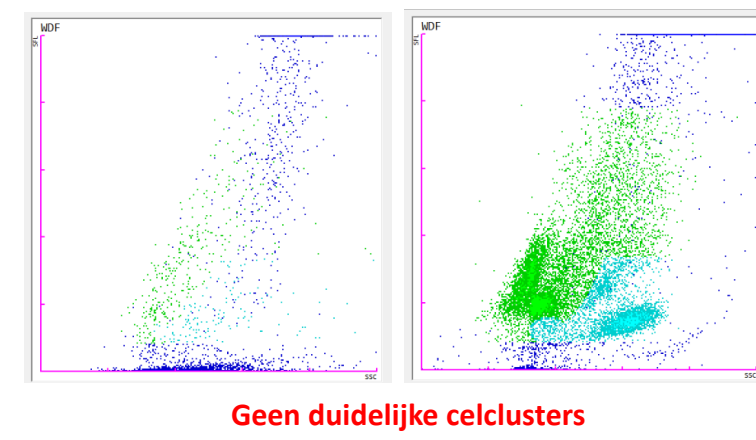
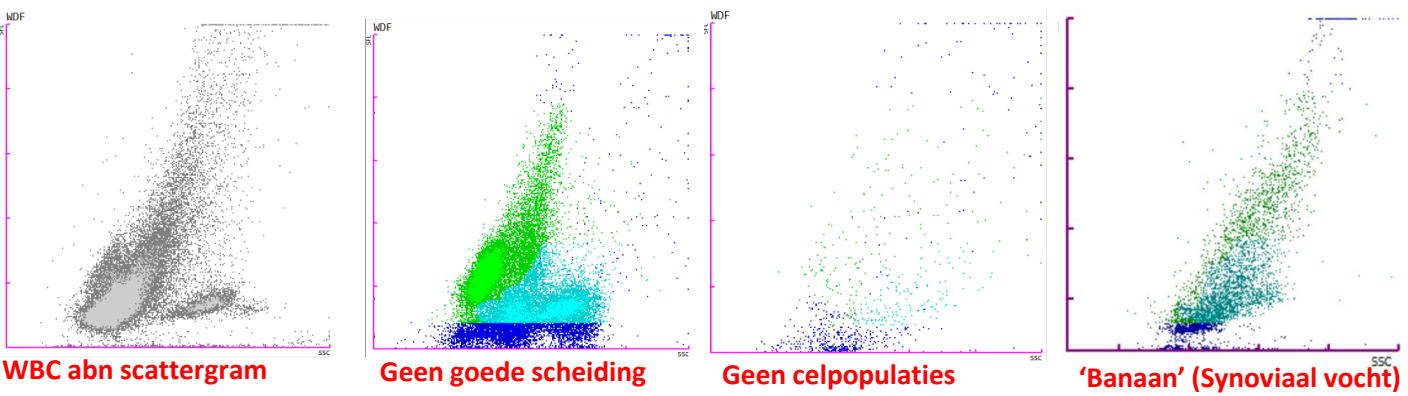
Synoviaal
UZL: geen criteria voor HF

EPU Body Fluid rule set

1. WBC Abn Scattergram
2. HF-BF cells
3. EO-BF *for CAPD*
4. Possible RBC interferences

+ scattergram interpretatie door MLT

+ specifieke aanvraag voor screening maligniteit



+ scattergram interpretatie door MLT

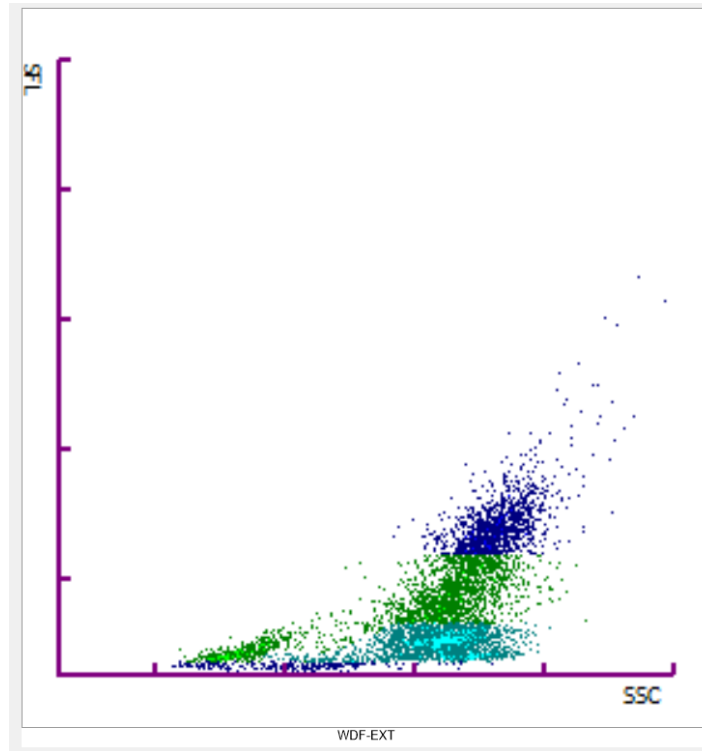
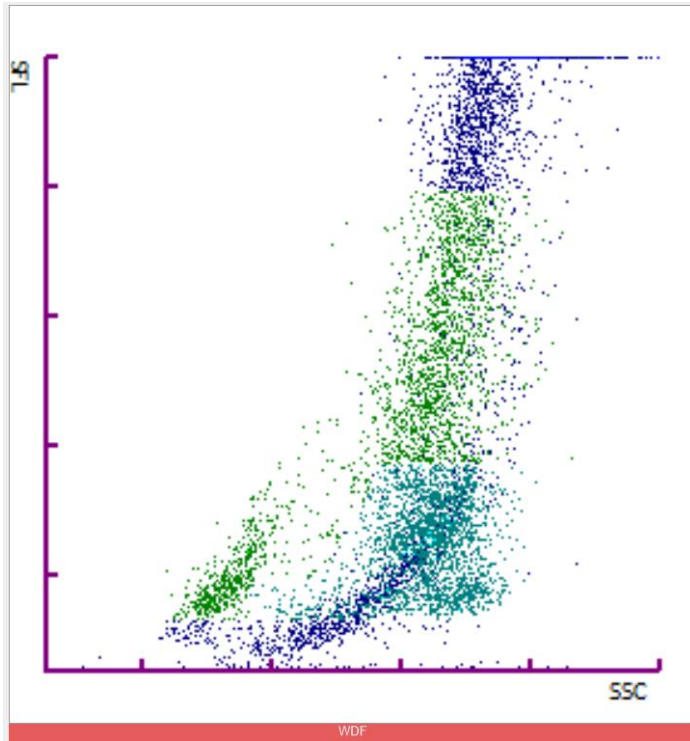
3 mogelijkheden rapportering en acties

BF_SCATTER	CYTOSE WBC		DIFFERENTIATIE (PMN – MN)
OK			
WBC OK DIFF niet OK	Order	Run	Test
			Result
NIET OK			Body Fluid Count
	R	1	BF_SCATTER
	R	1	DILUTION_FACTOR
	R	1	WBC-BF2

CASES: INTERPRETATIE SCATTERGRAM

Pleuravocht (M, 2d)

Niet ok



WBC	0,464 x10 ⁹ /L
MN	48,8 %
PMN	51,2 %

HF elevated 

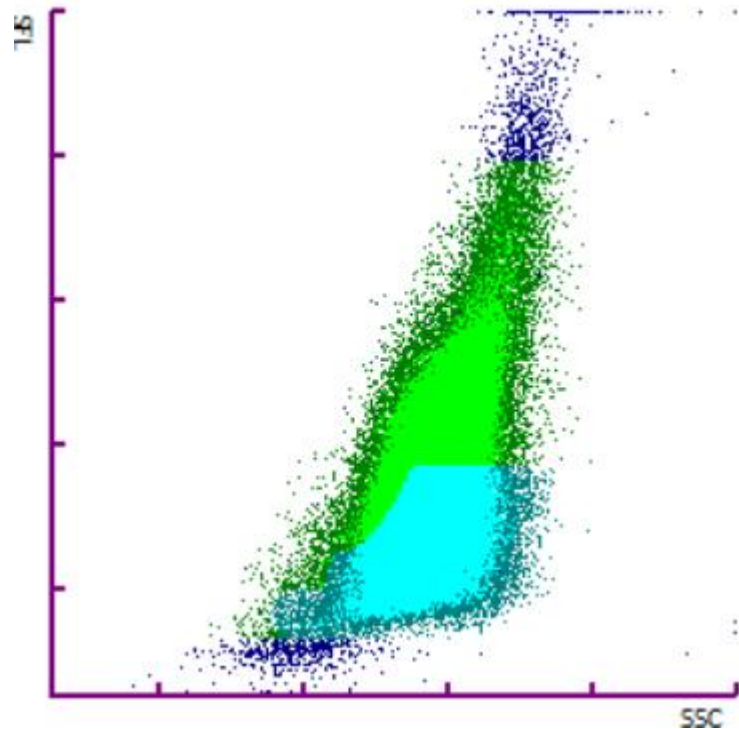


WBC 0,081 x10⁹/L

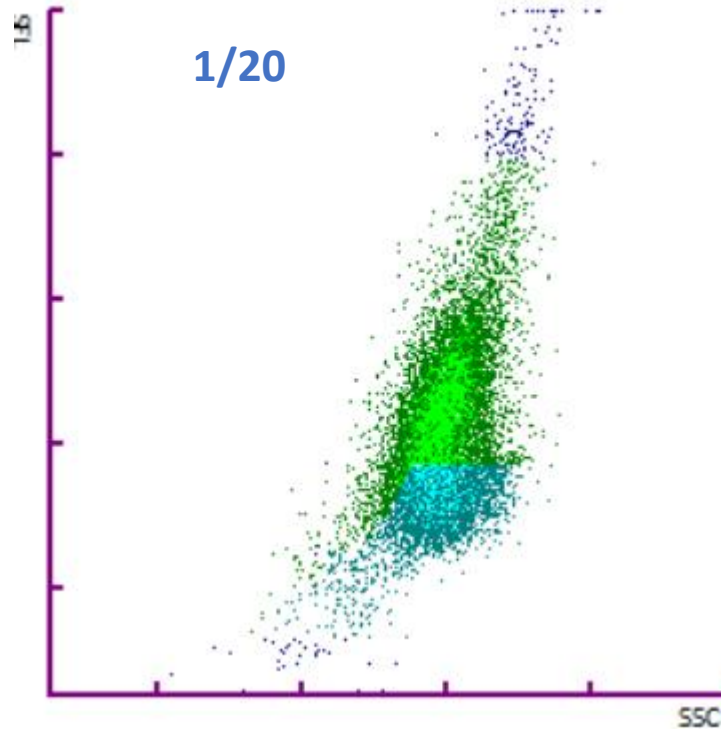
Geen WBC diff <0,1 10⁹/L

Pleuravocht (V, 2j)

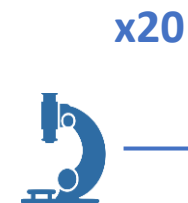
WBC OK
DIFF niet OK



WBC 24,503 x10⁹/L
MN 53,9 %
PMN 46,1 %



WBC 1,298 x10⁹/L
MN 69,9 %
PMN 30,1 %



WBC 25,960 x10⁹/L
NEUT 93 %
LYMF 1 %
MONO 6 %

TC-BF linearity limit

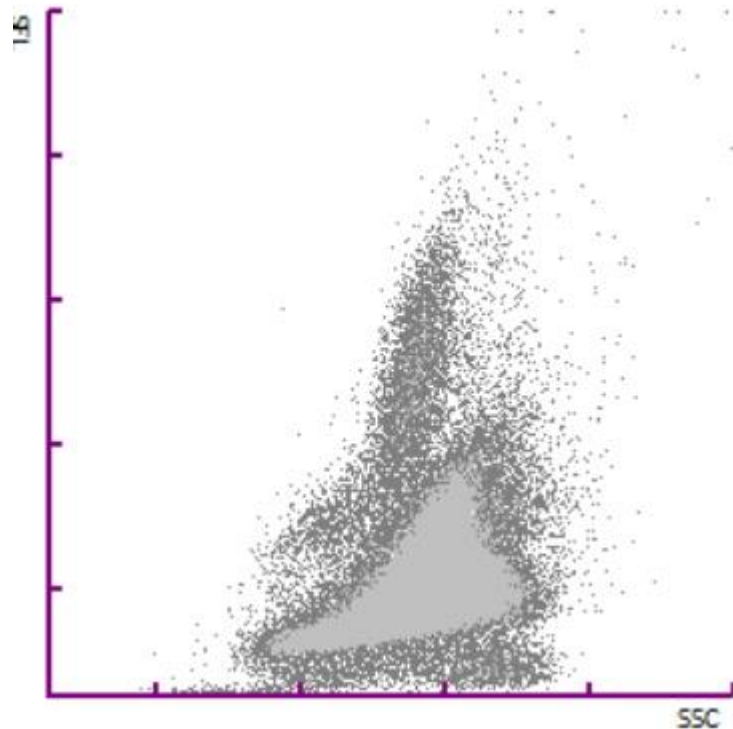


pleurapneumonie met empyeem

Pleuravocht (M, 85j)

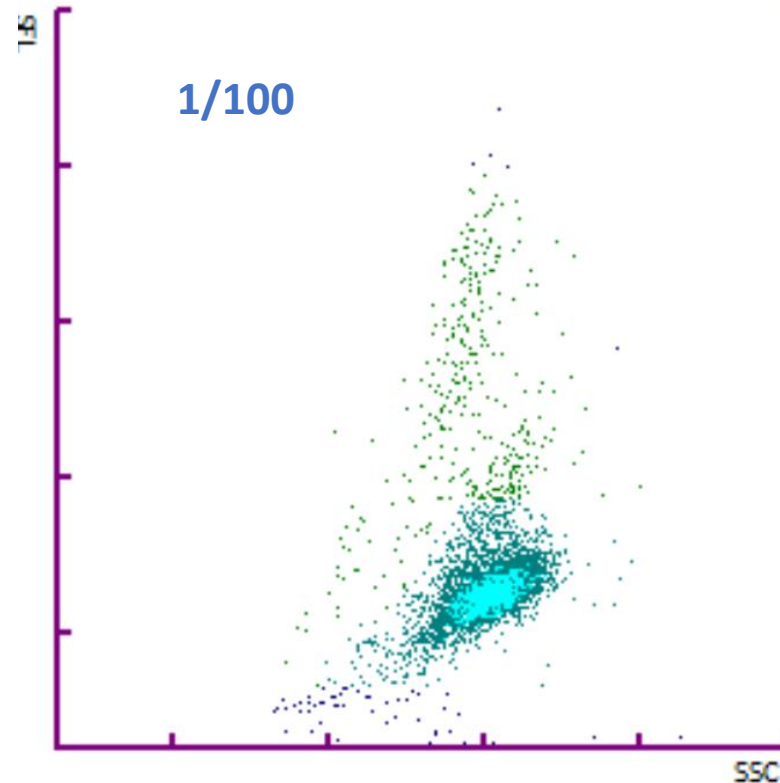
OK

Na verdunning



WBC 43,722 x10⁹/L
MN 93,7 %
PMN 6,3 %

WBC Abn Scattergram
TC-BF linearity limit



WBC 0,460 x10⁹/L
PMN 92,2 %
MN 7,8 %

x100

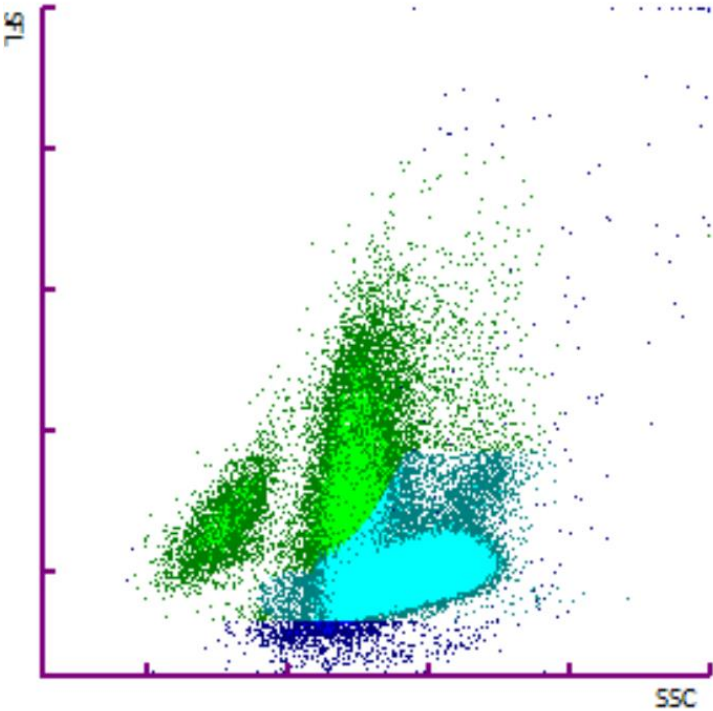
WBC 46,000 x10⁹/L

Gunstig effect verdunning vocht,
volledige rapportering XN

Pleuravocht (M, 34j)

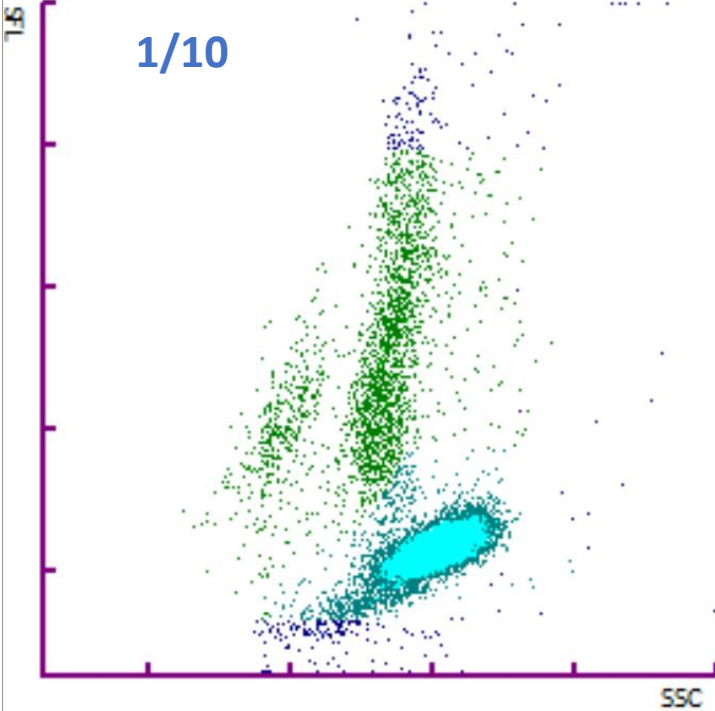
OK

Na verdunning



WBC 16,900 x10⁹/L
MN 11 %
PMN 89 %

TC-BF linearity limit 



WBC 0,234 x10⁹/L
MN 13,1 %
PMN 86,9 %

x10

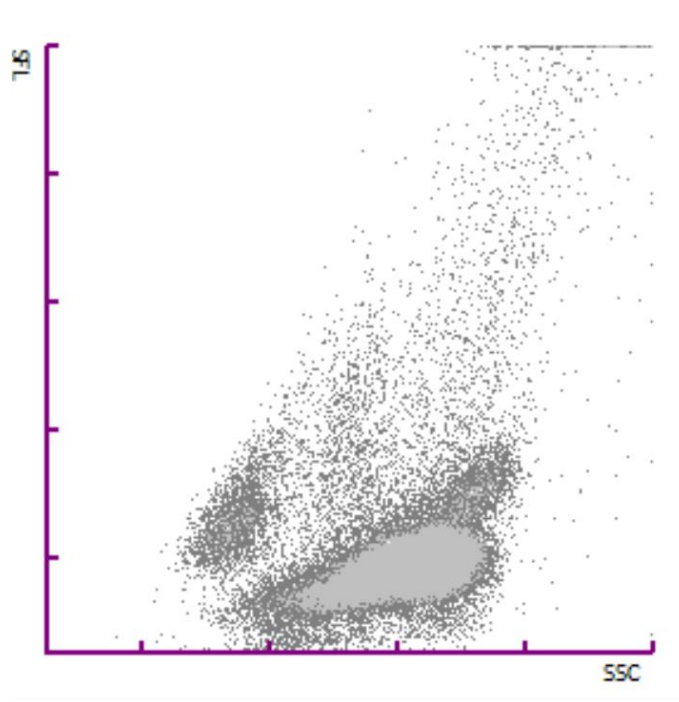
WBC 2,340 x10⁹/L

Gunstig effect verdunning vocht,
volledige rapportering XN

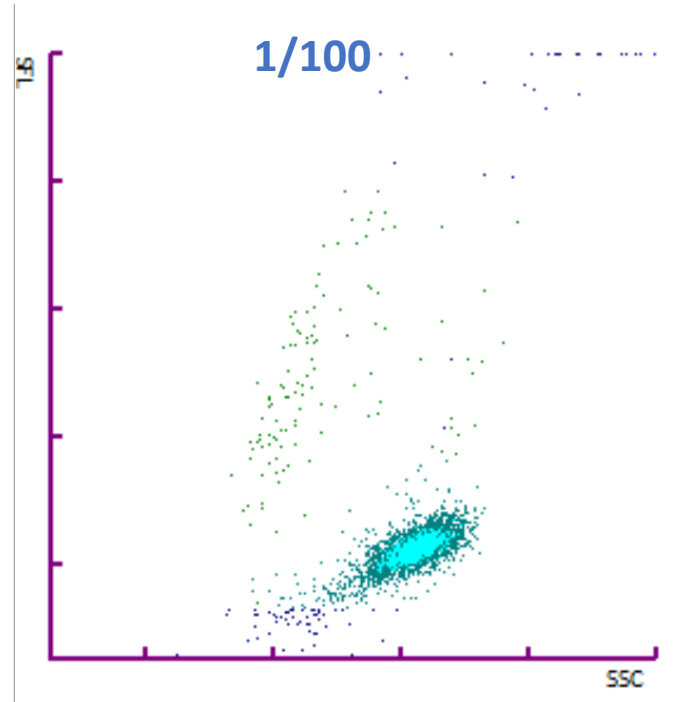
Synoviaal vocht (V, 88j, knie)

OK

Na verdunning



TC	39,131 x10 ⁹ /L
WBC	niet meetbaar
MN	3,5% *
PMN	96,5% *



WBC	0,398 x10 ⁹ /L
MN	3,1 %
PMN	96,9 %

X 100

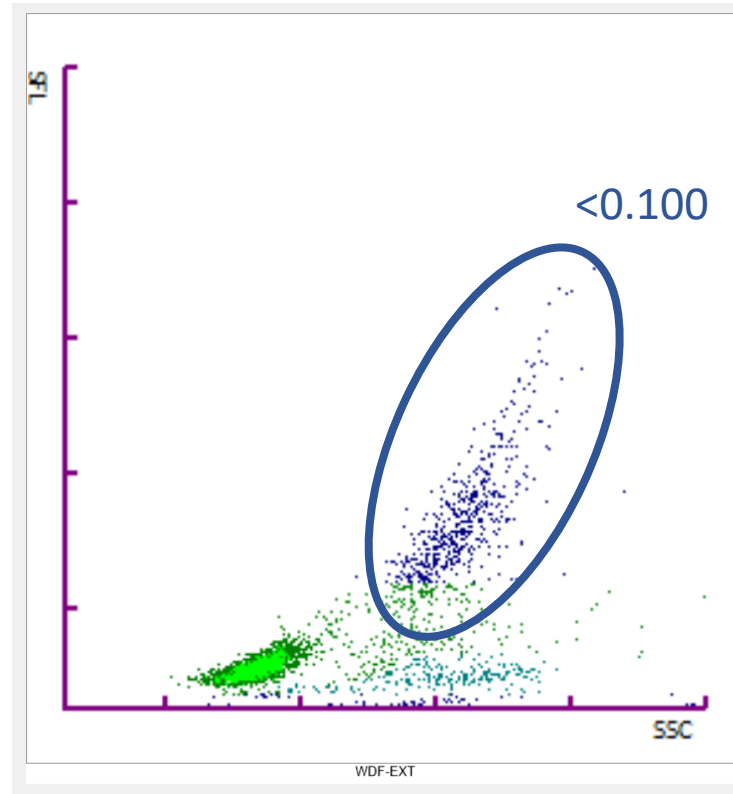
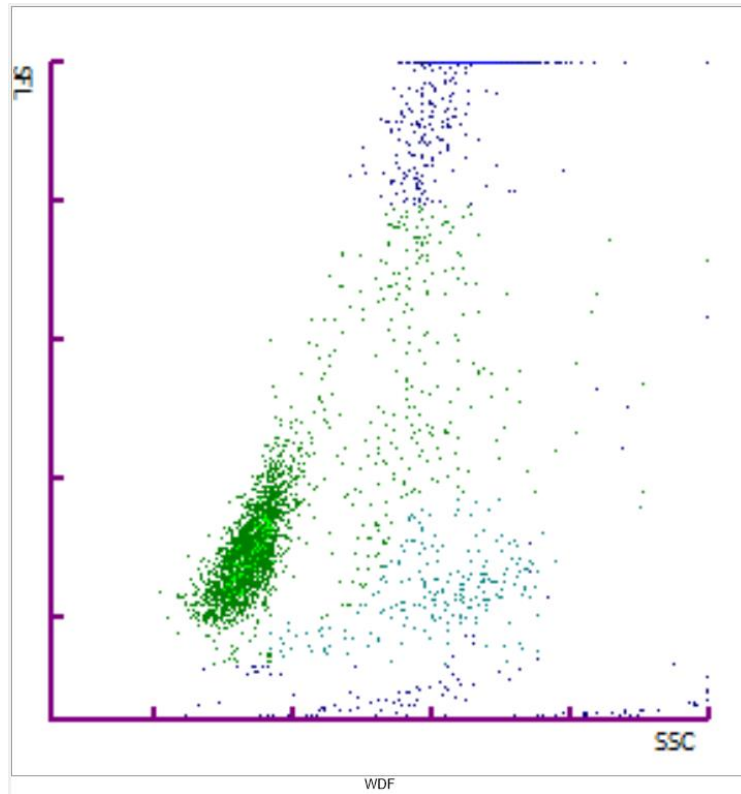
WBC	39,800 x10 ⁹ /L
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Gunstig effect verdunning vocht,
volledige rapportering XN

WBC Abn Scattergram

Pleuravocht (V, 80j)

WBC OK
DIFF niet OK



TC	0,350 x10 ⁹ /L
WBC	0,292 x10 ⁹ /L
MN	92,1%
PMN	7,9%
HF	0,058 x10 ⁹ /L

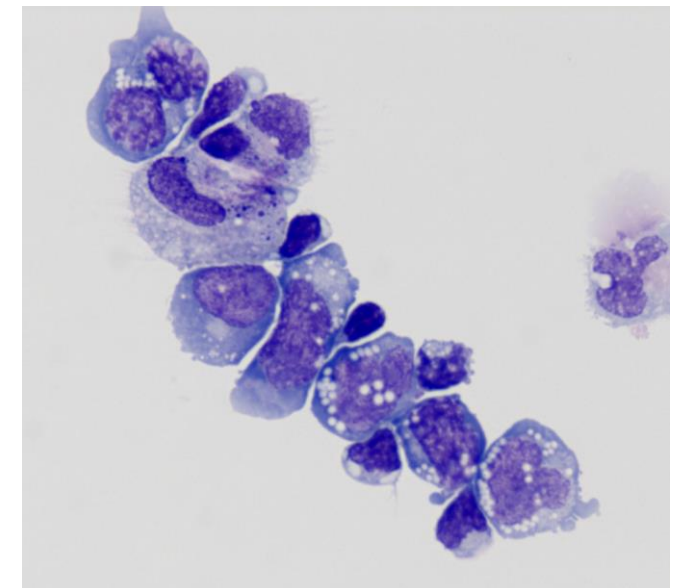
Hemato/onco afdeling



WBC	0,292 x10 ⁹ /L
-----	---------------------------

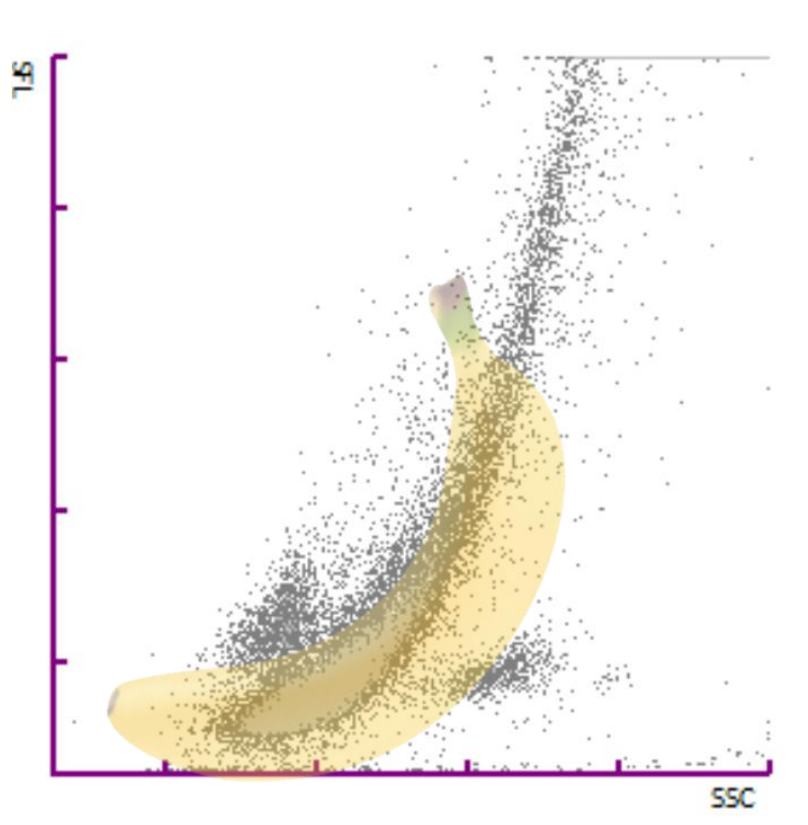
NEUT	4 %
LYMF	40 %
MONO	12%
ANDERE	44%

Morfologie:
Verdacht voor invasie door
lymfoom



Synoviaal vocht (heup)

Niet ok



WBC 1,732 x10⁹/L
MN 30,2 %
PMN 69,8 %

WBC Abn Scattergram

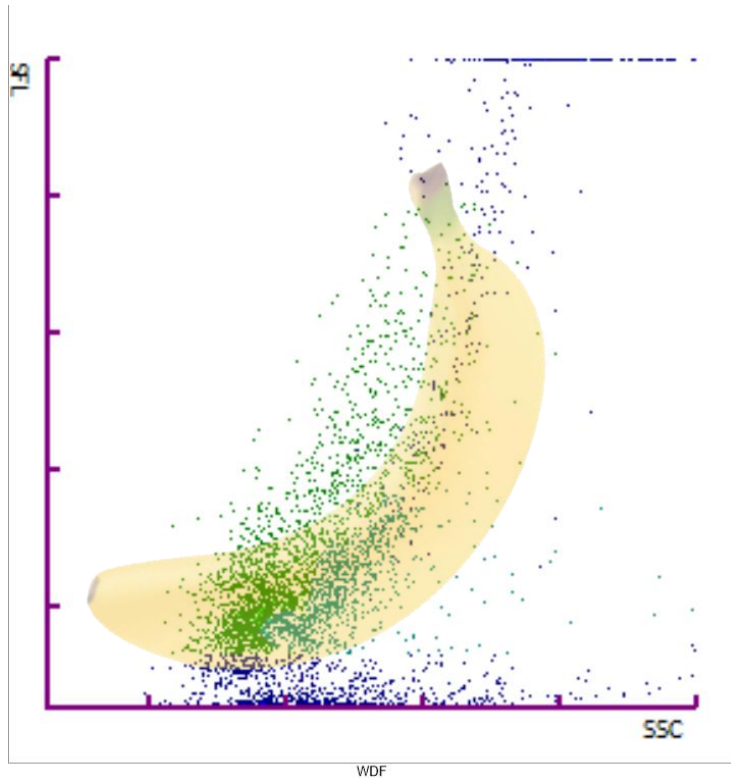


WBC 0,056 x10⁹/L

Geen WBC diff <0,1 x10⁹/L

Synoviaal vocht (knie)

Niet ok



WBC 0,303 x10⁹/L
MN 69 %
PMN 31 %

No flags 



WBC 0,100 x10⁹/L

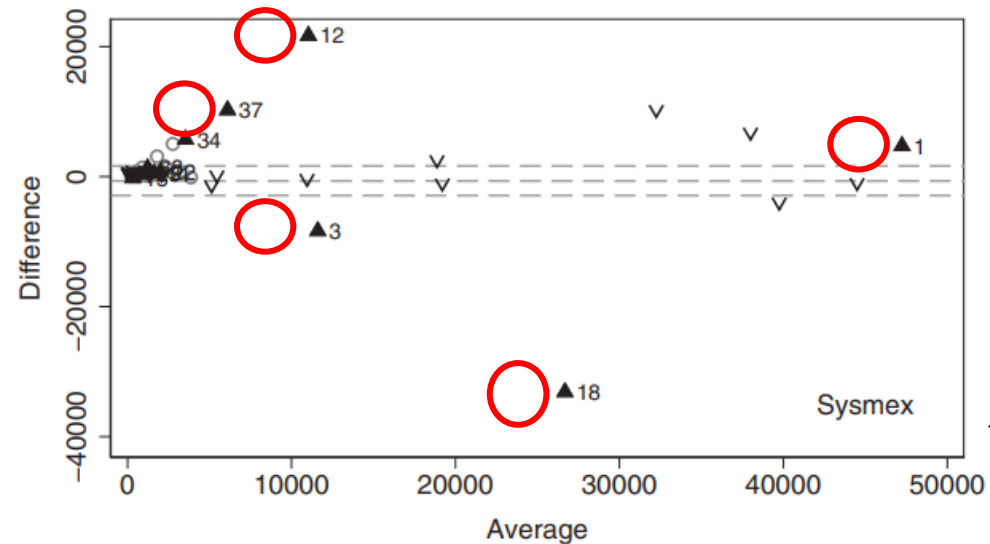
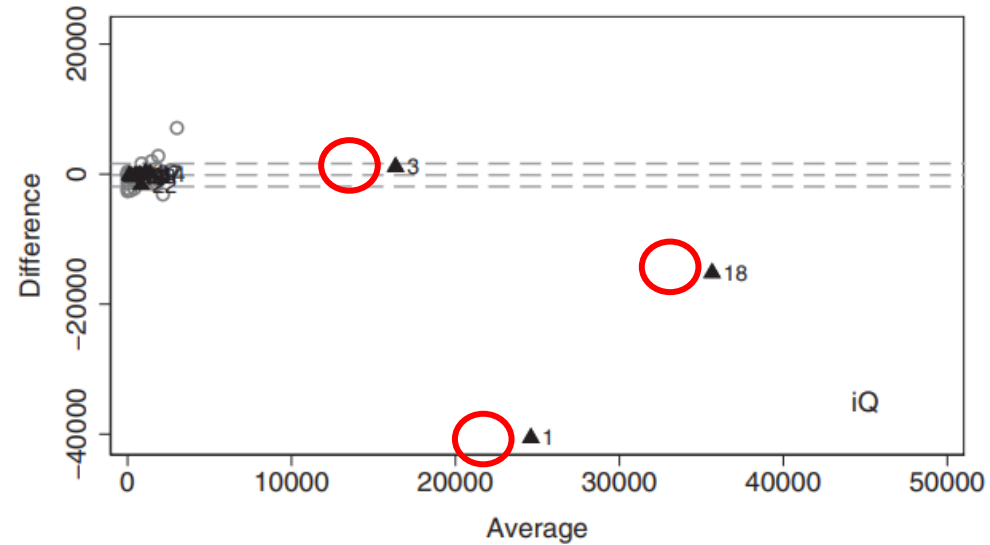


NEUT 81 %
LYMF 10 %
MONO 9 %

Potentiële interfererende niet-cellulaire elementen

Pearson L. et al (2021)

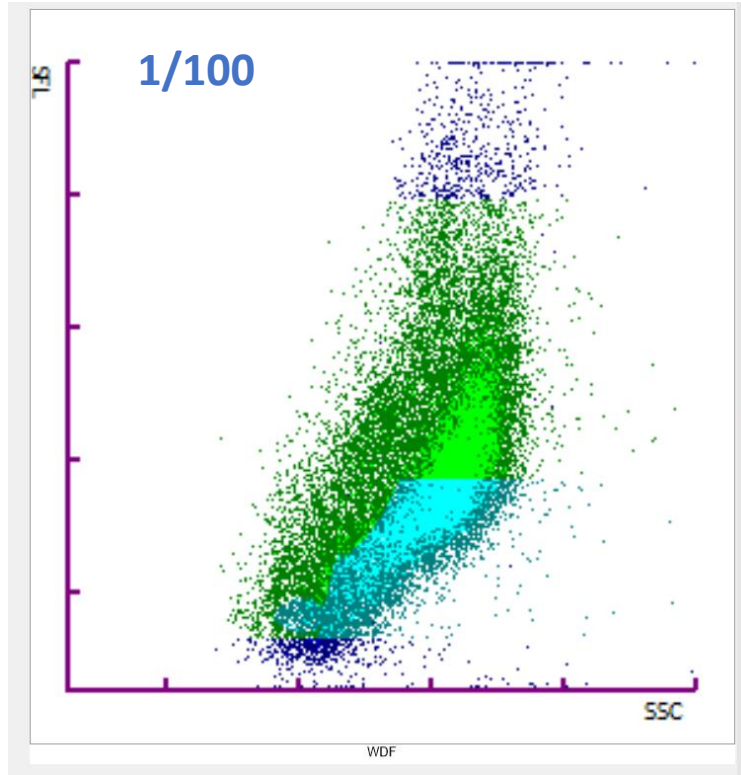
- Synoviaal vocht
- Metallose bij heupprothese



▲ Hip arthroplasty Metallosis

Synoviaal vocht (M, 70j)

Niet ok



WBC 3,405 $10^9/L$
MN 40,0 %
PMN 60,0 %

No flags 

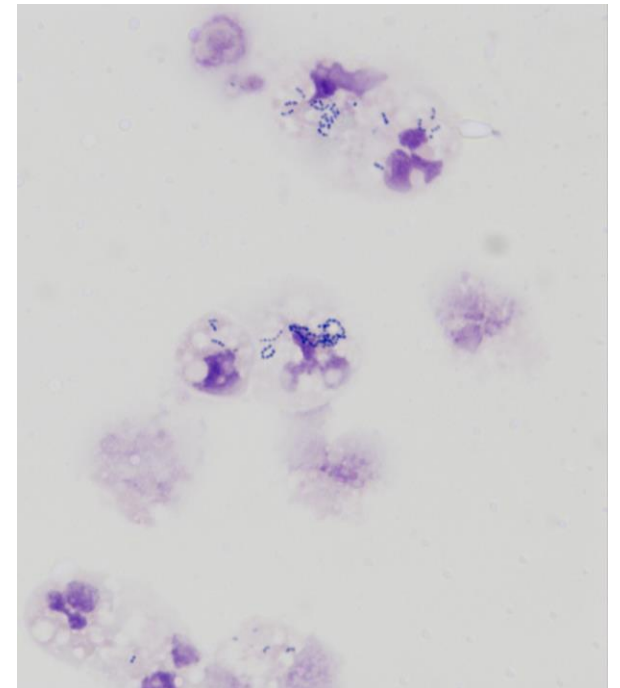
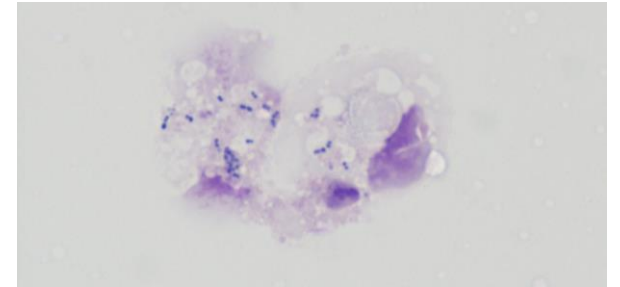


50,500 $\times 10^9/L$



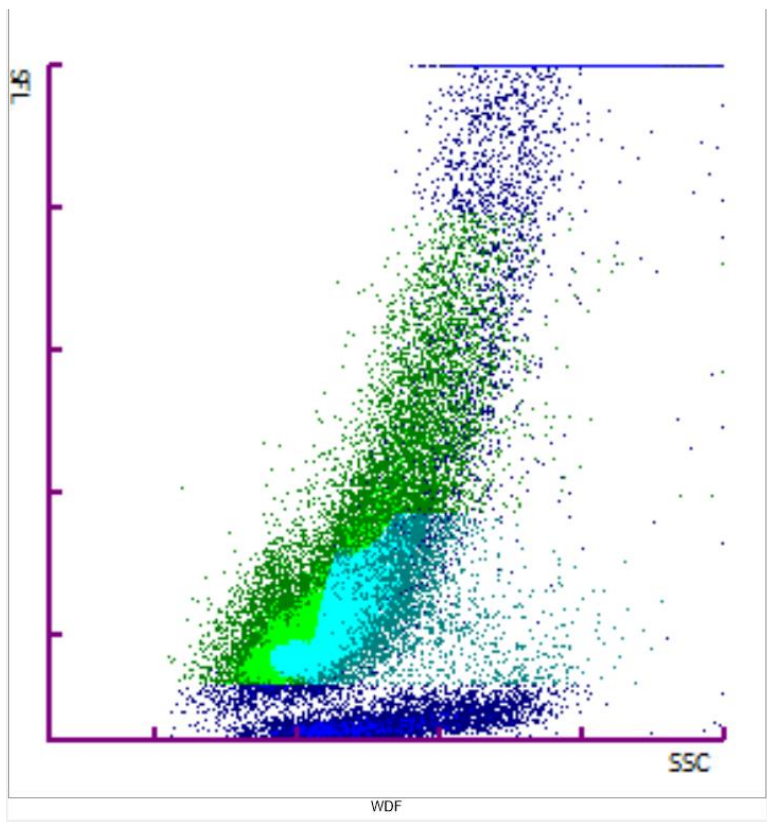
NEUT 95 %
LYMF 1 %
MONO 4 %

Groei van S. pyogenes



Synoviaal vocht (M, 77j)

Niet ok



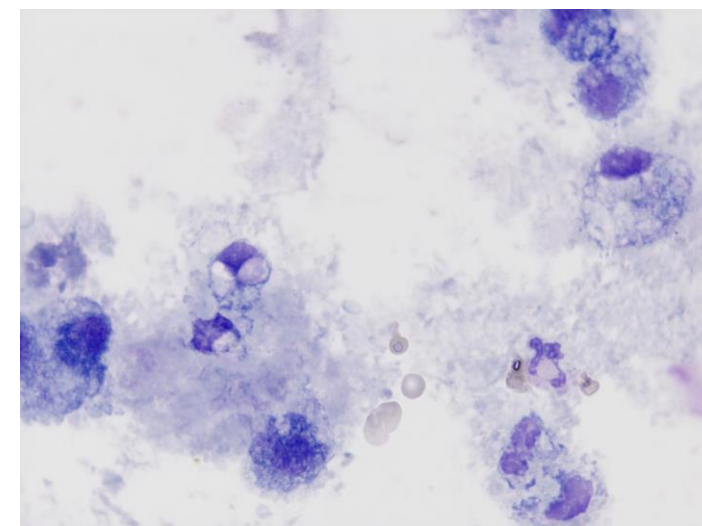
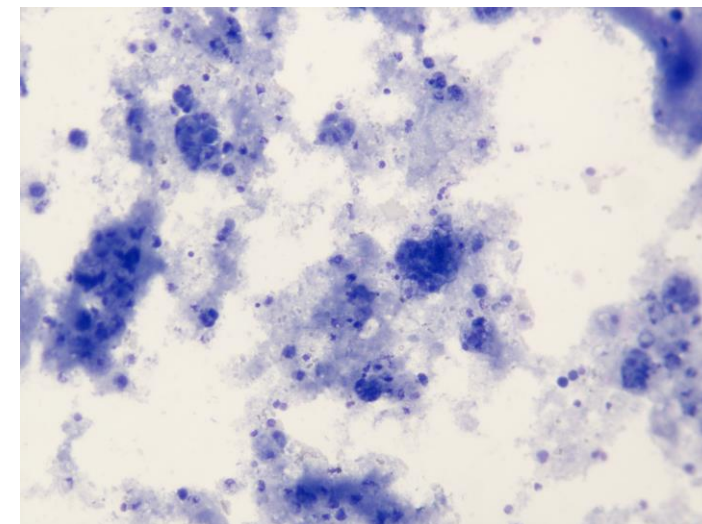
WBC $2,643 \times 10^9/L$
MN 45,8 %
PMN 54,2 %

No flags 

Pyrofosfaat kristallen 2+

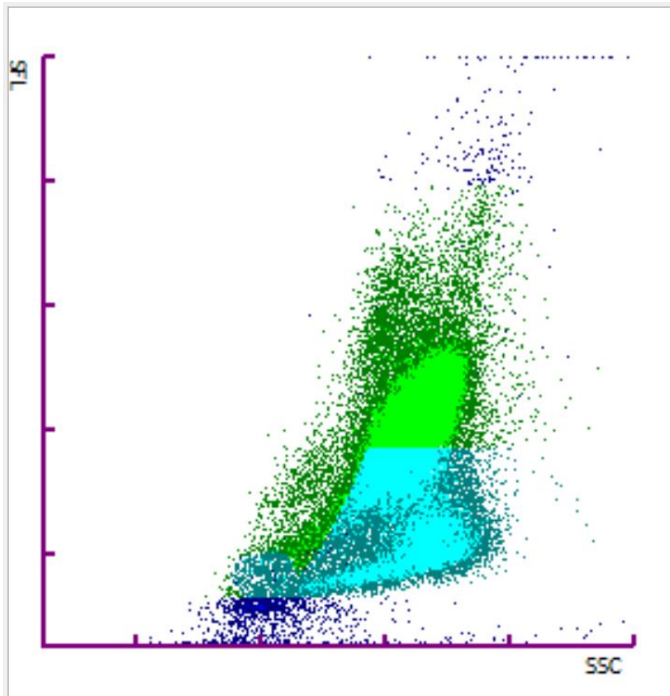
$0,350 \times 10^9/L$

NEUT 9 %
LYMF 34 %
MONO 57 %



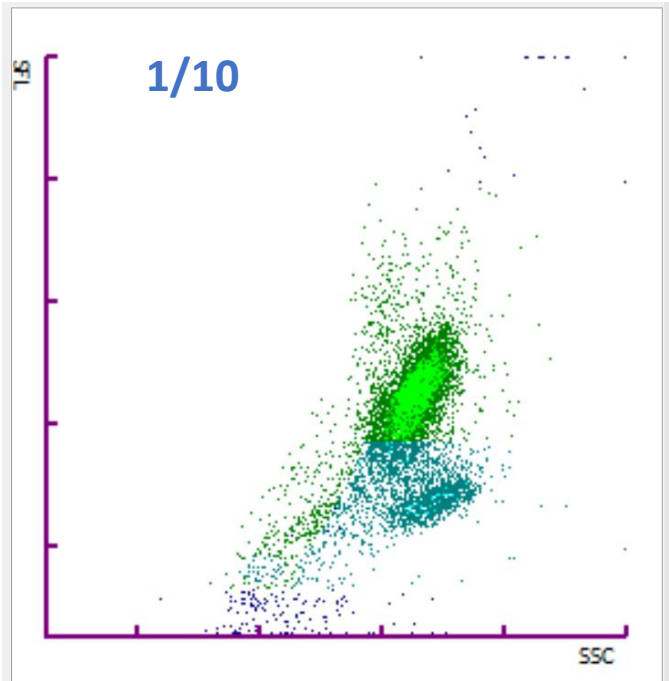
Ascites vocht (M, 75j)

WBC OK
DIFF niet OK



WBC 8,798 x 10⁹/L
MN 66%
PMN 34%

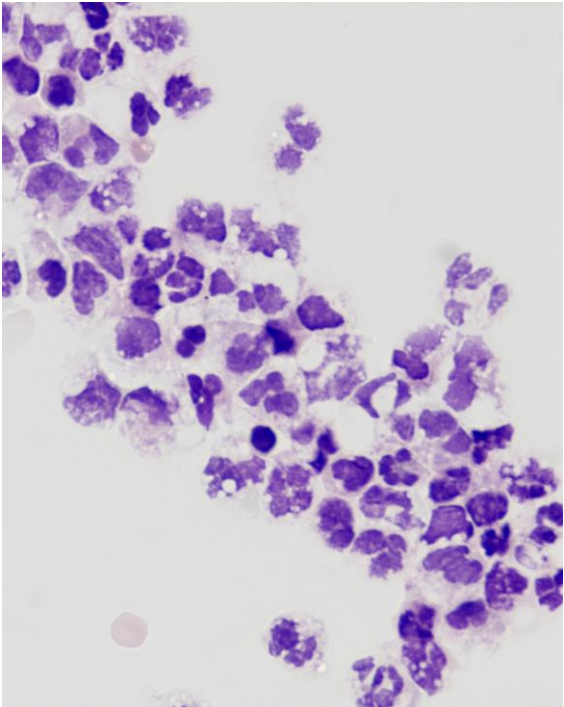
No Flags 



WBC 0,887 x 10⁹/L
MN 73%
PMN 26%

No Flags 

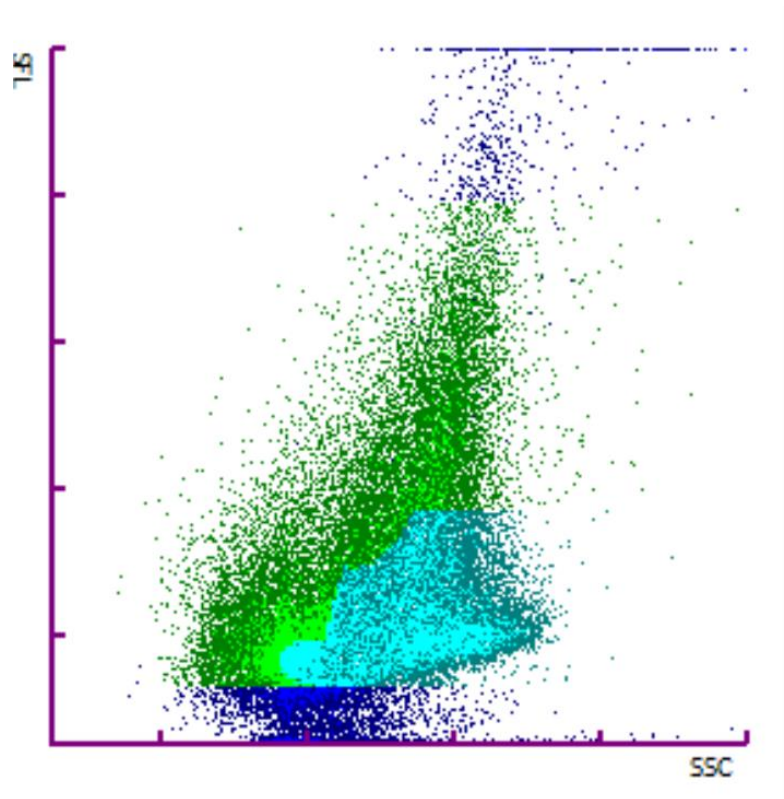
x10

WBC 8,87 x 10 ⁹ /L	
Neutrofielen	98%
Eosinofielen	2%
Lymfocyten	0%
Monocyten	0%

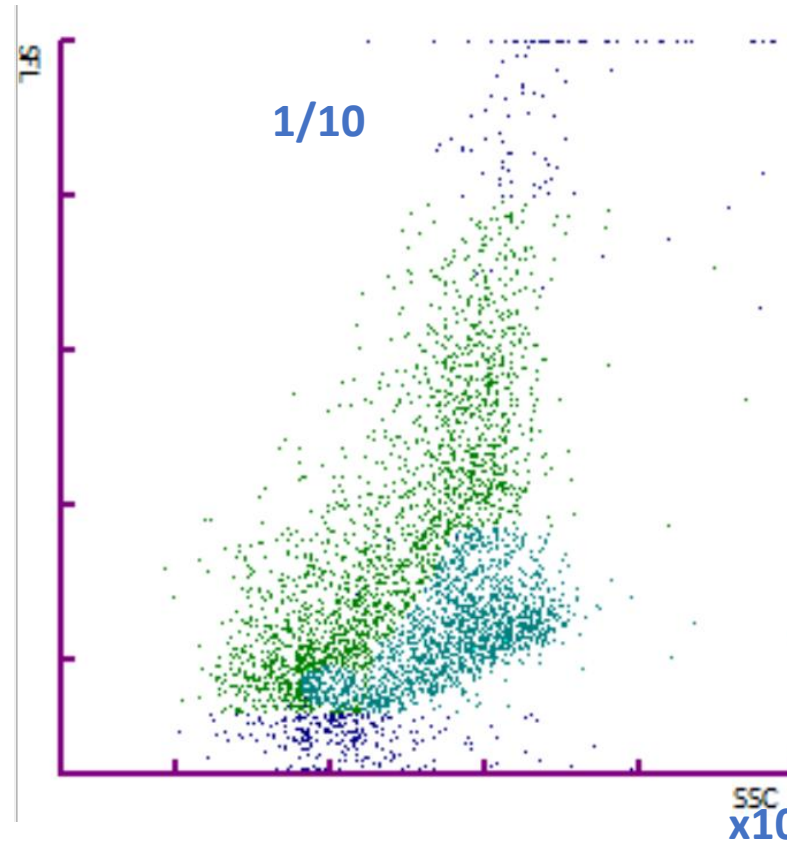
Synoviaal vocht (V, 48j)

WBC OK
DIFF niet OK



WBC 3,693 x10⁹/L
MN 46,5 %
PMN 53,5 %

No Flags 



WBC 0,397 x10⁹/L
MN 56,4 %
PMN 43,6 %

No Flags 

Bespreking
Segmentaire formule.
Enkele synoviaalcellen.

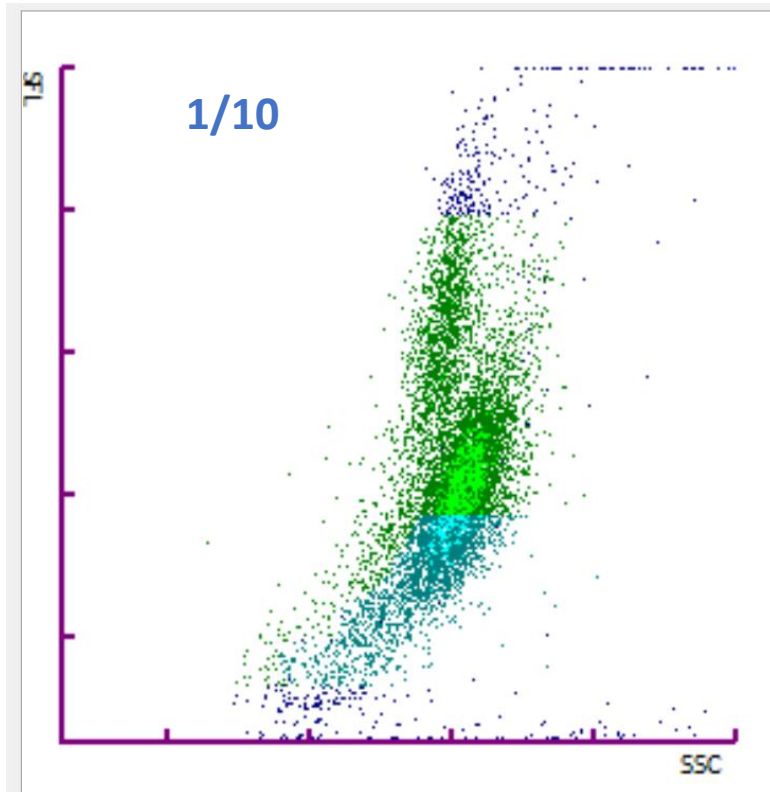
WBC 3,970 x10⁹/L

Neutrofielen 87%
Eosinofielen 1%
Lymfocyten 2%
Monocyten 10%



Pleuravocht, V 24j

WBC OK
DIFF niet OK



WBC 0,943 x10⁹/L
MN 71,1 %
PMN 28,9 %

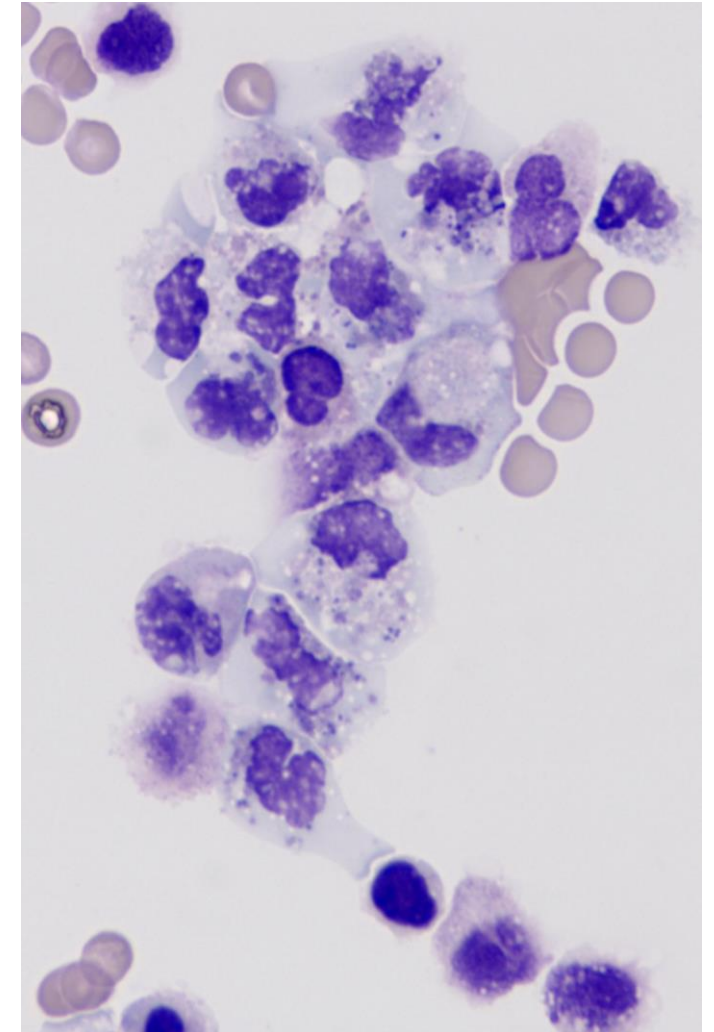
No Flags

x10

WBC 9,43 x10⁹/L

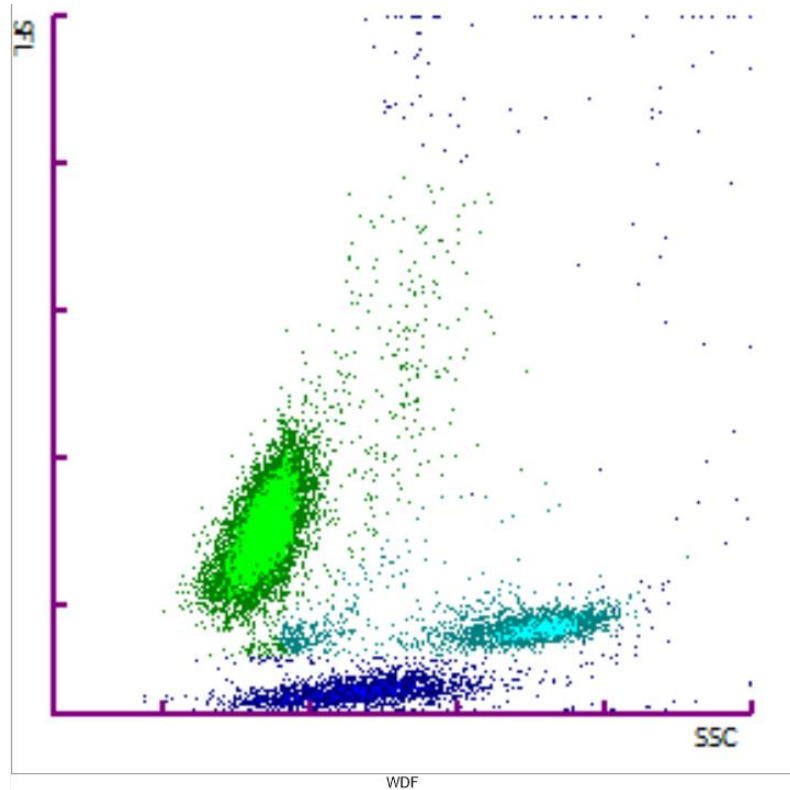
Neutrofielen 63%
Eosinofielen 0%
Lymfocyten 3%
Monocyten 34%

Groei van *S. pneumoniae*



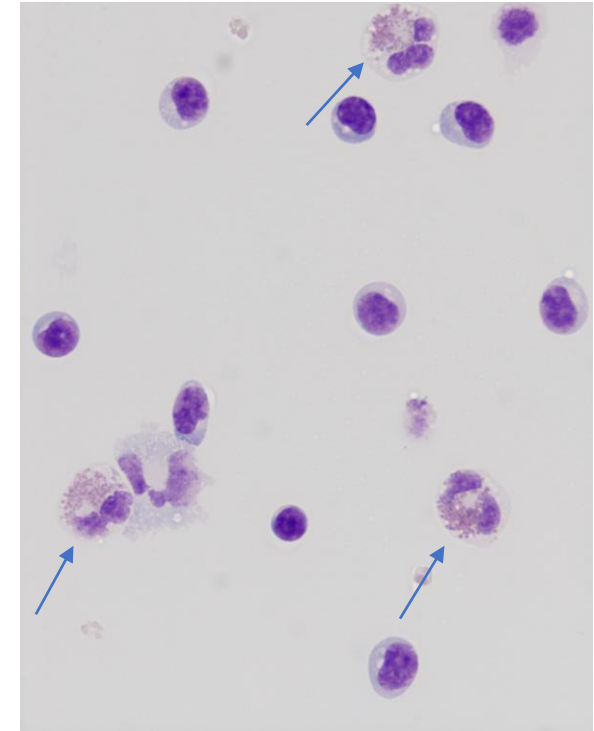
Pleuravocht, V 24j

WBC OK
DIFF niet OK



Pleurale eosinofilie

- Infectie
- Maligniteit
- Pancreatitis
- Bindweefselaandoeningen
- Overgevoelighedsreacties
- Parasieten
- Pneumothorax



WBC 1,289 x10⁹/L
MN 80,7 %
PMN 19,3 %

Eosinophilia → Cytospin 

Research diff

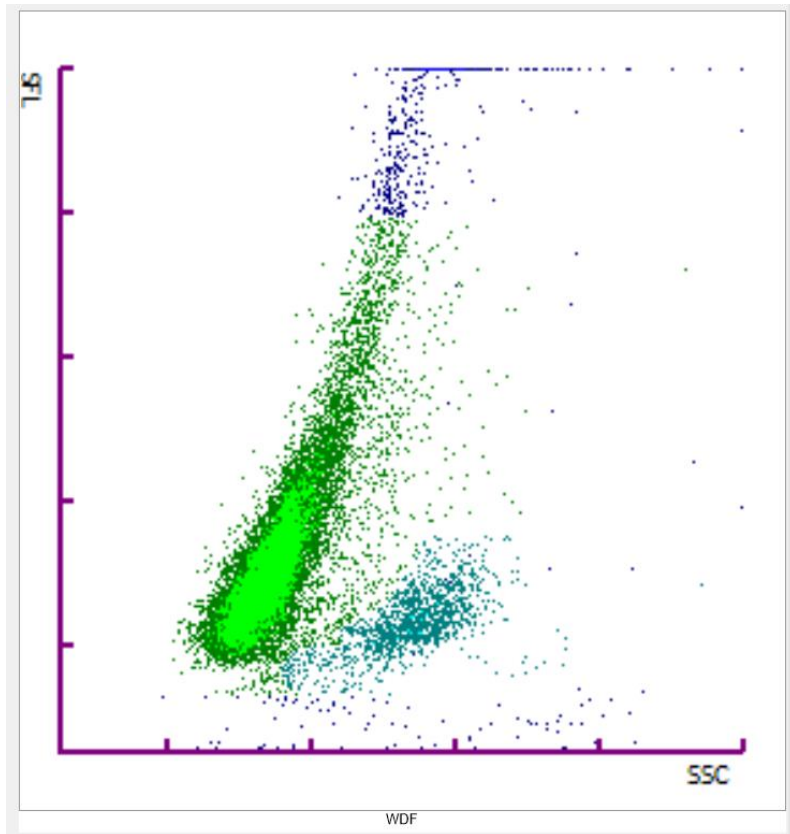
Neut 4,7%
Eo 14,6%
Lym 79,1%
Mono 1,6%



Neutrofielen	5 %
Eosinofielen	30 %
Lymfocyten	62 %
Monocyten	3 %

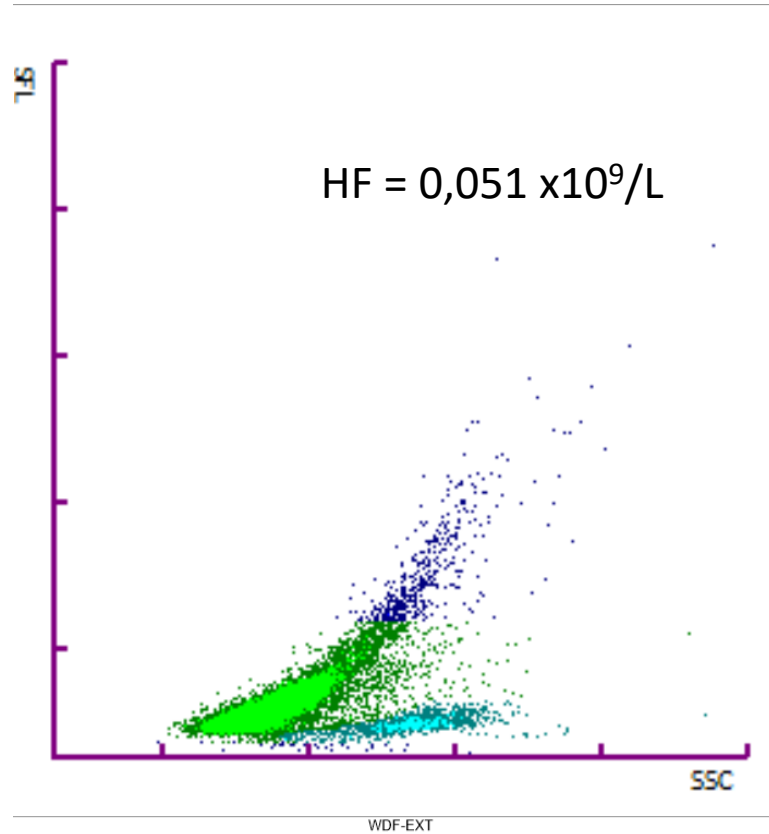
Pleuravocht (V, 62j)

OK



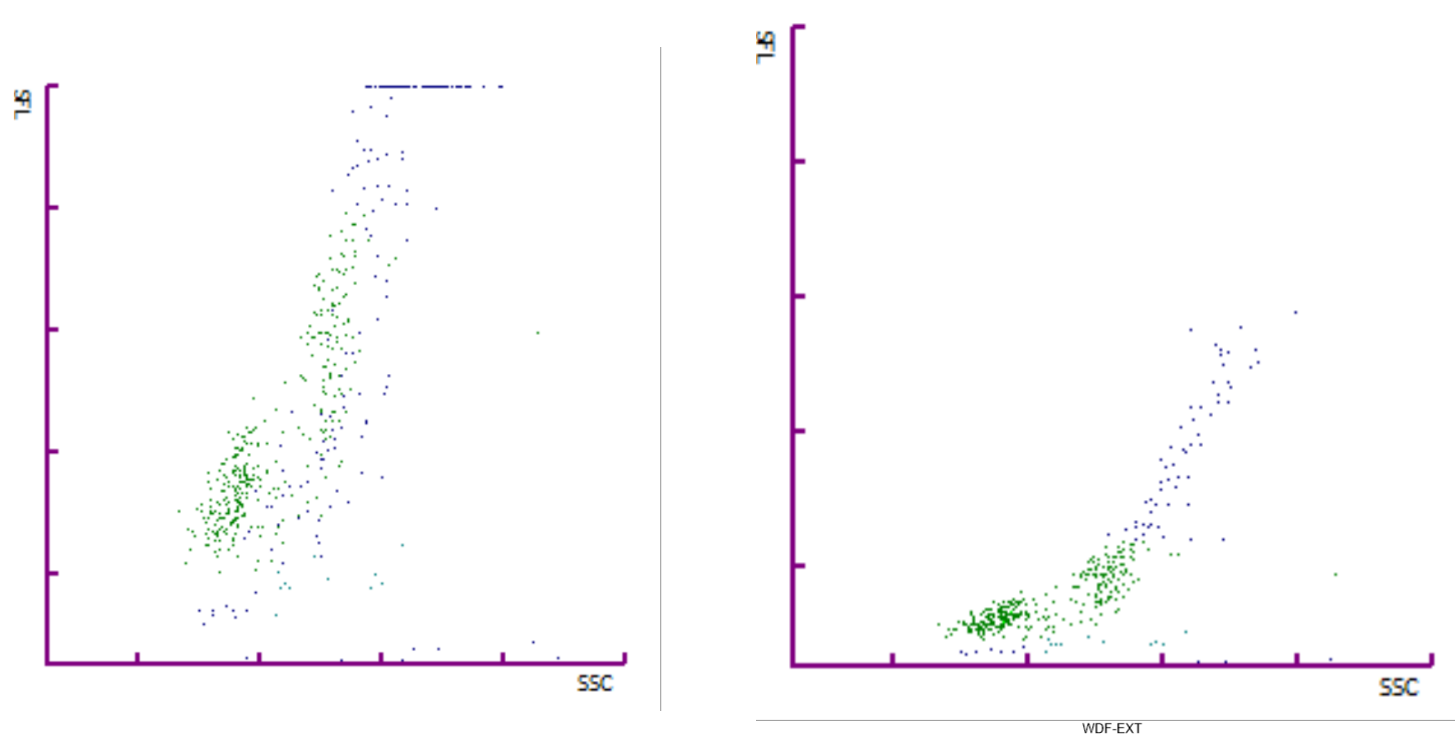
WBC 1,868 x10⁹/L
MN 92 %
PMN 8 %

No Flags 



CSV (M, 64j)

WBC OK
DIFF niet OK



WBC 36/ μ L
MN 97,2 %
PMN 2,8 %

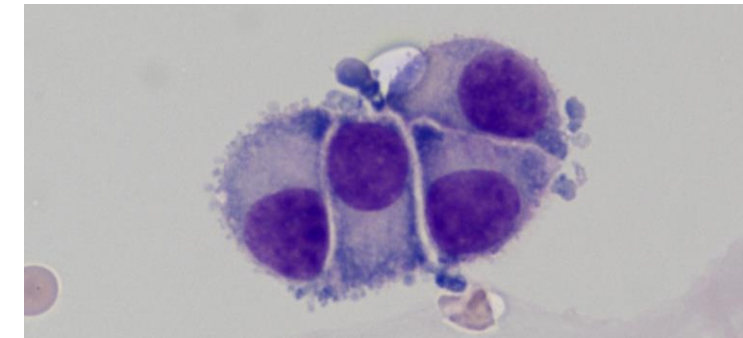
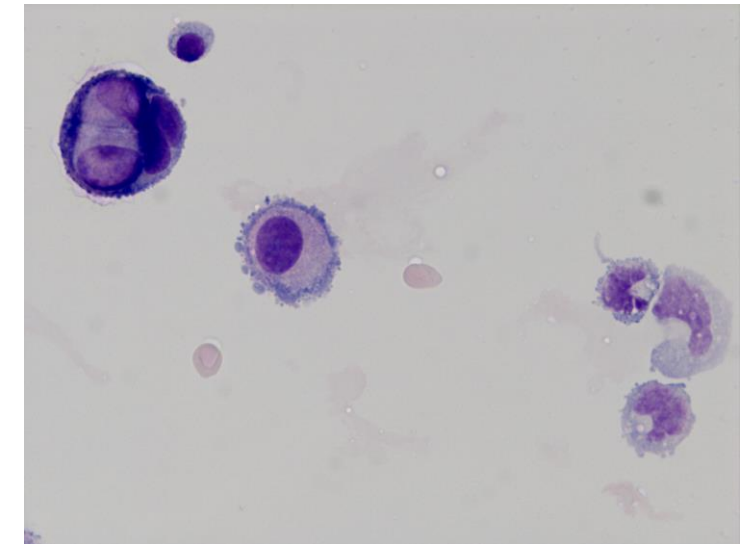
HF 6/ μ L

HF elevated 



Neutrofielen	4%
Lymfocyten	71 %
Monocyten	25 %

Morfologie:
Verdacht voor invasie door niet-hematologische maligniteit



Automatische celtellingen voor lichaamsvchten

Voordelen automatische celtellingen

- ✓ Meestal geen specifieke staalvoorbereiding vereist
- ✓ Reductie TAT
- ✓ Reductie blootstelling aan biologische risico's
- ✓ Beperkt staalvolume vereist
- ✓ Zeer lage LOD en LOQ's

➔ Complementair aan maar geen alternatief voor optische microscopie

Implementatie automatische celtellers voor lichaamsvochten

1. Correcte kennis van analytische kenmerken van het toestel
2. Verificatie volgens ICSH protocol
3. Toepassing van systemen met spoelsysteem om carry-over en contaminatie te vermijden
4. Geen specifieke staalvoorbereiding (uitgz. synoviaal vochten) vereist
5. Imprecisie opvolging vereist analyse kwaliteitscontrole
6. Ontwikkeling van algoritme met criteria voor indicatie voor microscopisch onderzoek

