KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Infection and Immune Dysregulation - Part One

Hey, everybody. In this presentation, we're going to discuss infection and immune dysregulation. As with other units in the blood chemistry module, we're only talking about using these markers as a screening tool. The basic CBC markers are not sufficient to make any conclusive diagnoses of infection or immune dysregulation. For that, we need to do much more extensive testing to determine the presence and cause of infection.

The diagnosis and treatment of infections—from tick-borne illnesses such as Lyme and Bartonella to intracellular infections such as Chlamydophila pneumoniae and mycoplasma to reactivated viral infections such as Epstein-Barr—is one of the most complex and murky topics in medicine. I will be covering this in more detail in a future advanced module. However, some markers on the CBC can be high or low in cases of infection and may highlight the need for further testing, so make sure to refer to the blood chemistry manual and the individual biomarker sheets for indications of specific markers outside of the patterns that we're going to cover in this presentation.

Lab and functional ranges for infection/immune markers

Marker	Lab range	Functional range
WBC	3.4–10.8 x 10^3/µL	5.0–8.0 x 10^3/µL
Neutrophils	Relative: 49–74% Absolute: 1.4–7.0 x 10^3/µL	Relative: 40–60% Absolute: N/A
Lymphocytes	Relative: 26–46% Absolute: 0.7–3.1 x 10^3/µL	Relative: 25–40% Absolute: N/A
Monocytes	Relative: 2–12% Absolute: 0.1–0.9 x 10^3/µL	Relative: 4–7% Absolute: N/A
Eosinophils	Relative: 0–5% Absolute: 0.0–0.4 x 10^3/µL	Relative: 0–3% Absolute: N/A
Platelets	150–379 x 10^3/µL	150–379 x10^3/µL

Here are the lab and functional ranges for the white blood cell markers that you'll find on the CBC that you need to pay attention to. Note that with neutrophils and lymphocytes, they measure both

absolute values and relative percentages. There is no lab range for relative percentage, but I do have a functional range for that. For absolute markers, there is a lab range but no functional range. We just use the lab range for absolute values.

Given the lack of specificity and sensitivity of the white blood markers for infection, I'm going to briefly cover a few general patterns to be aware of. Keep in mind you always need to follow up with more specific testing in order to confirm or rule out.

Acute bacterial infection

Marker	Value
WBC	High
Neutrophils	High
Lymphocytes	Low
Monocytes	High

The first pattern is acute bacterial infection. Typically, a high white blood cell count indicates acute infection, whereas low indicates something more chronic. Neutrophils are integral components of the innate immune system and are the first cells recruited to the sites of infection or inflammation. The most common cause of high neutrophil count is acute infection, especially certain bacteria, including pneumococcus, staphylococcus, and clostridium species. That said, certain viruses, fungi, and parasites can also increase the number of neutrophils in the bloodstream, and inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease are often also associated with increased neutrophil count. This is why we can't rely on these patterns' descriptions for making specific diagnoses.

Lymphocytes, on the other hand, may be low in cases of bacterial infection, but again, this is not a hard and fast rule. Monocytes are a general marker of inflammation and can be high in acute or chronic infections causing inflammation. When referring to high or low values with these patterns, we're talking either of functional elevations or decreases according to the lab range, either one.

Acute viral infection

Marker	Value
WBC	High
Neutrophils	Low
Lymphocytes	High
Monocytes	High

Acute viral infection also involves high white blood cell count, but lymphocytes in this pattern would typically be high, and neutrophils would typically be low, but again, we can't depend on this as a hard and fast rule. T-lymphocytes, on the other hand, are the prime players in cell-mediated immunity, and they play an important role in fighting viral infections.

Acute parasitic infection

Marker	Value
WBC	High
Eosinophils	High
Monocytes	High

In an acute parasitic infection, we'd expect high white blood cell count and high eosinophils. Eosinophils are drawn to areas of inflammation through chemotaxis, at which point they activate and release substances contained within their granules. Eosinophilia has many potential causes, grouped into seven broad categories: infection, allergy, neoplasm, lung disorders, skin disorders, and miscellaneous conditions. We can't assume that high eosinophils are necessarily caused by a parasite infection, but that's certainly one possibility. Since we're doing stool testing as part of the case review process, you'll often be able to determine whether a patient has parasitosis at the same time.

Chronic infection

Marker	Value
WBC	Low
Neutrophils	Low, Normal, or High
Lymphocytes	Low, Normal, High
Monocytes	High

In chronic infections, the white blood cell count will often be low—either functionally low or lab low. Neutrophils or lymphocytes could be low, normal, or high, so pretty nonspecific there. Monocytes will often be high because, as I said, monocytes play important roles in inflammation and the innate immune system response to pathogens, and they can be elevated in chronic infection.

Allergies

Marker	Value
WBC	Low, Normal, High
Eosinophils	High

When eosinophils are high, and the patient doesn't have parasites, allergies are another common possibility. This could involve allergies to environmental antigens such as dust and pollen, foods, or conditions such as eosinophilic esophagitis. Another cause of eosinophilia that is getting more attention lately is a condition known as mast-cell activation syndrome. The layman's term for this would be histamine intolerance. It involves an overactivation of the mast cells that produce histamine and leads to all of the signs and symptoms of histamine intolerance.

Autoimmunity

Marker	Value
WBC	Low
Lymphocytes	Low
Neutrophils	Low
Platelets	High or low
CRP	High
Ferritin	High
Vitamin D	Low
HDL	High

Here is what autoimmunity can look like on the CBC and case review blood panel: low white blood cell count, low lymphocytes and neutrophils are the most common, with high platelets and inflammatory markers, low vitamin D, and high HDL. HDL is a repair substance, so it can be very high in inflammatory states. These are not diagnostic for autoimmunity by any stretch, but you will often see a similar combo of markers in autoimmune patients.

Inflammation

Marker	Value
WBC	High
Neutrophils	High
Lymphocytes	High or Low
CRP	High
Ferritin	High
HDL	High

These are the markers you might expect to see in inflammatory states. Of course, the source of inflammation will determine which markers are elevated or low. For example, if it's an acute viral infection, lymphocytes may be high and neutrophils low, but this is just a kind of general idea of what you might see in a patient who is dealing with inflammation from any source, whether it is chronic inflammatory response syndrome caused by biotoxins, inflammatory bowel disease, or even something such as osteoarthritis.

Cancer

Marker	Value
WBC	High or Low
Neutrophils	Low
Lymphocytes	High or Low
Eosinophils	High
Monocytes	High or Low
Platelets	High or Low

Here are general markers that you might see in a patient with cancer. As you can see here, there is no way you can make a diagnosis with these markers, obviously. They are completely nonspecific, and in most cases, the markers can either be high or low, but I think what this is pointing to is that you'll often see some kind of dysregulation in the white blood cell indices on the CBC, which makes sense because, of course, cancer is characterized by that kind of immune dysregulation.

With cancer markers, they will typically be out of the lab range, not just functionally low or high, although if you catch it early, they could be only out of the functional range. The more significantly elevated or depressed the markers are out of the lab range, and the higher the number of markers that are out of the lab range, the more important it is to do follow-up testing and refer out.

Okay, let's look at a few cases. This patient is a 66-year-old female with a chief complaint of depression, inability to lose weight, irritability, anxiety, and other symptoms.

Marker	Value	Functional Range	Lab Range
Glucose	124	75 – 90	65 - 99
Hemoglobin A1c	6.4	4.4 – 5.4	4.8 - 5.6
Uric Acid	6.0	3.2 - 5.5	2.5 - 7.1
BUN	15	13 – 18	8 - 27
Creatinine	0.56	0.85 – 1.1	0.57 - 1
Sodium	142	135 – 140	134 - 144
Potassium	4.3	4.0 – 4.5	3.5 - 5.2
Chloride	104	100 – 106	97 - 108
C02	20	25 – 30	18 - 29
Calcium	9.2	9.2 – 10.1	8.7 - 10.2
Phosphorus	3.9	3.5 – 4.0	2.5 - 4.5
Magnesium	1.9	2.0 – 2.6	1.6 - 2.6
Protein, total	6.7	6.9 – 7.4	6.0 - 8.5
Albumin	4.5	4.0 – 5.0	3.6 - 4.8
Globulin	2.2	2.4 – 2.8	1.5 - 4.5
A/G ratio	2.0	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.5	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	118	42 – 107	39 - 117
LDH	178	140 - 180	119 - 226
AST	21	10 - 30	0 - 40
ALT	23	10 - 22	0 - 32
GGT	13	0 - 28	0 - 60
TIBC	261	250 – 350	250 - 450
UIBC	204	150 - 375	150 - 375
Iron	57	85 – 135	35 - 155
Iron saturation	22	15 – 45	15 - 55
Ferritin	697	MW: 30 - 150	15 - 150
Cholesterol, total	129	150 – 250	100 - 199
Triglycerides	96	50 – 100	0 - 149
HDL	49	55 – 85	> 39
LDL	61	0 – 175	0 - 99
T. Chol / HDL Ratio	2.6	< 3	0 - 4.4
Triglycerides / HDL Ratio	1.96	< 2	< 3.8
TSH	<0.006	0.5 – 2.5	0.45 - 4.50
T4, total	8.2	6.0 – 12	4.5 - 12.0
T3 Uptake	25	28 - 35	24 - 39
T3, Total	154	100 – 180	71 - 180
Vitamin D, 25-hydroxy	29.8	35 - 60	30.0 - 100.0

Marker	Value	Functional Range	Lab Range
WBC	10.0	5.0 – 8.0	3.4 - 10.8
RBC	5.75	4.4 – 4.9	3.77 - 5.28
Hemoglobin	15.7	13.5 - 14.5	11.1 - 15.9
Hematocrit	48	37 - 44	34.0 - 46.6
MCV	84	85 – 92	79 - 97
MCH	27.3	27.7 – 32.0	26.6 - 33.0
MCHC	32.7	32 – 35	31.5 - 35.7
RDW	14.9	11.5 – 15.0	12.3 - 15.4
Platelets	263	150 – 415	150 - 379
Neutrophils	73	40 – 60	
Lymphocytes	21	25 – 40	
Monocytes	5	4.0 – 7.0	
Eosinophils	1	0.0 – 3.0	
Basophils	0	0.0 – 3.0	
Additional Tests:			
T3, Free	3.6	2.5 - 4.0	2 - 4.4
T4, Free	1.14	1 - 1.5	0.82 - 1.77
CRP-hs	10.37	< 1.0	0.00 - 3.00
Copper	149		72 - 166
Zinc	95		56 - 134
Zinc / Copper Ratio	0.64	> 0.85	
Serum Methylmalonic Acid (MMA)	169	0 - 325	0 - 378
Homocysteine	7.3	< 9.0	0.0 - 15.0
Vitamin B-12	941	450 – 2000	211 - 946

Her white blood cell count and neutrophils are functionally high. Her lymphocytes were functionally low. Ferritin and C-reactive protein were also very high, suggestive of inflammation, and vitamin D was low. Also note that red blood cell count and hematocrit here are lab-high, and hemoglobin is functionally high. Alkaline phosphatase is high.

Elevated red blood cells, hemoglobin, and hematocrit can sometimes indicate a condition called polycythemia, so we would need to retest those markers to rule that out. The overall pattern here, I would say, is most suggestive of autoimmunity, and you probably notice that her TSH is practically zero. This patient, in fact, did have Hashimoto's and was taking a high dose of replacement hormone, so the Hashimoto's is what is causing these abhorrent white blood cell indices. This is pretty characteristic of what you might see in a Hashimoto's patient. Of course, this patient also has prediabetes, according to her red blood cell values, and we later found that she had type 1.5 diabetes presentation as well.

If you recall, if a patient has one autoimmune condition, they are likely to have more than one because autoimmunity is a pathology. It's an underlying process, and it can manifest in more than one autoimmune disease. Autoimmune disease describes the tissues that are being affected, whereas autoimmunity describes the mechanism.

The next patient is a 34-year-old female with chief complaint of decreased stress tolerance.

Marker	Value	Functional Range	Lab Range
Glucose	90	75 – 90	65 - 99
Hemoglobin A1c	5.8	4.4 – 5.4	4.8 - 5.6
Uric Acid	6.1	3.2 - 5.5	2.5 - 7.1
BUN	9	13 – 18	6 - 20
Creatinine	0.71	0.85 – 1.1	0.57 - 1
BUN/Creatinine Ratio	13	9 – 23	9 - 23
Sodium	138	135 – 140	134 - 144
Potassium	4.2	4.0 – 4.5	3.5 - 5.2
Chloride	101	100 – 106	97 - 108
C02	20	25 – 30	18 - 28
Calcium	9.0	9.2 – 10.1	8.7 - 10.2
Phosphorus	3.5	3.5 – 4.0	2.5 - 4.5
Magnesium	2.0	2.0 – 2.6	1.6 - 2.6
Protein, total	6.8	6.9 – 7.4	6.0 - 8.5
Albumin	4.4	4.0 – 5.0	3.5 - 5.5
Globulin	2.4	2.4 – 2.8	1.5 - 4.5
A/G ratio	1.8	1.5 – 2.0	1.1 - 2.5
Bilirubin, total	0.3	0.1 – 1.2	0.0 - 1.2
Alkaline Phosphatase	63	42 – 107	39 - 117
LDH	147	140 - 180	119 - 226
AST	20	10 - 30	0 - 40
ALT	16	10 - 22	0 - 32
GGT	9	0 - 28	0 - 60
TIBC	247	250 – 350	250 - 450
UIBC	215	150 - 375	150 - 375
Iron	32	85 – 135	35 - 155
Iron saturation	13	15 – 45	15 - 55
Ferritin	26	15 - 120	15 - 150
Cholesterol, total	121	150 – 250	100 - 199
Triglycerides	26	50 – 100	0 - 149
HDL	87	55 – 85	> 39
LDL	29	0 – 175	0 - 99
T. Chol / HDL Ratio	1.4	< 3	0 - 4.4
Triglycerides / HDL Ratio	0.30	< 2	< 3.8
TSH	2.100	0.5 – 2.5	0.45 - 4.50
T4, total	8.2	6.0 – 12	4.5 - 12.0
T3 Uptake	29	28 - 35	24 - 39
T3, Total	118	100 – 180	71 - 180
Vitamin D, 25-hydroxy	73.3	35 - 60	30.0 - 100.0

Marker	Value	Functional Range	Lab Range
WBC	9.6	5.0 – 8.0	3.4 - 10.8
RBC	4.97	4.4 – 4.9	3.77 - 5.28
Hemoglobin	14.7	13.5 - 14.5	11.1 - 15.9
Hematocrit	45	37 - 44	34.0 - 46.6
MCV	91	85 – 92	79 - 97
MCH	29.6	27.7 – 32.0	26.6 - 33.0
MCHC	32.7	32 – 35	31.5 - 35.7
RDW	13.6	11.5 – 15.0	12.3 - 15.4
Platelets	326	150 – 415	150 - 379
Neutrophils	72	40 – 60	
Lymphocytes	17	25 – 40	
Monocytes	10	4.0 – 7.0	
Eosinophils	1	0.0 – 3.0	
Basophils	0	0.0 – 3.0	

Additional Tests:			
T3, Free	3.1	2.5 - 4.0	2 - 4.4
T4, Free	1.42	1 - 1.5	0.82 - 1.77
Thyroid – TPO Ab			0 - 34
Thyroid – TGA			0 - 0.9
CRP-hs	6.35	< 1.0	0.00 - 3.00
Homocysteine	6.7	< 7.0	0.0 - 15.0
Vitamin B-12	652	450 – 2000	211 - 946
Copper	103		72 - 166
Zinc	92		56 - 134
Zinc / Copper Ratio	0.89	> 0.85	
Serum Methylmalonic Acid (MMA)	57	0 - 325	0 - 378

White blood cell count is functionally high. Neutrophils are functionally high. Lymphocytes are functionally low. Monocytes are functionally high. C-reactive protein is also high. Most likely it is inflammation here that is showing up in her CBC and white blood cell indices. This patient had all of the markers for chronic inflammatory response syndrome or biotoxin and mold-related illness. You'll often see abnormalities such as this in CIRS patients.

Here is another case, a 42-year-old female with chief complaint of GI issues, fatigue, and difficulty concentrating.

CBC, Platelet Ct, and Diff

WBC	7.8	x10E3/uL	4.0 - 10.5
RBC	4.69	x10E6/uL	3.80 - 5.10
Hemoglobin	14.2	g/dL	11.5 - 15.0

[redacted]

LabCorp
Laboratory Corporation of America

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[redacted]

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Hematocrit	42.7		%	34.0 - 44.0
MCV	91		fL	80 - 98
MCH	30.3		pg	27.0 - 34.0
MCHC	33.3		g/dL	32.0 - 36.0
RDW	13.3		%	11.7 - 15.0
Platelets	240		x10E3/uL	140 - 415
Neutrophils	**31**	**Low**	%	40 - 74
Lymphs	**61**	**High**	%	14 - 46
Monocytes	5		%	4 - 13
Eos	2		%	0 - 7
Basos	1		%	0 - 3
Neutrophils (Absolute)	2.4		x10E3/uL	1.8 - 7.8
Lymphs (Absolute)	**4.7**	**High**	x10E3/uL	0.7 - 4.5
Monocytes(Absolute)	0.4		x10E3/uL	0.1 - 1.0
Eos (Absolute)	0.2		x10E3/uL	0.0 - 0.4
Baso (Absolute)	0.1		x10E3/uL	0.0 - 0.2
Immature Granulocytes	0		%	0 - 2
Immature Grans (Abs)	0.0		x10E3/uL	0.0 - 0.1

Her white blood cell count is normal, but her neutrophils are low, and lymphocytes both percentage and absolute are high, and this is consistent with a viral infection.

Lab Test Results

Cytomegalovirus (Cmv) Ab, Igg

Test	Low	Normal	High	Reference Range	Units
Cytomegalovirus (Cmv) Ab, Igg		<0.60		0.00-0.59	

Vitamin D, 25-hydroxy

Test	Low	Normal	High	Reference Range	Units
Vitamin D, 25-hydroxy	27.8			30.0-100.0	ng/mL

Ebv Vca/ea Ab, Igg

Test	Low	Normal	High	Reference Range	Units
Ebv Early Antigen Ab, Igg			29.4	0.0-8.9	U/mL
Ebv Ab Vca, Igg			490.0	0.0-17.9	U/mL

Ebv Ab Vca, Igm

Test	Low	Normal	High	Reference Range	Units
Ebv Ab Vca, Igm		<36.0		0.0-35.9	

Follow-up testing for her suggested that she did, in fact, have Epstein-Barr virus previously but not currently, and that's not at all uncommon, as I'm sure you know. About 98 percent of people have been exposed to Epstein-Barr virus, so seeing IgG antibodies that are indicative of previous exposure generally are not a sign that the patient has a current infection. There may be some exceptions to that rule, but that's the general rule. Her cytomegalovirus and other viral antibodies that aren't pictured here were also normal. Her vitamin D was slightly low.

Component Results

Component	Standard Range	Your Value
White Blood Cell Count	3.4 - 10.8 x10E3/uL	16.8
Red Blood Cell Count	3.77 - 5.28 x10E6/uL	4.76
Hemoglobin	11.1 - 15.9 g/dL	14.2
Hematocrit	34.0 - 46.6 %	41.7
Mean Corpuscular Volume	79 - 97 fL	88
Mean Corpus Hgb	26.6 - 33.0 pg	29.8
Mean Corpus Hgb Conc	31.5 - 35.7 g/dL	34.1
RBC Distribution Width	12.3 - 15.4 %	14.1
Platelet Count	150 - 379 x10E3/uL	168
Neutrophil %		27
Lymphocytes %		67
Smudge cells present Atypical lymphocytes.		
Monocyte %		5
Eosinophil %		1
Basos		0
ANC-Neutrophil Absolute	1.4 - 7.0 x10E3/uL	4.5
Lymphcytes Absolute	0.7 - 3.1 x10E3/uL	11.3

She consistently had high lymphocytes, low neutrophils, and often high white blood cell count on retests. After ruling out a viral infection, I referred her to a hematologist because I was concerned about these persistently abnormal markers, and she was diagnosed with a condition called chronic lymphocytic leukemia or CLL, which is a cancer of the lymphocytes. It's a very slow-growing cancer. It often does not cause noticeable symptoms for many years, usually not diagnosed until after age 40. It can be so slow growing that treatment isn't always necessary, and the patient may live a normal life span. Fortunately, in this case, the patient was at stage 0. She is already in her mid-40s, so her prognosis is very good, but it's a good thing that we caught it and were able to figure out what was going on.