ACUTE PHASE REACTANTS

TERM DEFINITION

Acute phase reactants (APR) are a group of blood proteins (markers of inflammation) that exhibit significant changes (> 25%) in serum concentration during inflammation such as occurs with infection, rheumatological disorders, trauma or stress.

TYPES

ACUTE PHASE REACTANTS

Negative acute phase reactants associated with inflammation include decreased serum:

- Albumin
- Transferrin (total iron binding capacity)

ACUTE PHASE REACTANTS

Positive acute phase reactants associated with inflammation include elevated serum:

- C-reactive protein (CRP)
- Haptoglobin
- Ferritin
- Fibrinogen
- Hepcidin

CLINICAL PEARLS

APRs often associated with changes in the complete blood count, including anemia, leukocytosis, and thrombocytosis

ESR is not an acute phase reactant; it is a lab test whose result depends on the concentration of the APR, fibrinogen in the blood.

The acute-phase reactants commonly change in tandem, but not all of them change uniformly in all patients with the same illness.

ESR, erythrocyte sedimentation rate

CASE PRESENTATION

66 YEAR-OLD MAN WITH SEPTIC SHOCK

WHITE BLOOD CELLS	6.5	4.0 – 10.0
RED BLOOD CELLS	3.45*	3.9 – 5.2
HEMOGLOBIN	10.2*	11.2 – 15.7
HEMATOCRIT	33.9*	34 – 45
MCV	98	82 – 98
MCH	29.6	26 – 32
MCHC	30.1*	32 – 37
RDW	14.3	10.5 – 15.5
RDW-SD	50.4*	35.1 – 46.3

ALBUMIN	3.0*	3.5 – 5.2	g/dL
FIBRINOGEN, FUNCTIONAL	665*	180 – 400	mg/dL
IRON BINDING CAPACITY, TOTAL	218*	260 – 470	ug/dL
FERRITIN	628*	13 – 150	ng/mL
TRANSFERRIN	168*	200 – 360	mg/dL
C-REACTIVE PROTEIN	261.1*	0 – 5.0	mg/L

Normal ranges, right-most column

**Haptoglobin is missing*

IS THERE METHOD TO THE MADNESS?

Yes! The acute phase response is a highly coordinated, evolutionarily conserved response to microbial and non-microbial danger signals

Positive APR

- **CRP** - enhances phagocytosis by macrophages.
- **Haptoglobin** - binds and sequesters free hemoglobin (and therefore iron) in the circulation, depriving pathogens of iron.
- **Ferritin** - sequesters iron inside macrophages, depriving pathogens of iron.
- **Fibrinogen** - last step in clotting cascade, also plays a role in innate immunity by walling off pathogens.

Negative APR

- **Transferrin** - carries iron in the blood; downregulation reduces iron availability for pathogens.
- **Albumin** - possibly decreased so that the liver can reallocate resources to synthesize positive acute phase reactants.

CAVEATS

- Patients with cirrhosis or hemolysis may have normal or low haptoglobin.
- Patients with disseminated intravascular coagulation may have a low or normal fibrinogen level.
- Patients with inflammation and iron deficiency may have a ferritin in the 50-100 ng/ml range.

CAUSES OF ↓/↑ APR

- Infection
- Trauma
- Surgery
- Burns
- Tissue infarction
- Autoimmune disease
- Cancer

DIFFERENTIAL DIAGNOSIS

- High serum ferritin may also occur in the setting of iron overload or from cellular leak in the case of acute liver injury.
- Low albumin may also occur in the setting of chronic liver disease, proteinuria or malnutrition.

ESR VS. CRP

ESR and CRP are almost always increased concordantly. There are certain exceptions, for example:

High ESR, normal CRP: Multiple myeloma; SLE flare; **high ESR, normal CRP**

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

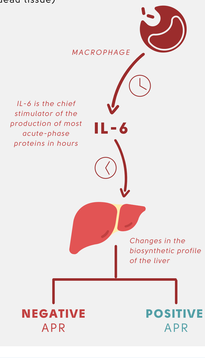
COMPARATIVE PHYSIOLOGY

The acute phase response is conserved across all

VERTEBRATES

PROXIMATE MECHANISMS

Innate immune response:
Activators (microbial, toxic compounds, dead tissue)



EVOLUTIONARY MECHANISMS

The acute phase response, which includes **changes in blood levels** of acute phase reactants, as well as alterations in blood counts, and a large number of behavioral, physiologic, biochemical, and nutritional changes, is highly evolutionarily conserved. It is considered an adaptive response that promotes homeostasis **after tissue injury or infection**. Though the overall framework is conserved between vertebrates from fish to mammals, the individual proteins involved, their level and rate of change, and their physiological functions vary.

There is an evolutionary trade-off here. In order to protect the host against danger, a highly complex system has evolved that can sometimes be over-played, and like every great weapon can turn on its bearer. This has been referred to as the **immune brinksmanship model**, whereby the host gambles that the APR-mediated harm inflicted on infected cells and pathogens will outweigh any collateral damage on normal tissue cells.

HISTORY OF MEDICINE

Of all the APRs, fibrinogen was the first to be recognized. In fact, it was named by Rudolf Virchow in 1847 and purified in 1879. The ESR, which depends on the fibrinogen level, was discovered by a Polish physician, **Edmund Faustyn Biernacki** in 1897. He noted that blood sedimentation rate depended on the level of plasma fibrinogen and that such levels were high in febrile diseases (including rheumatic fever). It would be many years before research tools were sufficiently honed to isolate other APRs. Notably, **C-reactive protein was discovered in 1930**. And it would take even longer for the various proteins to be incorporated into routine clinical assays.

NOTES

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