

The saline should always be given at body temperature to minimise any temperature gradient between the administered fluid and circulating mast cells – which seem to be unduly fragile to temperature gradients. A somewhat similar situation has been encountered in airmen baling out and parachuting into a freezing sea. Death can occur rapidly because mast cells in a warm body suddenly encountering very cold water have been known to trigger. This is likely due to the sudden and steep temperature gradient between freezing water and the warm internal milieu of the mast cells. The result is lethal anaphylactic shock.

Other problems: The reduction of oxygen and nutrient supply to the tissues as described above causes widespread disruption of normal metabolic functions. The finely balanced checks and balances of such functions are inevitably upset, with definable consequences. One of these is likely to be inappropriate mast cell activation, a frequent complication of both ME/CFS and Long Covid. The most destructive of these, short of anaphylaxis, is the tendency for mast cells in the gut lining to activate inappropriately when exposed to normally harmless food proteins. Histamine release is the result, together with other vasoactive substances. The most common clinical manifestation of this is severe abdominal pain, sometimes accompanied by vomiting and occasionally hives. A consequence of this is reduction of

food intake, with malnutrition being a real concern. Added to the generalised muscular weakness referred to earlier, food and fluid intake is likely to be drastically reduced, further compounding the problem and emphasising the vital importance of intravenous saline.

In summary: one of the most important (and straightforward) treatments involves re-expanding a reduced blood volume, as set out above. The effect will be to ameliorate and eventually reverse the problems caused by the reduction of capillary blood flow. In some patients, investigation of the failing pituitary gland is helpful in order to stop the kidneys from losing excessive water (as is the case with Addison's disease).

The next straightforward treatment involves the oral administration of a mast cell inhibitor such as sodium cromoglycate (Nalcrom) and an antihistamine in an attempt to alleviate inappropriate mast cell over-activity. Muscular weakness is sometimes so severe that nasogastric or nasojejunal tube feeding is required; the liquid feed given must always be at body temperature, as for the IV saline. Finally, the technique of immunoabsorption has shown promise; this removes the autoantibodies, with very encouraging results as shown in recent studies in Germany. *This technique is available in the UK.*

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A Short Synopsis of the Pathophysiology of Severe ME

There is a pathological sequence in such patients, which, in the light of current scientific findings, explains much of the clinical manifestations of this horribly disabling condition. An understanding of this sequence is key to its effective treatment. This sequence, starting with an immunological trigger in a previously healthy person, is as follows:

The immunological trigger: Viruses, bacteria and some vaccines have all been documented as acting in this fashion, including Covid-19. The biological intention of the immune response which follows is to neutralise the invading organism, amongst which are antibodies specific to this organism. In some cases, however this immune response includes antibodies which, far from being protective, have an affinity for the patient's own tissues, hence the term 'autoantibody'.

Autoantibodies: These may be harmful or relatively harmless depending on the tissue for which they have affinity. Autoantibodies triggered by Covid-19 infection appear, amongst other tissues, to have a particular affinity for the lining of blood vessels, causing

Inflammation. This damages the lining, with a major effect on blood flow in the smaller blood vessels, particularly the capillaries. An additional problem, due to the inflammation is the formation of 'micro clots' causing further obstruction to capillary blood flow. This is particularly the case in Long Covid, and anticoagulant medication is helpful in such patients. Other autoantibodies, found particularly in Long Covid, have an affinity for neurological receptor sites and block their function. These can be very disruptive of the normal autonomic control of subconscious bodily functions such as control of heart rate and blood pressure.

Capillaries: These are the smallest blood vessels in the body, with an average diameter of six microns. They are so narrow that red and white cells travel down them only in single file. They are practically the sole source of supply for the tissues of both oxygen and the other nutrients present in the blood. They also convey the breakdown products of tissue metabolism via the bloodstream to the kidneys for excretion. Any obstruction to blood flow through the capillaries is therefore potentially very serious. As previously stated, this happens in both Long Covid and ME/CFS, and one of the immediate – and detectable – effects is the accumulation of lactic acid in such patients. This occurs because the reduced blood flow through the capillaries starves the tissues of

oxygen – an essential component of the 'aerobic' metabolic process which generates energy. This causes the tissues to switch to a metabolic pathway which does not require oxygen – the less efficient 'anaerobic' pathway. The major byproduct of this pathway is lactic acid; this has been detected in excess in the blood, also in the muscles and brain in ME/CFS patients. Furthermore, oxygen is required in relatively large amounts to clear the excessive amounts of lactic acid which accumulate. This physiological requirement is well demonstrated by the hyperventilation seen in healthy subjects resting. Immediately after a 100-yard sprint, where the anaerobic pathway has been utilised. Some ME/CFS patients also experience this as "air hunger" – but after the slightest exertion only.

Reduced capillary blood flow: 'Downstream' of this fundamental problem there is a reduction in function of many tissues, particularly the muscles, mainly because they are being continuously starved of oxygen; they are therefore near or on their 'anaerobic threshold' at all times. Pituitary gland functional impairment is very likely due to this mechanism, and was first recognised in the 1990s. In particular, the production of ACTH, the pituitary hormone which stimulates the adrenal gland to produce hydrocortisone. Hydrocortisone instructs the

kidneys to retain sodium, which in turn means that water is retained as well.

A reduction of hydrocortisone levels because of failing pituitary function means that less sodium and water are retained by the kidneys, causing an abnormally high urinary output and a reduction in circulating blood volume. A continuous thirst is a very common feature because of this, and POTS is another consequence, due to the low blood volume. The other consequence is increased blood viscosity because of the reduction in the water component of blood – further affecting capillary blood flow. In some cases, other defects of the control of blood volume are suspected, particularly in respect of 'blocking' autoantibodies. The consequent reduction of blood volume from any of these mechanisms also reduces capillary blood flow, reducing oxygen and nutrient supply to the tissues even further. Blood volume reduction in ME/CFS has been well documented in the medical literature. The severe/very severe **always** require intravenous normal saline - in sufficient quantities, on a daily basis, as part of effective management. Restoration of blood volume by this method will help restore capillary blood flow, effectively reversing the damaging effects set out above. The daily amount required may well be up to two-three litres, given over approximately two hours.