

**The clinical and biological effects of ASEA ionized water /"redox supplement"
(co-administered with L-carnitine and omega-3 fatty acids plus multivitamins
dietary supplements) in a ~3-year-old boy with Duchenne muscular dystrophy (DMD)
from Romania – a case report**

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1st Motto: „ASEA works at some fundamental level in the body that we may never understand” (2011, [Dr. Chase N. Peterson](#) MD [1999-2014], the former president of the [University of Utah](#) from 1983 to 1991)

2nd Motto: „ASEA is based on technology that the scientist don't yet understand.” (2013, [Dr. A.S. Narain Naidu](#) MD Phd, microbiologist, immunologist and researcher, author of [the reference volume „Redox Life”](#))

3rd Motto: „We didn't think that drinking ASEA would shift metabolites chronically. We thought it would do something during exercise, but not after a week of drinking it [without concomitant exercise: author's note]. After working with the bioinformatics statistical division, we were able to determine that drinking ASEA over one week caused a shift in 43 metabolites, not a little shift: it was a large shift that caught us by surprise.” ([David Christopher Nieman](#) ^{[[URL2](#), [URL3](#)]} PhD and full professor at the College of Health Sciences at Appalachian State University, and director of the Human Performance Lab at the North Carolina Research Campus (NCRC) in Kannapolis, NC) ([video interview URL](#), from minute 5:40)

4th Motto: „Pediatrics – what a joy, what a feeling of accomplishment when helping Nature heal its children or prevent their diseases and accidents!” (Andrei-Lucian Drăgoi, pediatrician specialist and independent researcher)

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[2] Andrei-Lucian Dragoi research pages on: [ResearchGate](#), [Academia.edu](#), [ViXra](#), [GSJournal](#);

Abstract

This paper presents a case report on the clinical and biological effects of “[ASEA redox supplement](#)” ([ASEA-rs](#)) oral solution (co-administered with [L-carnitine](#) and [omega-3 fatty acids](#) plus [multivitamins dietary supplements](#)) in a ~3-year-old boy with [Duchenne muscular dystrophy \(DMD\)](#) from Romania.

[ASEA-rs](#) was tested on both animals and humans. [In vitro studies](#) on various human cells showed that [ASEA-rs is a very potent NRF2 selective activator \(with transient effect\)](#): the studies conducted [in vivo](#) (on both animals and humans) also support this main pharmacological mechanism of ASEA-rs, with no [toxicity](#) up to high doses (in contrast with [corticosteroids](#) which are usually reserved in Romania for DMD children with age above 4 years, given their toxicity profile and adverse effects including [immunosuppression](#), [growth delay](#), [osteopenia](#), [osteoporosis](#) and [overweight](#)) and a satisfactory [bioavailability](#) especially in the vital organs (in which NRF2 also reaches its highest intracellular cytoplasmatic concentrations), which assures the strong NRF2 activation effects of ASEA-rs indirectly observed in vivo.

[ASEA was clearly demonstrated to activate tissular lipases](#) (probably also via [NRF2](#) pathway) and to significantly increase some [fatty acids serum](#) levels that are further internalized by [skeletal muscles](#) and [myocardium](#) and used as “fuel” by [muscular cells \(myocytes\)](#) (and [cardiomyocytes](#)), partially sparing the [glycogen](#) reserves of [myocytes/cardiomyocytes](#) and so raising the resistance of skeletal muscles to effort and possibly the resistance and contractility of [myocardium](#).

Based on its demonstrated potent selective [NRF2](#) activation effect, its beneficial effects on muscle effort resistance and its [safety profile](#), I have prescribed ASEA-rs to this ~3-year-old child with DMD, with a minimal set of clinical signs at his age, but with significant biological alternations in the [biochemical markers of muscular damage \(rhabdomyolysis\)](#): the results (after the first 3 months with ASEA-rs, associated with [L-carnitine](#) and [omega-3 fatty acids](#) plus multivitamins supplements) were a significant reduction in the [creatinine \(phospho\)kinase \(CK/CPK\)](#) and [CK-MB isoform](#) serum levels.

Keywords: [ASEA](#) redox supplement ([ASEA-rs](#)) oral solution, 3-year-old boy, [Duchenne muscular dystrophy \(DMD\)](#), Romania, [NRF2](#) selective activator, tissular lipase activator, skeletal muscles and myocytes, myocardium and cardiomyocytes, [corticosteroids](#), [creatinine \(phospho\)kinase \(CK/CPK\)](#), CK-MB isoform

Important note (1). This atypical [URL](#)-rich paper (which maximally exploits the layer of hyperlinks in this document), chooses to use Wikipedia links for all the important terms used. The main motivation for this approach was that each Wikipedia web-article contains all the main reference (included as endnotes) on the most important terms used in this paper: it’s simply the most practical way to cite entire collections of important articles/books without using an overwhelming list of footnote/endnote references. The secondary motivation (for using Wikipedia hyperlinks directly included in keywords) was to assure a “click-away“ distance to short encyclopedic monographs on all the (important) terms used in this paper, so that the flow of reading to be minimally interrupted.

Important note (2). This paper also exploits the advantages of the hierarchic tree-like model of presenting informational content which is very easy to be kept updated and well organized.

I. Essential information on Duchenne muscular dystrophy (DMD)

- 1) **Etiology, epidemiology and pathophysiology.** [Duchenne muscular dystrophy \(DMD\)](#)^[URL2a, URL2b] is a severe [X-linked recessive muscular dystrophy](#) caused by a [mutation](#) (inherited from a person's parent in ~2/3 of DMD cases and non-inherited [de novo mutation](#) in ~1/3 of DMD cases) in the [gene](#) coding the [dystrophin \(dys\) protein](#), which is a [cytoplasmic](#) protein and a vital part of a protein complex (with many subunits) that connects the [myocyte cytoskeleton](#) to the surrounding [basal lamina](#) of the [extracellular matrix](#) through the muscular [cell membrane \(sarcolemma\)](#). Normal skeletal myocytes contain small amounts of dystrophin but its total/partial absence or abnormal length leads to excess calcium [cations](#) penetrating the [sarcolemma](#) and causing excess water to enter into all mitochondria which then burst and lead (by several [not clearly understood yet] aberrant intracellular signaling pathways) to increased intracellular [oxidative stress](#), sarcolemma permanent damage and myocytes [necrosis](#). [Skeletal muscles](#) progressive destruction ([rhabdomyolysis](#)) causes muscular fibers to be progressively replaced by [adipose](#) and [connective tissue \(pseudohypertrophic muscular dystrophy](#) or muscular pseudohypertrophy, for example [calf and tongue pseudohypertrophy](#)): that is why affected muscles may look larger than normal (which is due to increased fat content) and may show contractures (caused by muscle fibers shortening and fibrosis). DMD is the most common type of [muscular dystrophy](#) and has an incidence of ~1/3600 born male infants.
- 2) **Clinical signs and symptoms.** [Muscle weakness](#) associated with progressive [muscle atrophy](#) (with secondary [fatigability](#), frequent falls and progressive difficulty in walking and getting up from lying or sitting position) usually begins around the age of 4 years in boys and worsens quickly. Typically muscle loss initially occurs in the lower limbs (thighs, calves) and pelvis/hip (causing difficulties in standing up) followed by those of the upper arms (shoulders), neck, spinal and thoracic muscles: Most DMD boys are unable to walk by the age of 12 years. [Scoliosis](#) and [lumbar hyperlordosis](#) are common and due to [axial muscles](#) damage (with decrease in spinal muscular tonus). Advanced stages DMD patients may have respiratory disorders (due to respiratory muscles damage), swallowing difficulties (with high risk of [aspiration pneumonia](#)). DMD patients may also present neurobehavioral, learning and memory disorders (also believed to be the result of absent or dysfunctional dys in the brain). Females with a single copy of the defective dys-gene may also show mild signs and symptoms (without being classified as DMD) depending on their pattern of [X-inactivation](#): DMD may occur in females who have an affected father and a carrier mother, which is a very rare situation however.
- 3) **Labs and other tests.** DMD patients have extremely high [creatin kinase \(CK\)](#) and possibly (very) high CK-MB isomer serum levels: the serum levels of [aspartate transaminase \(AST\)](#) and [alanine transaminase \(ALT\)](#) are also very increased. Consequently, [myoglobin](#) (produced by [rhabdomyolysis](#)) also attains high concentrations in serum and urine. [Electromyography \(EMG\)](#) distinguishes the weakness caused by destruction of muscle tissue. [Echocardiography](#) may show [dilatative cardiomyopathy](#) secondary to myocardial fibrosis (which can occasionally lead to [congestive heart failure](#) and/or [arrhythmias](#))
- 4) **Positive diagnosis.** DNA testing demonstrating mutation(s) in one or more of the 79 exons of dys-gene (located on the short [p] arm of X chromosome, at locus 21 [Xp21]) can often make the diagnosis at birth or confirm the diagnosis in most suspected cases.
 - a. Muscle needle biopsy (with immunocytochemistry and immunoblotting for dystrophin) may be performed when DNA testing fails to find the mutation: dystrophin absence indicates DMD and dystrophin presence helps to distinguish DMD from milder dystrophinopathy phenotypes (depending on the amount and molecular size of dystrophin)
- 5) **Differential diagnosis (DD).** DD includes [Becker's muscular dystrophy \(BMD\)](#) (with incidence of 1.5-6/100 000 born boys, much less common than DMD) and other MDs.
- 6) **The pathophysiological and symptomatic DMD treatment.** DMD doesn't have a curative treatment, but only a pathophysiological and symptomatic treatment which may delay the onset of symptoms and increase the quality of life.

- a. Avoiding inactivity (such as prolonged bed rest), [physical therapies](#) (to minimize the development of contractures and deformity, to assist with breathing exercises and methods of clearing secretions), swimming, [orthoses](#) (to delay the onset of contractures) and corrective surgery may help in muscular symptoms and skeletal complications.
- b. Non-invasive/invasive [assisted ventilation](#) may be required in those with advanced respiratory muscles weakness.
- c. [Pacemaker](#) implant for patients with cardiac rhythm and conduction disorders.
- d. **Medications:** [steroids](#) such as [prednisolone](#) and [deflazacort](#) (which were demonstrated to slow muscle degeneration and to produce short-term improvements in muscle strength and function up to 2 years, including walking period prolongation according to some reports); [β2 agonists](#) such as [salbutamol](#) (which were demonstrated to increase muscle strength, but don't modify disease progression), [anticonvulsants](#) (to possible seizures control) and [immunosuppressants](#) (to delay damage to dying muscle cells). **Important note:** steroids were demonstrated to increase the myocyte production of [utrophin](#) (a protein homologous to dys, encoded by a 900 kb gene found on the long arm [q] of human chromosome 6) which closely resembles dystrophin and partially compensates its lack in DMD patients, in which utrophin expression is dramatically increased.
- e. **Genetic counseling** for people with family history of DMD.

7) The etiology-targeted DMD treatment (still under research).

- a. **Exon-skipping gene therapy (ESGT) with antisense oligonucleotides (oligos/AONs like [eteplirsen](#) or [drisapersen](#))** to trigger skipping of an exon (adjacent to the exon affected by mutation) so that to restore the reading frame and production of a (still-truncated but) more functional version of dys: ESGT essentially converts DMD phenotype into a BMD phenotype. Clinical improvement in 12 patients in a Phase 1-2a study was shown, in which patients whose performance had been declining instead improved, from 385 meters to 420 meters at the 6-minute walk distance test. For ESGT to be efficient on medium and long term, AONs must be periodically redelivered into muscles.
- b. **Stem cell replacement therapy (SCRT) with [pericytes](#)** (a type of multipotent stem cells which have the ability to be delivered systemically and uptaken by crossing the vascular barrier, then to fuse and form myotubes) injected arterially, crossing through arterial walls into muscles, where they can differentiate into potentially functional myocytes.
- c. **[CRISPR/Cas9-mediated genome editing](#)** (not currently feasible in humans, but potentially feasible in the future) which can precisely remove a targeted mutation of dys-gene, by allowing the DNA repair mechanisms of myocytes to replace that mutant dys-gene with a normal dys-gene.
- d. **[Ataluren](#)** (PTC124/ Translarna®) indicated for DMD patients that can walk and are more than 5 years old. Ataluren probably makes ribosomes less sensitive to premature [stop codons](#), especially for 'UGA' (by promoting insertion of certain near-cognate [transfer RNA \[tRNA\]](#) at the site of nonsense codons, with no apparent effects on downstream mRNA transcription, processing, stability nor on the resultant protein) thus helping to produce a functional dys similar to the non-mutated dys, as it was already demonstrated in DMD, where ataluren treatment increases expression of full-length dys. Unfortunately, Phase II trial of ataluren in DMD human patients was suspended when participants did not show significant increases in the 6-minute walk distance test.
- e. **[Sildenafil](#)** was demonstrated to improve the muscular blood flow in DMD boys (in a small study published in May 2014 in the journal "Neurology"): a larger and longer trial on [tadalafil](#) was designed and initiated so that to determine if this increased muscular blood flow will translate into clinical improvement in muscle function of DMD patients.
- f. **[Rimeporide](#)**, a [sodium–hydrogen antiporter 1](#) inhibitor is speculated to reduce sodium and calcium overload in cells of DMD patients: rimeporide is in preclinical trials as of May 2015.

- 8) **Prognosis.** The average life expectancy of DMD patients is 26 years (with a maximum between 30-50 years in rare cases who benefit from excellent care). Most DMD patients become wheelchair-dependent early in life, and the gradual development of [cardiac hypertrophy](#) and/or restrictive respiratory insufficiency typically results in premature death between ages of 20-30 years.

II. Essential information on ASEA “redox supplement” (ASEA-rs) and NRF2 activators

- 1) **Production, patents and chemical properties of ASEA-rs.** [ASEA-rs](#) is produced by an international direct selling and multi-level marketing company called “[ASEA](#)” ^[URL2] founded in 2007 and headquartered in Salt Lake City, Utah, USA. The present ASEA-rs is based on a technology developed and [patented](#) ^[URL2] by [Medical Discoveries, Inc.](#), and was previously called “MDI-P”.
 - a. ASEA-rs is a clear, colorless liquid generated by electrolysis of a highly purified sterile saline. ASEA-rs is distributed in [~1 liter plastic bottles](#). ASEA-rs has a saline concentration of ~0.27g [NaCl](#) /100ml (0.27%) and additionally contains (in a total concentration of about 1%) highly reactive chlorine and oxygen species: **the oxidant (OX) species from ASEA-rs** include [hydrogen peroxide](#) (H₂O₂), [superoxide](#) anions species (O₂⁻ and HO₂⁻), [hypochlorous acid](#) (HOCl), [hydronium cation](#) (H₃O⁺), [hypochlorite radical](#) (OCl^{*}), [singlet oxygen](#) ¹[O₂], (partially soluble) [oxygen](#) biatomic molecules (in [triplet](#) ground state) and triatomic molecules (O₃) ([ozone](#)) etc.; **the reductive (RED) species from ASEA-rs** include [hypochlorite anions](#) (ClO⁻) (also paired as [sodium hypochlorite](#) Na⁺ClO⁻ [NaOCl]), [chlorine](#) anions (Cl⁻), biatomic molecules (Cl₂), (partially soluble) [hydrogen](#) biatomic molecules (H₂), [hydrogen anions](#) (H) etc.
 - b. MDI-P had a relatively high concentration (~25-50%) of those reactive species and was initially tested for its microbicidal properties: it was found to be a very fast-acting, broad-spectrum microbicidal solution effective against [Staphylococcus aureus](#), [Pseudomonas aeruginosa](#), [Legionella pneumophila](#) and [Candida albicans](#) ^[URL1, URL2].
- 2) **Certifications of ASEA-rs.** After obtaining [its certificate of safety for oral consuming](#) ^[URL2a - ASEA-rs safety, classification and certifications brochure; URL2b, URL3a, URL3b], ASEA began selling ASEA-rs as a [dietary supplement](#) from 2009. ASEA-rs is currently produced in a production facility which is [FDA](#) registered, [NSF](#) certified, [GMP](#) compliant ^[URL2a - ASEA-rs safety, classification and certifications brochure; URL2b].
 - a. In 2015, ASEA partnered with [BioAgilytix Labs](#) (specialized in biomarker testing) which validates the existence of reactive oxygen species in ASEA-rs and product quality.
 - b. The first European country in which ASEA-rs was registered as a dietary supplement was Italy, under the name “ASEA advancing life” with index number 54229 in the official [list of dietary supplements approved in Italy](#) (see page 168 of the linked pdf list). ASEA-rs also appears in the [list of dietary supplements approved in EU](#) with no. NUT 1936 (see page 842 of the linked pdf list)
- 3) **ASEA-rs as a NRF2 selective activator.** ASEA-rs was tested on both animals and humans. [In vitro studies](#) on various human cells showed that **ASEA-rs is a very potent (but transient) selective NRF2 activator (even in low concentrations in vitro), avoiding the activation of NF-kb** (having interesting favorable [immunomodulating](#) properties) ^[URL2a - ASEA-rs main in vitro study, URL2b]; the studies conducted [in vivo](#) (on both animals and humans) also support this main pharmacological mechanism of ASEA-rs, with no [toxicity](#) up to high doses (calculated per kilogram of body mass) and a satisfactory [bioavailability](#) (which assures the strong effect demonstrated in vivo) ^[URL2a - ASEA-rs safety, classification and certifications brochure; URL2b]. **All studies on ASEA-rs are briefly presented in one official brochure published by ASEA** ^[URL1a - ASEA-rs studies - brochure, URL1b]. NRF2 governs the [Phase II cellular stress response](#) ^[URL2] so that NRF2 activation can induce over-expression in more than 150 genes (which are involved in the [Phase II cellular stress response](#)): five of these genes were demonstrated to be over-expressed by ASEA-rs oral consumption ^[URL1a - ASEA-rs gene study, URL1b, URL1c]. As NRF2 is ubiquitously expressed with the highest concentrations in the cytoplasm of cells from the vital organs (in descending order: the kidney, muscle, lung, heart, liver, and brain) ^[URL1], it is expected that ASEA-rs to mainly protect human vital organs (with the additional argument that these vital organs have the largest blood supply, which is directly proportional with the concentration ASEA-rs may reach in these vital organs).
 - a. “Brief Summary of Results for Objective (2): An 800% increase in GPx antioxidant efficacy in HMVEC-L cells was seen after 24 hours exposure from low-concentration ASEA (no concentration dependence seen). A transitory increase of up to 500% was seen in SOD antioxidant efficacy between 30 to 90 min. again after exposure to low-concentration ASEA (< 1%). In both cases, the low concentrations of ASEA were comparable to blood concentrations possible from oral dosing, though data is not available to confirm this. Concentration dependence at very low concentrations might be seen if such was carefully investigated. Exposure to high-concentration ASEA, in comparison, elicited only a small relative increase in GPx antioxidant efficacy that was not concentration dependent. An increase in SOD efficacy was not seen for either high-concentration ASEA or after long (24 hr) exposures. In subsequent investigations, this information will be used to determine optimal concentrations and time points to study concentration dependence (less than 0.1% and 0-120 minutes).” ^[URL1a - ASEA-rs main in vitro study, URL1b]
- 4) **ASEA-rs was also shown to be induce apoptosis** in “cultures of dysfunctional, stressed or damaged cells”. See below some paragraphs extracted from the cited study.

- a. “The induction of cell death in cultures of dysfunctional, stressed or damaged cells by ASEA infusion should also be explored. Natural healing processes involve a repair or replace mechanism by which marginally damaged cells are repaired, when possible, or undergo apoptosis, programmed death, if they cannot be repaired and then are replaced through mitosis of healthy neighboring cells. It is fairly evident that ASEA infusion, of itself, is not causing direct stress to exposed cells, however, it might tend to increase the efficiency of certain cytokine “death domain” messengers ([Cachexin](#)) that are designed to induce cell death in dysfunctional or damaged cells. The nuclear translocation of NRF2 can be considered part of the phase II oxidative defense response which includes expression of antioxidants, DNA repair molecules and other known repair mechanisms.” [[URL1a – ASEA-rs main in vitro study](#), [URL1b](#)]
- 5) **Additionally, ASEA activates human tissular lipases** (most probably via [NRF2](#) pathway) and significantly increases the [fatty acids serum](#) levels that are further internalized by [skeletal muscles](#) and [myocardium](#) and used as “fuel” by [muscular cells \(myocytes\)](#) (and [cardiomyocytes](#)), partially sparing the [glycogen](#) reserves of [myocytes/cardiomyocytes](#) and so raising the resistance of skeletal muscles to effort and possibly the resistance and contractility [myocardium](#): see prof. [D.C. Nieman’s](#) first metabolomics study on ASEA-rs [[URL-ASEA-rs first metabolomics study](#)].
- a. Based on prof. [D.C. Nieman’s](#) first metabolomics study on ASEA-rs (and its encouraging results), University of North Carolina (Chapel Hill) also started a second trial on ASEA-rs called “Effect of ASEA on Energy Expenditure and Fat Oxidation in Humans” [[URL – ASEA-rs second trial on metabolism](#)] with results summarized in ASEA-rs main “all-studies” brochure [[URL1a – ASEA-rs studies - brochure](#), [URL1b](#)] at page 2, in a rubric entitled “Influence of ASEA redox supplement ingestion on oxidative stress”.
- 6) **Antidoping certification of ASEA-rs.** Given its [antidoping certification](#), ASEA-rs is also widely used in the present by [various athletes](#) around the world.
- 7) **Comparison between ASEA-rs and other NRF2 activators.** There are many known natural molecules (especially [flavonoids](#)) and plant extracts that were demonstrated to be [NRF2](#) activators in vitro and/or in vivo [see also the author’s site subdomain [nrf2.dragoii.com](#)]: [sulforaphane](#) [[URL2](#)], [resveratrol](#) [[URL2](#)], [quercetin](#) [[URL2](#)], [curcumin](#) [[URL2](#)], [Ginkgo biloba](#) [[URL2](#)], [ginseng](#) [[URL2](#)], [catechins](#) [[URL2](#)] etc. There are also some synthetic NRF2 activators like: [dimethyl fumarate](#) [[URL2](#)], [monomethyl fumarate](#), [metformin](#) [[URL2](#)] etc. However, all these molecules have tissular toxicity (especially liver toxicity) at high doses in contrast with ASEA-rs which was demonstrated to have an excellent safety profile [[URL - ASEA main in vitro study](#)]. [Calorie restriction](#) (which was demonstrated to prolong life span in humans and animals) was also demonstrated to also imply a significant NRF2 activation effect (due to induced oxidative stress in calorie restricted cells): [physical exercise](#) has a similar activation effect on NRF2. **See below some paragraphs extracted from the main in vitro study on ASEA-rs:**
- a. “At this point it is worth mentioning that [NRF2](#) activity has been clearly detected in conjunction with low-concentration ASEA exposure without the normal prior [NF-kb](#) activity. This suggests that phase II antioxidant defense mechanisms have been stimulated without the normal prior phase I toxic response. This behavior has no precedent or is extremely rare. It appears from the data that ASEA is able to stimulate antioxidant expression without ever eliciting a prior low-level phase I toxic response.” [[URL1a – ASEA-rs main in vitro study](#), [URL1b](#)]
- b. “The infusion of a certain balanced mixture of redox signaling molecules, ASEA, into viable HMVEC-L and JB6 cell cultures has been seen to elicit distinct bioactivity. No indications of toxicity or the expression of inflammatory cytokines were observed and yet there was increased antioxidant and protective enzyme expression (as evidenced by increased nuclear NRF2) and greatly increased efficacy for the two master antioxidants, GPx [[glutathione peroxidase](#)] and SOD [[superoxide dismutase](#)]. This behavior suggests that ASEA infusion might tend to induce and enhance oxidative defense mechanisms without inducing toxic or inflammatory responses in such cells. Such action is unprecedented or extremely rare. Normally, low-level toxicity induces slight oxidative stress and inflammatory response which in turn induces oxidative defense and cell repair mechanisms. It would be of interest to determine concentration dependency of this effect with ultra-low-concentration ASEA infusions” [[URL1a – ASEA-rs main in vitro study](#), [URL1b](#)]
- c. “No toxic response was observed for any healthy cell culture in normal random phases(HMVEC-L or JB6) upon exposure to high concentrations (up to 20%) of serum ASEA. Two methods were used to determine toxic response, the translocation and accumulation of NF-kB and P-Jun in the nuclei. Both of these methods are known to be sensitive to low-levels of toxicity, as verified by the positive control. A complete lack of toxic indication and/or inflammatory cytokines was observed.” [[URL1a – ASEA-rs main in vitro study](#), [URL1b](#)]
- 8) **Topical forms of ASEA-rs.** ASEA-rs has also topical variants (gels), which have higher concentration in free radicals than the oral solution form: “[RENU 28](#)” and “[RENU Advanced Skin Care](#)”, which are briefly presented in one official brochure published by ASEA [[URL1a – RENU 28 studies - brochure](#), [URL1b](#)].

III. The main information on the child with Duchenne muscular dystrophy (DMD) clinical case (with ASEA-rs prescription motivations/arguments)

- 1) **Important argumentative note on ASEA-rs prescription in children with DMD under 12 years of age.** One of the warnings marked on its bottle recommends that ASEA-rs “should not be given to children under 12 years of age” (a warning mainly addressed to parents who can freely buy ASEA-rs dietary supplement from US and EU, as ASEA-rs doesn’t need a medical prescription to can be consumed for health preventive purposes or by sick adolescents and adults) . Given the safety profile of ASEA-rs (based on its extensive list of safety studies), I’ve personally considered that warning not an absolute but only a relative contraindication, because I’ve personally estimated (based on some published studies on steroids in DMD children) that benefits-to-risks ratio is much larger for ASEA-rs than for steroids when applied to DMD children under 4 years of age: that is why I have decided to prescribe ASEA-rs to this ~3-year-old DMD child (boy), a decision that showed biological and clinical benefits of ASEA-rs in this medical case, with no side effects until present (as shall be detailed next)
- 2) **Second argument for motivation of ASEA-rs prescription in a ~3-year-old DMD child.** Based on its demonstrated [immunomodulation](#) properties (including its strong selective [NRF2](#) activation effect), its beneficial effects on muscle effort resistance and its [safety profile](#) (no toxicity even for high doses, in contrast with corticoids which are usually reserved in Romania for DMD children with age above 4 years, given their toxicity profile and adverse effects including [immunosuppression](#), [growth delay](#), [osteopenia](#), [osteoporosis](#) and [overweight](#)), ASEA-rs was prescribed to this ~3-year-old child with DMD, with a minimal set of clinical signs at his age, but with significant biological alternations in the [biochemical markers of muscular damage \(rhabdomyolysis\)](#): the results (after the first 3 months with ASEA-rs, associated with [L-carnitine \[Carnil\]](#) solution produced by [Anfarm Hellas](#)] and [omega-3 fatty acids](#) supplement [[Omega 3 Junior](#) syrup produced by [Doppelherz](#)] were a significant reduction in the [creatine \(phospho\)kinase \(CK/CPK\)](#) and [CK-MB isoform](#) serum levels concomitant to only a slight increase in muscular [aspartate transaminase \(AST\)](#) and [alanine transaminase \(ALT\)](#).
- 3) **The first consult of the DMD boy in my pediatric office (from January 11th 2018, at 2 years and 8 months of age).** The DMD boy first came to my pediatric office for consult in **January 11th 2018** when he was aged approximately **2 years and 8 months**.
 - a. **Anamnesis.** When he was ~1-year-old (in the summer of year 2016), the boy had a high fever episode and he was suspected for high risk bacterial infection, so that he was hospitalized in [“Victor Gomoiu” Children Hospital](#) from [Bucharest](#) where he received a short cure (7 days) with antibiotics for [urinary tract infection \(UTI\)](#) with [Escherichia coli](#) (with a **slight enlargement of the left kidney**, but no other abnormalities on the [abdominal ultrasound](#)): with that hospitalization, the boy was discovered to have high serum levels of AST, ALT and CK. After being discharged from the “V. Gomoiu” hospital, the boy was redirected to the children neurology ward of [“Alexandru Obregia” Hospital](#) from Bucharest, for further investigations and diagnosis: the genetic tests (ready on September 12th 2016) of both the child and the mother showed **the same mutation in the 52nd exon of dys-gene** (a duplication of the nucleotide number 7547) which very probable implies a premature interruption of dys-gene reading from exon 53 to its last exon 79. Based on this genetic result, the boy was then diagnosed by the neurologist with **“oligosymptomatic progressive muscular dystrophy”** and was recommended physical therapy and periodic control (at every 6 months) in the children neurology ward (but with no reassessment of the muscle damage biological markers at that time). The mother also gave information about **her brother (the maternal uncle of her boy) who “couldn’t walk and was immobilized to bed from 7 years of age until his death at 18 years of age”** (but she couldn’t present any medical documents of her brother and his diagnosis). As expected, the mutation-carrier mother has no biological or clinical signs of muscle damage (including no biological markers of heart muscle damage and normal [electrocardiography \(ECG\)](#)). The parents were told by the neurologist to wait until the boy will be 4-year-old, for him to start a cure with [Prednisone](#) to delay the progress of the disease: this (quite long) Prednisone temporization (decided by the neurologist) and the symptoms/signs of the boy at that time (**impaired extension of one limb when walking and running plus calves enlargement**) worried parents and these were the main reason which determined the parents to ask a

second medical opinion from me as a pediatrician specialist at [Sika Medical clinic](#) (also from Bucharest).

- b. **Physical examination.** The main clinical signs found were: **impaired extension of the right limb (when walking), calves pseudohypertrophy (with 23/23cm maximum circumference of both calves), slight tonus deficit of the axial/spinal muscles, extreme anxiety at the physical exam, hyperkinetic child, moderate language delay (he only used ~20 correctly pronounced words at that age and only used pairs of words, but rarely sentences with verbs).** The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato/splenomegaly), but with **increased consistency stools (with defective discomfort),** normal diuresis and urination (with no kidney pain/sensibility), normal genital apparatus. **Body mass: 14kg** (Age: 2y8m) (in the normal range for sex and age). **Body height: 91cm** (Age: 2y8m) (in the normal range for sex and age).
- 4) **Based on diagnosis, anamnesis and physical examination (previously presented), I have requested some basic imaging and laboratory exams (see next).**
- 5) **Medical imaging exams of the DMD boy (in chronological order):**
- a. **Heart ultrasound (January 28th 2018):** echographically normal (with the reserve that the child was very anxious and hyperkinetic during this examination)
- b. **Abdominal ultrasound (*April 10th 2018; *parents delayed this exam because of objective reasons): minimal hepatomegaly;** all the other examined organs were echographically normal (with the reserve that the child was very anxious and hyperkinetic during this examination)
- 6) **Laboratory exams (rhabdomyolysis and inflammatory markers) of the DMD boy (in chronological order):**
- a. **Gamma-glutamyl-transferase (GGT)** (January 16th 2018): **10 U/ml** (within the normal range)
- b. **AST** – serum level (January 16th 2018): **473 U/L** (~10 times the superior limit of the normal range; of muscle origin, given the normal level of GGT)
- c. **ALT** – serum level (January 16th 2018): **558 U/L** (~17 times the superior limit of the normal range; of muscle origin, given the normal level of GGT)
- d. **CK** – serum level (January 16th 2018): **34 453 U/L** (~200 times the superior limit of the normal range; of muscle origin)
- e. **CK-MB** – serum level (January 16th 2018): **1241 U/L** (~52 times the superior limit of the normal range; of heart muscle origin)
- f. **Myoglobin (MG)** – serum level (January 22nd 2018): **2006 ng/mL** (~28 times the superior limit of the normal range; of muscle origin) (the child didn't want to cooperate for urine sampling for determining MG serum level)
- g. **C-reactive protein (CRP)** – serum level (January 22nd 2018): **0.61 mg/L** (within the normal range)
- h. **Erythrocyte sedimentation rate (ESR)** – serum level (January 22nd 2018): **9 mm/h** (within the normal range)
- 7) **Given all the DMD patient information previously given, I have decided to give the following recommendations (including medical treatment):**
- a. **ASEA-rs solution, per os** 30+30+0ml/day (~4ml/body_kg/day) (started from ~ January 22nd 2018)
- b. **L-carnitine** as **Carnil** oral solution (conc. 1g/10ml, 10ml vials) (produced by [Anfarm Hellas](#)), per os 0+1/2+0vials/day (after lunch, with fruit juice) (also started from ~ January 22nd 2018). **Important note.** L-carnitine acts as a transporter of long-chain fatty acids into the mitochondria (where to be oxidized for energy production): given the anticipated high levels of fatty acids produced by ASEA-rs (as shown by the metabolomics study conducted by [prof. Nieman](#) on ASEA-rs [see Part II]), I have used L-carnitine as an adjuvant for ASEA-rs.
- c. **Omega-3 fatty acids** plus multivitamins oral supplement as **Omega 3 Junior** syrup (produced by [Doppelherz](#)) (conc. ~8mg **DHA**/ml, 1.8mg **EPA**/ml; also containing vitamins **A**, **D**, **C**, **E**, **B1** (thiamine), **B2** (riboflavin), **B6**, **B12** (cobalamin), **niacin [vitamin B3]**, **pantothenic acid [vitamin B5]**, **biotin [vitamin B7]**) (started from ~ January 22nd 2018) 1.5+1.5+1.5ml/day (4.5ml/day in total).

Important note. I have chosen this DHA-EPA-multivitamin mix especially for the boy's language delay: I have chosen however a very small dose (4.5ml/day) given the age and the possibility that the multivitamin (antioxidant) mix may inhibit ASEA-rs effect (by partially/totally neutralizing the free radicals from ASEA-rs already absorbed in the blood)

- d. **Physical therapy:** the parents weren't compliant to this recommendation with the argument that their boy "is already very active and full of energy".
 - e. **Psychological Consult:** the parent's weren't compliant to this recommendation either, because of some prejudice on this kind of consult, as they consider their boy psychologically "normal".
- 8) I have then consulted the child monthly on: **January 22nd 2018** (for reading the imaging/laboratory exams results), **February 15th 2018** (for routine checkup), **March 22nd 2018** (for routine checkup and for the list of laboratory exams to be repeated after April 8th 2018 [the Easter period in Romania])
- 9) **(April 2018) Medical imaging exams of the DMD boy (in chronological order):**
- a. **Abdominal ultrasound (*April 10th 2018; *parents delayed this exam because of objective reasons): minimal hepatomegaly;** all the other examined organs were echographically normal (with the reserve that the child was very anxious and hyperkinetic during this examination).
- 10) **(April 2018, after ~3 months of ASEA-rs 60ml/day plus L-carnitine 0.5/day, omega-3 fatty acids supplement ~44mg/day and multivitamins mix) Laboratory exams (selected rhabdomyolysis markers) of the DMD boy (in chronological order):**
- a. **AST** – serum level (**April 17th 2018**): **453 U/L** (~9 times the superior limit of the normal range; of muscle origin, given the normal level of GGT; versus **473 U/L** on **January 16th 2018**)
 - b. **ALT** – serum level (**April 17th 2018**): **712 U/L** (~22 times the superior limit of the normal range; of muscle origin, given the normal level of GGT; versus **558 U/L** on **January 16th 2018**)
 - c. **CK** – serum level (**April 17th 2018**): **25 426 U/L** (~148 times the superior limit of the normal range; of muscle origin; versus **34 453 U/L** on **January 16th 2018**)
 - d. **CK-MB** – serum level (**April 17th 2018**): **632 U/L** (~26 times the superior limit of the normal range; of heart muscle origin; versus **632 U/L** on **January 16th 2018**)
- 11) **Checkpoint conclusion.** The ASEA-rs-based treatment from January-April 2018 (~3 months) was associated with a **slight AST serum level decrease of ~5%**, an **ALT serum level increase of ~28%**, a **CK serum level decrease of ~26%** and a **very significant CK-MB serum level decrease of ~50%** (which was the main target of my ASEA-rs recommendation and may be explained by the fact that ASEA-rs has stronger NRF2 activation effect on the myocardium, where the expression of NRF2 is larger than in skeletal muscles)
- 12) **ASEA-rs new increased daily dose.** Given the encouraging CK-MB serum level decrease of ~50% (as determined on **April 17th 2018**) I have transmitted to the family (without a new clinical consult until May 17th 2018) my updated recommendation to increase the ASEA-rs dose to 50+40+0ml/day (for a daily dose of 90ml/day, which is equivalent to ~6.5ml/body_kg/day) from April 18th 2018 until August 1st 2018. I
- a. I have also recommended a **new set of laboratory exams for the last week of July 2018:** AST, ALT, GGT, CK, CK-MB and MG serum levels.
- 13) **The last consult (up to present) from May 17th 2018.** The last consult (up to present) was on **May 17th 2018** (for routine checkup), when the boy was **~3 years old.**
- a. **Physical examination.** Normal extension of the right limb (when walking), **calves pseudohypertrophy (with ~23/23cm maximum circumference of both calves), no apparent tonus deficit of the axial/spinal muscles, no anxiety at the physical exam, no agitation, slight language delay (he uses ~30 correctly pronounced words at this age, but he builds true sentences using verbs and some simple phrases).** The rest of the physical examination exam results were normal: cranial nerves tests in normal limits, normal breath rate and pulmonary sounds, normal heart rate (with no heart murmurs), normal abdomen (without clinically detectable hepato/splenomegaly), but with **increased consistency stools (with defective discomfort),** normal diuresis and urination (with no kidney pain/sensibility), normal genital apparatus. **Body mass: ~14.1kg** (Age: 3 years) (in the normal range for sex and age). **Body height: 93.5cm** (Age: 3 years) (in the normal range for sex and age).

14) Discussions. Given the small age of the boy, the small number of signs/symptoms up to present, the fact that there is no “cut-off” exon number for a dys-gene mutation to exactly predict when an affected boy will develop a DMD phenotype and when he will develop a BMD phenotype (additionally, in 1990 England et al. even noticed that a patient with mild Becker muscular dystrophy was lacking 46% of his coding region for dystrophin [\[URL\]](#)), the diagnosis of DMD isn’t 100% sure yet; however, the severe form of MD of his maternal uncle (with loss of walking from 7 years of age until his death at 18 years of age) indicates this boy’s **duplication of the nucleotide number 7547 from 52nd exon of dys-gene** (which is probably shared with his maternal uncle and surely inherited from his maternal grandmother [also mother of his maternal uncle]) will more probably generate a DMD phenotype and that is why I have decided to start an aggressive therapy with ASEA-rs at least one year before the age of 4 years (when he was temporized to begin a corticosteroid treatment or other treatment like [ataluren](#) or even experimental treatments with AONs or stem cell [pericytes] replacement therapy)

- a. **The significant decrease of both CK and CK-MB serum levels (with ~28% and 50% respectively) may be explained by an important decrease of the oxidative stress in DMD myocytes: this effect may be produced by ASEA-rs via NRF2 pathway (an effect more pronounced in myocardium than in skeletal muscles, due to NRF2 higher concentration in the heart muscles versus skeletal muscles).**
- b. As ASEA-rs was not associated with any raise in AST/ALT (implying that ASEA-rs has no detectable liver toxicity) in prof. Nieman’s 1st metabolomics study (see pages 20 and 21 from [URL-ASEA-rs first metabolomics study](#)), **it is improbable that the increase of ALT serum level by ~28% (observed in this ~3years DMD boy) to be caused by ASEA-rs through liver toxicity.** ASEA-rs was demonstrated to be an inducer of apoptosis in damaged cells in vitro, so it is possible that the observed increased ALT serum level to be produced by a raise in apoptosis rate of skeletal (and possibly myocardial) myocytes: the increased apoptosis rate may be concomitant to an increase rate of new myocyte production (which may co-explain the decrease of CK and CK-MB, secondarily to the important decrease in the DMD myocytes plausibly produced by ASEA-rs).
- c. **The future extensive set of laboratory exams I have scheduled in the last week of July 2018 will surely clarify this observed increase in ALT serum level (from April versus January 2018).**

15) New possible future studies based on this specific DMD case treated with ASEA-rs.

- a. Given its clinical and biological effects in this DMD child case and its “prototype” selective NRF2 activator features, ASEA-rs and all the other known NRF2 activators may be tested in DMD and BMD patients (in future blinded [b] [randomized controlled trials](#) [bRCTs]).
- b. RCTs on NRF2 activators versus steroids in DMD/BMD cases (started before OR after 4 years of age) may also be conducted.

16) Final conclusions (at this stage of observation).

- a. **The significant decrease of both CK and CK-MB serum levels may be explained by a (significant) decrease of the oxidative stress in DMD myocytes, a decrease produced by ASEA-rs via NRF2 pathway (and more pronounced in the myocardium).**

17) Important note. I shall periodically update this paper with fresh information on DMD, ASEA-rs and this specifically DMD case.

IV. References were already integrated as URLs in the paper