A Second Case Report Regarding the Effects of "ASEA redox Supplement" in a ~5-year old boy with Duchenne Muscular Dystrophy from Bucharest, Romania (preprint)

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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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Abstract

This paper argues that "ASEA redox Supplement" (**ARS**) may show comparable or even stronger beneficial effects (with less or none adverse effects) than corticosteroids in children with Duchenne Muscular Dystrophy (**DMD**) and Becker muscular dystrophy (**BMD**). This paper presents a second case report on the effects of an ionized "saline water" called "ASEA redox Supplement®" (**ARS**) oral solution in a ~5-year-old boy with DMD from Bucharest, Romania. *In vitro* studies showed that ARS is a very potent selective NRF2 activator, thus a very potent (indirect) antioxidant and cytoprotective: the studies conducted *in vivo* also support this main pharmacological mechanism of ARS, with no toxicity up to high doses, in contrast with the much more toxic corticosteroids.

From the first months of ARS treatment the main rhabdomyolysis markers (with very high initial serum levels) dropped significantly, with no found toxicity until present.

The main conclusions of this second case report (on ARS effect in boys with DMD) are:

(**1**) ARS has remarkable antioxidant and immunomodulatory effects and should be studied on larger groups of children with DMD under the age of 4 years old (but also on other age groups of children and even young adults), as an alternative to early corticosteroids;

(**2**) Given its immunomodulatory effect (NRF2 selective activation and NF-kB inhibition), ARS deserves future cohort studies on its potential to replace corticosteroids and other non-steroidal immunosuppressants (at least partially) in many types of pulmonary/renal/hepatic/ articular/skin autoimmune and even malignant diseases of both children and adults;

(**3**) Given its very strong antioxidant effects (by highly selective NRF2 potent activation), ARS deserves future cohort studies on acute/chronic diseases that imply high levels of tissular oxidative stress, especially some acute/chronic cardiovascular and respiratory diseases like acute myocardial infarction with acute/chronic heart failure, stroke, Chronic Obstructive Pulmonary Disease (**COPD**), asthma etc. of both children and adults (so that ARS may help millions and even billions worldwide).

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For an introduction to DMD, NF-kB, NRF2, ARS and the 1st case report on ARS effects in DMD see the main reference of this paper [1,2]. All the essential aspects of this 2nd case report on ARS effects in DMD are included in the next table.

Table 1. The essential aspects of this 2nd case report on ARS effects in DMD

PEDIATRIC CONSULTS by Dr. Andrei-Lucian Drăgoi	Anamnestic and clinical essential aspects of this case	Paraclinical essential aspects of this case	Management -- essential measures recommended by dr. Dragoi
Consult no. 1 by dr. Dragoi on 9.12.2018 (home consult)	**Age**: 4 years & 8 months (**birth date**: 17.03.2014) **Sex:** male **Location:** Bucharest, Romania * **Diagnosis**: Duchenne muscular dystrophy (**DMD**) (genetic testing in November 2011 with DMD genotype confirmation in February 2017) * **Anamnesis**: - last neurologic consult in January 2018 at Clinical Hospital "Prof. Dr. Alex Obregia" - Pediatric Neurology Department (Bucharest, Romania) - parents refused oral corticoids (**OCs**) when proposed by the neurologist for their body with DMD and requested me a pediatric consult for an adjuvant therapy alternative to OCs with fewer or none adverse effects; -mother with gestational diabetes diagnosed in the 2nd trimester of this carriage (with normal glycemic levels after giving birth to this DMD boy) -up-to-date vaccine status * **Clinical aspects (the essentials)**: **Body mass (BM)**: ~15 kg (percentile ~25: under average, but normal BM) **Body exam**: loss of muscular strength (predominantly in axial muscles and lower limbs), pseudohypertrophy of calf muscles, low endurance, positive Gower's sign (clearly demonstrating weakness of the proximal muscles of the lower limbs); normal cranial nerves, normal intellect; **Previous treatment (until 9.12.2018) (all given at the initiative of boy's parents)**: Vitamin C (~100 mg/day), Coenzyme Q_{10} (120 mg /day), hemp oil with 1.35% Cannabidiol	**Genetic test result (Nov. 2016-Feb. 2018; Age:~4 years)**: hemizygous duplication of all exons from 8th to 43rd of dystrophin gene (dys-gene) which is a relatively rare type of (DMD) dys-gene mutation accounting for ~5% of the total known number of DMD cases [URL1, URL2] which duplications can be detected by multiplex ligation-dependent probe amplification (**MLPA**) screening of the dys-gene; the boy's mother was also demonstrated to carry exactly the same exons duplication; * **Heart ultrasound (selection) (Age: 3 months)**: large stenosis of the right pulmonary artery with no hemodynamic significance, thus no clinical signs * **LABS (11.10.2014)**: **Hgb: 14.5 g/dl;** **ASAT serum level: 279 U/l** **ALAT serum level: 285 U/l** **GGT serum levels: 8 U/l** (within the normal range for age and sex) * **LABS (2.11.2016)**: **CK serum level: 27 609 U/l** **CK-MB serum level: 704 U/l** **LDH serum levels: 4572 U/l** (a non-specific marker for tissular damage, including rhabdomyolysis, especially myocardium damage) **GGT serum levels: 10 U/l** (within the normal range for age and sex)	**-initial account for rhabdomyolysis markers** (CK, CK-MB, ASAT, ALAT, serum MG) **and specific liver toxicity marker** (GGT) (additionally to ASAT and ALAT which are non-specific for liver) **BEFORE starting ARS P.O.** and also the evaluate any possible (although improbable) paraclinical impact of all dietary supplements given to this DMD boy by his mother until December 2018 (HOWEVER, this initial labs checkup proposed by dr. Dragoi was refused by parents) * **-CK and CK-MB screening** for boy's healthy mother (carrying the dys-gene exonal duplication) and elder sister (a screening ALSO refused by parents) * **-starts ARS P.O. 30+30+0 ml/day (=60 ml/day ~ 4 ml/body_kg/day) from January 2019** (initiated from Jan 219 as indicated): the two 30 ml fraction should be administered before meals (and at least on 30 ml fraction before a physical therapy session); **after 1 month of ARS P.O., the daily dose may be increased to 60+30+0 ml/day (=90 ml/day ~ 6 ml/body_kg/day)** * **-discontinue vitamin C** (as it may interfere with ARS mechanism, as vitamin C may partially or totally neutralize the free oxygen radicals (**FORs**) contained in ARS, which FORS may not reach anymore the intracellular medium and thus may not accomplish NRF2 selective activation) * - may continue Coenzyme Q_{10} at the same dosing as previously applied: 120 mg /day * -may continue hemp oil at the same dose (5 ml/day) (as ARS stimulates the metabolism of fatty acids which lipid metabolism is also fueled by this hemp oil) * -(optionally) may continue omega-3 dietary supplement at the same dose (1

	(**CBD**) concentration (5 ml/day), omega-3 dietary supplement (1 capsule x 3/day), laminin dietary supplement (1 capsule/day), a brain/memory stimulating dietary supplement (containing a mix of: UMP, a bitartrate salt of DMAE, Acetyl-L-carnitine, Vinpocetine, Alpha-GPC and standardized extracts of Huperzine A, Ginkgo biloba, Ashwagandha and Wild Blueberry), homeopathic remedies, acupuncture sessions * **Specific clinical test results**: North Star Ambulatory Assessment (**NSAA**) **score** (**Jan 2018**): 17 points, which represent 50% of the maximum possible score of 34 points. **The 6-minute walk test (6MWT)** (**Jan 2018**): **the 6-minute walk distance (6MWD)** 292 meters (**m**), without any stops, falls and no need for any external physical support during testing. **Important note.** According to a multicenter study published in 2013 [URL1, URL2], a baseline 6MWD<350 m was associated with greater functional decline: loss of ambulation was observed only in the group with baseline 6MWD <325 m.		capsule x 3/day) and laminin dietary supplement (1 capsule/day); * - (optionally) may continue the naturist brain/memory stimulating dietary supplement (see **Paraclinical essential aspects column**) * - (optionally) may continue homeopathic remedies and acupuncture sessions (presuming that these treatments won't decrease the predicted efficiency of ARS in decreasing the rhabdomyolysis markers) * -continues physical therapy sessions (1 hour/ session, 2 sessions/week) (including special stretching exercises) -also home physical therapy daily sessions (30-45 minutes/session and even 2 sessions/day when starting ARS P.O.) * -continues therapeutic swimming (hydrotherapy) sessions (45-60 minutes/ session; 2 sessions/week) * -annual neurologic consults * -annual heart ultrasound * - while under ARS P.O., repeat North Star Ambulatory Assessment (**NSAA**) and the 6-minute walk test (**6MWT**) each 6 months

Consult no. 2 by dr. Dragoi (23.07.2019) (short online consult for minimal anamnesis and labs reading)	**Age**: 5 years & 4 months (**birth date**: 17.03.2014) * **Anamnesis**: -meals with a high percentage of raw fruits and vegetables, gluten-free and sugar-free aliments, milk derivates; - after: ~7 months of **ARS** P.O. 60 ml/day (~4 ml/body_kg/day from January 2019 until present), physical therapy sessions (1 hour/ session, 2 sessions/week, from Feb. 2018 until present), therapeutic swimming (hydrotherapy) sessions (45-60 minutes/ session; 2-3 sessions/week; from the summer 2018 until present), ***Vitamin C** (1g/day in the interval [**iti**] 9.12.2018-31.01.2019), **Coenzyme Q10** (250 mg/day iti 15.02.2019-15.04.2019), ***L-carnitine** (340 mg/day iti 15.02.2019-15.04.2019), ***whole-grain lipids and sterols supplement** (1 cps/day iti 01.02.2019-15.05.2019), ***homeopathic remedies** (iti 01.02.2019 – present), *Milena fungus tincture (10 drops x 2/day iti 01.02.2019 – present), *Calcarea carbonica (2 granules/day, 7 days / month iti 9.12.2018-31.01.2019), *Kal-Mag plus D (iti 01.02.2019-15.05.2019), *"Liquid Gold"® omega-3, 6, vitamins K2 (its MK-7 subvariant), *D3 (1/2 teaspoon/day iti 21.03.2019 - present), *"Laminine"® oral supplement (produced by Lifepharm® and containing laminin) (1 cps/day iti 15.05.2019 – present), *"Laminine Immune +++"® oral supplement (produced by Lifepharm® and containing laminin, Polysaccharide Complex and Reishi, Maitake and Turkey Tail Mushrooms [URL1, URL2]) (1 tablet/day iti 15.05.2019 – present), *raw bee pollen (5 ml/day iti summer 2018 - present), hemp oil with	**LABS (11.03.2019) (after ~3.5 months of ARS P.O. 60 ml/day (~4 ml/body_kg/day):** **Hgb: 13.8 g/dl;** **ASAT serum level: 213 U/l** **ALAT serum level: 264 U/l** **CK serum level: 8979 U/l** **CK-MB serum level: 295 U/l** **LDH serum levels: 806 U/l** **GGT serum levels: 10 U/l** (within the normal range for age and sex) ASLO: 317 IU/ml Ferritin: 87 ng/ml	**-continues ARS P.O. 30+30+0 ml/day (=60 ml/day ~ 4 ml/body_kg/day); the ARS dose may optionally be increased to 60+30+0 ml/day until the last week of August 2019, when the next pediatric consult is scheduled** * -may continue hemp oil at the same dose (5 ml/day) (as ARS stimulates the metabolism of fatty acids which lipid metabolism is also fueled by this hemp oil) * -(optionally) may continue omega-3 dietary supplement at the same dose (1 capsule x 3/day) and laminin dietary supplement (1 capsule/day); * - (optionally) may continue homeopathic remedies and acupuncture sessions (presuming that these treatments won't decrease the predicted efficiency of ARS in decreasing the rhabdomyolysis markers) * -continues physical therapy sessions (1 hour/ session, 2 sessions/week) (including special stretching exercises) -also home physical therapy daily sessions (30-45 minutes/session and even 2 sessions/day when starting ARS P.O.) * -continues therapeutic swimming (hydrotherapy) sessions (45-60 minutes/ session; 2-3 sessions/week) * -annual neurologic consults * -annual heart ultrasound * - while under ARS P.O., repeat North Star Ambulatory Assessment (**NSAA**) each 6 months and the 6-minute walk test (**6MWT**) each month

	1.35% Cannabidiol (**CBD**) concentration (5 ml x 3/day iti summer 2018 - present) (*all these marked treatments were administered by parent's own initiative) - hasn't repeated NSAA and 6MWT from 9.12.2018 until the date of this online consult by Dr. Dragoi (23.07.2019) - the mothers states that her boy "can walks for ~1 hour [almost without any pause]" - the mother states that her boy was given ARS 60 ml/day from Jan 2019 until present (23.07.2019) - the mother states that her boy also continues physical therapy, hydrotherapy and acupuncture		
Meeting no. 3 by dr. Dragoi (29.07.2019)	**Age**: 5 years & 4 months **Note**. The purpose of this scheduled meeting was to perform the 6MWT on a professional stadium. * **Important note:** On 29.07.2019 we've found the proper technical conditions for this boy to repeat the **6MWT** for the 2nd time (after the 1st 6MWT from January 2018). * **Technical condition description**: we had access to a professional stadium with multiple 60-meter plane tracks covered with anti-shock rubber. * **6MWT result**: In the first ~ 4 minutes (**min**), the boy walked 4 tracks (of 60 m each), thus a total distance of 240 m (=60 m * 4), with an average speed of 1 track/min=60 m/min. The boy fell down at minute 4:18 (when we has at his 5th track): after a pause of about ~20 seconds (when he was encouraged by his mother) he restarted the walk so that he accomplished ~5.3 tracks (~320 m) in 6 minutes (which is better than the 6MWT result of 294 m from January 2018, if not considering that fall). After the 6 minutes, the		**Important note**. This 6MWT (from 29.07.2019) results should be carefully interpreted as possibly falsely lower, because the boy's mother had the initiative (2 days before this 6MWT) to test the child at home on a corridor of ~9.45 m in length saying that he had walked 38 tracks in 6 minutes, which means ~359 m (without falling). As this track was too short (9.45 m), this previous 6MWT could have a falsely lower result possibly caused by slowing down more often at the ends of this corridor. A result >350 m is considered a good result (and obviously better than the 294 m result of the 6MWT from January 2018). It is known that, to be reliable, a 2nd 6MWT should be repeated after at least 1 week from another previous one. The mother told me about that 1st (2 days before) 6MWT and I assumed to repeat the 6MWT again, with the risk of getting a falsely lower result and that is because organizing this 6MWT on a professional stadium was a chance for this child not to be missed. * **Observation 2**. We consider this 6MWT result from 29.07.2019 a reasonable one, given the fact that there is a recent study [URL] showing that 6MWT wouldn't necessarily bring more information than a 2-minute walk test (**2MWT**) if the child sustains a good walk speed of >50 m/min in the first 2 minutes, then he is very probably capable of maintaining a

	boy wanted however to continue the test so that he accomplished ~5.6 tracks until minute 6:20 (considering the 20 seconds of initial pause). The boy had finished 6 tracks (360 m) in ~6 minutes and 55 seconds.		comparable speed in the next 4 minutes. The 6MWT from 29.07.2019 can be regarded as a two-stages test composed from a 4-minute walk (sub-)test (**4MWT**) and a 2MWT, "coupled" to one another by that after-fall 20 seconds pause. * **Recommendation**. The boy was scheduled to repeat the 6MWT monthly (two tests departed by at least 5-6 days in the first week of each month)

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Results and Interpretations

1. The ARS-based treatment in the first ~3.5 months (from a total of 8 months of ARS po: from the ~middle of January 2019 until present) was associated with:
   - **a.** ***** *a slight ALT serum level total decrease* of **~8%** (from **285 U/l** [on 11.10.2014, the last determination before starting ARS] to **264 U/l** [on 11.03.2019])
   - **b.** ***** *a significant AST serum level total decrease* of **~31%** (from **279 U/l** [on 11.10.2014, the last determination before starting ARS] to **213 U/l** [on 11.03.2019]) (with **normal GGT serum levels** from 11.10.2014 [**8 U/l**] until 11.03.2019 [**10 U/l**], thus no detectable liver toxicity of ARS at least in the Jan-March 2019 interval)
   - **c.** ***** a *marked CK serum level total decrease of* **~307%** (from **27 609 U/l** [on 2.11.2016, the last determination before starting ARS] to **8979 U/l** [on 11.03.2019])
   - **d.** ***** *a very significant CK-MB serum level decrease of* **~239%** (from **704 U/l U/l** [on 2.11.2016, the last determination before starting ARS] to **295 U/l** [on 11.03.2019])
   - **e.** ***** *a spectacular LDH serum level (*a non-specific marker for tissular damage, including rhabdomyolysis, especially myocardium damage*) decrease of* **~567%** (from **4572 U/l** [on 2.11.2016, the last determination before starting ARS] to **806 U/l** [on 11.03.2019])
   - **f.** (all * markings): under the reserve that boy's mother refused to determine all the rhabdomyolysis markers immediately before the initiation of ARS P.O.: additionally myoglobin (**MG**) serum/urinary level was never determined by the mother and never specifically requested by any doctor except dr. Drăgoi;
   - **g.** These significant decreases of the (previously) listed rhabdomyolysis markers (especially CK, CK-MB and LDH) may be explained by the fact that **ARS has strong global NRF2 activation effect (on all types of muscles/myocytes) and a very strong NRF2 activation effect on the myocardium**, where the expression of NRF2 is larger than in skeletal muscles, an additional indirect subtle potential "proof" that ARS acts via NRF2 pathway). These results suggest that *ARS may have very potent muscular (including myocardial) protective effects* (the basis of which *we propose the study of ARS on large cohorts with acute or chronic cardiac diseases*), *significantly limiting the muscular damage in DMD patients, with the potential of even stronger effects in (milder) BMD phenotypes*: this comes in the "same pack" with *no liver toxicity, no adverse effect on growth and development of the child* and *no other adverse effects* in other clinical spheres until the present.
   - **h.** For extensive **interpretations** of ARS effects in these two DMD cases (published by the author) see reference [1] (section "*Results and Interpretations*").
   - **i.** The next labs are scheduled in the last week of August 2019 and are still under work.

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Discussions

1. For previous extensive discussions on ARS effects in these two DMD cases (published by the author) see reference [1] (section "*Discussion*").

2. **Pathophysiology**. The pathological mechanisms of DMD are generally complex and dramatic: the main hallmark of DMD is a very high oxidative stress (**OS**) level in DMD-phenotype myocytes including cardiomyocytes (leading to chronic muscle inflammation, repeated cycles of degeneration and impaired muscle regeneration) [URL1, URL2, URL3, URL4, URL5, URL5, URL6, URL7, URL8, URL9, URL10, URL11, URL12, URL13, URL14, URL15, URL16]
   - **a.** OS is two sided: whereas excessive OS causes intracellular molecular damage, maintenance of a physiological level of oxidant challenge (mainly by superoxide molecules generation), termed "oxidative eustress" (**OES**), is essential for governing life

processes through redox signaling. “Redox balance is maintained by prevention, interception, and repair, and concomitantly the regulatory potential of molecular thiol-driven master switches such as NRF2/Keap1 or NF-κB/IκB is used for system-wide OS response. Non-radical species such as hydrogen peroxide (H_2O_2) or singlet molecular oxygen, rather than free-radical species, perform major second messenger functions. Chemokine-controlled NADPH oxidases and metabolically controlled mitochondrial sources of H_2O_2 as well as glutathione- and thioredoxin-related pathways, with powerful enzymatic back-up systems, are responsible for fine-tuning physiological redox signaling. This makes for a rich research field spanning from biochemistry and cell biology into nutritional sciences, environmental medicine, and molecular knowledge-based redox medicine.” [URL1, URL2, URL3].

b. ARS contains both superoxide and H_2O_2 species (in small concentrations<1%) and not only hyper-activates NRF2, but also "injects" cells with various free radical species, thus keeping OES while preventing a possible cytotoxic reductive stress (**RS**): that is what makes ARS unique from all known natural/artificial antioxidants; in contrast, common antioxidants may easily induce RS when given/administered in excess or when too strongly activating the NRF2 pathway [URL1, URL2, URL3, URL4, URL5, URL6, URL7, URL8] (although there may be cases in which a slight RS may prevent OS: see URL). **More specifically**, even if ARS is a solution in which there is a relatively good redox balance between free oxidant species (**FOS**) and free reductive species (**FRS**), ARS has an ~3-4 acid ph (as its superoxide and other FOS slightly predominate over FRS). The direct antioxidant effect of ARS is probably low, although "injecting" ARS in a cell under oxidative stress actually (and at least partially) restores the balance between FOS and FRS in that cell. In the same time FOS from ARS strongly (and very selectively) activates NRF2 and all the endogenous antioxidant enzymatic systems controlled by NRF2: apparently this may lead to RS, but this probably does not happen in case of ARS just because ARS ALSO “injects” cells with some additional FOS (which probably remain partially non-neutralized by endogenous antioxidant systems) and that is unique among all direct antioxidants and among all known NRF2 activators. In a cell under high OS, ARS strongly lowers the global oxidative level/potential from/of that cell (not mainly by direct mechanism, but mainly by NRF2 activation and consequent endogenous antioxidant enzymes genetic overexpression) and in the same time "injects" additional FOS species in the cell, thus preventing reductive stress. It is true that ARS also "injects" FRS in that same cell, but those FRS are in minority (when compared to FOS predominance in ARS). **Prudence is however advised so that ARS should be administered in progressively higher doses (correlated with the body mass of the patient) so that to effectively treat OS without causing RS: (explanation 1) RS may have also caused the slight re-increase of ASAT, ALAT, CK and CK-MB (in the last 8-9 months) in the 1st published case of an ARS-treated boy with DMD [1]**; **(explanation 2)** another possible explanation for this slight re-increase (of those rhabdomyolysis markers) may be an autoimmune response to a possible increase in the number of normal dys revertant fibers (plausibly induced by ARS) to which organisms with DMD phenotypes (**DPs**) haven’t normally gained an immune tolerance because the low levels of normal dys in these DPs (a phenomenon already demonstrated after exon-skipping therapy in a mdx mouse model: see URL). Furthermore, there is a very high variability between human individuals in their cellular response to physical exercise (**PE**) (aka “redox individuality”): because ARS grossly contains the same redox molecules that are usually produced in cells by PE, the response to ARS is also expected to be very variable (concerning the possible induction of OS and/or RS) in general, and even more variable in DMD cases in which there is a very large spectrum of possible dys gene mutations (affecting dys structure and functions in the human cells). **Given its uniqueness in possibly preventing RS, ARS should replace common antioxidants in all those past studies (which should be redesigned by including ARS) in which those tested antioxidants or NRF2 activators were demonstrated to not help and even to induce RS.**

c. The spectrum of diseases (including genetic syndromes) which have an important component of acute and/or chronic OS is immense, that is why ARS has a significant potential to help in all these diseases, and that is why ARS deserves systematic extensive studies in many diseases from this OS-centered spectrum of diseases.

d. ARS is such a potent indirect antioxidant (via NRF2 pathway) that it can be also used as a research tool to indicate/verify if any disease has a significant oxidative stress component or not: for example, the significant decrease of all rhabdomyolysis markers (when under ARS P.O.) in these published cases of DMD clearly indicates that DMD has an important oxidative stress component. More specifically, ARS can be administered in any clinical case even when no

specific/exact diagnostic is known: if there will be any clinical or paraclinical amelioration in that clinical case with unknown diagnosis, then OS is probably one important link in the pathophysiology of that unknown/undiagnosed disease.

3. **Additional lab/imaging and other tools for studying DMD cases treated with ARS**. Impaired muscle regeneration is a hallmark in DMD, that is why several indices of regeneration (centronucleation, fibre size, embryonic myosin, utrophin serum levels [URL]) can also be measured in ARS-treated DMD/BMD cases.
   - **a.** LDH [URL2], which is expressed extensively in almost all body tissues: it is released from the intracellular medium during tissue damage, it is a marker of common injuries and disease such as muscles damage (from DMD/BMD), heart failure etc. [URL1a, URL1b, URL2, URL3, URL4, URL5]
   - **b.** Diaphragm ultrasonography may also be used in the future as a practical non-invasive assessment of the diaphragm function in ARS-treated DMD cases [URL].
   - **c.** Various questionnaires and scores can be used to quantify the quality of life in children and adults with DMD [URL].
   - **d.** FORT [URL2] and FORD [URL2] tests may also be used to periodically monitor the antioxidant properties in any ARS-treated patient (not only in ARS-treated DMD/BMD patients).
   - **e.** hand-held myometry [URL1, URL2, URL3, URL4, URL5]
   - **f.** 6 Minute Walk Test [URL2] (**6MWT**) [URL1, URL2a, URL2b, URL3, URL4a, URL4b, URL5, URL6, URL7, URL8, URL9, URL10, URL11] and its 2MWT variant (URL1)

4. **Additional diets and molecules which may have synergic effects with ARS**. Possible synergic combinations between ARS and other therapeutic molecules also deserve extensive studies:
   - **a.** Various diet-charts for DMD patients [URL]
   - **b.** Specific physical therapies [URL]
   - **c.** creatine monohydrate (URL)
   - **d.** simvastatin (URL1, URL2)
   - **e.** N-acetylcysteine (**NAC**) (URL; ARS may even be studied in combination with [or as a replaces of] NAC in paracetamol/acetaminophen intoxication/poisoning, because, similarly to NAC, ARS also increases the concentration of glutathione in all cells, including hepatocytes by activating glutathione synthase via NRF2 pathway)
   - **f.** melatonin [URL]
   - **g.** Medical laser [URL]
   - **h.** SIRT1 activators [URL]
   - **i.** Protandim® (a NRF2 activating combination of herbal dietary supplements) [URL]

5. **Other potential uses of ARS**.
   - **a.** Given the spectrum of NRF2 cellular/tissular different concentrations (kidney > muscles > lungs > heart > liver > brain), ARS (as a very efficient NRF2 activator with excellent bioavailability in all these listed vital organs) has a significant therapeutic potential in renal, hepatic, pulmonary, heart, liver and even brain infectious and/or inflammatory and/or degenerative diseases (possibly also including mental disorders like depression, anxiety etc). Given that kidneys have the highest NRF2 tissular concentration, ARS deserves a special focus in studying the treatment with ARS PO in various nephrologic/kidney disease like: various types of (progressive) glomerulonephritis, nephrotic syndrome, urinary tract infections (**UTIs**) (especially pyelonephritis), chronic kidney disease (**CKD**) and even hemolytic-uremic syndrome (**HUS**), so that to prevent renal scaring or other possible mild or serious complications of these kidney diseases.
   - **b.** Given its "hybrid" antimicrobial and anti-inflammatory effects (plus its demonstrated stability in nebulized form), ARS deserves extensive studies on its possible capacity to prevent airway tract infections similarly to inhaled antibiotics in recent specific studies on DMD patients with respiratory distress/insufficiency [URL]
   - **c.** ARS may be tested in various doses (2-3-4-5-..10 ml x 1-2-3/day) as adjuvant treatment with possible good results on pulmonary/airways inflammation (because of its anti-inflammatory properties via NRF2 pathway) and viral/bacterial infections (because of its direct bactericidal and virucidal properties).
   - **d.** Given its corticoid-like anti-inflammatory effects, ARS also deserves extensive studies (alone or in various combinations with inhalatory, oral or parenteral corticosteroids) in all diseases which usually respond to corticoids, like pulmonary sarcoidosis, primary or secondary pulmonary fibrosis, cystic fibrosis (because of its hybrid anti-microbial and anti-inflammatory mechanism), scleroderma with pulmonary determination (because ARS significantly diminishes chronic inflammation and thus may prevent fibrosis). The results may be even better when ARS nebulizations are associated with ARS consumption PO. Of course that ARS may be first tested on various mouse models of chronic pulmonary inflammation of various infectious, autoimmune, genetic and non-genetic diseases.
   - **e.** ARS may also have some interesting effects on extracellular matrix (**EM**) and interstitial (stromal) cells (**ICs**), especially on telocytes, which are a novel defined type of ICs (in the field of stem cells), with very long

(tens to hundreds of micrometres) and very thin prolongations called "telopodes": these telopodes present an alternation of thin segments called "podomeres" (with caliber mostly < 200 nm, below the resolving power of light microscopy) and dilated segments called "podoms", which accommodate a relatively large number of mitochondria (on which ARS was proven to have some significant effects via NRF2 pathway but also via other genetic pathways [see the 1st published case on ARS effects in DMD]), (rough) endoplasmic reticulum and caveolae - the so-called "Ca2+ uptake/release units".

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Final conclusions

1. ARS is plausibly the strongest (artificial) NRF2 selective activator ever produced by humans in a lab: that is why ARS may be regarded as a very important discovery in redox medicine and human/animal medicine/biology in general.
2. ARS effects in DMD patients appear to be reproducible, because the response to ARS is quite similar in both these published ARS-treated DMD cases: that makes ARS a very promising new strategy in DMD and BMD treatment/management. Furthermore, we predict that ARS effects in BMD patients (which have a less affected phenotype) may be even more spectacular.
3. Obviously, further extensive studies are needed to better understand the cellular effects of various ARS dosages and ARS combinations with other (possibly synergistic) therapeutic molecules/drugs.
4. ARS therapy is significantly more expensive than corticosteroids but ARS therapy has the advantage to have zero toxicity (in principle) and to be significantly less expensive than ataluren or exon skipping therapy for example.

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2. **Author contributions:** The conceptualization, data curation, formal analysis, investigation, methodology, project administration, software (used for keeping the evidence of all patients, including this boy), supervision, validation, visualization, writing (the original draft plus review & editing) were all done by dr. Andrei-Lucian Drăgoi, the single author of this article. Funding acquisition and resources were mainly supported by the parents of this boy and secondarily supported by RNHIS; we have also obtained the oral consent of the mother to publish this medical case in both English and Romanian, with the only condition to not mention the names of the boy, parents or other relatives;
3. **Competing interests:** the author of this paper was invited a couple of times to present ARS and his clinical experience with ARS, but with no financial remuneration and no competing interests.

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References

(some of the references were already included as URLs in the text)

[**1**] Andrei-Lucian Drăgoi (July 2019). (ASEA in DMD - CJBRT article - 20.07.2019) **The Remarkable Effects of "ASEA redox Supplement" In A Child with Duchenne Muscular Dystrophy – A Case Report,** Canadian Journal of Biomedical Research and Technology (CJBRT) 2019; volume 1, issue 4:8. URLs: URL1a, URL1b, URL1c (CJBRT original sources); URL2a (Research Gate source); URL2b & URL2c (Academia sources); URL2d (Vixra source); URL3 (Research Gate **preprint** source).

[**2**] Andrei-Lucian Drăgoi (May 2018). (ASEA in DMD preprint – version 1.1 – 1.08.2018 – 13 pages) **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**. Research Gate preprint. DOI: 10.13140/RG.2.2.21420.36486. URL (Research Gate source). The article based on this preprint was published in July 20th, 2019 under the title "**The Remarkable Effects of "ASEA redox Supplement" In A Child with Duchenne Muscular Dystrophy – A Case Report"** in the Canadian Journal of Biomedical Research and Technology (**CJBRT**) 2019; volume 1, issue 4:8. URLs: URL1a, URL1b, URL1c (CJBRT original sources); URL2 (Research Gate source)