Environmental diseases, oxidative stress and genetic polymorphism

Francesco Cosentino, MD *
Maria Concetta Giuliano, GP #
Fabio Biscichia GP Trainee #

* Gastroenterology and Hepatology Dept -
Milton Keynes G.H. - NHS FT UK
# General Practice NHS - Sicily Italy
Enviromental Diseases
Sensitivity Related Illnesses (SRI)

Adverse clinical states elicited by exposure to low dose of enviromental phisical, chemical or biological factors mainly xenobiotic chemicals drugs and metals

Multiple Chemical Sensitivity (MCS)

Crhonic Fatigue Syndrome (CFS) / Myalgic Encefalomyelitis (ME)

Fibromyalgia (FM)

Electromagnetic Hypersensitivity (EHS)
~ 15–30% of USA population exhibit milder forms of chemical hypersensitivity

~ 3% of Canadians have been diagnosed with environmental sensitivities

~ 3–4% of Americans suffers with severe forms of chemical sensitivity

Comparable data in other countries such as Germany, Sweden, Netherlands
Sensitivity Related Illness (SRI)

The marked similarity of symptoms may support common organic etiological biomarkers of disease.

Clinical overlapping of the different syndromes which may represent separated clinical settings sharing some common molecular pathways.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM) and Multiple Chemical Sensitivities (MCS) in Quebec

MCS = 170,991

ME/CFS = 91,962

FM = 75,742

Total reporting one or more diagnoses = 297,953
Sensitivity Related Illness (SRI)

Clinical data prove that functional or genetic defects may cause chronic oxidative stress and consequent metabolic and immunologic alterations characteristic for the patients with enviromental SRI.

Emerging model of disease etiology

Gene polymorphism phase I/II
Detoxification enzymes gene
Free radical antioxidant
Homeostasis disturbances
Epigenetic and metabolic factors

Phase I and phase II reactions

**PHASE I**
- Expose or add functional group
- Oxidation
- Reduction
- Hydrolysis

**XENOBIOTIC** → **PRIMARY PRODUCT**

**PHASE II**
- ROS
- Conjugation

**SECONDARY PRODUCT**

**EXCRETION**

**LIPOPHILIC**  →  **HYDROPHILIC**
Gli enzimi antiossidanti

- I radicali liberi sono alla base del danno che caratterizza molte situazioni fisiopatologiche.

I più importanti ROS sono:
- anione superossido $O_2^-$
- perossido d'idrogeno $H_2O_2$
- radicale ossidrilico $\cdot OH$

- **Superossido-dismutasi**
- **Catalasi**
- **Glutatione perossidasi**
- **Glutatione riduttasi**

Converte l'anione superossido in $H_2O_2$:

$2O_2^- + O_2 \rightarrow R' + 2H_2O$
Nitric oxid - Peroxynitrite at the base of lipid peroxidation and epigenetic alterations
Peroxynitrite induced cytotoxicity


Fig. 1. Peroxynitrite-induced cytotoxic pathways. Nitric oxide and superoxide react to form peroxynitrite which damages cells via various damaging effects such as lipid peroxidation, inactivation of metalloenzymes and other proteins by oxidation and nitration. Peroxynitrite also acts on mitochondria triggering the release of proapoptotic factors such as apoptosis-inducing factor (AIF) and cytochrome c. These factors mediate caspase dependent and independent apoptotic death pathways. Moreover, peroxynitrite-induced DNA breakage activates PARP leading to NAD and ATP depletion and consequently to necrosis.
**Sensitivity Related Illnesses (SRI)**

Functional Changes in Genoma occur without a change in nucleotide sequence.

- **DNA Methylation**
- **Histone Modifications**
- **microRNAs**

**EPIGENETIC FACTORS**

**EPIGENETIC MECHANISMS**
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

**HEALTH ENDPOINTS**
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

**DNA methylation**
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histones are proteins around which DNA can wind for compaction and gene regulation.

Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
Sequelae of toxicant exposure induce loss of Tolerance (TILT) with consequent Allergy, Food Intolerance and Chemical Hypersensitivity.

After primary toxicant individuals become sensitive to low levels of diverse triggers in environment (chemical, inhalant or food antigens).

Cytokine levels in the blood plasma of control subjects ($C$, $n = 52$), and patients with diagnosed MCS ($MCS$, $n = 77$)

Inter-group significant differences ($P< 0.05$ or $0.01$) are reported under each panel.

MCP-1 (macrophage chemotactic protein), PDGF (platelet-derived growth factor), VEGF (vascular endothelial growth factor).

Metabolic redox parameters in the blood components

- control subjects (C 52)
- MCS Patients (MCS 133)
- Suspected MCS Patients (S-MCS 93)

GSH (glutathion reduced)
GPX (glutathion peroxidase)
GSSG ((glutathion oxidized)
NO2 (nitric oxide)
CL (luminol-dependent chemiluminescence)
AOA (anti-oxidant activity)

Co-morbidities registered in the MCS group (226) through evaluation of anamnesis. % of patients affected by each single category of organ pathologies.

Gastro-intestinal
Thyroideal
Allergies/intollerances
Respiratory
Cardiovascular

NO COMORBIDITIES

POSSIBILI IRRITANTI LUMINALI NELL’IBS

ACIDI BILIARI
Malassorbimento riportato nell’IBS
*Niaz 1997*
Possono indurre infiammazione colica
*Fernandez-Banares 2001*

ANTIBIOTICI
Associazione fra uso di antibiotici ed IBS nei bambini
*Mendall 1998*
Sviluppo di sintomi funzionali intestinali dopo uso di antibiotici
*Maxwell 2002*

MICROFLORA
Fermentazione colica anormale
*King 1998*
Ridotti coliformi e lattobacilli
*Balsari 1982*
Invasione batterica
*Swidinski 1999*

ALLERGENI ALIMENTARI
Elevata prevalenza di allergie alimentari nell’IBS
Allergeni alimentari inducono rilascio di mediatori della infiammazione intestinale
*Maluenda 1984*

GASTROENTERITI INFETTIVE
Fino ad 1/3 dei pazienti sviluppa IBS dopo una gastroenterite infettiva acuta
*Barbara 2002*
Working hypothesis on the role of low grade inflammation in the pathogenesis of irritable bowel syndrome.

- Previous gastroenteritis
- Genetic factors
- Food allergies
- Altered microflora

Gut 2002;51:i41-i44 doi:10.1136/gut.51.suppl_1.i41
CELLULE INFAMMATORIE NELLA MUCOSA COLICA DI PAZIENTI CON IBS

BARBARA ET AL, 2000

p<0.01

0 5 10 15 20 25 30 35
% DI CELLULE / AREA

CONTROLLI IBS

MASCHI FEMMINE
CELLULE INFiammatorie nella mucosa colica di pazienti con IBS: Mastociti

Barbara et al., 2000

% of cells / area

Ctrl

IBS

p<0.01

C

IBS

0

2

4

6

8

10

12

% of cells / area
AUMENTATA ATTIVAZIONE DEI MASTOCITI NELL’IBS

DEGRANULAZIONE DEI MASTOCITI

Barbara et al, 2000

N° MC DEGRANULATI/CAMPO

LIBERAZIONE DI ISTAMINA (ng/mg)

C IBS

6540

Barbara et al, 2000
INTERAZIONE TRA MASTOCITI E NERVI NELL’IBS

Barbara et al, Gastroenterology 2004

MC within 5 µm of nerves

* P<0.001

N° degranulated mast cells

r = 0.72
p = 0.002

N° mast cells < 5 µm to nerves
Severità del dolore addominale

Frequenza del dolore addominale

n° mastociti < 5 μm dai nervi

Barbara et al, Gastroenterology 2004
Nitric Oxide is a Unique Signaling Molecule

- The small size, lipophilic nature, and chemical lability of Nitric Oxide allow it to act as a unique signaling molecule.
- Diffusion of Nitric Oxide rapidly occurs across cell membranes without the need for cell surface channels.
- In target cells, Nitric Oxide directly activates intracellular enzymes, mainly guanylyl cyclase (sGC) which catalyzes the synthesis of cyclic guanosine monophosphate (cGMP) - a key second messenger that translates Nitric Oxide signaling into a physiologic effect.

Non-cholinergic non-adrenergic (NA-NB) neural mechanisms involving nerves containing NO have been showing to modulate smooth muscle in the gastrointestinal tract;

It has been suggested that release from tonic NO inhibition may be important in the regulation of cyclical fasting small intestinal motility (MMC)

Abnormalities of phase III activity (MMC) are frequently associated with clinical problems such as bacterial overgrowth or diarrhoea

Manipulation of small intestinal motility by NO synthase inhibitors (L-NMMA) applications induces premature intestinale phase III and may also have potential therapeutic effect

Gut 1999;44:72-76 doi:10.1136/gut.44.1.72
Figure 1
Manometric tracing showing example of early stimulation of phase III by 4 mg/kg/h L-NMMA. The position of the sensor is shown on the vertical axis (A, antrum; P, pylorus). Values are distance in cm from the pylorus in the duodenum and upper jejunum.
Motility

Evidence that nitric oxide mechanisms regulate small intestinal motility in humans

Table 1
Pressure waves per minute, velocity, duration and length of migration of phase III of the migrating motor complex during infusion of saline and three doses of L-NMMA

<table>
<thead>
<tr>
<th></th>
<th>L-NMMA (mg/kg/h)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>0.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Pressure waves per min</td>
<td>11.4 (11.1–12.7)</td>
<td>11.4 (10.8–11.8)</td>
<td>11.1 (10.7–11.5)</td>
<td>11.3 (10.7–11.8)</td>
</tr>
<tr>
<td>Velocity (cm/min)</td>
<td>7.7 (5–10.4)</td>
<td>10.3 (5–12.9)</td>
<td>6.7 (4.7–8.7)</td>
<td>5.5 (1.8–9.1)</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>6.0 (4.0–8.0)</td>
<td>7.4 (3.2–10.8)</td>
<td>5.7 (4.3–7.1)</td>
<td>4.7 (2.8–6.6)</td>
</tr>
<tr>
<td>Length of migration (cm)</td>
<td>64.3 (62.8–65.8)</td>
<td>72.5 (69.7–75.3)</td>
<td>57 (26.5–87.5)</td>
<td>75 (75–75)</td>
</tr>
</tbody>
</table>

Data are means and 95% confidence intervals.
MECCANISMI DEL RGE IN SOGGETTI DI CONTROLLO E IN PAZIENTI CON MRGE

- Rilasciamento transitorio dello SEI
- Mancata ipotonia dello SEI
- Incremento pressione addominale

A cura del Dott. Fabio Baldi e del Dott. Sandro Passaretti

(da J. Dent et al, 1988)
Different Reflux Mechanisms With Hiatal Hernia

* $P < 0.001.$
† $P < 0.005.$

Diagram illustrating the potential targets for TLOSRs inhibition

5-HT₃ antagonist
GABAB agonist
mGLUR5 antagonist
(mGLUR8 agonist)

GABA_B agonist

Vagal afferent

Fundic mechano receptors

CCK₁ antagonist

CNS

Vagal efferent

Interneuron

Atropine
L-NMMA
Cannabinoid agonist

Morphine

Inhibitory Motor Neuron

NO

Galmiche J P et al. United European Gastroenterology Journal 2013;2050640613484021

J. Tack Gut Jan 2002;50(1) 6-7
Lower oesophageal sphincter relaxation is lost in neuronal nitric oxide synthase (n-Nos) deficient mice.
Abnormal 24-Hour Esophageal pH Monitoring in the Different GERD Groups

- NERD: 50% (n=71)
- Erosive Esophagitis: 75% (n=40)
- Barrett's Esophagus: 90% (n=40)
BMP4  This protein belongs to the transforming growth factor β (TGF-β) family. Members of the TGF-β family are thought to be involved in controlling cellular differentiation, migration and proliferation.

CDX2  A key gene in the differentiation of gastrointestinal cells is the homeobox gene. Abnormal genetic expression of this gene, resulting from epigenetic changes has been shown to be associated with the development of Barrett esophagus. Demethylation of the promoter region of this gene has been shown to induce its expression in quiescent cell lines, thus inducing intestinal differentiation. Animal models have also shown that exposure to duodenal contents induces the expression of CDX2.
Eosinophilic Oesophagitis (EoE)

Interventi dietetici
- Dieta elementare
- Dieta di eliminazione

Terapia Farmacologica
- Steroidi topici e sistemici
- Inibitori dei leucotrien (montelukast)
- Anti-IL-5 (mepolizumab)
- PPI

Dilatazioni perendoscopiche

<table>
<thead>
<tr>
<th>Tipo di dieta</th>
<th>N. bambini</th>
<th>Risposta*</th>
<th>Riferimento bibliografico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di eliminazione</td>
<td>35</td>
<td>26 (74%)</td>
<td>Kagalwalla et al 2006 (19)</td>
</tr>
<tr>
<td>Elementare</td>
<td>25</td>
<td>22 (88%)</td>
<td>Kagalwalla et al 2006 (19)</td>
</tr>
<tr>
<td>Elementare</td>
<td>10</td>
<td>10 (100%)</td>
<td>Kelly et al 1995 (20)</td>
</tr>
<tr>
<td>Elementare</td>
<td>51</td>
<td>51 (100%)</td>
<td>Markowitz et al 2003 (21)</td>
</tr>
<tr>
<td>Elementare</td>
<td>172</td>
<td>172 (100%)</td>
<td>Lacouras et al 2005 (5)</td>
</tr>
<tr>
<td>Di eliminazione</td>
<td>75</td>
<td>75 (100%)</td>
<td>Lacouras et al 2005 (5)</td>
</tr>
<tr>
<td>Di eliminazione</td>
<td>146</td>
<td>112 (76%)</td>
<td>Spergel et al 2005 (9)</td>
</tr>
<tr>
<td>Elementare</td>
<td>40</td>
<td>39 (97%)</td>
<td>Spergel et al 2005 (9)</td>
</tr>
</tbody>
</table>

*Definita come n. (%) di pazienti con miglioramento clinico e istologico

<table>
<thead>
<tr>
<th>Steroidi</th>
<th>Tipo di studio</th>
<th>N. pazienti</th>
<th>Risposta clinica</th>
<th>Risposta istologica</th>
<th>Riferimento bibliografico</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone</td>
<td>Serie di casi</td>
<td>4 bambini</td>
<td>100%</td>
<td>25%</td>
<td>Faubon et al 1998 (26)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Serie di casi</td>
<td>5 adulti</td>
<td>20%</td>
<td>60%</td>
<td>Langdon et al 1993 (27)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Serie di casi</td>
<td>11 bambini</td>
<td>100%</td>
<td>100%</td>
<td>Tettelbaum et al 2002 (11)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Retrospettivo</td>
<td>20 bambini</td>
<td>50%</td>
<td>50%</td>
<td>Noel et al 2004 (28)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Serie di casi</td>
<td>19 adulti</td>
<td>100%</td>
<td>21%</td>
<td>Remedios et al 2006 (8)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Serie di casi</td>
<td>21 adulti</td>
<td>90%</td>
<td>------</td>
<td>Arau et al 2003 (29)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Retrospettivo</td>
<td>20 bambini</td>
<td>80%</td>
<td>80%</td>
<td>Aceves et al 2007 (30)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>RCT</td>
<td>20 bambini</td>
<td>------</td>
<td>50%</td>
<td>Konikoff et al 2006 (14)</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Fard. prosp.</td>
<td>30 bambini</td>
<td>97%</td>
<td>94%</td>
<td>Schaefer et al 2008 (16)</td>
</tr>
<tr>
<td>Budesonide</td>
<td>RCT</td>
<td>24 bambini</td>
<td>87%</td>
<td>87%</td>
<td>Dohr et al 2010 (15)</td>
</tr>
</tbody>
</table>

RCT: studio randomizzato controllato
Efficacy of Dietary Interventions for Inducing Histologic Remission in Patients With Eosinophilic Esophagitis: A Systematic Review and Meta-analysis

**Gastroenterology**
146, Issue 7, Pages 1639–1648, June 2014

**Conclusions**

Dietary interventions are effective in producing histologic remission in patients with EoE. Elemental diets and SFEDs were the most effective, achieving <15 eosinophils/high-power field in 90.8% and 72.1% of patients, respectively.
Chemical Intolerance in Primary Care settings
Prevalence Comorbidity and Outcomes

Figure 1. Prevalence of Chemical Intolerance vs Number of Possible Mental Disorders

Note: Possible disorders were major depressive disorder, generalized anxiety disorder, panic disorder, and alcohol abuse disorder.
Neural Sensitization (SRI)

Pesticide and Organic Solvent Action

- Organophosphorus/carbamate pesticides
- Organochlorine pesticides
- Organic solvents
- Pyrethroid pesticides
- Sodium channels

Acetylcholinesterase
Acetylcholine
Muscarinic activity

GABA<sub>a</sub> receptors
TRPV<sub>1</sub>, TRPA<sub>1</sub>
Other TRP receptors

NMDA: N-metil-D-aspartato recettore
Recettore post-sinaptico

NITRIC OXIDE

Mercurio
Solfuro di Idrogeno
Monossido di Carbonio
Neural Sensitization

THE FOUR MECHANISMS

- 1. Nitric oxide acts as a retrograde messenger, stimulating the presynaptic cells to become more active in releasing the neurotransmitter glutamate

- 2. Peroxynitrite depletes ATP pools via two different mechanisms, causing NMDA receptors in depleted cells to be hypersensitive to stimulation

- 3. Peroxynitrite increases permeability of the blood brain barrier (BBB), increasing accessibility of organic chemicals to the central nervous system (CNS)

- 4. Nitric oxide inhibits cytochrome P450 metabolism of organic compounds, producing increased levels of organic compounds which may stimulate NMDA activity
Neural Sensitization Cycle

NMDA Receptor

Stimulation of Neurotransmitter Release
(presynaptic cell)

Stimulation of NMDA stimulation
(postsynaptic cell)

Increased Nitric Oxide

Increased Peroxynitrite

Retrograde Messenger

ATP (energy) depletion

Martin L. Pall
Prof Emeritus of Biochemistry and Basic Medical Sciences
Washington State University USA
Nitric oxide and the NMDA excitatory neurotransmission system are implicated in long term potentiation (LTP)

Long-term potentiation (LTP), is a central mechanism involving learning and memory where the synapses show long term increases in sensitivity to stimulation. Excessive NMDA activity leading to excessive levels of nitric oxide and peroxynitrite has been implicated in several neurodegenerative diseases including Parkinson’s disease and Alzheimer’s disease.
NMDA

Nitric Oxide

E-NOS

I-NOS

BH$_4$: Tetrahydrobiopterina

NF-Kappa-B

TRP rec

Ca$^{2+}$

superoxide

ATP

oxidative stress

PRN

BH$_4$

IL-1$\beta$, IL-6

IL-8, TNF-\(\alpha\)

IFN$\gamma$
The search for reliable Biomarkers of Disease in Multiple Chemical Sensitivity and other environmental Intolerances

### Table 1. Genetic Polymorphisms Influencing MCS Susceptibility

<table>
<thead>
<tr>
<th>Gene</th>
<th>Study</th>
<th>Function-chemical metabolism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON1</td>
<td>H,M</td>
<td>Detoxification of organophosphorus toxicants including pesticides</td>
<td>May be expected to increase activity of strictly hydrophobic solvents on the TRPV1 receptor</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>M</td>
<td>Hydroxylation of hydrophobic compounds</td>
<td>May produce more or less activity, depending on substrate</td>
</tr>
<tr>
<td>NAT2</td>
<td>M,S</td>
<td>Acetylation</td>
<td>Should increase detoxification and excretion</td>
</tr>
<tr>
<td>GSTM1</td>
<td>S</td>
<td>Provides reduced glutathione for conjugation</td>
<td>Should increase detoxification and excretion</td>
</tr>
<tr>
<td>GSTT1</td>
<td>S</td>
<td>Glutathione conjugation</td>
<td></td>
</tr>
<tr>
<td>UGT1A1</td>
<td>M&amp;S</td>
<td>Glucuronidation, leading to increased excretion</td>
<td></td>
</tr>
</tbody>
</table>

H=Hailey et al, 1999 (11); M=McKeown-Eyssen et al, 2004 (12); S=Schnakenberg et al, 2007 (13); M&S= Müller and Schnakenberg, 2008 (14).

DE Luca C. *Int J Environ Res. Public Health* 2011, 8, 2770-2797
Clinical Audit

MCS Prospective Study

Background

Previous community based studies showed an increasing chemical intolerance and allergy

AIMS

Assess MCS prevalence and comorbidities in a sample of Primary Care Clinic patients

Assess the impact of Genetic and Epigenetic Factors as the cause of MCS
Clinical Audit

MCS Prospective Study

Methods

Patients will be recruited from 10 General Practice Catania Health District Board ASP 3 (Sicily)

Patients will complete the validated QUEESI Quick Enviromental Exposure and Sensitivity Inventory
Clinical Audit

MCS Prospective Study

QUEESI

Chemical intolerance

Primary Care Evaluation of Mental Disorders

Screen for possible Psychiatric disorders

Dott. Francesco Cosentino - Dott.ssa Maria Concetta Giuliano - Dott. Fabio Bisicchia
ECIM 2012
Quick Environmental Exposure Sensitivity Inventory (QUEESI)

Criteria for Low, Medium and High scale scores

Table 1. Criteria for low, medium, and high scale scores

<table>
<thead>
<tr>
<th>Scale/Index</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Severity</td>
<td>0-19</td>
<td>20-39</td>
<td>40-100</td>
</tr>
<tr>
<td>Chemical Intolerance</td>
<td>0-19</td>
<td>20-39</td>
<td>40-100</td>
</tr>
<tr>
<td>Other Intolerance</td>
<td>0-11</td>
<td>12-24</td>
<td>25-100</td>
</tr>
<tr>
<td>Life Impact</td>
<td>0-11</td>
<td>12-23</td>
<td>24-100</td>
</tr>
<tr>
<td>Masking Index</td>
<td>0-3</td>
<td>4-5</td>
<td>6-10</td>
</tr>
</tbody>
</table>

Dr Claudia Miller Dept. Family & Community Medicine Texas University USA
### LEVEL 1 Criteria

- Patient case history suggestive of MCS
- Daily activities affected by exposure to chemicals
- Impairment of at least two systems after exposure to chemicals known
- **QUEESI** score $\geq 21$
Clinical Audit

MCS Prospective Study

Level 2 Criteria

Olfactory Assessment
Near Infrared Spectroscopy

Psychological Assessment
MMP1  MMP2
Rorschach Test, Zulliger Test

Neurophysiologic Testing
Clinical Audit

MCS Prospective Study

Level 2 Criteria

Assessment of Oxidative Stress

D-Roms Test

PAB test

**Erythrocyte** Superoxide Dismutase, Catalase, Glutation peroxidase activity
D-ROMs Test (Reactive Oxygen Metabolites) is a spectrophotometry that determines the concentration of hydroperoxides (ROOH) generated in the cells from the attach of ROS.
D-ROMs test

The test is evaluated in a conventional measuring unit called U CARR (from the chemist Carratelli, the inventor of the test). Normal values are from 250 to 300 U CARR; above 300 U CARR there is the oxidative stress, but for a thin borderline range (301-320 U CARR).

<table>
<thead>
<tr>
<th>IDROPEROSSIDI (U-CARR)</th>
<th>IDROPEROSSIDI (mg H₂O₂/dl)</th>
<th>Stress Ossidativo (gravità)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 - 320</td>
<td>24.08 - 25.60</td>
<td>Border-line</td>
</tr>
<tr>
<td>321 - 340</td>
<td>25.68 - 27.20</td>
<td>Mild</td>
</tr>
<tr>
<td>341 - 400</td>
<td>27.28 - 32.00</td>
<td>Moderate</td>
</tr>
<tr>
<td>401 - 500</td>
<td>32.08 - 40.00</td>
<td>High</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>&gt; 40.00</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Dott. Francesco Cosentino - Dott.ssa Maria Concetta Giuliano - Dott. Fabio Bisicchia
ECIM 2012
PAB test
Prooxidant-Antioxidant Balance

Rate the effectiveness of the barrier antioxidant which is able to oppose the action of damaging free radicals.

Normal range 1.30 – 1.70 mmol/L
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MCS Prospective Study

Level 2 Criteria

Autoimmunity Markers
Cytokine Panel
Total IgG IgA IGE
Aga IgA IgG  TtG IgA IgG
Iron - Ferritin - Vit B12- Folate
Homocisteynemi *
MTHFR *
Restriction Diet
Food Allergy Test  IgE * – IgG4 *
Patch test *

* Facoltative
Clinical Audit
MCS Prospective Study

Level 3 Criteria

Genetic Polymorphism

- PON 1
- CYP2D6
- NAT2
- GSTM1
- GSTT1
- UGT1A1
The assessment of concentration of hydroperoxides (ROOH) and prooxidant-antioxidant balance by D-ROMs and PAB Test could be a useful and cheap diagnostic device to confirm the suspected diagnosis of SRI in patients with QUEESI score positive.

D-ROMs and PAB test could be a useful diagnostic address in search of Genetic Polymorphism associated with MCS and Epigenetic Factors.