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The ESS Statement of Support to the Ukraine



Any professional society should maintain impartiality, inclusivity and collegiality, focusing activities on the area of its expertise. However, adhering to these premises should never replace basic human decency in the face of immoral actions and the need for empathy towards fellow

human beings in need. The European Shock Society (ESS), stands for the European spirit of free, diverse and peaceful coexistence of all people, and feels compelled not to remain indifferent but to issue a strong condemnation of the Russian Federation's recent premeditated invasion of sovereign and democratic Ukraine. Although we fully realize that such a statement is only symbolic, we collectively believe that symbols matter. Above all, we wish to express our deepest sympathy to Ukraine and its suffering citizens, with a special regard to our Ukrainian scientist colleagues. ESS will attempt its best to extend its collegial support to the Ukrainian research community within the Society's resources and potential.

Message from the ESS President



I had drafted the below letter before the invasion of Ukraine began. The recent events eclipse all other news below. We, the ESS, have not remained indifferent – see our official Statement of Support (above). Neutrality is definitely a good thing but sometimes it is inexcusable. These are such times. Dear ESS executive committee, I am very proud of you for rallying together to do it! Please read the rest of the Newsletter.

The current times have been trying and each one of us has been somehow impacted by the rampant pandemic; we all had to make adjustments to

our professional and private existence. I sincerely hope that each one of you was able to find their small niche of tranquility in this turbulent reality - any activity that frees up the mind from a seemingly unending list of to-do-things (paper, grant, report, audit, ...), organizational challenges (Ouch, another zoom in 20min! Enough laptops/bandwidth at home?), logistic twists and turs (Oops, half of my staff on quarantine. Again.). All of those on the top of the long days at lab/ward/ER/ICU/home-office. Please hang on there! Ask for help if you feel overwhelmed. One of "a silver lining" elements in such tough times is the robust rise in selfishness and collegiality. Hope you have been experiencing some of it too... (this sentence has a brand new meaning in the current situation).

In our small attempt to "undemonize" the above hardships and bring a smile to your faces, we are launching an ESS "*ZOOMosis Competition*" with an attractive price to entice your participation (see details on page 33 in the Newsletter). Another new item we would like to introduce are webinars. I have been already working on this concept and hopefully this works out at some point in 2022.

We are few months after our ESS congress. A true regret it did not take place in sunny Greece but we are no different from countless other societies who reverted to the online format. Despite the general exhaustion with on-line conferences, the 19th ESS congress was supersuccessful and the laurel leaf for this goes to Evangelos Giamarellos, our past ESS President. Evangelos organized in a warp-speed time the scientific program and the digital congress platform (with a great support of the Congress World team) and most all recruited an excellent and topic-diverse crowd of experts. Thank you very much, Evangelos!

Life goes on and our ESS moves with it. We have some fine news to share. One of the finest is that Borna Relja is our ESS president-elect – the first ever female upcoming ESS president. One could ask why the commotion? Is it not a self-evident event? Indeed, but I am joyful about this undeniable upgrade in the ESS diversity and simply share it with you (keeping my fingers crossed for Borna!). Mark Maegele is another fine reinforcement to the ESS executive committee by becoming our ESS treasurer. His great organizational experience in IFSS and ESS makes him a true asset. Last but not least, we are very jubilant about new and returning ESS members. Our sincere thanks and welcome to all of you for deciding to (re-)join us!

Though the future is unclear, a cautious optimism is allowed and thoughts of subsiding pandemic somewhat justified. I cling to that optimism hoping the 20th ESS congress will be a physical-presence one. We are facing a notable anniversary: 40 years of ESS existence. An onsite congress would be a delightful change of the mundane digital routine and an imperial Vienna is a deserving location to enjoy it. The preparations are underway (I tweet on the progress; *@osuchm*); the dates are fixed (21-23 September 2023) and the chosen venue is the University of Vienna. Keep your fingers crossed for this to successfully transpire!

Sincere regards and digital hugs from your current ESS captain, especially to all Ukrainians,

Marcin Osuchowski

Message from the past ESS President



The word crisis is coming from the Greek verb crinomai ($\kappa \rho (v \circ \mu \alpha \iota)$) which means to become evaluated. In other terms, crisis is the period of life where the level of stress is so extensive where each and everyone of us will be criticized either in a good way or in a bad way from this/her actions. This applies not just for individuals but also for scientific societies.

The COVID-19 pandemic is probably the biggest challenge our generation has come across so far. When the pandemic arrived, I have just started by

term as President of the ESS. At that time, I was considering the risk for a severe impact on ESS. This is where crisis comes and proves that good people can prove their merit when challenges emerge. I was one of the luckiest presidents of the ESS because I had one Executive Board of highly qualified people who worked hard to expand the international merit of the society. Early during the pandemic under the leadership of Marcin Osuchowski, the current President, and of Marc Maegele, the current Treasurer, we published a guiding map for the new coronavirus. As the pandemic progressed, many of our members actively participated in big international collaborations like the European Group of Immunology of Sepsis or in local Back to Contents

scientific activities to fight the pandemic. Thanks to the efforts of our General Secretary, Andrea Szabò our website was fully updated. As a result, awareness for ESS and its activities increased substantially, and this led to more than 700 registrations during our e-conference of November 2021 whilst many European colleagues became members of our Society. The proceedings of the sessions will soon become available in a supplement volume of Shock and this is anticipated to further increase awareness for our activities.

The European Shock Society is fundamentally relying on tight scientific and emotional bonds between members who aim to promote the diverse aspects of shock research. The enormous productivity over the last two years of the pandemic crisis guarantees the future of ESS.

Long-live ESS!!!

Evangelos J. Giamarellos-Bourboulis

Message from the General Secretary



Dear Colleagues, dear members and friends of ESS,

I trust that the pandemic has not affected your health, your daily work and your commitment to the ESS. On behalf of the entire ESS community, I would like to thank President Evangelos J. Giamarellos-Bourboulis and Maria Papapanagiotou (from CongressWorld) for their excellent organisation of the 29th ESS congress! Special thanks go to the distinguished speakers of the congress for the very high quality of their presentations and to the moderators of the sessions for the active

communication during the congress.

Our five council meetings in preparation for the congress were also held online, as was the General Assembly during the WEB Conference. I would like to take this opportunity to thank all members of the Council and all participants in the General Assembly for their active collaboration.

I also thank our long-standing members for their perseverance in renewing their ESS membership and welcome our new members (including those who have rejoined the ESS community).

We remain committed not only to retaining our membership, but also to improving communication between and within the membership and the board. The <u>ESS website</u> provides new opportunities for this. It is not only a way to find colleagues working in a similar research area for those who are registered in the membership database, but also to express interest in ESS webinars and to indicate if someone would like to participate in organizing them.

ESS / Membership / Join the Members' Database

Join the Members' Database

Webinars

Please suggest topics for future webinars organised by ESS (please provide keywords / suggest speakers)

Please suggest topics you would like to present on future webinars organised by ESS.

Likewise, information on the current status of membership payments may also be available (as classified information of the actual member).

Membership Status	
Last Payment Date	8th Dec 2021
Paid Until End	2023

Therefore, I would like to encourage everyone (if they have not already done so) to join the <u>ESS Members' database</u>. An important condition for this is that the email addresses provided at the time of registration must be confirmed (this has not been done for several applicants). Finally, I would like to wish Marcin Osuchowski a very successful congress in 2023, which I look forward to assisting with and participating in person in the beautiful Vienna. Together with our Past-President Evangelos J. Giamarellos-Bourboulis and the newly elected President-Elect Relja Borna, we wish to support the successful realization of the congress in every way possible.

Yours, Andrea Szabó

The (last and first) Treasurer's Corner



Borna:

Dear friends of the ESS, dear ESS team, I am taking this opportunity to express my thanks to all "permanent" and new members and the ESS board for your support over the last two years. My quite short treasurer experience is ending given my new role of ESS presidentelect. After taking over from Marcin Osuchowski in 2019, my main challenge was to continue an open dialogue with you during the global crisis and maintain the overall financial stability of the society. First,

you might have noticed that I sent you some reminders; and luckily many of you have responded and wired the money for your memberships. Thank you very much! The surplus from Chania meeting and kind donations by Jean-Marc Cavaillon and Anna Herminghaus secured an overall stable financial stance of the ESS. Thanks to the continuous activity and support of our past presidents Markus Huber-Lang, Jean-Marc Cavaillon and Evangelos J. Giamarellos-Bourboulis! A snapshot from our balance sheet shows major expenses for legal counseling and website hosting with the refresh of our ESS website essentially impacting our

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visual appearance. Second, money is not necessarily the most desirable store of value, though Marc Maegele our new treasurer will keep you active to avoid episodes of financial distress and dysfunctions. There's not a big difference between engaging new members and engaging a friend face to face. Instead of one-directionally talking to members, we all need to think about how we can involve them into the ESS conversation. In the past two years, such conversations became rarer but the outcomes made it all worthwhile. We, the ESS council, are happy to welcome our new ESS members on board, who have joined us during this difficult time. Dear ESS friends, dear ESS board, dear Mr. President Marcin, dear Marc, the fiscal development is only one pillar of the ESS sustainability, and I am just happy and feel privileged to be part of it with you.

And Chockey -

Marc:

Dear colleagues, members, students and friends of the ESS, fiscal stability is of utmost importance for our society as it provides a sound basis for all our activities now and in the future. In troubling times, I take over the responsibility of serving the ESS as new treasurer. I am humbled and proud simultaneously to follow Borna Relja in this position, who successfully controlled and guided the ESS finances over

the past term. It will be with your support and the income from the membership fees that the ESS will stay and hopefully become financially even sounder, more stable and more flexible in the years to come. The society should be attractive for new and young members to join but also alternative sources of fiscal influx need to be explored in different directions. With these aims in mind, the ESS will be able to continuously support and educate the next generation of investigators in the fields of shock, trauma and sepsis and to provide corresponding platforms of exchange. It is self-explanatory that fiscal development is integral to the continuously evolving strategy of the ESS and I am looking forward to this new "team challenge"!

Borna and Marc: Ending our joint treasurer's corner piece, allow us to remind you about a very important change that took place at Paris congress in 2017: **The ESS collects membership fees separately of the registration fee for the biennial congress.** This means if you are an ESS member and fail to pay the membership on time, you make the life of the ESS (and the treasurer) much harder. We sincerely ask you to pay your ESS membership fee. Thank you!

Your past treasurer, Borna Relja Your new treasurer, Marc Maegele

Congratulations to our new council members: Councillors appointed by the President



I graduated from Athens Medical School in 2006. The same year, I became a member of Hellenic Sepsis Study Group as a Scientific Associate at 4th Department of Internal Medicine at ATTIKON University Hospital with special interest in genetic of sepsis, cell culture and flow cytometry. I finished my PhD in 2012 with thesis titled "Genomic polymorphism in sepsis". I finished my clinical specialty in Internal Medicine in 2015 and began my work as an academic scholar with special interest in conducting and supervising

clinical trials especially in sepsis field. I finished my training as an Infectious disease specialist at 2020, and I am currently a consultant at 4th Department of Internal Medicine at ATTIKON. In the context of my evolving interest for clinical trials, I also completed MsC programme in "Clinical Pharmacology and Therapeutics", at the Medical School of Democritus University of Thrace. I currently serve as a Senior Clinical Research Associate at Hellenic Institute for the Study of Sepsis with main interests in clinical trials oriented toward sepsis (especially viral sepsis in COVID-19 times) as well as molecular and pathophysiologic background of sepsis/viral sepsis manifestations. I participate at several educational master programmes and I am a co-author of 37 journal papers.

"It was a great honor to be appointed by my mentor Prof. Giammarelos-Bourboulis (and reconfirmed by the ESS council vote) as a council member of this fruitful organization. The merger of basic research and clinical science in an effort to unravel the mysteries behind the entity of acute states makes ESS successful and unique. After fifteen years in the field of sepsis, I really look forward to contributing with all my efforts to fulfill ESS goals and be part of its great vision."

Yours, Antigoni Kotsaki



PD Dr. Christoph Schlimp, is Consultant in Anaesthesiology & Intensive Care at the Trauma Hospital Linz, Austria; a Group Leader at the Ludwig Boltzmann Institute for Traumatology (LBI Trauma), the Research Center in Cooperation with AUVA; and a freelancing flight physician for primary retrieval and secondary intensive care transport with the helicopter emergency service HEMS-ÖAMTC, Austria.

Over the last 25 years, Christoph has developed scientific interest in four

defined topics: 1) in the patho-mechanism of venous and cerebral gas embolism; 2) electromagnetic interference in defibrillators; 3) theragnostic guidance of coagulation management in traumatic or perioperative bleeding patients; 4) preclinical shock models.

In 2012-13, Christoph absolved a full-time research fellowship at LBI Trauma, where he investigated improvement/validity of assays and quick diagnosis to estimate fibrinogen levels/functionality as well as on treatment options for traumatic or perioperative acquired coagulopathy. Christoph has over 70 peer-reviewed publications in the areas of anaesthesia, critical care and emergency medicine; in 2015 he was granted the *venia docendi* at the Medical

University of Innsbruck, Austria. In 2016, Christoph was grated a fellowship at the Royal Infirmary Edinburgh, Scotland, focusing on perioperative bleeding management in major vascular surgery. Christoph has a wealth of clinical experience, having studied, worked and taught across the world in the fields of anaesthesia, critical care medicine, preclinical emergency medicine and trauma management. He is member (and currently chair 2019-2022) of the Task Force on Perioperative Haemostasis (AGPG) of the Austrian Association of Anesthesiology, Resuscitation and Intensive Care (ÖGARI). Welcome Chris!

Reminiscence of the ESS Congress 2021



When it became clear that the 19th Congress of the European Shock Society will be exclusively digital meeting, I was afraid that it would be diluted by multiple other online meetings that took place during the COVID-19 pandemic. To my joyful surprise, it was absolutely not the case! And I know that it is not only my own opinion. The ESS congress committee but especially Evangelos Giamarellos-Bourboulis made a great effort to gather some of the best researchers in the field of shock, sepsis and COVID-19 to share their work and knowledge. It was also due to the excellent digital platform that enabled a true interaction between the speakers and audience. The thematic composition of sessions and the talks themselves triggered lively discussions which made the virtual meeting of a full and wholesome value. Another positive twist was that the online format made the attendance much higher than anyone could have expected. This also significantly contributed to making the congress special. Even though we all miss the in-person interactions, it was great to see many friends and the ESS general assembly online. Seeing so many 'shock' fellows from across a few continents built a strong feeling of belonging to a very special society. Hope to finally see you all in person in less than 2 years!

Tomasz Skirecki

Reminiscence of the ESS Congress 2021 – by a new member



I was ecstatic for the opportunity to join the 19th congress of ESS. There were many interesting and informative presentations on diverse topics related to sepsis and trauma, and ranging across clinical, translational, and animal model studies. I enjoyed the stimulating talks by renowned PIs and research groups, and learned a lot! I was also very impressed by the high level of collaboration and participation widely across international borders, and was in awe to learn more about the Global Sepsis Alliance and the European Sepsis Alliance, the ImmunoSep consortium and the Hellenic Sepsis Study

Group. The conference was well-run by the brilliant adoption of a highly interactive online platform. The possibility of watching talks recordings was another great organizational plus. I am extremely grateful to the organizers for this outstanding congress and applaud all the speakers for their excellent presentations. I am looking forward to participating again next year.

Welcome new ESS members!



Full members

Stelios Assimakopoulos Geece

> **Roman Hajek** Czech Republic

Eleni Karakike Greece

Antigoni Kotsaki Greece

Matthijs Kox The Netherlands Andreas Limmer Germany

Magdalena Milewska Poland

Hercules Tsangaris Greece

> Amy Tsurumi USA

Marcin Zasadowski Spain

Student members

Nadia Ehteshamzad Germany Ludmila Lupu Germany

Maria Siabli Greece

Welcome back (full members)

Tanja Eichhorn Austria

Evdoxia Kyriazopoulou Greece

> Mihai Netea The Netherlands

Pierre Raeven Austria

Christoph Schlimp Austria

Viktoria Weber Austria

Martin Wepler Germany

Anakinra personalized treatment in COVID-19 patients



Immunotherapy for severe infections and sepsis is an old therapeutic concept. From the beginning of the 90s and for 15 years onwards, several small and large-scale randomized clinical trials (RCTs) were done on the safety and efficacy of biologicals. Therapy was aiming to normalize the dysregulated immune response of the host. Unfortunately, none of these drugs succeed in clinical development. These failures led to the realization that immunotherapy in severe infections should be tailored to the specific needs of each host and that the concept of "one size fits all" should be

abandoned. However, treatment through personalized approaches mandates the application of biomarkers which are translated into the level of activation of specific mechanisms inside the human body.

The most worrisome feature of pneumonia by the novel coronavirus SARS-CoV-2 (known as COVID-19 disease) is that most patients with significant radiological findings affecting large parts of the lung parenchyma may remain at a relatively good state for several days after infection. They are hospitalized under low flow supplemental oxygen until they suddenly deteriorate into acute respiratory distress syndrome (ARDS) and require mechanical ventilation. This translates into a relatively wide window-of-opportunity (W-O) for intervention to prevent progression into ARDS. Widely applied biomarkers like C-reactive protein inform about the presence of a systemic inflammatory response but they are not specific on the mechanism taking place during this W-O. suPAR (soluble urokinase plasminogen activator receptor) is increased earlier than the other biomarkers in patients who will eventually deteriorate into ARDS¹⁻³. A concentration of 6 ng/ml (and above) indicates the presence of alarmins which stimulate the excess production of interleukin (IL)-1 α and of IL-1 β and may frequently lead to unfavorable outcomes. Anakinra is the recombinant nonglycosylated form of the IL-1 receptor antagonist. Once bound to the IL-1 receptor, it blocks the action of both IL-1 α and IL-1 β . This instigated an idea that the early increase of suPAR should guide a treatment with anakinra to prevent progression to ARDS.

This hypothesis was tested in an open-label trial phase 2 using parallel comparators under similar standard-of-care (SoC) therapy. The study was given the acronym SAVE (<u>suPAR-guided Anakinra treatment for Validation of the risk and Early Management Of seveRE</u> respiratory failure by COVID-19). 950 individuals with moderate to severe COVID-19 pneumonia and suPAR \geq 6 ng/ml without the need of non-invasive or invasive ventilation were treated with anakinra. Findings reported in the published interim analysis on the first 130 treated patients⁴ showed that 22.3% progressed into ARDS or died by day 14 compared to 59.2% of SoC comparators.

Advice was then provided from the Emergency Task Force for COVID of the European Medicines Agency for the design, conduct and analysis of the large-scale SAVE-MORE pivotal phase 3 trial. The trial was double-blind 1:2 randomized, it was conducted in 37 study sites in Italy and Greece and SoC contained dexamethasone. The primary endpoint was the WHO-CPS

(World Health Organization Clinical Progression Scale) by day 28 which elaborates the allocation of patients into fully recovered, long COVID persistence, remaining hospitalized at the general ward without/with supplemental oxygen, remaining hospitalized at severe disease or having died. Results showed that anakinra treatment led to 0.36 odds ratio for worse outcome compared to placebo treatment which translated to 64% global improvement of the WHO-CPS after 28 days (Figure 1). This is also translated into 64% relative increase of the rate of full recovery and into 54% relative decrease of the risk for remaining under severe disease or dying. By day 14, 31.7% of patients treated with placebo and SoC developed ARDS or died compared to 20.7% of patients on anakinra and SoC⁵.

These extremely favorable results led to the approval of anakinra treatment guided by suPAR for hospitalized adults with COVID-19 pneumonia in need of supplemental oxygen (low-flow or-high flow) by the European Medicines Agency⁶. This indication is the start of applied theragnostics for severe infections. The concept of theragnostics is built on huge worldwide scientific collaborations over the last decade aiming to deliver biomarkers which can be translated at bedside into information for a specific underlying mechanism of pathogenesis and guide decision-making with drugs targeting the mechanism. In this aspect, findings of the SAVE and SAVE-MORE trials prove that the theragnostics approach may bring considerable clinical efficacy.

Patient state	SoC + Placebo		SoC + Anakinra	
Fully recovered, PCR(-)	Ĩ	26.5%	ŴŴŶŶ	50.4%
Asymptomatic, PCR (+)	Ŷ	3.2%	n în	9.9%
Ambulatory, with symptoms	^^^^	50.3%	ŤŤŤ	29.3%
Hospitalized, moderate disease	î î	6.9%	ŕ	4.2%
Hospitalized, severe disease	Ť Ť	6.3%	Ŷ	3.1%
Dead	††	6.9%	Ť	3.2%

Figure Global efficacy of anakinra treatment by day 28

The figure shows the allocation of patients under the different strata of severity of the World Health Organization Clinical Progression Scale

PCR: polymerase chain reaction; SoC: standard-of-care containing dexamethasone

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Evangelos Giamarellos-Bourboulis

Legal/ethical problems with animal experimentations

Over 100 million animals are employed in experimental research around the globe annually. In the EU, this number approximates 10 million (based on the 2019 EU report). The main areas of animal uses include basic research (45%), followed by translational/applied research (23%) and regulatory use (23%). The ethical component has accompanied animal-based research for decades, yet, the intensity of those considerations have been rapidly growing over the recent years.



Annual polling of the American public on the topic of animal experimentation and its moral justifications demonstrate an gradually increasing trend against the acceptability (Fig. 1).

Similar trends were recorded in the UK (75% in 2002, 66% in 2016). There are at least two key elements that have contributed to this effect: i) an increasing societal awareness regarding animal well-being and ii) a rise in aggressive lobbying against the use of animals in research by various anti-animal research organizations and/or activists. While the former is overtly positive, the latter is controversial insofar that it has frequently become populistic, bias-ridden

and not based on facts. The research community is typically very careful in disclosing their animal-based research to the lay public creating a strong imbalance in the coverage of that type of research activities and their undeniable benefits (see the text by K. Leech below). While there are some notable activities explaining the role and need of animal-based experiments to general public (e.g. <u>https://www.understandinganimalresearch.org.uk</u>; UAR; <u>www.EARA.eu</u>), these initiatives have not yet achieved a worldwide recognition of the anti-animal research organizations (e.g. PETA).

The pre-clinical intensive care research (ICR) is especially vulnerable to this criticism given that it relies on a relatively high proportion of severe and non-recovery models (representing 17% of the total in 2017 in the EU). While the new directive 2010/63/EU on the protection of animals used for scientific purposes has brought about many positive improvements (e.g. enhanced focus on the 3Rs and alternative methods, harm/benefit assessment), it also contains a tangible threat to animal research given that its ultimate aim is full replacement of animal experiments. The ICR research will likely be the first domain, in which hard restrictions will be implemented (e.g. ban mortality as a study endpoint in the Netherlands). This will be very damaging to the advance of ICR given that complex physiological phenomena can be hardly studied in cell-based systems. Furthermore, mortality/survival as endpoints are an inherent part of the ICR given that it reflects true events (i.e. death, acute and severe states) in human patients. A hypothetical shift toward milder models (supporting less burdensome scenarios for animals) will do more harm than good. The existing scientific evidence clearly demonstrates that low-burden models of critical care conditions do not adequately reflect pathophysiological characteristics of the same critical states in human patients. Thus, such an animal (low burden) model-to-human (severe states) mismatch will generate misleading evidence (that is not translatable to human scenarios) and further fuel the criticism of ICR.



Interestingly, the recent COVID-19 pandemic may be an important public opinion influencer. Despite an aggressive denial by some organizations regarding the utility of animal modeling in development of anti-COVID-19 drugs and vaccines, it appears that a (favorable) public awareness on the importance of ICR in that particular area has rapidly increased. This is reflected by the recent (2020) poll conducted by UAR (Fig. 2) demonstrating an unusually high

acceptance of the animal modeling in COVID-19 research (which is inherently severe given the specificity of the disease). Also the outcome of the most recent Swiss referendum on a complete ban on the use of animals in research (13 Feb 2022) has been likely influenced by the pandemic; an overwhelming 79% of voters did not support the ban. In that context, it is interesting whether the 2020 trend-reversal (in favor of animal experimentation) in the Gallup

poll (Fig.1) is purely accidental or rather foretells a marked and protracted perception-change in that topic.

Marcin Osuchowski

EARA – the voice of the biomedical sector on the use of animals in biomedical research



European Animal

Since its founding, just eight years ago, EARA has been the Research Association principal voice on the European stage in advocacy and communication about the important role the use of animals

plays in biomedical research. With more than 125 member organisations, representing both public and private research, as well as breeders and suppliers, EARA has gained a seat at the table when the subject of animal research is discussed and recent events has made our input more important than ever.

Events last autumn, at the European Parliament, appear to show that we are reaching a watershed moment on the use of animals in scientific research in the EU. Although the September 2021 vote by MEPs for an EU-level action plan to facilitate the transition to innovation without the use of animals in research, regulatory testing and education – in other words a staged phase-out - carries no weight in law, it is likely to put further pressure on the European Commission to go beyond the terms of existing regulations in Directive 2010/63 on the use of animals for scientific purposes.

Certainly the vote will put wind in the sails of the activist groups, across the EU, that have recently launched a European Citizens' Initiative (ECI), which combines a call for a ban on animal testing - under REACH regulations - of potentially hazardous substances used in cosmetics, plus a demand for the EU to plot a roadmap to phase-out all animal testing in the EU before the end of the current legislative term.

The main concern of EARA is that many MEPs have been misled by activist groups into believing that non-animal methods of biomedical research are ready and waiting to replace animal models currently in use for safety testing, drug development and basic research. However, the reality is that the usefulness of non-animal methods remains limited, and they do not serve as suitable alternatives for huge areas of research and development.

EARA believes that the scientific community in Europe needs to improve its engagement with MEPs and the Commission to ensure that they receive a more balanced narrative on the use of animals in scientific research. We have now begun a series of meetings with politicians and policymakers to ensure this happens.

EARA also encourages researchers to be more open and transparent about their use of animals to increase awareness of the benefits their use brings to society, through fresh biomedical insights and new drugs and treatments. For instance, the use of animal models in neuroscience where there are virtually no alternative methods available and throughout the development process of all Covid-19 vaccines. This openness initiative is demonstrated through our network of <u>Transparency Agreements</u>, which is now established in seven countries in Europe (Belgium, France, Germany, Portugal, Spain, Netherlands and the UK).

At this potentially historic juncture it is important for the research sector to improve its communication efforts. If you would like to collaborate with EARA please contact kleech@eara.eu.

By Kirk Leech, European Animal Research Association executive director

Revisiting Metchnikoff's work in light of the COVID-19 pandemic

Jean-Marc Cavaillon and Jack Levin. Innate Immunity 2022 in press

I was invited by the Metchnikoff Institute of Microbiology and Immunology in Karkhov (Ukraine) to revisit Elie Metchnikoff's work in the light of COVID-19. Although I thought initially it was a tough challenge, then I realized how much the polymath Elie Metchnikoff would have been fascinated by this new infectious pathology and how much his own work and that of his closest collaborators were in connection with this disease.

COVID-19 has led to a profusion of scientific articles. Few among us can claim to have read even one percent of those. Alexandre Besredka (1870-1940), who took over the laboratory of his mentor after his death on July 15th, 1916, said of Metchnikoff: "*his eyes sheltered behind glasses, sparkling with mischief and kindness; his simplicity, his invariably welcoming approach [...] his erudition and his prodigious memory made of Metchnikoff a living bibliography, all the more pleasant to consult that one seemed to oblige him in doing so. Some emphasize his talent as a teacher, exercising over the audience a hold that no one escaped; the youthful ardor he brought to the discussions in academies and especially in international congresses, his fiery temper that his opponents feared so much". It must be said that he was among his colleagues at Institut Pasteur, the only one to master Russian, German, French and English, which allowed him to read the scientific articles published at the time in the language of their authors. This taste for reading is illustrated by a famous painting by the Russian painter Ossip Perelmanov, known as Ossy de Perelma (1876–1949), representing Metchnikoff seated at a desk in front of a mountain of books, newspapers and papers and leafing through articles, a painting close to the photo of Metchnikoff in front-off the shelves of the library:*

COVID-19 was undoubtedly a tremendous incentive for international cooperation; Metchnikoff welcomed in his laboratory no less than a hundred collaborators from Europe and even from Japan, with whom he published over two hundred articles. With my colleagues from the European Shock Society and the European Group on Immunology of Sepsis we published reviews on what we now call a new medical entity ¹. Thirteen nationalities were thus represented.

Metchnikoff worked on aging, coining the term gerontology. Indeed, it turns out that mortality due to COVID-19 mainly concerns the elderly. We call "immunosenescence" the alteration of the immune system in aged people and "inflammaging" the ability of the elderlies to produce more inflammatory cytokines. These terms would have certainly delighted Metchnikoff.



In addition to inoculating himself with the blood of a patient with a relapsing fever and drinking a cholera culture broth, Metchnikoff studied many infectious pathologies including syphilis and tuberculosis. It turns out that the scientific community agrees to consider the most severe cases of COVID-19 as a viral sepsis. One of his collaborators, Félix Mesnil (1868-1938) published a work on "Vibrionian" sepsis.

We know that macrophages in general and alveolar macrophages in particular are an integral part of the pathogenesis of COVID-19, just like neutrophils, called in Metchnikoff's time, microphages. In particular, a process called "netosis" consists of a particular death of neutrophils, which release all of their intracellular material outside the cell. This phenomenon has been observed in the lungs of patients developing acute respiratory distress syndrome. Of course, Metchnikoff is renowned for being the father of phagocytes(sis). With Nicolaï Tchistovitch (1860-1926), they described the alveolar macrophages present in the lungs. Furthermore, it turns out that Constantin Levaditi (1874-1953) in Metchnikoff's laboratory was the first to report the process of netosis, mentioning that dead neutrophils could still contribute to killing bacteria.

Metchnikoff's lessons on inflammation are famous and were translated into English. Metchnikoff was fully aware that there is a beneficial physiological inflammation and a pathological one; in other words, the yin yang of the host response to infection combining beneficial and deleterious effects ². This ambivalence, this dichotomy, these two faces of Janus was nicely illustrated when it was shown that treatment with interferon- α was beneficial

¹ Osuchowski MF et al. SARS-CoV-2/COVID-19: evolving reality, global response, knowledge gaps, and opportunities. Shock. 2020 Oct; 54(4): 416-437

Osuchowski MF et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med. 2021 Jun; 9(6): 622-642

² Alfred I. Tauber. Metchnikoff and the phagocytosis theory Nature Reviews | Molecular Cell Biology November 2003, 4: 897-901

when initiated early in COVID-19 patients, but on the contrary harmful when administered late. Of course, a deleterious inflammation is strongly present in the lungs of the most severe COVID-19 patients. It is further exacerbated in obese patients in whom a contribution of macrophages in an activated state within adipose tissue is suspected. These cells present in these tissues were known and mentioned by Metchnikoff. He was also fully aware of the role of the various parts of the body in the fight against microbial invasion. And no doubt he would have subscribed to the concept of "compartmentalization" I had developed to illustrate that different or even opposing processes occur during a systemic inflammatory pathology such as sepsis ³. A cytokine storm has been claimed to characterize COVID-19, but in the periphery, it is more of a small drizzle ⁴, while indeed in the most severe patients, this storm occurs in their lungs where cytokines act in synergy to induce tissue damage that can lead to death.

Many pieces of data and/or phenomena already known for more than twenty-five years were re-discovered during current investigations on COVID-19 including for example the synergy between TNF and IFNgamma⁵. This confirmation of old works is also illustrated on the occasion by the contribution of the complement system in the aggravation of pulmonary inflammation. The complement system was particularly studied in Metchnikoff's laboratory by Jules Bordet (1870-1961) - the work, for which he was awarded the 1919 Nobel prize. With his brother-in-law, Octave Gengou (1875-1957), Bordet also studied the coagulation process, a phenomenon closely associated with severe forms of COVID-19.

Metchnikoff carried out numerous studies on the digestive tract, yet COVID-19 is associated in more than 17% of cases with gastrointestinal manifestations. Metchnikoff discovered microglial cells in the brain which he called "neuronophages" and became interested in the damage to nerve cells during rabies infection. We now know that COVID-19 can be pathogenic to the nervous system.

COVID-19 was associated with many psychological disorders, some were amplified by the locked-down and in some countries the frequency of suicides increased during that period. It is a theme dear to Metchnikoff, who wrote two books on the nature of man with an optimistic philosophical vision. As a young man, however, Metchnikoff was psychologically very fragile. Very distressed by the serious infectious diseases of his wives, Metchnikoff attempted suicide twice. The first time was after the death of his first wife, Ludmilla Federovnain, in Madeira. He swallowed a large dose of morphine; he survived but became dependent on this drug for some time. The second time was after his second wife, Olga Belokopytova, was diagnosed with typhoid fever. In his first work "Studies on human nature. Essay on optimistic philosophy" (1903), isn't it funny to read this self-portrait: "*I know in a completely intimate way a man of science who felt very unhappy during his youth. Endowed with a kind of hypersensitivity for*

³ Cavaillon J-M., Adib-Conquy M., Cloëz-Tayarani I., Fitting C. Immunodepression in sepsis and SIRS assesed by *ex vivo* cytokine production is not a generalized phenomenon : a review. J. End. Res., 2001, 7, 85-93

⁴ Stolarski AE, Kim J, Zhang Q, Remick DG. Cytokine drizzle - the rationale for abandoning "cytokine storm". Shock. 2021 Nov 1;56(5):667-672.

⁵ Wang N, et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host Microbe. 2020; 28: 455-464.

suffering, he tried to calm it by all possible means. Any annoyance was capable of plunging him into a state of real prostration which he remedied by narcotics. To escape certain moral pains, he inoculated himself with morbid viruses. Later, when he reached a mature and advanced age, his hypersensitivity gave way to less acute feelings. He no longer felt evil in a certain way, as violent as in his youth. On the other hand, he much more appreciates the positive side of life and, even in cases where he feels unhappy, he never thinks of shortening his life. He was pessimistic and admitted that the bad far outweighs the good. At a more advanced age, his appreciation of existence has completely changed."

In addition to various tiny pathogens, Metchnikoff also worked (early in his career) as an embryologist; he performed investigations on more than thirty animal species and studies of COVID-19 were possible thanks to the establishment of animal models ⁶. It should be recalled in this regard that COVID-19 is a zoonosis derived from bats; Metchnikoff published works on that animal species as well.

COVID-19 triggered an unprecedented research in the field of vaccination. Although Metchnikoff is rightly considered as the father of innate immunity and cellular immunity, he did not deny busying his collaborators with projects associated to humoral immunity. This included vaccine-derived protection as it was the case with the Belgian Jules Bordet, the Russian Vassiliy Issaevitch Issaeff (1854-1911), or the Italian Giuseppe Sanarelli (1864-1940). After heading the Institute of Bacteriology in Odessa to promote vaccination against rabies and anthrax developed by Pasteur, Metchnikoff himself worked on vaccination by developing a vaccination against cholera toxin (using guinea pigs, rabbit, goat and horse) and against typhoid fever (using chimpanzees). Of note, Waldemar Haffkine (1860-1930), the Katalin Kariko of the early XXth century who proposed vaccines to fight cholera and plague epidemics, had been trained in Metchnikoff's laboratory ⁷.

The photo of Metchnikoff posing like Pasteur in his most famous painting made by the Finnish artist Edelfelt, could be a tribute to Louis Pasteur, we are celebrating the 200th anniversary in 2022, who welcomed him in his institute, and also to the vaccines he had developed, and which have played such a major role to address this current pandemic.

Jean-Marc Cavaillon

⁶ Winkler MS, et al. Bridging animal and clinical research during SARS-CoV-2 pandemic: A new-old challenge. EBioMedicine. 2021 Apr; 66:103291.

⁷ Cavaillon J-M., Osuchowski M. Pandemics, COVID-19, sepsis and vaccines: a historical perspective. J Intensive Medicine, 2021, 1, 4-13

New European/International guidelines for patients on antithrombotic drugs requiring regional anaesthesia in the perioperative or intensive care setting



Neuraxial (spinal/epidural) and peripheral nerve blocks are an integral part of the daily work of anaesthetists around the world to ease or eliminate pain in patients. Bleeding is a potential complication and the risk is increased in perioperative patients on antiplatelet and/or anticoagulant drugs. Even intensive care physicians might face a challenging clinical situation of parenteral anticoagulant therapy with an epidural or deep nerve catheter in situ.

In a collaborative effort, the <u>European Society of Anaesthesiology and Intensive Care (ESAIC)</u> and the <u>European Society of Regional Anaesthesia (ESRA)</u> nominated a joint panel of experts to evaluate the available literature on the prevention of bleeding complications of nerve blocks in patients on antithrombotic drugs. The aim was to prepare an evidence based pragmatic guideline about reducing the risk of antithrombotic drug-induced haematoma formation related to the practice of regional anaesthesia and analgesia.

A systematic literature search was performed, examining seven drug comparators and 10 types of clinical intervention with the outcome being peripheral and neuraxial haematoma. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used for assessing the methodological quality of the included studies and for formulating recommendations. A Delphi process was used to prepare a clinical practice guideline. The guidelines have now been published in the European Journal of Anaesthesiology. The document illuminates the current state of knowledge in a clear form and provides 40 practical recommendations.

Besides recommended drug specific time intervals, an important new input/update has been given to the emerging availability of drug measurement used to guide certain time intervals.

In order to increase the reach and promote broad application, the guidelines are freely accessible via the ESRA website: <u>Regional anaesthesia in patients on antithrombotic drugs</u> Joint ESAIC/ESRA guidelines.

Christoph Schlimp



Eur J Anaesthesiol 2022; 39:100-132

GUIDELINES

Regional anaesthesia in patients on antithrombotic drugs

Joint ESAIC/ESRA guidelines

Sibylle Kietaibl, Raquel Ferrandis, Anne Godier, Juan Llau, Clara Lobo, Alan JR Macfarlane, Christoph J. Schlimp, Erik Vandermeulen, Thomas Volk, Christian von Heymann, Morné Wolmarans and Arash Afshari

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Prehospital use of tranexamic acid (TXA) in traumatic brain injury (TBI): New data emerging!



Haemostatic derangements may complicate initial TBI leading to exacerbation of lesions and haemorrhagic progression [1]. Recent observational data have confirmed laboratory coagulopathy in 20 percent of patients with isolated TBI upon hospital admission [2]. Fibrinolysis is meanwhile recognized as one key driver of TBI-associated coagulopathy and haemorrhagic progression of lesions [3,4]. The results from the CRASH-3 trial [5] including its benefits when given within three hours of injury, have promoted the antifibrinolytic tranexamic acid (TXA) into prehospital Emergency Medical Services (EMS) protocols. Indeed, early prehospital administration of 1g TXA iv to trauma patients on-scene was linked to blood clot stabilization, reduced fibrinolytic activity and decreased fibrin

degradation products [6]. The efficacy and safety of early out-of-hospital administration of TXA was recently assessed in two clinical trials [7,8].

The randomized, double-blind, three-group, multicenter phase II "Prehospital TXA for TBI"-trial examined whether different dosing regimen of TXA administered out-ofhospital within two hours of injury would result in improved six-month neurologic outcome (GOSE) in 966 non-shocked patients >/= 15 years with moderate/severe blunt/penetrating TBI [7]. The "Brain Injury: Prehospital Registry of Outcome, Treatments and Epidemiology of Cerebral Trauma (BRAIN-PROTECT)"-Study was a



retrospective multicenter cohort study (n = 1.827) on observational data into the Dutch prehospital cerebral trauma registry on patients treated for suspected severe TBI [8].



After controlling for confounders, the observational BRAIN-PROTECT cohort study reported increased mortality among patients with severe isolated TBI with 1g iv TXA prehospital [8]. The adjusted 12-month mortality was also higher in isolated severe TBI patients, and the sensitivity analyses showed consistent evidence for increased mortality after TXA in the same subgroup [8]. In the "Prehospital TXA for TBI"-trial, out-of-hospital TXA within two hours of injury showed

only an uncertain and small benefit on 6-month functional neurologic outcome in patients with suspected moderate/severe TBI [7]. In CRASH-3 in which one third of patients had a GCS </= 8 only small differences were reported in the primary efficacy analysis between TXA and placebo [5]. However, some benefit with TXA was reported for specific TBI subgroups and with specific dosing, e.g. in CRASH-3 after exclusion of patients with a GCS of 3 or bilateral unreactive pupils at baseline [5] or in the "Prehospital TXA for TBI"-trial among patients with intracranial haemorrhage on initial CT scan [5]. Secondary exploratory analyses of the "Prehospital TXA for TBI"-trial also indicated less progression of intracranial haemorrhage in the combined TXA group versus placebo [7].



In patients with isolated TBI current evidence is likely to be insufficient to recommend routine use of TXA as benefits, if present, are small, restricted to subgroups and with the mechanistic effect in these cohorts still insufficiently explained. It may be that the effect of TXA depends on the magnitude of TBI sustained, timing and dosing as well as on whether the patient is at risk for major or ongoing intracranial haemorrhage. Negative side effects with TXA, such as thromboembolism, occur with higher dosing and need to be considered. Using TXA cautiously seems prudent when best prehospital clinical judgment suggests that a patient has isolated severe TBI (based on GCS score ≤8 in combination with other suggestive clinical findings) without evidence of relevant extracranial injuries. Further sub-group and sensitivity analyses differentiated for injury severity and based upon individual patient data should be considered.

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Upcoming events



ISICEM 2021 - 41th International Symposium on Intensive Care and Emergency Medicine March 22-25, 2022, Brussels, Belgium https://www.isicem.org/1/Programme_new.asp

2022 Critical Care Congress, Virtual April 18 - 21, 2022 <u>https://www.sccm.org/Annual-</u> Congress/critical-care-conference





21th^h European Congress of Trauma & Emergency Surgery April 24–26, 2022, Oslo, Norway <u>https://www.estes-congress.org/</u>

ESICM LIVES 40, May 12-14, 2022, Madrid, Spain https://www.esicm.org/events/esicm-lives-40/





The Society for Cardiovascular Angiography and Interventions (SCAI) SCAI 2022 Scientific Sessions May 19-22, 2022, Atlanta, GA https://scai.org/scai2022



European Congress on Surgical Infections (SIS-E) June, 2023, Madrid, Spain https://sis-e.org/2022/



45th Annual Conference on Shock

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20th Congress of ESS September 21-23, 2023, Vienna, Austria





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by Andrea Szabó

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OUR SHOCK JOURNAL: SHOCKING CHANGES



On July 1, 2021 Daniel Remick, Boston University, Boston USA became the new Editor-in-Chief (EIC) for the Society's journal, *Shock[®]*. The journal thrived under the inspired leadership of the former EIC, Irshad Chaudry, and the interim EIC Mark Clemens. *Shock[®]* has several strong attributes including 1) An expert and dedicated Editorial Board, who also served as reviewers, 2) A robust impact factor, and 3) recognition as a journal that published mechanistically based studies.

Methods

Building on this base and Shock's strategic plan, several important changes have been instituted or will be shortly. First, the entire editorial board was substantially restructured by replacing the prior Associate Editors with four newly designated Associate Editors (AE). The new AEs include: Stefanie Flohé, University Hospital Essen, Germany, Marc Jeschke, University of Toronto, Canada, Yong-ming Yao, PLA General Hospital, Beijing, China and Basilia Zingarelli, University of Cincinnati, USA. These AEs have defined duties including managing manuscripts and recommending acceptance and continue our Asian and European collaborations. The second change is streamlining the submission of manuscripts by creating SIMple Submit (SIMS). SIMS allows authors to submit their papers in just two steps, replacing the prior 16 step process. SIMS includes a manuscript, since the process is now so easy. The fee is waived for active Shock members, or for investigators from resource poor countries. Third, editors may now reject manuscripts without sending them out for review. This will significantly decrease reviewer fatigue and allow reviewers to focus their energies on providing feedback to improve papers submitted to *Shock*[@].

<u>Results</u>

The journal has also recruited new and enthusiastic editorial board members. We will also start to have quarterly regular virtual meetings with the editorial board members with a formal agenda and minutes to increase communication and transparency. Other new initiatives will be implemented shortly, including increased use of social media to promote our papers, podcasts that highlight the important findings and initiating brief, but informative, reviews. Other journals have been contacted to allow referral to *Shock*[©] if they have a high quality but out-of-scope rejected manuscript. We will also begin recruiting Trainee Editors – trainees who will be mentored by an Associate Editor or EIC to learn how to evaluate manuscripts.

These changes allowing easier submission and streamlined expert review should help grow the reputation of *Shock*[©]. Please consider *Shock*[©] when submitting your next manuscript (but only if it is high quality).

Daniel Remick Editor-in-Chief, Shock[©]

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Last words about the ESS newsletter



Dear present ESS member,

If you like your ESS Winter Newsletter, please feel free to share it with your colleagues in the lab, department and/or institute. Perhaps, you could use this opportunity to suggest them to join us (a registration form can be found at the end of this Newsletter). Do not forget that we need you to keep improving our society so it stands proud and strong among other international Shock Societies.

This Newsletter, put together by your peers, belongs to you! We invite you to identify with it as members of the ESS. Moreover, we ask you to help us make it even better. Accordingly, we would be delighted to publish in our next issue any input you might be wishing to share with us (e.g. discussion on a given research/popular science topic, announce available positions in your lab, a contribution to the journal club corner, historical memories, comments about sepsis 3.0 etc.)

Dear past ESS member,

Please do not forget to renew your membership. We need all colleagues, junior and senior alike, to enable the ESS to host in its ranks the best representatives of the European Shock research - at the bedside and/or at bench alike.



Jean-Marc Cavaillon our Past-President

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