Volume: 4 **Issue: 2**
Year: 2023
DOI: 10.53811/ijtcmr.1330957

International Journal of Traditional and Complementary Medicine Research

Publisher
Duzce University

REVIEW

Fever and the Ageing Immune System, A Review

Seema Mahesh[1, 3*], Esther van der Werf[2], Mahesh Mallappa[3], George Vithoulkas[4, 5], Nai Ming Lai[6]

[1] Taylor's University, Faculty of Health and Medical Sciences, Subang Jaya, Malaysia.
[2]Louis Bolk Institute, Department of Infectious Diseases, Bunnik, Netherlands.
[3]Centre For Classical Homeopathy, Bengaluru, India.
[4]University of the Aegean, Department of Homeopathy, Mytilini, Greece.
[5]International Academy of Classical Homeopathy, Alonissos, Greece
[6] Taylor's University, Faculty of Health and Medical Sciences, Subang Jaya, Malaysia.

* Corresponding Author: Seema Mahesh, e-mail: bhatseema@hotmail.com

Received: 30.07.2023 Accepted: 24.08.2023

Abstract
Whether to treat fever in the elderly, is a question that has not yet been answered. This review examines the available evidence so far, to arrive at a comprehensive picture about this question. Aged population are a special category due to their lower basal body temperature, blunted fever response and existing co morbidities. The aging immune system undergoes many changes in all its faculties, which alters its ability to mount an efficient acute inflammatory response. In such a scenario, fever is mostly absent and there is a need to revise the fever criteria in the elderly. Having said that, the most successfully aging, centenarians, mount efficient febrile response during infections, indicating that aging itself may not be the reason for the reduced febrile response. Holistic medicine, such as homeopathy, views the fever scenario differently and advocates interference only when the immune system is helpless. The 'levels of health theory' explains that the healthiest benefit from fever while those with reduced immunity suffer from it. This theory may prove to be an invaluable clinical tool to arrive at definite clinical guidelines concerning the treatment of fever, especially in the elderly. However, it requires scientific investigation before it can be used as a clinical tool.
There is no conclusive evidence on whether fever must be treated or not in the elderly and whether holistic medicine may have a solution to this dilemma. This is a research gap that needs to be filled with quality studies in the current health scenario.
Keywords: Fever, Agieng, Elderly, Older Adults, Immunosenescence.

INTRODUCTION

Evolutionary mechanisms were not designed for longevity and yet, the world is aging today. The need to understand the aging immune system is more relevant than ever before in history. Fever in the elderly requires special consideration because of the inflammaging and immunosenescence that occur with age. This review examines the literature available regarding the special scenario of fever in the elderly in the context of acute inflammatory response and its modification with changes in the aging immune system.

ACUTE INFLAMMATION AND FEVER

The acute inflammatory response (AIR) was developed and maintained through evolution as a defence mechanism against injury and infection.[1] Galen considered it an essential process in healing, whereas Virchow identified it as a pathological process, that may be detrimental.[2] Immunology has come a long way since then and today we know the truth to be lying somewhere in between these two extremes. For example, it is known that AIR is essential for dealing with infecting pathogens effectively but, when it continues beyond necessary or when the response is stronger than required, it is detrimental to the organism.[3]

One of the cardinal features of AIR is fever.[1] Fever is defined as regulated elevation of core temperature achieved through the integrated behavioural,

physiological and biochemical processes that determine the balance between heat generation and elimination.[4] Heat seeking behaviour appeared 600 million years ago, even before the advent of adaptive immunity. Evolution has developed and maintained fever as a means to mount defence response during tissue injury and conserved it despite the heavy metabolic cost, implying a survival advantage from fever.[5]

With breach in tissue integrity by pathogens, the resident immune cells, recognize the foreign antigen, engulf it, and release pro inflammatory cytokines. IL1, in humans, is a pyrogenic cytokine that stimulates the conversion of arachidonic acid into prostaglandins. Prostaglandin E2 (PGE2), thus produced, acts upon the preoptic area of the hypothalamus through EP3 receptors to generate fever, which has manifold roles to play during AIR.[6] It acts as a systemic alarm whereby all the components of the immune system are primed for inflammation and neutralization of the pathogen.[7 – 10]

FEVER – THE YAY AND THE NAY

To begin with, febrile temperature was found to be detrimental to most pathogens and immune cells such as macrophages require febrile range temperature for efficient functioning.[11,12] Both the innate and adaptive immune systems of most organisms are programmed to respond with defensive functions at febrile range temperatures.[13] Increased recruitment of lymphocytes to the site of injury or infection occurs and the fever range thermal stress also acts on distinct cell types and regulates the adhesion cascade, necessary for lymphocytes to reach the site of infection. The 'lymphocyte – high endothelial venules - IL6' axis is responsive to thermal element of fever and improves immune surveillance in secondary lymphoid organs.[8] The lymphocytes neutralize the pathogens through aerobic and anaerobic killing, thus completing the task.[2]

Many studies have shown the benefit of survival from fever in an infected host.[2] Pathogen clearance is enhanced by fever and hindering fever during infections with antipyretic drugs has been shown to increase mortality in a trial.[13,14] Many researchers have used fever induction as a therapy for cancer and it has been observed, albeit not definitively, that children with autism improved considerably in their behaviour during a fever.[2,15,16]

Evidence suggests that the most important sequel to inflammation, viz. resolution of inflammation requires an efficient acute inflammatory response to be activated.[17] Studies in the last two decades have shown that the return of the tissue environment and the immune system to the normal state is an active process and does not passively result from removal of the pathogen.[18,19] If this fails, the tissue environment fails to return to its normal state as the pro inflammatory factors remain in the tissue environment, leading to the activation of chronic inflammatory phenomenon.[20,21] The acute inflammatory response itself has various checkpoints that it must pass through for the downstream resolution to be stimulated.[17,22] For example, PGE2, a *proinflammatory* cytokine, responsible for fever generation as stated, after the neutralization of bacteria, turns *anti-inflammatory* and signals for the phagocytosis of apoptotic neutrophils and their efferocytosis from the tissue environment. This ensures onset of the resolution.[23] In addition, febrile temperature of >38ºC inhibits further production of pro inflammatory cytokines but not anti-inflammatory cytokines, ensuring smooth resolution and return of homeostasis.[24] Many theories have proposed that interfering with the acute inflammatory process may result in the activation of chronic inflammatory diseases, which may contribute to the increasing trend of non-communicable diseases today.[25–27] The Immune system is constantly reorganizing itself to identify optimal functioning points.[28] When its efforts are thwarted by drugs, its response is subnormal, which may increase the inflammatory stimulus and in a deeper tissue than otherwise would have occurred.[21] This may lead to chronic inflammation in the deeper/more vital organ systems.

Despite evidence of fever as a beneficial phenomenon, there is widespread practice of suppressing fevers.[29–32] However, while exaggerated, or sometimes misplaced due to anxiety, putative damage from fever does exist.[33,34] Fever causes heavy metabolic burden and may cause death in people with compromised cardiorespiratory reserve such as the frail elderly.[13,31,35,36] In children, it is known to cause febrile convulsions and behavioural alterations.[10] Organ damage due to cell death and protein synthesis impairment is a real danger in high fevers.[37,38] Even though pathogen load decreased, febrile mice could still die from high fevers and fever in post-operative scenario was fatal.[13,39] In many conditions of decreased cardiorespiratory respiratory reserve, such as cardiac arrest and ischemic stroke, therapeutic hypothermia is practiced to avert major organ damage.[40,41] In fact,

in many situations, naturally occurring hypothermia was observed during infections which seemed to confer a survival advantage.[42]

Such opposing and equally strong evidence for and against fever behoves immunologists to investigate this further. Bhavani et al., have shown that fever patterns are not uniform in sepsis, and each pattern has a different outcome. The basic state of the individual seems to have a great bearing on the temperature developed, the effect on pathogen and on the host.[43] Therefore, many researchers believe that fever must be considered in each individual case before deciding the therapy.[44,45] The benefit seems to lie in a balance between pathogen clearance and tissue injury.[46]

IMMUNOSENESCENCE

The evolutionary theory of aging posits that evolution never really programmed for longevity. Its focus was on the continuity and survival of the species.[47] Therefore, many adaptive genes selected for optimal functioning and defence such as acute inflammatory response with high metabolic cost are required for the preservation of the individual until the reproductive age.[48] Post reproductive age, the same genes turn maladaptive and aging sets in as a chronic inflammatory process, termed as *antagonistic pleiotropy*.[48,49] This implies a regulated progressive decline of the organism. However, immunological studies have shown that it may not be as simplistic as that.[28] There are many other theories that propose different factors as instrumental in aging. For example, the *network theory*, considers the aging process to be controlled by various defence functions and their influence on the organism.[28,50] Each organism is subject to various stressors, physical, chemical, biological, and radiational. The network of defence against these stressors in an organism includes antioxidants (e.g., superoxide dismutase), heat shock proteins, Poly ADP Ribosyl Polymerase (PARP), DNA repair enzymes and other stress proteins. Genes that regulate these factors are stimulated by stress and the organism copes with stress. These stresses are beneficial to the organism at low levels and maintain the immune system in shape (hormetic effect). However, when they become overwhelming, they have a detrimental effect.[28] When the organism is unable to cope, macrophage activation occurs, resulting in a subclinical chronic inflammatory state. The theory further suggests that the outcome of longevity is a balance between the hormetic and detrimental effects of stress. Better coping capability implies increased longevity as seen in centenarians.[28] Chronic inflammation itself may not be responsible for frailty or decreased life span as it is present in both healthy and the diseased elderly. However, the ability to cope with pro-inflammatory status may make all the difference. There is a genetic component that decides the capacity to cope with stress. The theory suggests there are two such genetic factors involved – one that is responsible for inflammatory response – adding up over time and the second that confers robustness or frailty. This implies a combination of high inflammatory status and frailty gene will result in unsuccessful aging.[28]

Other theories of aging consider metabolic activity itself as responsible for aging - Effect of accumulation of cellular debris and telomere shortening over the years. Similarly, cellular oxidation products accumulating in the cells with increased reactive oxygen species are responsible for aging.[28,50,51]

They all seem to consider facets of a complex phenomenon and it appears that all of them are probable. A common thread running through all these theories is the existence of chronic inflammation in the process – a cause, or result of aging, known as *inflammaging*.[28,49,50,52-54] This is evidenced by changes in the immune system that is seen commonly in the elderly.[44,55,56] There is a global reduction in the activity of the innate, cellular, and humoral immunity. All elderly, whether healthy or with the disease, demonstrate increased IL6 – an indicator of inflammation. Thymic involution with age implies a decrease in lymphocytes.[57] Lymphocytes are reduced in number and changed in composition so that naïve T cells are lacking but activated T cells are increased in proportion in the elderly.[55] Cytokine production is predominantly Th2, and there is an increased expression of Cellular Adhesion Molecules (CAM).[49,55,56] Almost all immunoglobulins are expressed more in the elderly (except IG4) and so are non-organ-specific autoantibodies, while organ-specific autoantibodies are decreased. B lymphocytes, Natural Killer cells, and tissue-resident macrophages are decreased. Somatic cells reach a cell proliferation exhaustion, and lymphocytes cannot undergo clonal expansion during a pathogen challenge.[52,55]

These changes are relevant clinically as the elderly are shown to be more susceptible to infections with a lack of optimal response leading to serious complications of infections and increased mortality. This is especially so with novel pathogens. While the elderly maintain a good defence against known

pathogens, the inability for clonal expansion of T cells translates to subnormal defence to novel pathogens. Other factors such as predominant Th2 response and lack of febrile response also contribute to the severity of infections. The existence of comorbidities in the aged is associated with an increased risk of infections.[55] However, it was demonstrated through studies in centenarians that the process of aging is not uniform. Those with a better genetic endowment, the centenarians, and their offspring, showed better adaptive capability.[28,58]

FEVER IN THE ELDERLY

Body temperature in the elderly also adapts to the changed need according to the above-mentioned changes in the immune system. Basal body temperature, like the basal metabolic rate, is lower in the elderly.[59] This has been shown to confer survival advantage from the decrease in metabolic demand.[59] While successful aging is associated with adaptive hypothermia, it renders detecting infections in the aged difficult, as the body does not readily raise the temperature to the established febrile range. With every decade increase in age, a temperature drop of 0.15ºC was observed during the first 3 days of infections, emphasizing the lack of robust febrile response and the danger of missing a diagnosis in the elderly.[59,60,61] Many researchers have recommended a reduction of febrile range for the elderly to avoid missing an infection in diagnosis.[62] Most elderly seem to have a basal body temperature of <98.6ºF. Fever criteria for the elderly, therefore, have been recommended to be: even a single temperature reading of ≥2ºF above baseline or oral temperature of ≥99ºF or rectal temperature of ≥99.5ºF.[63]

Fever seems to be ambivalent in its effect on this age group. While many studies have shown the increased mortality from high fever, due to the extra cardiopulmonary stress and metabolic demand, many studies have also shown increased mortality from lack of fever, especially in septic patients. Ahkee et al. showed that lack of fever and leucocytosis, both characteristics of efficient AIR, was associated with increased mortality in community-acquired pneumonia scenarios in the elderly.[31,63,64,65,66] In the latest COVID 19 pandemic, the clinical presentation of severe dyspnoea and tachypnoea in the elderly was associated with decreased survival while those who presented with fever and headache, tended to survive.[54] While it is true that there have not been definitive studies to investigate the effect of fever in this age group, the elderly have been a majority population in many studies investigating the effect of fever.[67,68] Schulman et al. endeavoured to study the effect of reducing temperature with drugs in septic patients and had to abort their study due to the unacceptably high mortality in the treatment group when compared to those who were not treated for fever.[14] However, epidemiological studies of dengue have demonstrated that the elderly are more prone to develop severe dengue fever and dengue shock syndrome although, they did not present with the classical signs of dengue fever as described by the WHO for diagnosis, including fever.[68,69] Most of the elderly did not develop a high fever during infections but presented with discomfort or altered sensorium.[63] Over 60% of infected elderly did not mount a fever in response to even severe infections. Such blunted fever response was shown to be associated with increased mortality.[62,65] Hypothermia, a defence response to infection seems to confer a survival advantage in some elderly while being associated with increased mortality in others.[42,70] While therapeutic hypothermia is practiced[40,41] in ischemic stroke and myocardial infarction, in the infections scenario, there is ambiguity over the benefit/damage from fever.[40,41,31,33-35,42,70-75]

Antipyresis is practiced due to fear in the general population regarding harm from fever. While known to reduce discomfort in the febrile patient, the effect of these drugs on the immune response is ambiguous.[14,76-82]

IT IS A SPECTRUM REALLY!

Febrile response, as stated above requires effective cytokine response from the innate immunity, to which the adaptive immunity must react with downstream stimulation of the appropriate cells, cytokines, and eventually, the anti-inflammatory factors.[2,6,7,83] However, the effect of aging on these systems implies poor cytokine release, so that fever is not generated efficiently.[63,68,84] With activation of pro-inflammatory status, the anti-inflammatory response may be late or absent, causing undue damage, even end organs failure as seen in many dengue cases of the aged.[68] However, centenarians, who have ideal immune systems show febrile responses as efficient as young adults, indicating that unsuccessful aging is associated with damage caused by fever and successful aging implies efficiency of the AIR.[55,58] Two homeostatic mechanisms are shown to be at work during inflammation – linear and nonlinear.[47] The linear path involves a dose-response relationship to an

inflammatory stimulus. As the inflammatory stimulus increases, so does the immune response, establishing homeostasis. The nonlinear path involves an unpredictable chaotic path, where small changes in the initial conditions stimulate an amplified response, characterized by an undue explosion of inflammation and organ dysfunctions clinically.[47] The aged, with multiple co-morbidities and inflammaging may often develop the nonlinear response. This was demonstrated in the current pandemic of Corona Virus Disease – cytokine storm that occurred in the aged caused increased morbidity.[54,85,86]

As demonstrated, multiple factors, including genetics, oxidation, exposure to stress, influence the efficiency of the immune system in the aged.[28,47,51,58] In this context, the theory propounded by Vithoulkas may explain these confounding observations.[87] The *levels of health theory* states that each person is born with a certain possibility for health, determined by genetic and epigenetic influences at the moment of fertilization.[87] This is the potential that one may achieve if one lives right. Living right implies a healthy lifestyle, minimal psychological stress, relatively less exposure to infections, and least use of drugs/medications of any kind. Under such circumstances, a person ages successfully and preserves the ability to put up an efficient AIR well into old age. However, any of these conditions not being optimal tends to reduce the efficiency of the organism and bring down the 'level of health'.[87] These levels are relative and make up a spectrum with the healthiest people with a potential for the lifespan of over ninety years at the top and those born with severe genetic disorders and pathologies causing them to die in infancy at the bottom. Everyone else makes up the spectrum in between. The healthiest are characterized by the ability to mount efficient AIR and a lack of chronic inflammatory tendency. As we go down, there are people who develop recurrent infections, followed by those in whom chronic inflammations have set in and AIR is impaired. In these people, we may not perceive efficient AIR, but an altered, chaotic AIR which is detrimental to the being. The AIR which was beneficial to the 'higher level' people, will kill in the 'lower levels' due to the magnitude of the response and the inability of the body to control it.[87] Fundamentally, the level of health, decided by the influence of genetic inheritance and allostatic load, decides the ability to mount and the outcome of an AIR, especially fever.

This, to a great extent, explains the widely different outcomes from fever observed in the elderly. If a person has a well-preserved immune system, fever is beneficial, and it is advisable to let the fever run and achieve its ends. If the immune system is compromised in any way, then fever is detrimental.[58] This is supported by many immunological studies as well. It is seen that when there is a subnormal response to inflammatory stimulus in the local tissue, the inflammatory stimulus becomes stronger and attacks a deeper tissue than would have happened in the healthier systems.[21] Further, as shown in a study, fever patterns differed in the infection scenario and each pattern was shown to have a different outcome. Those who quickly mounted a high fever and showed quick resolution of fever were the least likely to die or suffer during sepsis. However, those who did not mount fever or developed hypothermia during sepsis were most likely to die.[43]

This means that every individual's response to an inflammatory stimulus may be peculiar to that individual. Mechanisms have been detected that help the body in this defence. It has been suggested that the preoptic hypothalamus may be involved in sensing the inflammatory stimulus and judging the energy resources available for mounting a response. It may decide whether a fever or hypothermia was more adaptable in that individual.[6] Further, glutathione, an antioxidant in the cells has been shown to direct the ability to raise fever in response to inflammatory stimulus.[88] This research is in the same vein as the levels of heath theory. Here, the researchers found that the level of glutathione in the cells is determined by the presence of chronic inflammation in the environment. In very healthy individuals without chronic inflammation, glutathione is very high and during AIR, there is barely any fever recognized as the process of inflammation is carried out with barely any cost to the individual. When the chronic inflammation is strong and deep and has been established, the glutathione is used up for combatting the oxidative stress and is very low in the cells. In such conditions, the body adapts to the absence of defence and develops hypothermia instead of fever. The people in between these two extremes are shown to be able to raise a high/efficient fever response during AIR as in them, the glutathione is available in moderate quantities.[88,89]

Thus, we see that while evolution developed fever as a defence, in the current scenario of increased longevity of organisms (humans and their domesticated animals), a new outlook and

understanding is necessary to interpret the AIR and fever response. Indiscriminate use of fever suppressive drugs has been proven to be detrimental, while fever suppression is necessary in many. The levels of health theory may have the answer to this and investigating the real-life truth behind this theory is warranted. If practical clinical diagnostic parameters may be developed to detect the level of health of the person developing fever, a more logical and beneficial approach may be advised to the physicians, leading to preservation of the efficiency of the immune system.

CONCLUSION

Fever has evolved as a defence against pathogenic invasion. However, in the scenario of increased longevity, it is shown to cause both increased survival and increased morbidity/mortality especially in the elderly. So far, there is no conclusive evidence for or against the administration of antipyretic drugs in the special scenario of the aging immune system. Individualised approach may be the solution with levels of health theory providing the tools for such an assessment. Until such tools are developed, each case may have to be clinically assessed before prescribing.

Author contributions: Conceptualization: [SM, MM]; Design: [SM]; Writing: [SM, MM, EvdW, GV, NML]; Supervision: [EvdW, GV, NML].

Conflict of interest: There is no potential conflict of interest relevant to this article.

Funding: We would like to thank Taylor's University Ageing Flagship Programme.

Declaration: This work was presented at 1st International Rumeli Congress on Food and Health Sciences.

REFERENCES

1. Kumar V, Abbas AK, Aster JC. *Robbins Basic Pathology E-Book*. Saintt Louis: Elsevier, 2017.
2. Korniluk A, Koper O, Kemona H *et al.* From inflammation to cancer. *Ir. J. Med. Sci. (1971 -)*2016;186:57–62.
3. Frangogiannis NG. Inflammation in cardiac injury, repair and regeneration. *Curr. Opin. Cardiol.* 2015;30:240–5.
4. Hasday JD, Thompson C, Singh IS. Fever, immunity, and molecular adaptations. *Compr. Physiol.* 2014;4:109–48.
5. Hasday JD, Fairchild KD, Shanholtz C. The role of fever in the infected host. *Microbes Infect.* 2000;2:1891–904.
6. Blomqvist A, Engblom D. Neural Mechanisms of Inflammation-Induced Fever. *Neuroscientist* 2018;24:381–99.
7. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat.Rev. Immunol.* 2015;15:335–49.
8. Fisher DT, Vardam TD, Muhitch JB *et al.* Fine-tuning immune surveillance by fever-range thermal stress. *Immunol.Res.* 2009;46:177–88.
9. Lin CD, Zhang YH, Zhang K *et al.* Fever Promotes T Lymphocyte Trafficking via a Thermal Sensory Pathway Involving Heat Shock Protein 90 and α4 Integrins. *Immunity* 2019;50:137–51.e6.
10. El-Radhi AS. *Clinical Manual of Fever in Children*. Cham: Springer International Publishing, 2018:179–92.
11. Kluger MJ, Ringler DH, Anver MR. Fever and Survival. *Science* 1975;188:166–8.
12. Lee C-T, Zhong L, Mace TA *et al.* Elevation in Body Temperature to Fever Range Enhances and Prolongs Subsequent Responsiveness of Macrophages to Endotoxin Challenge. *PLoS One* 2012;7:e30077.
13. Jiang Q, Cross AS, Singh IS *et al.* Febrile Core Temperature Is Essential for Optimal Host Defense in Bacterial Peritonitis. *Infect Immun.* 2000;68:1265–70.
14. Schulman CI, Namias N, Doherty J *et al.* The Effect of Antipyretic Therapy upon Outcomes in Critically Ill Patients: A Randomized, Prospective Study. *Surg Infect.* 2005;6:369–75.
15. Hobohm U. Fever therapy revisited. *Br. J.Cancer* 2005;92:421–5.
16. Megremi ASF. Is fever a predictive factor in the autism spectrum disorders? *Med.Hypotheses* 2013;80:391–8.
17. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat. Immunol.* 2005;6:1191–7.
18. Serhan CN. Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms. *FASEB J.* 2017;31:1273–88.
19. Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. *Semin. Immunol.* 2015;27:149–60.
20. Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution? *Int. J. Exp. Pathol.* 2006;88:85–94.
21. Nathan C, Ding A. Nonresolving Inflammation. *Cell* 2010;140:871–82.
22. Chan MM-Y, Moore AR. Resolution of inflammation in murine autoimmune arthritis is disrupted by cyclooxygenase-2 inhibition and restored by prostaglandin E2-mediated lipoxin A4 production. *J. Immun.* 2010;184:6418–26.
23. Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat.Rev. Immunol.* 2015;16:51–67.
24. Boneberg E-M, Hartung T. Febrile Temperatures Attenuate IL-1β Release by Inhibiting Proteolytic Processing of the Proform and Influence Th1/Th2 Balance by Favoring Th2 Cytokines. *J. Immun.* 2003;171:664–8.
25. Vithoulkas G, Carlino S. The "continuum" of a unified theory of diseases. *Med. Sci. Monit.* 2010;16:15.

26. Earn DJD, Andrews PW, Bolker BM. Population-level effects of suppressing fever. *Proc. R. Soc. B: Biol.* 2014;281:20132570.
27. Barnig C, Bezema T, Calder PC *et al.* Activation of Resolution Pathways to Prevent and Fight Chronic Inflammation: Lessons From Asthma and Inflammatory Bowel Disease. *Front.immunol.* 2019;10:1699.
28. FRANCESCHI CLAUDIO, BONAFÈ MASSIMILIANO, VALENSIN SILVANA *et al.* Inflamm-aging: An Evolutionary Perspective on Immunosenescence. *Ann. N. Y. Acad. Sci.* 2006;908:244–54.
29. El-Radhi AS. Fever management: Evidence vs current practice. *World J. Clin. Pediatr.* 2012;1:29–33.
30. Carey JV. Literature review: should antipyretic therapies routinely be administered to patient fever? *J. Clin. Nurs.* 2010;19:2377–93.
31. Kiekkas P, Velissaris D, Karanikolas M *et al.* Peak body temperature predicts mortality in critically ill patients without cerebral damage. *Heart & Lung* 2010;39:208–16.
32. Hew YH, Blebil AQ, Dujaili JA *et al.* Assessment of knowledge and practices of parents regarding childhood fever management in Kuala Lumpur, Malaysia. *Drugs Ther. Perspect.* 2018;35:29–35.
33. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med.* 1999;25:668–73.
34. Laupland KB, Shahpori R, Kirkpatrick AW *et al.* Occurrence and outcome of fever in critically ill adults. *Crit. Care Med.* 2008;36:1531–5.
35. Donoso A, Arriaga D. Fever and antipyretic therapy in the septic patient in the intensive care unit: an update. *Bol. Med. Hosp. Infant. Mex. (English Edition)* 2019;75,
36. Lee J-C, Cia C-T, Lee N-Y *et al.* Causes of death among dengue patients causes of death among hospitalized adults with dengue fever in Tainan, 2015: Emphasis on cardiac events and bacterial infections. *J. Microbiol. Immunol. Infect.* 2022;55:207–14.
37. Rice P, Martin E, He J-R *et al.* Febrile-Range Hyperthermia Augments Neutrophil Accumulation and Enhances Lung Injury in Experimental Gram-Negative Bacterial Pneumonia. *J. Immun.* 2005;174:3676–85.
38. Walter EJ, Hanna-Jumma S, Carraretto M *et al.* The pathophysiological basis and consequences of fever. *Crit. Care* 2016;20,
39. Barie PS, Hydo LJ, Eachempati SR. Causes and Consequences of Fever Complicating Critical Surgical Illness. *Surg. Infect.* 2004;5:145–59.
40. Chan PS, Berg RA, Tang Y *et al.* Association Between Therapeutic Hypothermia and Survival After In-Hospital Cardiac Arrest. *JAMA* 2016;316:1375–82.
41. Kurisu K, Yenari MA. Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise. *Neuropharmacology* 2018;134:302–9.
42. Liu E, Lewis K, Al-Saffar H *et al.* Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and Escherichia coli-induced systemic inflammation. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2012;302:R1372–R1383.
43. Bhavani SV, Carey KA, Gilbert ER *et al.* Identifying Novel Sepsis Subphenotypes Using Temperature Trajectories. *Am. J. Resp. Crit. Care Med.* 2019;200:327–35.
44. Caruso C, Buffa S, Candore G *et al.* Mechanisms of immunosenescence. *Immun. Ageing* 2009;6,
45. Doyle JF, Schortgen F. Should we treat pyrexia? And how do we do it? *Crit. Care* 2016;20:303.
46. Niven DJ, Laupland KB. Pharmacotherapy of fever control among hospitalized adult patients. *Expert Opin Pharmacother* 2013;14:735–45.
47. Vitale B. Holistic Approach to the Immunobiology of Aging (view on the turn of millenium). *Acta Clin.Croat.* 2019,
48. Zainabadi K. A brief history of modern aging research. *Exp.Gerontol.* 2018;104:35–42.
49. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat.Rev. Cardiol.* 2018;15:505–22.
50. Franceschi C, Campisi J. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. *J. Gerontol. - Biol. Sci. Med. Sci.* 2014;69:S4–S9.
51. Skwarło-Sońta K. Functional connections between the pineal gland and immune system. *Acta Neurobiol. Exp. (Wars)* 1996;56:341–57.
52. Jenny NS. Inflammation in aging: cause, effect, or both? *Discov. Med.* 2012;13:451–60.
53. Meftahi GH, Jangravi Z, Sahraei H *et al.* The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging." *Inflamm. Res.* 2020;69:825–39.
54. Perrotta F, Corbi G, Mazzeo G *et al.* COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging clin. exp. res.* 2020;32:1599–608.
55. Ginaldi L, Loreto MF, Corsi MP *et al.* Immunosenescence and infectious diseases. *Microbes Infect.* 2001;3:851–7.
56. Dunn RM, Busse PJ, Wechsler ME. Asthma in the elderly and late-onset adult asthma. *Allergy* 2017;73:284–94.
57. MILLER R. Aging and immune function: Cellular and biochemical analyses. Exp.Gerontol. 1994;29:21–35.
58. Cossarizza A, Ortolani C, Monti D *et al.* Cytometric analysis of immunosenescence. *Cytometry* 1997;27:297–313.

59. Waalen J, Buxbaum JN. Is Older Colder or Colder Older? The Association of Age With Body Temperature in 18,630 Individuals. *J. Gerontol. - Biol. Sci. Med. Sci.*2011;66A:487–92.
60. Roghmann M-C, Mackowiak PA, Warner J. The Relationship between Age and Fever Magnitude. *Am. J. Med. Sci.* 2001;322:68–70.
61. Turkulov V, Brkic S, Sevic S *et al.* Fever of unknown origin in elderly patients. *Srp. Arh. Za Celok. Lek* 2011;139:64–8.
62. Norman DC. Fever in the Elderly. *Clin. Infect. Dis.* 2000;31:148–51.
63. Cristofaro PA. Infection and Fever in the Elderly. *J. Am. Podiatr. Med. Ass.* 2004;94:126–34.
64. Guzmán MG, Kouri G, Bravo J *et al.* Effect of age on outcome of secondary dengue 2 infections. *Int. J. Infect. Dis.* 2002;6:118–24.
65. Wiewel MA, Harmon MB, van Vught LA *et al.* Risk factors, host response and outcome of hypothermic sepsis. *Crit. Care* 2016;20:328.
66. AHKEE SUNKET, SRINATH LATHA, RAMIREZ JULIO. Community-Acquired Pneumonia in the Elderly: Association of Mortality With Lack of Fever and Leukocytosis. *South. Med. J.* 1997;90:296–8.
67. Zhang Z, Chen L, Ni H. Antipyretic Therapy in Critically Ill Patients with Sepsis: An Interaction with Body Temperature. *PLoS One* 2015;10:e0121919.
68. Lin RJ, Lee TH, Leo YS. Dengue in the elderly: a review. *Expert. Rev. Anti. Infect. Ther.* 2017;15:729–35.
69. Rowe EK, Leo YS, Wong JG *et al.* Correction: Challenges in Dengue Fever in the Elderly: Atypical Presentation and Risk of Severe Dengue and Hospita-Acquired Infection. *PLoS Negl. Trop. Dis.* 2014;8:e 2777, corrected: e2886.
70. Brody GM. Hyperthermia and Hypothermia in the Elderly. *Clin. Geriatr. Med.* 1994;10:213–29.
71. Tiruvoipati R, Ong K, Gangopadhyay H *et al.* Hypothermia predicts mortality in critically ill elderly patients with sepsis. *BMC Geriatr.* 2010;10:70.
72. Peres Bota D, Lopes Ferreira F, Mélot C *et al.* Body temperature alterations in the critically ill. *Intensive Care Med.* 2004;30:811–6.
73. Egi M, Makino S, Mizobuchi S. Management of fever in critically ill patients with infection. *J. Emerg. Crit. Care Med.* 2018;2:10–.
74. Jampel HD, Duff GW, Gershon RK *et al.* Fever and immunoregulation. III. Hyperthermia augments the primary in vitro humoral immune response. *J. Exp. Med.* 1983;157:1229–38.
75. Sundén-Cullberg J, Rylance R, Svefors J *et al.* Fever in the Emergency Department Predicts Survival of Patients With Severe Sepsis and Septic Shock Admitted to the ICU*. *Crit. Care Med.* 2017;45:591–9.
76. Rajakariar R. COX-2 in Inflammation and Resolution. *Mol.Interv.* 2006;6:199–207.
77. Veteikis D. Anthropogenic and temporal components in a complex trigger of type 1 diabetes suggest the active participation of antipyretics. *Med. Hypotheses* 2016;93:126–31.
78. Young P, Saxena M, Bellomo R *et al.* Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. N Engl J Med 2015;373:2215–24.
79. Deen J, von Seidlein L. Paracetamol for dengue fever: no benefit and potential harm? *Lancet Glob.Health* 2019;7:e552–e553.
80. Ludwig J, McWhinnie H. Antipyretic drugs in patients with fever and infection: literature review. *Br. J. Nurs.* 2019;28:610–8.
81. Lell B, Sovric M, Schmid D *et al.* Effect of Antipyretic Drugs in Children with Malaria. *Clin. Infect. Dis.* 2001;32:838–41.
82. Eyers S, Weatherall M, Shirtcliffe P *et al.* The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analyis. *J. R. Soc. Med.* 2010;103:403–11.
83. Eskilsson A, Matsuwaki T, Shionoya K *et al.* Immune-Induced Fever Is Dependent on Local But Not Generalized Prostaglandin E(2) Synthesis in the Brain. *J. Neurosci.* 2017;37:5035–44.
84. Hubbard RE, Woodhouse KW. Frailty, inflammation and the elderly. *Biogerontology* 2010;11:635–41.
85. Nikolich-Zugich J, Knox KS, Rios CT *et al.* SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. *GeroScience* 2020;42:505–14.
86. Pence BD. Severe COVID-19 and aging: are monocytes the key? *GeroScience* 2020;42:1051–61.
87. Vithoulkas G. *Levels of Health*. 3rd ed. Alonissos, Greece: International Academy of Classical Homeopathy, 2019.
88. Wrotek S, Sobocińska J, Kozłowski HM, *et al.* A. New insights into the role of glutathione in the mechanism of fever. *Int. J. Mol. Sci.*. 2020;19:1393.
89. Surana NK, Kasper DL. Approach to the Patient with an Infectious Disease. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. *Harrison's Principles of Internal Medicine.* 20th ed. McGraw-Hill;2018:Chapter 115. Accessed October 15, 2020. https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192019106