Stress-induced hyperglycemia is a valuable biomarker in febrile neutropenia

Stress-induced hyperglycemia (SIH) is a transient condition that occurs in patients with acute diseases such as trauma, stroke, surgery and sepsis. Claude Bernard, the eminent French physiologist, described for the first time in 1855 that critically-ill patients tended to show hyperglycemia (1). In the beginning, it was supposed to be an ancient and adaptive response back to 1925 when Otto Warburg discovered that cancer cells obtained a selective advantage by glycolysis (8), thus the "Warburg effect" can be viewed as the result of the trade-off between the energetic and the plastic needs of cancer cells to sustain rapid proliferation. Wen et al. have suggested similar mechanisms for the inflammatory response that even Otto Warburg apparently missed (Figure 1). Pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS) are able to provoke insulin resistance in the liver and smooth muscle, contributing to SIH, and thereby sparing and diverting glucose to monocytes and other immune cells involved in the inflammatory response. At the same time, sepsis induces profound metabolic changes in these immune cells, including a switch to anaerobic glycolysis, resembling the "Warburg effect" (9). It is possible that the biological meaning of SIH could precisely involve a fine-tuning of their metabolic routes, to obtain a maximum performance during sepsis, while limiting the rise of reactive oxidative species coming from the stressed mitochondria. An early adaptive response is feasible at the beginning of infection (10), and astonishing as it might be, glucose itself behaves
as a pro-inflammatory molecule\(^{(11)}\). In the late phase of sepsis, this physiological program could turn into a deleterious feedback loop with higher releases of pro-inflammatory molecules and a stronger response to LPS\(^{(12)}\). Thus, SIH might be considered as a compound biomarker indicating both the presence of sepsis and its progression.

In the field of FN, there is already some clinical support to sustain this biological scenario. In a recent report, we analyzed 692 cancer patients with FN and apparent clinical stability at the onset of infection. We developed a prediction model for sepsis-related complications combining an expression of the individual vulnerability (chronic diseases and the performance status), severe mucositis and two biological parameters: precisely monocytopenia and SIH\(^{(13)}\). The prevalence of SIH among patients with neutropenic infections is elevated (16-67\%), and it predicts unfavorable outcomes as shown in Table 1. However, the majority of these reports are retrospective and small-sized, so the clinical associations are, at best, hypothesis-generating. Variability in the design and the definition of SIH in each study does not allow drawing definitive conclusions, but are encouraging for further research to validate the role of SIH as a prognostic marker in large prospective studies. Interestingly, these results are also consistent with previous research in the non-cancer population. SIH is one of the major physiological changes in non-neutropenic patients with sepsis, in which it might represent a useful tool for prognostic evaluation and diagnosis of site-specific infections\(^{(14)}\). Moreover, SIH is an independent predictor of adverse outcome, in a pleiad of diseases and clinical settings, such as trauma\(^{(15)}\), surgery\(^{(16)}\), brain injuries\(^{(17)}\), stroke and myocardial infarction.

In summary, it is said that: “There is nothing new under the sun but there are lots of old things we do not know”\(^{(18)}\). SIH is probably one of those integrative “old concepts” that is now being revisited with increasing interest in the field of acute diseases. A new piece in this puzzle is provided by Matias et al. in the specific setting of acute leukemia induction treatment\(^{(19)}\). Future prospects may transform this easily available information into new approaches to stratify and treat neutropenic infections.

### Table 1 - The relationship between stress-induced hyperglycemia and clinical outcomes in immunosuppressed cancer patients

| Author                  | Clinical setting | n  | Clinical outcome according to SIH                                                                 |
|-------------------------|------------------|----|--------------------------------------------------------------------------------------------------|
| Matias et al.\(^{(20)}\)| Adult AL         | 280| SIH was associated to life-threatening complications and infection-related mortality.              |
| Roberson et al.\(^{(20)}\)| Childhood ALL    | 871| There were not significant differences in CR rate, EFS or OS.                                    |
| Sonabend et al.\(^{(20)}\)| Childhood ALL    | 135| Patients with SIH were more likely to be admitted for FN, and suffered more documented infections.|
| Derr et al.\(^{(21)}\)   | Adult BMT        | 382| SIH was associated to infections and bacteremia.                                                  |
| Weiser et al.\(^{(22)}\) | Adults ALL       | 278| Shorter CR duration and median survival is reported.                                               |
| Soysal et al.\(^{(23)}\) | FN               | 86 | Sepsis and complicated infections were more likely in patients with SIH.                          |
| Carmona-Bayonas et al.\(^{(13)}\)| FN       | 175| SIH was an independent predictor of life-threatening complications in apparently stable patients.  |
| Ali et al.\(^{(24)}\)    | Adult AML        | 289| SIH is associated to increased hospital mortality.                                                 |
| Fuji et al.\(^{(24)}\)   | Adult BMT        | 112| Increased risk of organ dysfunction, GVHD and NRM.                                                 |

SIH: stress-induced hyperglycemia; AL: acute leukemia; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: complete remission; EFS: event-free survival; OS: overall survival; FN: febrile neutropenia; BMT: bone marrow transplantation; GVHD: graft versus host disease; NRM: non-relapse mortality

### References

1. Bernard C. Leçons de physiologie experimentale appliqué a la medicine. vol. 1. Paris: Bailleure; 1855.
2. Wolf RE, Birbara CA. Meningococcal infections at an army training center. Am J Med. 1968; 44(2):243-55.
3. Matias CN, Lima V, Teixeira HM, Souto FR, Magalhães V. Hyperglycemia increases complicated infection rate and mortality during induction therapy of adult acute leukemia patients. Rev Bras Hematol Hemoter. 2013;35(1):39-43.
4. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006;106(10):2258-66.
5. Ahn S, Lee YS. Predictive factors for poor prognosis febrile neutropenia. Curr Opin Oncol. 2012;24(4):376-80.

6. Ali NA, O’Brien JM, Blum W, Byrd JC, Klisovic RB, Marcucci G, et al. Hyperglycemia inpatients with acute myeloid leukemia is associated with increased hospital mortality. Cancer. 2007;110(1):96-102.

7. Zhai L, Ballinger SW, Messina JL. Role of reactive oxygen species in injury-induced insulin resistance. Mol Endocrinol. 2011;25(3):492-502.

8. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124(3215):269–70.

9. Wen H, Ting JP, O’Neill LA. A role for the NLRP3 inflammasome in metabolic diseases--did Warburg miss inflammation? Nat Immunol. 2012;13(4):352-7.

10. Yeh MC, Mukaro V, Hii CS, Ferrante A. Regulation of neutrophil-mediated killing of Staphylococcus aureus and chemotaxis by c-jun NH2 terminal kinase. J Leukoc Biol. 2010;87(5):925-32.

11. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med. 2004;30(5):748-56.

12. Layendyk JP, Schabbauer GA, Tencati M, Holscher T, Pawlinski R, Mackman N. Genetic analysis of the role of the PI3K-Akt pathway in lipopolysaccharide-induced cytokine and tissue factor gene expression in monocytes/macrophages. J Immunol. 2008;180(6):4218-26.

13. Carmona-Bayonas A, Gómez J, González-Billalabeitia E, Canteras M, Navarrete A, Gonzálvez ML, et al. Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. Br J Cancer. 2011;105(5):612-7.

14. Richards JE, Kauffmann RM, Zuckerman SL, Obremskey WT, May AK. Relationship of hyperglycemia and surgical-site infection in orthopaedic surgery. J Bone Joint Surg Am. 2012;94(13):1181-6. Comment in: J Bone Joint Surg Am. 2012;94(13):e98.

15. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma. 2004;56(5):1058-62.

16. Ata A, Lee J, Bestle SL, Desemone J, Stain SC. Postoperative hyperglycemia and surgical site infection in general surgery patients. Arch Surg. 2010;145(9):858-64. Comment in: Arch Surg. 2011;146(3):368-9; author reply 370; Arch Surg. 2011;146(3):369-70; Arch Surg. 2010;145(9):864;Arch Surg. 2011;146(3):369; author reply 370.

17. Jeremitsky E, Omert LA, Dunham CM, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma. 2005;58(1):47-50.

18. Bierce A. The Devil’s Dictionary. Oxford University Press, USA; 1999.

19. Roberson JR, Spraker HL, Shelsjo J, Zhou Y, Inaba H, Metzger ML, et al. Clinical consequences of hyperglycemia during remission induction therapy for pediatric acute lymphoblastic leukemia. Leukemia. 2009;23(2):245-50.

20. Sonabend RY, McKay SV, Okcu MF, Yan J, Raymond MW, Margolin JF. Hyperglycemia during induction therapy is associated with increased infectious complications in childhood acute lymphocytic leukemia. Pediatr Blood Cancer. 2008; 51(3):387-92.

21. Derr RL, Hsiao VC, Saudek CD. Antecedent hyperglycemia is associated with an increased risk of neutropenic infections during bone marrow transplantation. Diabetes Care. 2008; 31(10):1972-7.

22. Weiser MA, Cabanillas ME, Konopleva M, Thomas DA, Pierce SA, Escalante CP, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone / methotrexate cytarabine regimen. Cancer. 2004;100(6):1179-85. Comment in: Cancer. 2004;101(5):1100-1; author reply 1101.

23. Soysal DE, Karakus V, Seren AR, Tatar E, Celik M, Hizar S. Evaluation of transient hyperglycemia in non-diabetic patients with febrile neutropenia. Eur J Intern Med. 2012;23(4):342-6.

24. Fuji S, Kim SW, Mori S, Fukuda T, Kamiya S, Yamasaki S, et al. Hyperglycemia during the neutropenic period is associated with a poor outcome in patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation. Transplantation. 2007;84(7):814-20.