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The series *Annual Update in Intensive Care and Emergency Medicine* is the continuation of the series entitled *Yearbook of Intensive Care Medicine* in Europe and *Intensive Care Medicine: Annual Update* in the United States.

Common Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPB	Cardiopulmonary bypass
CT	Computed tomography
CVP	Central venous pressure
DO_2	Oxygen delivery
EKG	Electrocardiogram
EVLW	Extravascular lung water
FiO_2	Inspired fraction of oxygen
GEDV	Global end-diastolic volume
ICU	Intensive care unit
IL	Interleukin
LV	Left ventricular
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor kappa-B
NO	Nitric oxide
OR	Odds ratio
PAC	Pulmonary artery cather
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
PET	Positron emission tomography
RBC	Red blood cell
RCT	Randomized controlled trial
ROS	Reactive oxygen species
RRT	Renal replacement therapy
RV	Right ventricular
$ScvO_2$	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced lung injury
V_T	Tidal volume

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Infections and Sepsis

Fever Management in Intensive Care Patients with Infections

P. Young and M. Saxena

Introduction

> 'Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever' [1].

Fever is one of the cardinal signs of infection and, nearly 120 years after William Osler's statement in his address to the 47th annual meeting of the American Medical Association [1], infectious diseases remain a major cause of morbidity and mortality. Despite this, it is unclear whether fever itself is truly the enemy or whether, in fact, the febrile response represents an important means to help the body fight infection. Furthermore, it is unclear whether the administration of antipyretic medications or physical cooling measures to patients with fever and infection is beneficial or harmful [2, 3]. Here, we review the biology of fever, the significance of the febrile response in animals and humans, and the current evidence-base regarding the utility of treating fever in intensive care patients with infectious diseases.

The Biology of Fever

Regulation of Normal Body Temperature

Thermoregulation is a fundamental homeostatic mechanism that maintains body temperature within a tightly regulated range. The ability to internally regulate body temperature is known as endothermy and is a characteristic of all mammals and birds. The thermoregulatory system consists of an afferent sensory limb, a central

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processing center, and an efferent response limb. In humans, the central processing center controlling the thermoregulatory set-point is the hypothalamus. Both warm-sensitive and cold-sensitive thermoreceptors are involved in the afferent limb. Stimulation of the cold-sensitive receptors activates efferent responses relayed via the hypothalamus that reduce heat loss and increase heat production. These responses include reducing blood flow to the peripheries and increasing heat production by mechanisms including shivering. Conversely, stimulation of warm-sensitive receptors ultimately increases heat loss through peripheral vasodilation and evaporative cooling caused by sweating.

The Cellular and Molecular Basis of the Febrile Response

Upward adjustment of the normal hypothalamic thermoregulatory set-point leading to fever is typically part of a cytokine-mediated systemic inflammatory response syndrome that can be triggered by various infectious etiologies including bacterial, viral, and parasitic infections as well as by a range of non-infectious etiologies including severe pancreatitis and major surgery.

In patients with sepsis, the febrile response involves innate immune system activation via Toll-like receptor 4 (TLR-4). This activation leads to production of pyrogenic cytokines including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. These pyrogenic cytokines act on an area of the brain known as the organum vasculosum of the laminae terminalis (OVLT) leading to the release of prostaglandin E_2 (PGE_2) via activation of the enzyme cyclo-oxygenase-2 (COX-2). PGE_2 binds to receptors in the hypothalamus leading to an increase in heat production and a decrease in heat loss until the temperature in the hypothalamus reaches a new, elevated, set-point. Once the new set-point is attained, the hypothalamus maintains homeostasis around this new set-point by the same mechanisms involved in the regulation of normal body temperature. However, in addition, there are a number of important specific negative feedback systems in place that prevent excessive elevation of body temperature. One key system is the glucocorticoid system, which acts via nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1). Both these mediators have anti-inflammatory properties and downregulate the production of pyrogenic cytokines, such as IL-1β, IL-6, and TNF-α. The febrile response is further modulated by specific antipyretic cytokines including IL-1 receptor antagonist (IL-1RA), IL-10, and TNF-α binding protein.

Heat Shock Proteins and the Febrile Response

The negative feedback systems outlined above are not the only mechanisms that exist to protect cells from being damaged by the febrile response. In addition, the heat shock proteins (HSPs) provide intrinsic resistance to thermal damage. Genes encoding the HSPs probably first evolved more than 2.5 billion years ago. They

represent an important system providing protection to cells, not only against extremes of temperature, but also against other potentially lethal stresses including toxic chemicals and radiation injury. During heat-stress, transcription and translation of HSPs is upregulated. HSPs can then trigger refolding of heat-damaged proteins preserving them until heat-stress has passed or, if necessary, can transport denatured proteins to organelles for intracellular degradation. As well as providing protection against cellular damage from the thermal stress induced by fever, the HSPs may themselves be important regulators of the febrile response. For example, HSP 70 inhibits pyrogenic cytokine production via NF-κB. HSPs also inhibit programmed cell death, which might otherwise be induced by an invading pathogen.

The Physiological Consequences of Fever

The febrile response leads to a marked increase in metabolic rate. In humans, generating fever through shivering increases the metabolic rate above basal levels by six-fold [4]. In critically ill patients with fever, cooling reduces oxygen consumption by about 10 % per °C decrease in core temperature and significantly reduces cardiac output and minute ventilation [5]. Any potential benefit of the febrile response needs to be weighed against this substantial metabolic cost.

The Immunological Consequences of Fever

Temperatures in the physiological febrile range stimulate the maturation of murine dendritic cells. This is potentially important because dendritic cells act as the key antigen presenting cells in the immune system. Human neutrophil cell motility and phagocytosis are enhanced by temperatures in the febrile range, and growth of intracellular bacteria in human macrophages *in vitro* is reduced by temperatures in the febrile range compared to normal temperatures. Murine macrophages demonstrate a range of enhanced functions at temperatures in the febrile range. These effects include enhanced expression of the Fc receptors that are involved in mediating antibody responses, and enhanced phagocytosis. Temperatures in the physiological febrile range enhance binding of human lymphocytes to the vascular endothelium. This L-selectin-mediated binding is important in facilitating lymphocyte migration to sites of tissue inflammation or infection. In mice, T lymphocyte-mediated killing of virus-infected cells is increased by temperatures in the febrile range and helper T-cell potentiation of antibody responses is enhanced. In contrast to other cells of the immune system, the cytotoxic activity of natural killer cells is reduced by temperatures in the febrile range compared to normal body temperature. Although their functions are enhanced by temperatures in the physiological febrile range (38–40 °C), neutrophils and macrophages have substantially reduced function at temperatures of $\geq$ 41 °C.