

## Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

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## Figure Legends

**Figure 1.** At rest glucocorticoids (e.g., cortisol) are produced from the zona fasciculata of the adrenal cortex upon stimulation by adrenocorticotropic hormone (ACTH) released in the blood from the anterior pituitary gland. Both corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) synthesized in the hypothalamus contribute to the synthesis and release of ACTH by pituitary cells. During stress, the synthesis of ACTH is additionally stimulated by norepinephrine, mainly produced in the Locus Ceruleus. At the level of inflamed tissues, terminal nerve endings of afferent fibers of the autonomic nervous system (ANS) have receptors for damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) allowing them to sense the threat and activate the noradrenergic/CRH system. These DAMPs and PAMPs can also directly stimulate adrenal cortex cells that possess Toll-like receptors (TLR), resulting in ACTH-independent cortisol synthesis. In addition, paracrine routes allow the medulla to also stimulate glucocorticoid synthesis independently of ACTH.