

## Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

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DOI:

[10.1007/s00134-017-4914-x](https://doi.org/10.1007/s00134-017-4914-x)

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*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Annane, D, Pastores, S, Arlt, W, Balk, R, Beishuizen, A, Briegel, J, Carcillo, J, Christ-Crain, M, Cooper, MS, Marik, P, Umberto Meduri, G, Olsen, K, Rochweg, B, Rodgers, S, Russell, J & Van den Berghe, G 2017, 'Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)', *Intensive Care Medicine*, vol. 43, no. 12, pp. 1781-1792. <https://doi.org/10.1007/s00134-017-4914-x>

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**Table 1.** Main Mechanisms of Critical Illness Related Corticosteroid Insufficiency

General defect	Main mechanisms	Key factors
Decrease in cortisol production	Necrosis/hemorrhage	Acute kidney failure; hypo-coagulation; disseminated intravascular coagulation; cardiovascular collapse; tyrosine kinase inhibitors
Altered adrenal synthesis of cortisol	Decreased availability of esterified cholesterol	Depletion in adrenal storage regulated by annexin A1 – formyl peptide receptors Down-regulated Scavenger Receptor-B1
	Inhibition of steroidogenesis	Immune cells / Toll like receptors /cytokines
		Drugs (e.g., sedatives, corticosteroids) ACTH-like molecules (e.g., corticostatins)
Altered synthesis of CRH/ACTH	Necrosis/hemorrhage	Cardiovascular collapse; disseminated intravascular coagulation; treatment with vasopressor agents
	Inhibition of ACTH synthesis	Glial cells / nitric oxide mediated neuronal apoptosis
		Increased negative feedback from circulating cortisol following up-regulation of ACTH-independent mechanisms of cortisol synthesis
		Drugs (e.g., sedatives, anti-infective, psychoactive agents) Inappropriate cessation of glucocorticoid treatment
Alteration of cortisol metabolism	Decreased cortisol transport	Down-regulation of liver synthesis of cortisol-binding globulins and albumin
	Reduced cortisol breakdown	Decreased expression and activity of the glucocorticoid inactivating 5-reductase enzymes in the liver with putative role of bile acids; Decreased expression and activity of the hydroxysteroid dehydrogenase in the kidney
Target tissue resistance to cortisol	Inadequate glucocorticoid receptor alpha (GR- $\alpha$ ) activity	Decreased expression and decreased transcription; unclear mechanisms – NF-kappa B driven?