

**Genes list:** CALCA, CRP, TREM1, PLAUR, LBP, IL6, HMGB1, ELANE, CXCL8, IL10, IL1B, S100A8, S100A9, S100A12, CD14, FCGR1A, ITGAM, C3AR1, C5AR1, LCN2, CXCL10, IFNG, IFNA, IFNB, CCL19, CCL25, CX3CR1, P2RX7, PTX3, TNFSF10, MMP8, MMP9, HLA-DR, TNF, MYD88, NLRP3, TLR2, TLR4, NOTCH1, BCL2, PDCD1, CCL2, ARG1, IL1R2, CD177, OLFM4, MAPK14, VCAM1, ICAM1, SOCS3, GATA3, CCR7, CCR2, HIF1A .

11 pathways in sepsis, with an updated genes:

## 1. Inflammatory and Immune Pathways

- **Key Genes:** TNF, IL1B, IL6, IL10, TLR2, MYD88, NLRP3, CD14, CXCL8, CXCL10, PDCD1 (PD-1), SOCS3, CCR2, CCR7, FCGR1A, S100A8/S100A9/S100A12, TREM1, HMGB1, ITGAM, IFNG, IL1R2.
- **Role:** Dysregulated inflammation leads to cytokine storm, immune activation, and immune suppression in late-stage sepsis.

## 2. Pathogen Recognition Pathways

- **Key Genes:** TLR2, TLR4, CD14, MYD88, P2RX7, NLRP3, LBP, CEACAM4, TREM1, HMGB1.
- **Role:** Recognizes **PAMPs** (pathogen-associated molecular patterns) and **DAMPs**, initiating inflammatory signaling through PRRs (pattern recognition receptors).

## 3. Adaptive Immune Pathways

- **Key Genes:** HLA-DR, PDCD1 (PD-1), IL10, GATA3, CCR7, CCR8, BCL2, CCL25, CCL19.
- **Role:** Governs T-cell activation, differentiation, and survival, balancing pro-inflammatory and anti-inflammatory responses.

## 4. Coagulation Pathways

- **Key Genes:** PLAUR, C3AR1, C5AR1, S100A8/S100A9, VCAM1, ICAM1, PTX3, CRP.
- **Role:** Links inflammation and coagulation, contributing to **disseminated intravascular coagulation (DIC)**, thrombosis, and bleeding.

## 5. Vascular and Endothelial Pathways

- **Key Genes:** VCAM1, ICAM1, HIF1 (HIF1A), TNF, IL1B, MMP8, MMP9, CX3CR1, CALCA, TREM1, HMGB1, ITGAM, IFNG, NOTCH1.
- **Role:** Endothelial activation and dysfunction lead to vascular leakage, hypoperfusion, and tissue ischemia.

## 6. Oxidative Stress Pathways

- **Key Genes:** P2RX7, CD177, OLFM4, MMP8, MMP9, S100A8/S100A9, NLRP3, CEACAM4, ELANE, IFNA, IFNB.
- **Role:** Overproduction of ROS damages lipids, proteins, and DNA, exacerbating tissue injury.

## 7. Hypoxia and Metabolic Pathways

- **Key Genes:** HIF1 (HIF1A), ARG1, LCN2, IL10, MAPK14, PTX3, CALCA.
- **Role:** Hypoxia-induced metabolic shifts (e.g., glycolysis) and mitochondrial dysfunction impair energy production and worsen organ failure.

## 8. Apoptosis and Cell Death Pathways

- **Key Genes:** BCL2, TNFSF10 (TRAIL), NLRP3, P2RX7.
- **Role:** Excessive apoptosis (e.g., lymphocyte death) and inflammatory cell death (e.g., pyroptosis) weaken immune defenses and increase tissue damage.

## 9. Complement Activation Pathways

- **Key Genes:** C3AR1, C5AR1, PTX3, LBP, CRP, FCGR1A.
- **Role:** Amplifies inflammation and opsonization but contributes to tissue damage and endothelial dysfunction when dysregulated.

## 10. Organ-Specific Pathways

- **Key Genes:** LCN2, PTX3, ARG1, HIF1 (HIF1A), MMP9.

- **Role:** Impaired organ function (e.g., kidneys, liver, heart, lungs) due to tissue hypoxia, inflammation, and vascular injury.

## 11. Epigenetic and Transcriptomic Regulation Pathways

- **Key Genes:** SOCS3, HIF1 (HIF1A), GATA3, MYD88.
- **Role:** Sepsis-induced epigenetic changes and transcriptional reprogramming alter immune and inflammatory responses.

Pathway	Subpathway	Genes
Inflammatory and Immune Pathways	Cytokine Storm	TNF, IL1B, IL6, CXCL8, CXCL10, HMGB1, TREM1, IFNG, IFNA, IL1R2
	Anti-inflammatory Signals	IL10, SOCS3, PDCD1
	Immune Cell Recruitment	CCR2, CCR7, CCL2, CD177, CEACAM4
Pathogen Recognition Pathways	PAMP/DAMP Detection	TLR2, TLR4, CD14, MYD88, LBP, HMGB1, TREM1, CEACAM4
	Inflammasome Activation	NLRP3, P2RX7, IL1B
Adaptive Immune Pathways	T-cell Activation	HLA-DR, PDCD1, BCL2, GATA3, CCL19, CCL25
	Regulation of Differentiation	CCR7, CCR8, GATA3, PDCD1
Coagulation Pathways	Clot Formation	C3AR1, C5AR1, PLAUR, S100A8, S100A9, S100A12
	Fibrinolysis	PTX3, CRP, PLAUR

Vascular and Endothelial Pathways	Endothelial Activation	<b>NOTCH1, ITGAM, VCAM1, ICAM1, HMGB1, TREM1, IFNG, CX3CR1</b>
	Vascular Integrity	<b>HIF1, MMP8, MMP9, CALCA</b>
Oxidative Stress Pathways	ROS Generation	<b>P2RX7, CD177, ELANE, OLFM4, CEACAM4, IFNA, IFNB</b>
	Neutrophil Function	<b>ELANE, S100A8, S100A9</b>
Hypoxia and Metabolic Pathways	Metabolic Shift	<b>HIF1, ARG1, LCN2, MAPK14</b>
	Hypoxia Response	<b>PTX3, CALCA, MAPK14, IL10</b>
Apoptosis and Cell Death Pathways	Apoptosis	<b>BCL2, TNFSF10, PDCD1, TNFSF10</b>
	Pyroptosis	<b>NLRP3, P2RX7, IL1B</b>
Complement Activation Pathways	Complement Amplification	<b>C3AR1, C5AR1, PTX3, CRP</b>
	Opsonization	<b>LBP, CRP, FCGR1A</b>
Organ-Specific Pathways	Kidney Damage	<b>LCN2, ARG1, PTX3, HIF1</b>
	Liver Dysfunction	<b>S100A8, MMP9</b>
Epigenetic and Transcriptomic Regulation Pathways	Gene Expression Modulation	<b>SOCS3, HIF1, MYD88, HIF1A</b>
	Immune Gene Transcription	<b>GATA3, MAPK14</b>