Table S1. Treatment strategies directed at pathogenic bacteria in sepsis.

Treatment strategies	Mechanisms of action	Refs (Publication date)
Free antibiotics	Interfering with metabolic processes of bacteria	[1-3] (2021, 2016, 2020)
Antibiotic loaded NPs	Increasing antibiotic potency due to improved pharmacokinetics	[4] (2021)
Metal and metal oxide NPs	The disruption of the bacterial cell membrane, denaturation of protein, and DNA damage and disruption of the respiratory chain	[4] (2021)
Free AMPs	Physically destroying the lipid bilayers of bacteria	[5, 6] (2021, 2020)
Self-assembling chimeric peptide NPs with PEGylation	Alleviating the pharmacokinetic defect of peptide-based antibacterial drugs with the improved cytocompatibility	[7] (2022)
Liposome with a combined AMP and antibiotic	Synergism with significant improvement of bacterial clearance	[8] (2015)
Lipidic nanocapsules encapsulating essential oils	Antimicrobial activity of phenolic, aldehyde and alkene compounds in essential oils	[9, 10] (2016, 2016）

AMP: antimicrobial peptide; PEG: polyethylene glycol; NP: nanoparticle.

Table S2. Treatment strategies directed at toxins in sepsis.

Treatment strategies	Mechanisms of action	Refs (Publication date)
AMPs	Binding to LPS and LP	[11] (2018)
Gas gangrene antitoxin	Neutralizing a-toxin secreted by *C. perfringens*	[12] (2018)
Anti-endotoxin monoclonal antibody	Binding to endotoxin	[13] (2000)
J5 antiserum	Binding to LPS core	[14] (2000)
J5 immune plasma	Binding to LPS core	[14] (2000)
Intravenous immunoglobulins	Nonspecifically neutralizing bacterial toxins	[15] (2013)
Polymyxin B fiber column	Removing circulating endotoxin by adsorption	[16] (2017)
HDL like NPs	Scavenging and neutralizing LPS	[17] (2016)
Engineered liposomes	Sequestering bacterial toxins as decoy	[18] (2015)

AMP: antimicrobial peptide; HDL: High-density lipoprotein; LP: lipoprotein; LPS: lipopolysaccharide.

Table S3. Treatment strategies directed at inflammatory cytokines in sepsis.

Treatment strategies	Mechanisms of action	Refs (Publication date)
CytoSorb	Nonspecifically eliminating many proinflammatory cytokines	[16] (2017)
TLR4 Inhibitor	Inhibiting TLR4 signaling	[16] (2017)
APS loaded NPs	Inhibiting the activity of TLR4/NF-κB pathway with improved pharmacokinetics	[19] (2000)
Anti-TNF monoclonal antibody	Antibody-specific inactivation of circulating TNF	[20-22] (2003, 2001, 2001)
Soluble TNF receptors	Receptor-specific inactivation of circulating TNF	[20-22] (2003, 2001, 2001)
IL-1 receptor antagonists	Receptor-specific inactivation of IL-1	[20-22] (2003, 2001, 2001)
PAF receptor antagonist	Receptor-specific inactivation of PAF	[20-22] (2003, 2001, 2001)
Bradykinin inhibitor	Inhibiting the kallikrein/kinin cascade	[20-22] (2003, 2001, 2001)
Ibuprofen	Inhibiting the production of prostaglandin	[21, 22] (2001, 2001)
Glucocorticoids	Inhibiting the synthesis of almost all proinflammatory cytokines	[23, 24] (2002, 2005)
Cerium oxide NPs	Decreased transcriptional action of ROS, iNOS, COX-2, and NF-κB	[25] (2018)
Curcumin-loaded solid lipid NPs	Suppressing NF-kB activation and IkBa degradation levels	[26] (2015)
Bone marrow stromal cells	Reprograming host macrophages to increase their IL-10 production	[27] (2009)

APS: astragalus polysaccharide; COX-2: cyclooxygenase-2; IkBa: NF-kappa-B inhibitor alpha; IL: interleukin; iNOS: inducible nitric oxide synthase; NF-κB: nuclear factor kappa-B; NP: nanoparticle; PAF: platelet-activating factor; ROS: reactive oxygen species; TLR4: toll-like receptor 4; TNF: tumor necrosis factor.

Table S4. Some of transmembrane PRRs and corresponding PAMPs and DAMPs participating in the inflammation in sepsis.

PAMPs/DAMPs	TLRs	Roles in inflammation
Triacyl lipopeptide soluble factors	TLR1	
Lipoproteins	TLR2	
Matrix metalloproteinase 2	TLR2	
Peptidoglycan	TLR2	
mRNA	TLR3	
Fibrinogen	TLR4	
Envelope proteins	TLR4	
Heparan sulfate	TLR4	
Atypical LPS, LPS	TLR2 / TLR4	Producing
Hsp60, hsp70,hsp72, hsp22	TLR2 / TLR4	proinflammatory
Glycoprotein 96	TLR2 / TLR4	cytokines
Hyaluronic acid	TLR2 / TLR4	
HMGB1	TLR2 / TLR4 / TLR5	
Di-acyllipopeptides from mycoplasm	TLR2 / TLR6	
Amyloid β	TLR2 / TLR6	
Oxidized LDL	TLR2 / TLR6	
CpG-containing DNA from bacteria, host DNA from dying cells, mitochondrial DNA (mtDNA),	__	
HMGB1-DNA complex	__	
Flagellin	TLR5 / TLR11	

Note: "__" represents no.

HMGB1: high-mobility group box 1; hsp: heat-shock protein; LDL: low-density lipoprotein; LPS: lipopolysaccharide; TLR: Toll-like receptor.

Table S5. Some of cytoplasmic PRRs as well as corresponding PAMPs and DAMPs engaged in the inflammation in sepsis.

PAMPs	DAMPs	Intracellular PRRs	Roles in inflammation
g-D-glutamyl-mesodiaminopimelic acid (bacterial peptidoglycans)	__	NOD1	
muramyl dipeptide (bacterial peptidoglycans)	__	NOD2	
Bacillus anthracis lethal toxin		NLRP1	
Staphylococcus aureus, Candida albicans, Saccharomyces cerevisiae, Listeria monocytogenes, Neisseria gonorrhoeae, pore-forming toxins	Uricacid crystals, extracelluar ATP, HMGB1, hsp70, hsp90	NLRP3	Activating casp-1 causes pyroptosis
Listeria monocytogenes, Salmonella typhimurium, Shigella flexneri, Legionella pneumophila, Pseudomonas aeruginosa, Cytosolic flagellin	__	NLRC4	
Double-stranded DNA from Francisella tularensis	__	AIM2	
Cytosolic LPS	__	Cytosolic LPS sensor	Activating casp-11 causes pyroptosis

Note: "__" represents no.

ATP: adenosine triphosphate; hsp: heat-shock protein; LPS: lipopolysaccharide.

Supplemental References

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