

# Estradiol Towards Sepsis : Pengaruh Estradiol Terhadap Sepsis

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## ORIGINAL ARTICLE

## Estradiol Towards Sepsis

## Pengaruh Estradiol Terhadap Sepsis

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## ABSTRACT

Sepsis is an emergency condition as a result of host dysregulation systemic immune response to infection that is related to the end stage of organ dysfunction. Both sepsis and septic shock conditions are the main problems in ICU especially, those that affect millions of people in the whole world every year. Studies in line with immune-neuroendocrine related to sepsis get high attention about factors that play roles in sepsis pathogenesis and prognosis, like correlation to gender, hormones, and other factors. In this case, lots of experimental studies and clinical studies showed that sepsis has significant sexual dysmorphic. The female gender has proven protective against sepsis, meanwhile, males could have worse sepsis because of decreasing immunologic response that mediates cell and cardiovascular function. Estrogen is a hormone in women that plays important roles in not only reproductive function but also non-reproductive function. Physiological estrogen in women is divided into three forms: estrone (E1), estradiol (E2 or 17 $\beta$ - estradiol), and estriol (E3). Several experimental studies in animals showed that estradiol has a protective response when infection occurs. Estrogen generally stimulates cytokine release, induction of HCR, and restoration of organ function due to sepsis. Potential pathogenesis for this condition is a specific expression of cytokine and anti-inflammation. This pathological inflammatory condition is related to gender that is found in surgical patients at the molecular level.

**Keywords:** Estradiol; estrogen; inflammation; inflammatory cytokine; sepsis

## ABSTRAK

Sepsis adalah suatu kondisi gawat darurat yang diakibatkan oleh disregulasi respon imun sistemik host terhadap infeksi yang berhubungan dengan tahap akhir disfungsi organ. Baik sepsis maupun syok sepsis merupakan salah satu masalah utama di ICU, yang mempengaruhi jutaan orang di seluruh dunia setiap tahunnya. Penelitian-penelitian yang berkaitan dengan imun-neuroendokrin yang berhubungan dengan sepsis mendapatkan lebih banyak perhatian terkait faktor-faktor yang berperan dalam patogenesis dan prognosis sepsis, seperti hubungannya dengan jenis kelamin, hormon, dan faktor lainnya. Banyak penelitian eksperimental dan studi klinis menunjukkan sepsis secara signifikan memiliki hubungan dengan jenis kelamin. Jenis kelamin perempuan terbukti protektif terhadap sepsis, sedangkan jenis kelamin laki-laki memperburuk sepsis karena menurunnya respon imunologi yang memediasi fungsi sel dan kardiovaskular. Estrogen merupakan hormon pada wanita yang berperan penting tidak hanya pada fungsi reproduksi namun juga pada fungsi non-reproduksi. Estrogen fisiologis pada wanita dibagi menjadi tiga bentuk: estron (E1), estradiol (E2 atau 17 $\beta$ -estradiol), dan estriol (E3). Beberapa penelitian eksperimental pada hewan menunjukkan bahwa estradiol memiliki respons protektif ketika terjadi infeksi. Estrogen secara umum merangsang pelepasan sitokin, induksi HO-1 dan pemulihan fungsi organ akibat sepsis. Patogenesis potensial untuk kondisi ini adalah ekspresi spesifik dari sitokin pro dan anti-inflamasi. Kondisi inflamasi patologis ini terkait dengan jenis kelamin yang ditemukan pada pasien bedah pada tingkat molekuler.

**Kata Kunci:** Estradiol, estrogen, inflamasi, sitokin inflamasi, sepsis

## INTRODUCTION

Sepsis is a condition related to the systemic immunologic response of infection that causes the end stage of organ failure and death. Both sepsis and septic shock conditions are the main problems in ICU especially, those that affect millions of people in the whole world every year.<sup>1,2</sup> This condition causes one of three to one of six sepsis that is related to death. In sepsis, tissue, cytokine, immune system, and complex endothelial interaction affect disruption in microcirculation. This mechanism causes organ dysfunction to organ failure.<sup>3-5</sup>

Lately, studies in line with immune-neuroendocrine have high attention to factor that affects the system, like correlation to gender, hormones, and other factors that relate to pathogenesis in sepsis. In this case, lots of experimental studies and clinical studies showed that sepsis has significant sexual dysmorphic. To that, the female has a lower level of severity and lower death risk. The potential mechanism in this observation is specifically expression related to gender from pro-inflammatory cytokine in patients who underwent surgery at the level of biomolecular.<sup>6,7</sup>

The female gender has proven protective against sepsis, meanwhile, males could have worse sepsis because of decreasing immunologic response that mediates cell and cardiovascular function. Male hormonal, androgen, could lower immune response. <sup>8</sup> contrast, female hormonal could show protective effects that contribute to natural advantages in septic conditions. Thus, hormonal status has to be considered <sup>8</sup> when doing hospital care in septic patients. In line with this fact, potential therapy could appear from this fact. In this case, the administration of female hormones (estrogen and its precursor) could have a better effect. Administration of an agent that affects synthesizing hormone enzyme decreases the level of pro-inflammatory agent and thus has a good effect in patients with sepsis.<sup>8</sup>

4

## METHODS

For this review, we used a variety of sources by searching through PubMed, Embase, Scopus, Current Content, and Iran Medex from January 1990 up to December 2014. The search was performed by using combinations of the following keywords and or their equivalents: 'sepsis, human, estradiol'. Manuscripts published in English languages, as full-text articles, and or as abstracts were included in the study. Unfortunately, we did not specifically hand-search conference proceedings and manuscripts published in other languages.

## RESULTS

### Definition, Pathophysiology, and Diagnostic of Sepsis

Sepsis is a condition as a result of the host's systemic immunologic response to the infection process that relates to the end stage of organ dysfunction and death. Sepsis definition continues to develop into the newest one that focuses on the impairment of organ dysfunction. Death cases for patients with sepsis have decreased because of improvement management that was declared by the *Surviving Sepsis Campaign*. The sample of hospitalized patients in the *United States National Inpatient Sample (NIS)* from 2009 to 2012 shows a decreasing level of mortality from 16.5% to 12.8%. Besides, almost 50% of patients with sepsis shock will die. Mortality in general from sepsis syndrome varied from 30% to 50% depending on demographic factors such as age, gender, comorbid, and organ dysfunction.<sup>9</sup>

Practically, organ dysfunction is shown by Sequential (sepsis-related) *organ Failure Assessment (SOFA)* score. A SOFA score of 2 points or more is related to 10 % more mortality in hospitals.<sup>2,10</sup>

Table 1. Sepsis Definition from 1992 to 2016<sup>11-13</sup>

Definition	Sepsis 1	Sepsis 2	Sepsis 3
Sepsis	Systemic Inflammatory Response Syndrome (SIRS) cause by infection	No change	Impairment of organ function causes by host response to infection that life threatening
Severe Sepsis	Sepsis define is at least one of this: organ function impairment, hypoperfusion. Hypotension, lactat acidosis, oligouria, altered mental status.	No change	no definition of severe sepsis
Shock Sepsis	Sepsis with hypotension after adequate fluid therapy and with support inotropic or vasopressor	No change	Sepsis with disturbance of circulation, cellular, and metabolic that life threatening

In 2019, the European Prevalence of Infection on Intensive Care (EPIC) declared that infection from gram-negative bacteria became the most common cause at 62% followed by gram-positive infection

at 47%. It has an increasing prevalence related to enhancing nosocomial infection. A microorganism that causes the most sepsis is *Staphylococcus aureus* (20%), *Pseudomonas* (20%) dan *E. coli* (16%) with most locations in the respiratory tract (42%), vascular (21%), and genito-urinary (20%).<sup>14</sup>

Sepsis pathophysiology is divided into two mechanisms, level in cellular and molecular. Both of these mechanisms contribute to an imbalance of host inflammation response, immune dysfunction, and coagulopathy. At the cellular level underwent destruction of the endoplasmic reticulum and autophagia. In the end, in this order, this destructive mechanism causes organ impairment. Molecularly, exogen exposure in this case known as Pathogen-Derived Molecular Patterns (PAMP). This PAMP includes endotoxin, exotoxin, lipopolysaccharide (LPS), or DNA sequence or from endogen exposure. This is called a *Damage-Associated Molecular Pattern (DAMP)*.<sup>15-18</sup>

In *Surviving Sepsis Campaign Bundle 2021*, sepsis is a sign of organ dysfunction marked with an enhancement qSOFA score to 2 points or more towards *Glassgow Comma Score* <15, respiration rate  $\geq 22$ x/minutes, and systolic blood pressure  $\leq 100$  mmHg. If qSOFA is less than 2 points but suspicious of sepsis thus re-evaluated for clinical that direct to possibility of sepsis. qSOFA score is more specific but less sensitive compared to the SIRS score. For patients with sepsis suggested to evaluate blood lactate. Septic shock is related to the escalation of lactate based on the definition from Sepsis-3. The cut-off value for lactate is 1.6-2.5 mmol/L.<sup>19</sup>

Sofa score calculates when the patient is in ICU and re-asses per 24 hours next. 6 criteria in SOFA show organ function (respiratory, cardiovascular, kidney, neurological, and hematology). Every item gives 0 for the lowest score and 4 for the maximum score.<sup>1</sup>

Table 2: SOFA score criteria<sup>20</sup>

Parameter	Skoring SOFA
<b>Respiratory system</b>	
PaO <sub>2</sub> / FIO <sub>2</sub> (mmHg)	
> 400	0
< 400	1
< 300	2
< 200 with respiratory device	3
< 100 with respiratory device	4
<b>Neurology system</b>	
Glasgow Coma Scale	
15	0
13-14	1
10-12	2
6-9	3
< 6	4
<b>Cardiovascular system</b>	
Hypotension	
MAP > 70 mmHg	0
MAP < 70 mmHg	1
Dopamine 5 µg/kg/min or dobutamine	2
Dopamine > 5 µg/kg/min or epinephrine 0.1 µg/kg/min or norepinephrine 0.1 µg/kg/min	3
Dopamine > 15 µg/kg/min or epinephrine > 0.1 µg/kg/min or norepinephrine > 0.1 µg/kg/min	4
<b>Liver</b>	
Bilirubin (mg/dl) [µmol/L]	
<1,2 (<20)	0
1,2-1,9 [20-32]	1
2,0-5,9 [33-101]	2
6,0-11,9 [102-204]	3
>12,0 [>204]	4

### Estradiol pharmacodynamic and pharmacokinetics

Estrogen is a hormone in women that plays important roles in not only genital but also systemic conditions. Estrogen is desensitization in systemic conditions related to tissue and organs like the liver, cardiovascular, musculoskeletal, and central nervous system. Physiologically estrogen in women is divided into three types: estrone (E1), estradiol (E2 or 17β-estradiol), and estriol (E3). The fourth estrogen is estetrol (E4) which dominantly and potently works before menopause. Each form of estrogen produces a dis-similar product formed by cholesterol through the reaction order of estrogen biosynthesis.<sup>21,22</sup>

Estrogen deactivation for E2 is controlled by estrogen metabolism that includes E2 conversion to a less functioning form like E1 or E3, and producing E2 sulfation by estrogen sulfotransferase to 17beta-estra-1,3,5-trien-3,17-diol 3-sulfate.<sup>20,23</sup> This form has no interaction with estrogen receptors. Aromatase regulation in female rats decreases to inhibit E2 synthesis. This condition is related to lipocalin 2 deficiency, cytokine derivate from new adipose when aromatase hormones decrease.<sup>22,24</sup> Thus, the estrogen ratio that circulates might function as a dynamic metabolism indication: balance between synthesis and deactivation of estrogen. One of the mechanisms that is frequently used to control estrogen synthesis is controlling aromatase enzyme.<sup>24</sup> This enzyme is responsible for to last process of E2 synthesis. Aromatase is one of the superfamily cytochrome p450 and it is expressed



widely in a lot of organs including the brain, gonad, vascular, musculoskeletal, liver, skin, adipose tissue, and endometrium. Aromatase expression specifically depends on three factors: alternative binding, promoting specific tissue, and varying transcription factors.<sup>25,26</sup>

The focus product from the biosynthesis process is E2 is the most potent estrogen in the premenopausal period. Meanwhile, E1 has a role after a menopausal period when synthesized in adipose tissue from dehydroepiandrosterone of the adrenal. E3 is the least potent estrogen that is formed through 16 $\alpha$ -hydroxylation. It has a bigger role when in pregnancy relates to the placenta that produces E3.

Volume distribution and protein binding from several components of estrogen have been known for their properties. Balance volume distribution around 73 $\pm$ 24 L for micronized estradiol, 6 $\pm$ 0.5 L for 17 $\beta$  dihydroequilin sulfate, 23 $\pm$ 1.3 L for 17 $\beta$  dihydroequilin, dan 12.4 $\pm$ 1.6 L for equilin sulfate. Total volume and all distribution lowered after intravenous administration from various components of estrogen. Estrogen binds tightly with protein. Although several estrogens weakly bind to albumin, most estradiol strongly binds to sex hormone-binding globulin.<sup>27</sup>

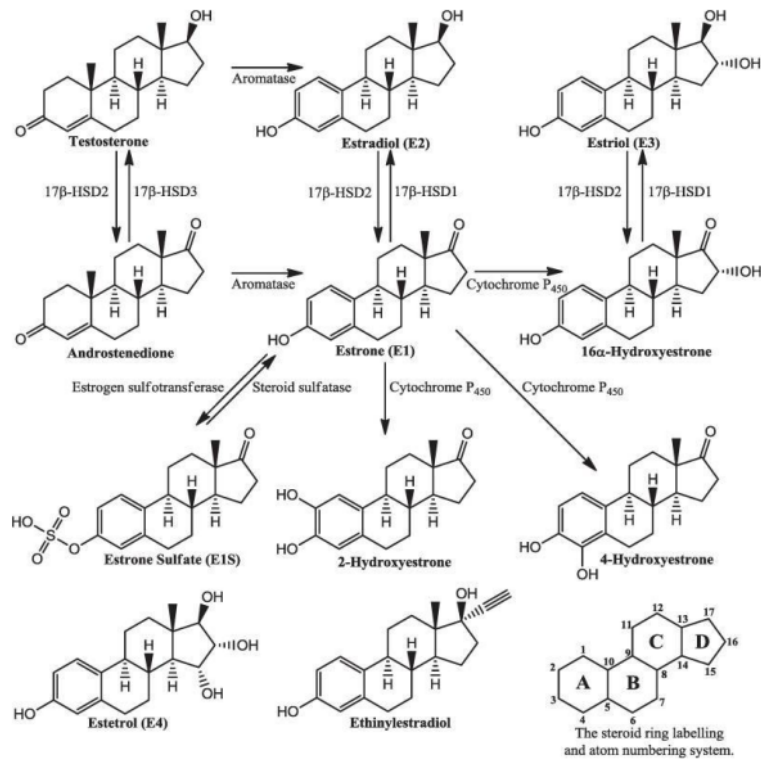


Figure 1. Structure and metabolism of estrogen. There are three types of physiological estrogen for women: estrone (E1), estradiol (E2 atau 17 $\beta$ -estradiol), and estriol (E3). (Adapted from Birkhauser M. Treatment of pain in estrogen deficiency. Arch Gynecol Obs)<sup>22</sup>

Metabolism of estradiol undergoes three competitive pathways that involve hydroxylation which is catalyzed by cytochrome P450 (CYP). This mechanism depends on NADPH appertain to CYP1A1, CYP1B1, and CYP1A2. Estrone and estradiol underwent hydroxylation in C2, C4, and C16 positions and changed into estrogen catechol (2-hydroxy estrone, 4-hydroxy estrone, 2-hydroxy estradiol, and 4-hydroxy estradiol), and 16 $\alpha$ -hydroxy estrone.<sup>28,29</sup>

Estrogen catechol metabolized (methylation) into methoxy estrogen (2-methoxy estrone, 4-methoxy estrone, 2-methoxy estradiol dan 4-methoxy estradiol) by enzyme catechol-O-methyltransferase (COMT). Besides the methylation process, core estrogen and catechol estrogen are conjugated with glucuronate acid and liver enzyme phase II including UDP glucuronosyltransferases and sulfotransferases. This conjugation is assumed detoxification reaction in which a hormone becomes soluble in water and excreted into urine or feces or transforms into part that is more lipophilic with a short half-life.<sup>28,29</sup>

Pharmacodynamically, estrogen has a strong anti-gonadotropin effect in high concentrations. This process is through negative feedback in Hypothalamic–pituitary–gonadal axis (HPG-axis) that compress gonadotropin, LH, and FSH secretion. This mechanism inhibits gonad sex hormone production and levels of sex hormones that circulate. However, estrogen can induce positive feedback that is needed for fertility which decreases with age.

#### Anti-inflammation properties of Estradiol

Inflammation which involves immune cells, vascular, and molecular mediators generally classified into acute or chronic state. To avoid inflammation, the body localizes and decreases damaged tissue thus modulating improvement. The role of the estrogen immunomodulation complex in the inflammation process shows that estrogen affects vulnerability towards chronic inflammation and infection response. This role is related to the menstruation cycle, pregnancy, and menopause.<sup>21</sup> Besides, in research with rats, estrogen lowered inflammation in cerebral vascular with inhibits the induction pathway NF- $\kappa$ B/siklooksigenase-2 (COX-2) mediated by interleukin (IL) -1 $\beta$ .<sup>22</sup> One study showed that intracellular estrogen receptor activation shortens the proinflammation phase that is induced with LPS. E2 facilitates the development of the inflammation process towards phenotype-dependent “deactivation acquired” to IL 10 and is responsible for tissue remodeling and repair to a hemostasis state. It can be concluded that increasing of suffering from chronic disease after menopause.<sup>30</sup>

Another research referred to E2 as its ability to lower inflammation response towards CRP in bone marrow-derived macrophages (BMM) and vascular smooth muscle (VSMC). This mechanism decreases the formation of neointima in the carotid artery. Expression of Era dalam BMM decreases along with age. In this research showed that vasoprotective of E2 depends on age and place and reveals the effect of vasotoxic.<sup>31</sup>

Cytokine stimulation enhances nitrit and protein iNOS.<sup>32</sup> The Most important property of iNOS is their potency to induce a level of nitric oxide compared to other iNOS isoforms. High levels of NO produced by iNOS result in strong anti-microbe effects to control infection.<sup>33</sup> An increase of nitrite that is induced by cytokine significantly lowered by estrogen with lowered levels of mRNA, iNOS, and protein expression is in cells that are stimulated by cytokine.<sup>31</sup>



### Estradiol for sepsis

Several studies have demonstrated that sepsis has notable sexual dimorphism and women have valuable lower rates of sepsis severity and mortality. In a multicenter analysis study that included more than 20,000 patients, it was found that there was a significant survival rate in female patients under 50 years of age.<sup>34</sup>

Sexual dimorphism in sepsis makes some studies that carry out sexual hormone research in animals and patients. The result shows that in animals, estradiol has a protective response when infection occurs.<sup>35</sup> Estrogen generally stimulates cytokine release, induction of iNOS, and restoration of organ function due to sepsis. Potential pathogenesis for this condition is a specific expression of cytokine pro and anti-inflammation. This pathological inflammatory condition is related to gender that is found in surgical patients at the molecular level.<sup>36</sup> Estrogen receptors are present in several important organs such as the heart, lungs, and liver which in turn are organs associated with sepsis. There are two divided of subtypes ER, namely ER- $\alpha$  and ER- $\beta$ . ER- $\alpha$  is the dominant receptor for estrogen in the liver. ER- $\beta$  has this role in the heart and lungs. In the small intestine, both ER- $\alpha$  and ER- $\beta$  promote estrogen-dependent effects.<sup>37</sup>

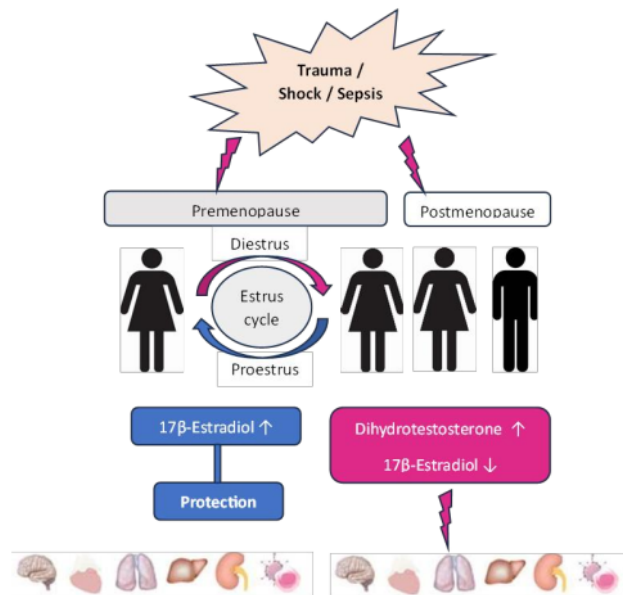


Figure 2. Illustration correlation between gender and sex hormones that protected organ (adapted from Bösch F, Angele MK, Chaudry IH. Gender differences in trauma, shock and sepsis)<sup>38</sup>

Findikli, et al conducted a study on for role of sex hormones in 160 sepsis patients by examining the serum concentration of G protein-coupled estrogen receptor-1 (GPER-1) which modulates the estrogen immune response.<sup>39</sup> These receptors are found on endothelial cells, vascular smooth muscle cells, and endocrine organs (liver and pancreas). The signal from GPER-1 is a precursor that can stimulate an immune response in septic patients.<sup>40</sup> The results in this study found that the

optimal dose, which is 2.58 pg/mL of serum GPER-1 concentration, was used to predict mortality in septic patients leading to the possible dose-dependent effects of the hormone. Although serum concentrations of GPER-1 were not found to differ in men and women or the convalescent or deceased groups, this finding is track with the results of other studies which found that sex hormone concentration levels in patients with sepsis were found equally in men and women.<sup>35</sup> In another study, Sakr, et al found that although sex hormones may affect sepsis and the disease they can erase the difference in male and female patients. This could explain the contradictory results regarding incidence and mortality in septic patients.<sup>41</sup>

For the infection, macrophages are needed to produce NOX2 and ROS. Its inflammatory factors play a role in diminishing pathogens and releasing infection. Pathogens that are attached to infection bond to the cell surface of immune receptors. When pathogens bind to cell surface immune receptors TLRs and FcγR during phagocytosis, LC3 is recruited to macrophage phagosomes, thereby promoting phagocytosis. Due to the recruitment of LC3 to the phagosome surface. This process is termed LC3B-associated phagocytosis (LAP). LAP initiation requires RUBICON and NADPH oxidase. A study by Sun et al demonstrated that β-glucan-induced trained immunity could help female mice fight sepsis better than males. When it comes to OVX mice (which have undergone ovariectomies), the effect of trained immunity is diminished, leading to a loss of advantage against sepsis. Meanwhile, trained immunity induced by β-glucan can increase the expression of RUBICON and NOX2 in macrophages, and facilitate the production of ROS, thus promoting the LAP process to enhance pathogen engulfment. RUBICON is an inhibitor of autophagia which stabilizes the structure of NOX2 in producing ROS. In addition, in vitro experiments show that E2 can further promote trained immunity to facilitate PAP. Results from this study show that higher E2 levels in women can enhance macrophage LAP to remove pathogens, thereby making women more resistant to sepsis. This may explain the reason for sex dimorphism in sepsis.<sup>42-44</sup> Besides, estrogen-dependent mediating effects in sepsis are not limited to a single ER-α or ER-α downstream pathway. Estrogen binding to ER-α or ER-β can lead to activation of signaling proteins such as MAPK, TLR4, HSPs, PGC-1α, CREB, NF-κB, P-1 and kt/HO-1.<sup>24</sup> E2 initially has significant potential to suppress NF activation NF-κB; it completely blocked activation NF-κB that induced by tumor necrosis factor alpha (TNFα).<sup>45</sup>

Gender dysmorphic is possible because of different expressions from cytokine pro and anti-inflammation. During sepsis, cytokine pro-inflammation like IL-6, IL-8, IL-10, and TNF-α, increased in male patients.<sup>34</sup> Administration of exogen estrogen can enhance macrophage and dendritic function that is mediated by ER-α. Treatment in rats that underwent ovariectomy with agonis ER-α significantly lowered interaction between leucocyte-endothelial induced by sepsis (attachment of leucocyte and neutrophil extravasation) and increased bowel integrity.<sup>35</sup> Estrogen might increase the life survival rate.

Tonnaer et al. in a study showed that ovariectomy and sub-chronic estradiol-17 therapy induced down-regulation of dopamine D1 and the lower level of D2 receptor in rat's atrium. Intracellular mechanism mediates down-regulation of DA receptors because vary of estrogens do not interact with DA receptors which attached to the membrane in vitro.<sup>46</sup>

A study from Hassan et al. demonstrated that 17β-estradiol (E2) dan 2-methoxy estradiol (2ME) offer protection against kidney injury induced by ischemia reperfusion. 2ME is the main effector molecule that mediated to reno-protective effect from estradiol. Reno-protective properties induced by 2ME through inhibition of HIF-1α and the gene that is controlled by the expression of TH and COMT will show the level of catecholamine in tissue.<sup>44</sup> Previous studies reported that 17β-estradiol (E2) compressed renal sympathetic activity that in contra should increase during Renal Ischemia-Reperfusion. This condition is a consequence effect from overflow nor-epinephrine in the terminal

nerve and for this reason, estradiol has renoprotection properties towards RIR-induced-AKI. It has an important role in metabolizing estrogen into 2ME.<sup>47-49</sup> Suppression of E2 to the activity of sympathetic in renal becomes the mechanism of renoprotection towards RIR-induced AKI. This condition related to E2 conversion that is mediated by COMT becomes 2 ME. 2 ME decreases production or activity of several mediator pro-inflammation and pro-fibrotic like TNF- $\alpha$ , TGF- $\beta$ , dan HIF-1 $\alpha$ .<sup>50,51</sup>

Xu, et al in their study conducted on 28 mice of different sexes that had been previously induced with LPS for sepsis, found that estrogen could reduce liver damage caused by sepsis. This condition was proved by decreased serum levels of AST and ALT, as well as improved mitochondrial dysfunction and activation of pyroptosis signaling pathways. This condition is followed by decreased mitochondrial superoxide production and decreased protein expression of pyroptosis-related proteins in the septic liver. It could happen because the administration of estrogen in mice has been shown to reverse the regulation of GSDMD, caspase 1, and NLRP3. NLRP3 plays an important role in mediating the activation of the pyroptosis signaling pathway associated with sepsis-induced liver damage. Thus, the inhibition/suppression of NLRP3 can reduce liver damage caused by sepsis.<sup>52</sup>

Estradiol was found to induce heme-oxygenase-1 (HO-1) expression. HO-1 is an enzyme that functions in the degradation of heme to signal bioactive molecules free of iron, biliverdin, and carbon monoxide.<sup>38</sup> Otterbein, et al in their research found that induction of HO-1 and its products can provide cardioprotective effects.<sup>53</sup> Another study conducted by Xerri, et al found that estradiol can prevent cardiac dysfunction caused by sepsis.<sup>54</sup>

17 $\beta$ -estradiol (E2) is also considered to reduce muscle weakness caused by polymicrobial sepsis in ovariectomized rats. Furthermore, E2 also reduces atrophy, and lipopolysaccharide (LPS)-induced production of inflammatory cytokines, an endotoxin in C2C12 myotubes. On the other hand, E2 does not alter proteolytic pathways such as LPS-induced atrogen-1/MAFbx up-regulation and autophagosome formation in C2C12 myotubes. These findings suggest that E2 protects skeletal muscle from septic damage by reducing inflammatory cytokines. In this study, it was concluded that estrogen should be a factor in sex differences in sepsis.<sup>55</sup>

17 $\beta$ -Estradiol decreases cytokine-stimulated iNOS expression and NO production.<sup>94</sup> An important feature of iNOS is its ability to induce higher nitric oxide levels compared to the other two NOS isoforms. The high levels of NO generated by iNOS exert a strong anti-microbial effect to control infection and are therefore critical in immune defense. Downregulation of iNOS expression may explain the beneficial role of estrogen in models of sepsis and shock.<sup>56</sup>

In the early stages of sepsis, macrophages will help defense by releasing proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 to kill pathogens. However, activated macrophages can overproduce proinflammatory cytokines, causing microvascular damage to endothelial cells and activating the coagulation and complement cascade reactions. NLRP3 is a complex polymer protein that functions to secrete proinflammatory cytokines IL-1 $\beta$  and IL-18. The inactivation of NLRP3 can induce the release of proinflammatory cytokines. NLRP3 has a 3'-UTR site that can bind directly to miR-29a-5p. miR-29a-5p that was directly transfected at the 3'-UTR site showed decreased NLRP3 levels and a decrease in the amount of miR-29a-5p through its inhibitor could increase the amount of NLRP3.<sup>56</sup>

Estradiol can induce the production of mucous in the nose that contains mucin, electrolytes, IgA and IgG, lysozyme, lactoferrin, and oligosaccharides. This component is known to have antiviral and antibacterial properties that had an important role in the mechanism of action of neutralizing upper respiratory tract infection. In the lower respiratory tract, estrogen can induce a local immune response that activates dendritic cells, phagocytes, neutral killers, and CD8+ cells. This immune

response might destroy the virus thus preventing diffusion and reducing viral load.<sup>57</sup> This study is in line with the study conducted by Arellano, et al. Its research demonstrated that estradiol can activate B cells from antibodies, augmentation from dendritic cells enhance cytotoxicity of NK in lower concentrations, and increase CD8+ lymphocytes that are specified to certain viruses.<sup>58</sup>

Results of a study by Lakbar, et al showed that estradiol can reduce the symptoms that arise due to sepsis. High estradiol levels might reduce mortality in septic patients.<sup>35</sup> This is inversely to the research conducted by Tsang, et al. Its study found that serum estradiol levels were found to be higher in critically ill septic patients than in healthy patients of the same age and sex. Patients who died related to sepsis and were previously treated at the hospital were also found higher concentrations of estradiol than those who survived sepsis. High levels of estradiol concentrations are also associated with the severity of sepsis. This might be related to the limitations of the study design. The observational design prevented the establishment of a causal relationship between estradiol concentrations and sepsis or death. Second, this study was unable to investigate the relationship between estradiol, inflammation, and physiological stress because Tsang et al did not measure markers of inflammation and stress response. Third, study samples were obtained on average 27 hours after patients met diagnostic criteria, and results might have differed if samples were obtained earlier. Third, we cannot determine whether the findings are unique to sepsis or characterize critical illness more generally.<sup>59</sup> Therefore, more detailed studies are concerned with markers of the inflammatory response in sepsis and their relation to estradiol concentrations.



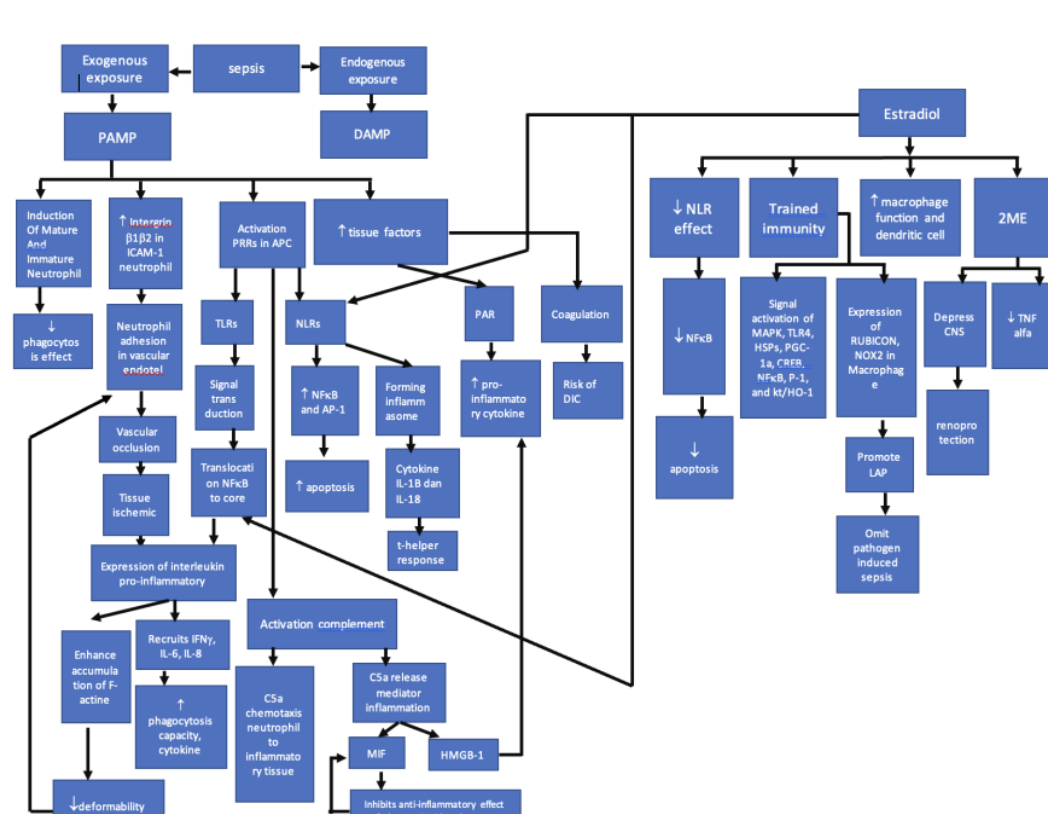


Figure 3. Scheme for sepsis and inflammatory factor related to estradiol as a protective agent against sepsis

Macrophages produce NOX2 and ROS to fight infection, and inflammatory factors help diminish pathogens. During phagocytosis, LC3 recruits to macrophage phagosomes, promoting LC3B-associated phagocytosis (LAP). RUBICON and NADPH oxidase are involved in LAP initiation. Sun et al. found that  $\beta$ -glucan-induced trained immunity can help female mice fight sepsis better than males.<sup>42-44</sup> Estrogen-dependent mediating effects in sepsis involve activating signaling proteins like MAPK, TLR4, HSPs, PGC-1 $\alpha$ , CREB, NF- $\kappa$ B, P-1, and kt/HO-1.<sup>24</sup> Estrogen administration can enhance macrophage and dendritic function, potentially increasing life survival rates. Gender dysmorphism in sepsis is possible due to different expressions of cytokine pro and anti-inflammation.<sup>28</sup>

## CONCLUSIONS

Several studies have demonstrated that sepsis has significant sexual dimorphism and demonstrated that women have significantly lower rates of sepsis severity and mortality. Estradiol for sepsis has several important effects such as reducing the incidence of apoptosis, reducing the production of proinflammatory cytokines, acting as renoprotection, and increasing macrophage function. E2 was also found to reduce lipopolysaccharide (LPS)-induced inflammatory cytokine production and atrophy. Estradiol has the potential to protect skeletal muscle from septic damage by reducing inflammatory cytokines. The administration of estradiol according to the time and dose can inhibit inflammation caused by macrophages by increasing



the regulation of miR-29a-5p expression. It is miR-29a-5p which binds directly to the 3'UTR site and can reduce NLRP3 levels thus inflammation can be reduced.

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## AUTHOR CONTRIBUTION

All authors read and approved the final manuscript.

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## CONFLICT OF INTEREST

No relevant disclosures of competing interests.

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