OLGU ÖRNEKLERİ İLE COVID-19 TEDAVİSİNİN DÜNÜ, BUGÜNÜ VE YARINI

Oturum Başkanı: İftihar Köksal

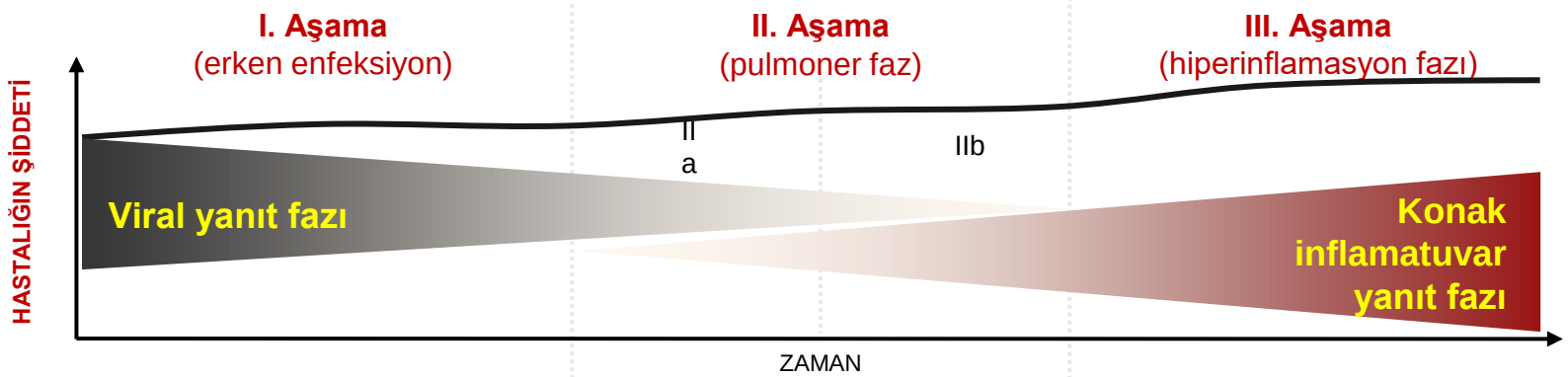
Tartışmacılar: İftihar Köksal, Yeşim Taşova, Füsun Eyüboğlu, Burçin Halaçlı

25 Mayıs 2022, EKMUD 2022

Sunum Planı

- Giriş konuşması
- Olgu sunumları ve tartışma
- Dünden geleceğe tedaviler

COVID-19'un klinik evreleri

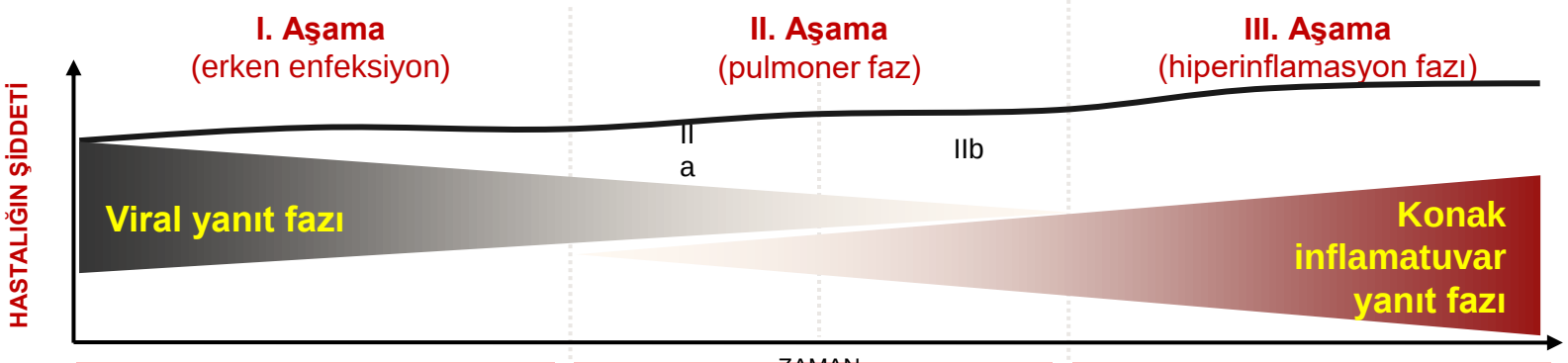


Klinik semptomlar	Hafif genel semptomlar Ateş >37,6°C; Kuru öksürük, ishal, baş ağrısı	Solunum güçlüğü Hipoksi (PaO2/FiO2 ≤300 mmHg)	ARDS SIRS/şok Kalp yetmezliği

1. Siddiqi H & Mehra M. J Heart Lung Transp (2020). In press. doi: https://doi.org/10.1016/j.healun.2020.03.012.

COVID-19'un klinik evreleri

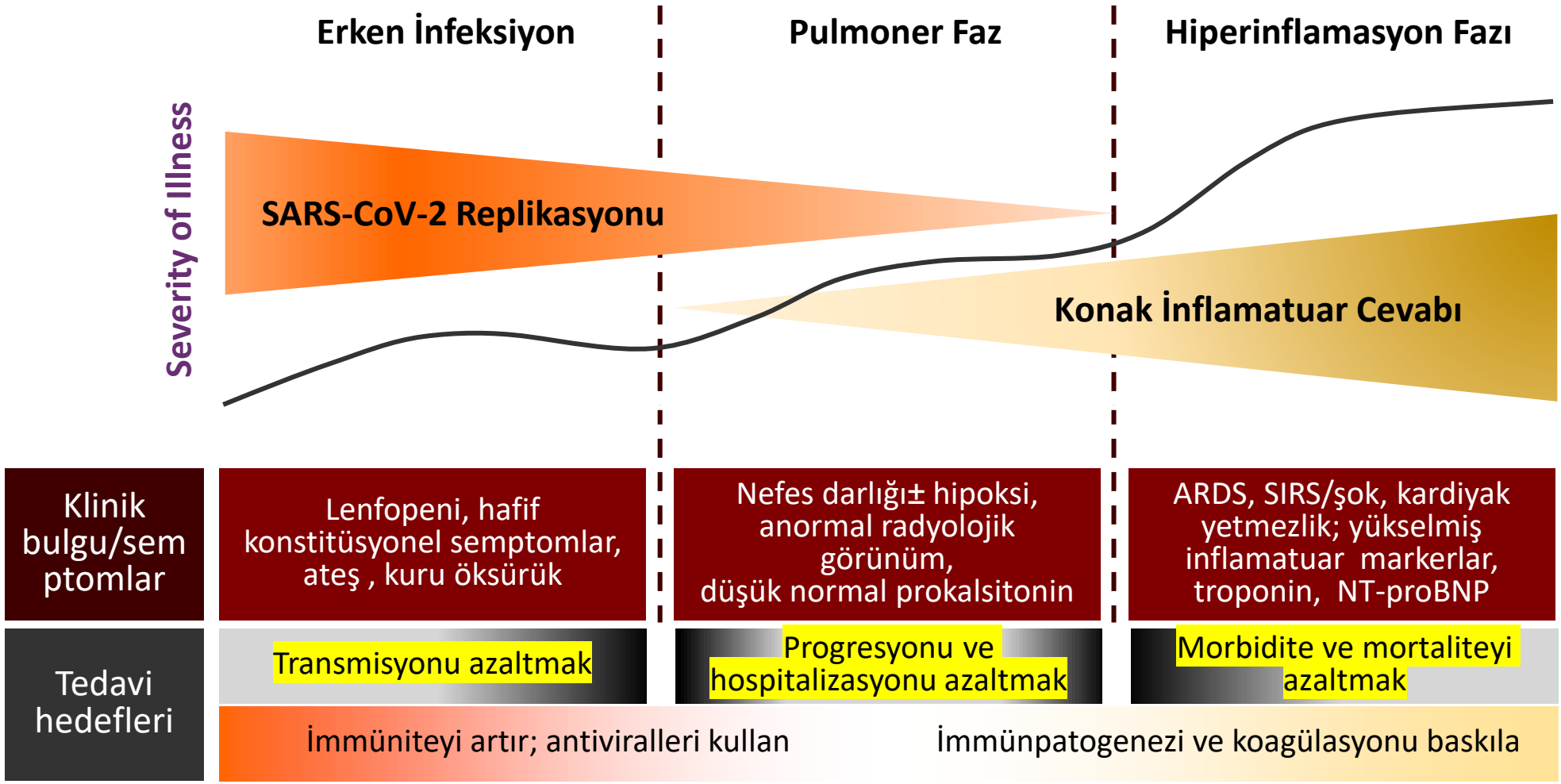
- *Potansiyel terapötik yaklaşımlar*



Klinik semptomlar	Hafif genel semptomlar Ateş >37,6°C; 99,6°F Kuru öksürük, ishal, baş ağrısı	Solunum güçlüğü Hipoksiya (PaO_2/FiO_2 ≤300 mmHg)	ARDS SIRS/şok Kalp yetmezliği
Klinik belirtiler	Lenfopeni Protrombin zamanının uzaması D-dimer ve LDH yükselmesi	Toraks görüntülemesinde anormal sonuç Transaminitis Düşük-normal prokalsitonin	İnflamatuvar belirteçlerde yükselme (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP yükselmesi
Potansiyel tedaviler	Remdesivir, klorokin, hidroksiklorokin, konvalesan plazma transfüzyonları		
	İmmünsüpresyonun azaltması	Kortikosteroidler, insan immünoglobulini, IL-6 inhibitörleri, IL-2 inhibitörleri, JAK inhibitörleri	

1. Siddiqi H & Mehra M. J Heart Lung Transp (2020). In press. doi: https://doi.org/10.1016/j.healun.2020.03.012.

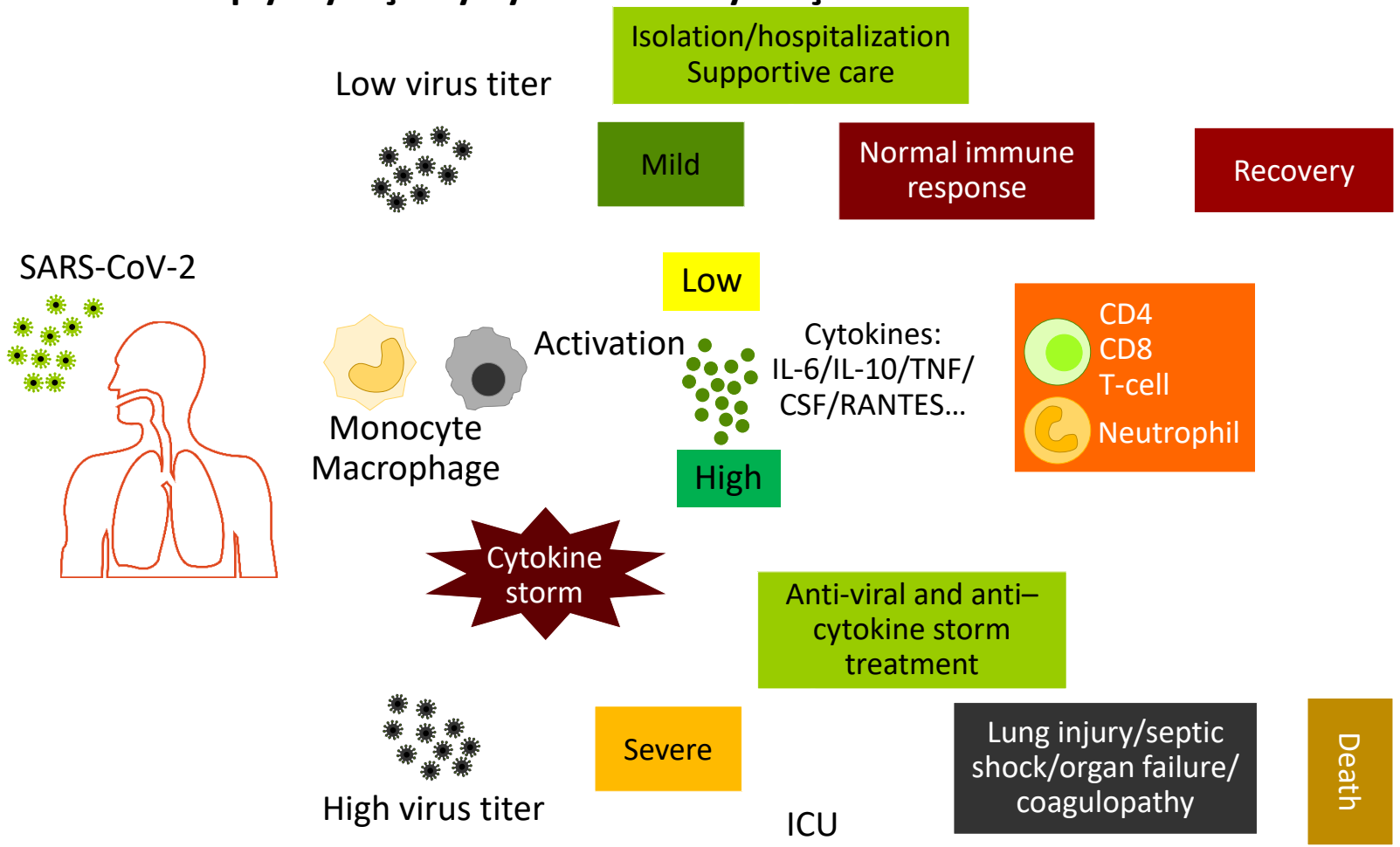
SARS-CoV-2 Patogenezinde Tedavinin Beklenen Yararı



NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated April 8, 2022.
Siddiqi. J Heart Lung Transplant. 2020;39:405.

SARS-CoV-2'de immün cevap

İmmün cevap ya iyileşmeye ya da ölüme yol açar [1]



Yeterli immün cevap

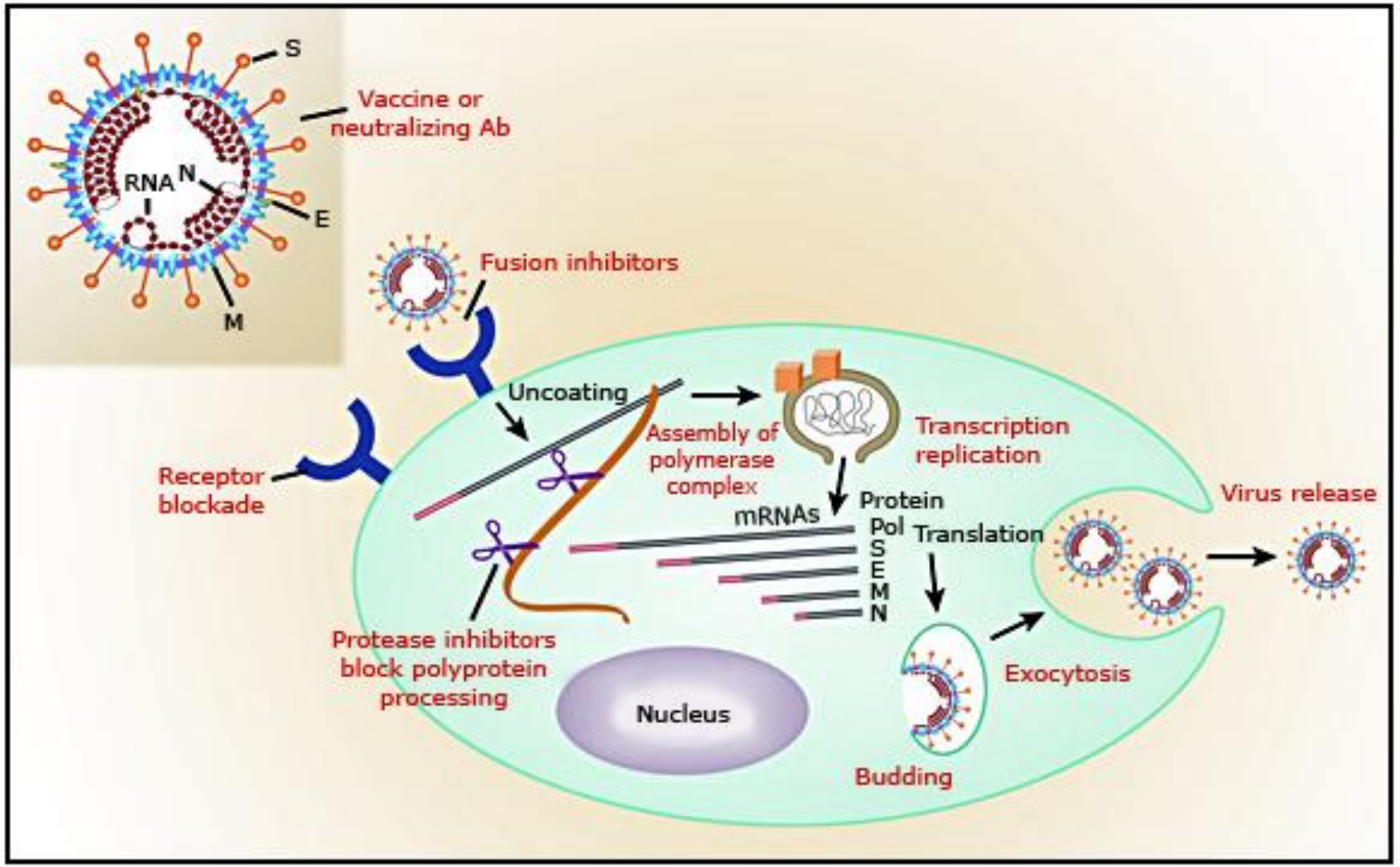
- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Yetersiz immün cevap

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. J Leukoc Biol. 2020;108:17. 2. Sokolowska. Allergy. 2020;75:2445.

Antiviral İlaçların ve Aşıların Potansiyel Hedefleri



Ciddi COVID-19 Riskini Artıran Medikal Durumlar

- Kanser
- Kardiyak hastalık
- Kronik böbrek /karaciğer hastalığı
- Kronik akciğer hastalığı
- Demans
- Diyabet
- Down sendromu
- HIV enfeksiyonu
- Immun yetmezlik
- Mental sağlık durumu
- Aşırı kilo, obezite
- Gebelik
- Sickle cell hastalığı, thalassemia
- Sigara
- Solid organ, kök hücre nakli
- İnme
- Tüberküloz

cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

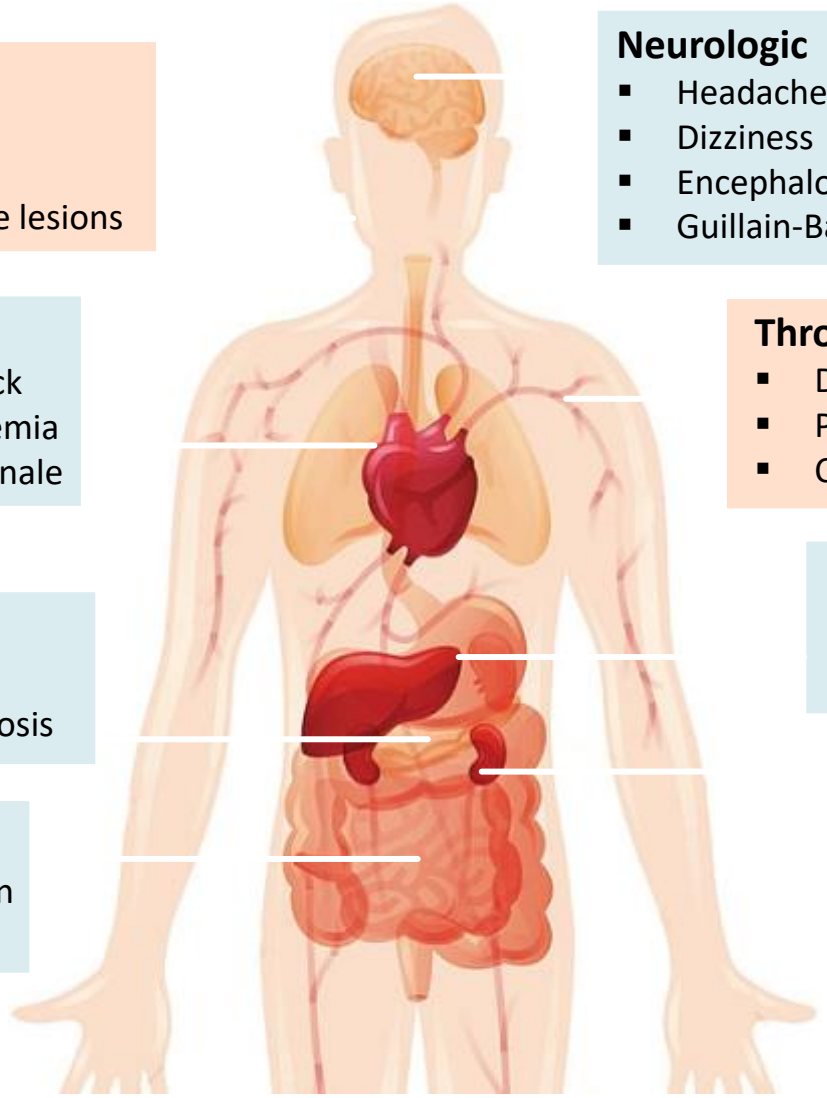
Ekstrapulmoner Belirtiler

Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis



Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta. Nat Med. 2020;26:1017.

OTURUM-1: **Olgu örnekleri ile COVID-19 Tedavisinin Dünü, Bugünü ve Yarını**

Oturum Başkanı: İftihar Köksal

Tartışmacılar: İftihar Köksal, Yeşim Taşova, Füsun Eyüboğlu, Burçin Halaçlı

Olgu-1: Esma Eryılmaz Eren
COVID-19'lu Bir Hastada Aspergillus Terreus ve Lichtemia Corymbifera ile Invaziv Sinüzit Ko-enfeksiyonu

Olgu-2: Esma Eryılmaz Eren
Otolog Hematopoietik Kök Hücre Alıcısı, COVID-19 ve Mukormikoz

Olgu-3: Kağan Şevik
Menenjit Tanılı bir Olguda COVID-19 ile İlişkili MIS-A

Olgu-4: Emirhan Işık
COVID ECMO YB Hastası

Olgu-5: Seichan Chousein Memetali
Zor COVID-19 Olgusu

Olgu-6: Emrullah Ataş
COVID-19 Pnömonisinin Renal Transplantlı Bir Hastadaki Seyri

Olgu-7: Merve Bozdağ
Covid 19'da Pirfenidon Deneyimi

Olgu-8: Serpil Oğuz
COVID-19 Pnömoni Tanısıyla İzlenen, Tedavi Sırasında Spontan Pnömomediastinum Gelişen Olgu

Nontherapeutic Management of Mild COVID-19

WHO[1]
▪ Isolate suspected/confirmed cases to contain SARS-CoV-2 transmission; isolation can occur at home, in a designated COVID-19 health or community facility
▪ Treat symptoms (eg, antipyretics for fever/pain, adequate nutrition, appropriate rehydration)
▪ Educate patients on signs/symptoms of complications that, if developed, should prompt pursuit of urgent care

NIH[2,3]
▪ Majority of cases managed in ambulatory setting or at home (eg, by telemedicine)
▪ No imaging or specific lab tests indicated if otherwise healthy
▪ Close monitoring advised for older patients, those with underlying comorbidities due to increased risk of disease progression
▪ In non-hospitalized patients, do not initiate anticoagulants or antiplatelet therapy to prevent VTE or arterial thrombosis unless other indications exist or patient is participating in clinical trial

1. WHO. COVID-19 clinical management: living guidance. November 23, 2021.
2. NIH COVID-19 Treatment Guidelines. Clinical spectrum of SARS-CoV-2 infection. Last updated October 19, 2021.
3. NIH COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last updated February 24, 2022.

Nontherapeutic Management of Moderate COVID-19

Management[1]

- Monitor closely, as pulmonary disease can rapidly progress
- Administer empiric antibiotics if bacterial pneumonia/sepsis suspected; re-evaluate daily and de-escalate/stop treatment if no evidence of infection

Isolation (Home vs Healthcare Facility)[2]

- Dependent on clinical presentation, requirement for supportive care, presence of vulnerable household contacts; if high risk of deterioration, hospitalization preferred

Initial Evaluation[1]

- May include chest x-ray, ultrasound, or CT
- Perform ECG if indicated
- Obtain CBC with differential and metabolic profile including liver/renal function
- Inflammatory markers (eg, CRP, D-dimer, ferritin) may be prognostically valuable

1. NIH COVID-19 Treatment Guidelines. Clinical spectrum of SARS-CoV-2 infection. Last updated October 19, 2021.
2. WHO. COVID-19 clinical management: living guidance. November 23, 2021.

Nontherapeutic Management of Severe COVID-19

Severe Pneumonia Treatment[1]

- Equip patient care areas with pulse oximeters, functioning oxygen systems, and disposable, single-use, oxygen-delivering interfaces
- Provide immediate supplemental oxygen to patients with emergency signs during resuscitation (eg, obstructed/absent breathing, severe respiratory distress, central cyanosis, shock, coma/convulsions) and to stable hypoxemic patients
- Monitor for clinical deterioration (eg, rapidly progressive respiratory failure, shock); provide immediate supportive care
- Practice cautious fluid management in patients without tissue hypoperfusion and fluid responsiveness

Acute Coinfection Treatment[1]

- Administer empiric antimicrobials within 1 hr of initial assessment based on clinical judgment, patient host factors, and local epidemiology; knowledge of blood cultures before antimicrobial administration ideal
- Assess daily for antimicrobial de-escalation
- Treat other nonbacterial acute coinfections based on lab-confirmed diagnoses or epidemiologic/clinical criteria

Evaluation[2]

- Perform evaluations outlined for **moderate** disease

1. WHO. COVID-19 clinical management: living guidance. November 23, 2021.
2. NIH COVID-19 Treatment Guidelines. Clinical spectrum of SARS-CoV-2 infection. Last updated October 19, 2021.

Supportive Management of Critical COVID-19: ARDS

Patients With ARDS	Recommendation
Any	▪ Provide advanced oxygen/ventilatory support if patient in respiratory distress does not respond to standard oxygen therapy and develops acute hypoxemic respiratory failure ▪ Reserve performance of endotracheal intubation with airborne precautions for trained/experienced providers ▪ Reserve trials of HFNO and NIV for select patients with mild ARDS; monitor for deterioration
Mechanically ventilated	▪ Use lower tidal volumes (4-8 mL/kg PBW), inspiratory pressures (plateau pressure <30 cmH_2O) ▪ Apply prone ventilation 12-16 hr/day in adults with severe ARDS ▪ Practice conservative fluid management if no tissue hypoperfusion and fluid responsiveness ▪ In case of moderate-to-severe ARDS, higher vs lower PEEP suggested with individualized titration and monitoring; avoid neuromuscular blockade by continuous infusion ▪ Avoid disconnecting ventilator; clamp endotracheal tube if transferring to transport ventilator ▪ Consider airway clearance techniques in patients with excessive secretions or difficulty clearing secretions, if deemed medically appropriate ▪ Consider ECMO referral if refractory hypoxemia persists despite lung-protective ventilation

WHO. COVID-19 clinical management: living guidance. November 23, 2021.

Supportive Management of Critical COVID-19: Prevention of Complications

Attempted Outcome Reduction	Intervention
Days of invasive mechanical ventilation	▪ Assess daily for readiness to breathe spontaneously ▪ Minimize sedation (continuous or intermittent) with specific titration targets in mind
Ventilator-associated pneumonia	▪ Use oral vs nasal intubation in adolescents/adults ▪ Maintain semirecumbent patient positioning (ie, head of bed elevation 30-45°) ▪ Use closed suctioning system; drain condensate periodically ▪ Use new ventilator circuit per patient; exchange for same patient only if soiled/damaged ▪ Replace heat moisture exchanger if malfunctioning, soiled, or every 5-7 days
Thromboembolism	▪ Monitor for signs/symptoms (eg, stroke, DVT, pulmonary embolism, acute coronary syndrome); standard vs therapeutic/intermediate anticoagulation dosing suggested for thromboprophylaxis
Catheter-related bloodstream infection	▪ Use checklist and real-time observer to confirm steps for sterile insertion, as daily reminder to remove catheter if unneeded
Pressure ulcers	▪ Turn patient every 2 hr
Stress ulcers and GI bleeds	▪ Administer enteral nutrition within 24-48 hr of admission, H2RAs or PPIs if risk for GI bleed
Antimicrobial resistance	▪ Use empiric antimicrobials for shortest period possible, de-escalating as soon as no evidence of infection and patient clinically stable; avoid antimicrobial use if low suspicion of bacterial infection
Side effects and DDIs	▪ Consider pharmacokinetic and pharmacodynamic effects of all medications

WHO. COVID-19 clinical management: living guidance. November 23, 2021.

Supportive Management of Critical COVID-19: Septic Shock

Diagnosis
▪ **Adults**[2]: Infection suspected/confirmed, vasopressors required to maintain MAP ≥ 65 mm Hg, and lactate ≥2 mmol/L without hypovolemia
▪ **Children**[2]: Any hypotension or ≥2 of the following—altered mental state, brady/tachycardia, prolonged capillary refill or feeble pulses, tachypnea, mottled/cold skin or petechial/purpuric rash, increased lactate, oliguria, hyper/hypothermia

Resuscitation Strategies[2]
▪ **Adults**: Give buffered/balanced crystalloids; give vasopressors if shock continues during/after fluid resuscitation
▪ Assess for fluid overload after each bolus; if present (or no response to fluid), reduce or discontinue fluid
▪ Avoid hypotonic crystalloids, starches, or gelatins
▪ Place arterial catheter for adult patients who require vasopressors
▪ Consider dobutamine if poor perfusion and cardiac dysfunction persist after reaching MAP target

- First-line vasopressors
  - Norepinephrine for adults[1,2]
  - Epinephrine for children[2]

1. NIH COVID-19 Treatment Guidelines. Care of critically ill patients with COVID-19. Hemodynamics. Last updated July 8, 2021.
2. WHO. COVID-19 clinical management: living guidance. November 23, 2021.

Extrapulmonary Manifestations

Manifestation	Recommendation
Renal dysfunction[1]	▪ When renal replacement therapy is indicated for critically ill COVID-19 patients, continuous renal replacement therapy (CRRT) is recommended, if available ▪ If CRRT is unavailable or not possible, prolonged intermittent renal replacement therapy rather than intermittent hemodialysis is recommended
Hematologic[2]	▪ Administer prophylactic dose anticoagulation to hospitalized adults with COVID-19; do not use anticoagulant or antiplatelet therapy to prevent arterial thrombosis outside of usual standard of care ▪ COVID-19 diagnosis should not influence the recommendation for VTE prophylaxis in hospitalized children

1. NIH COVID-19 Treatment Guidelines. Acute kidney injury and renal replacement therapy. Last updated December 17, 2020.
2. NIH COVID-19 Treatment Guidelines. Antithrombotic therapy in patients with COVID-19. Last updated February 24, 2022.

Tedavi Yönetimi

IDSA: Suggestions FOR Treatment of Hospitalized Patients With COVID-19

IDSA Guidance	Patient Population	Treatment
Suggests	▪ Hospitalized with severe‡ COVID-19 ▪ Hospitalized with progressive severe‡ or critical* COVID-19, elevated markers of inflammation ▪ Hospitalized with severe‡ COVID-19 ▪ Hospitalized with severe‡ COVID-19, elevated markers of inflammation, no invasive ventilation ▪ Hospitalized with severe‡ COVID-19, no invasive ventilation ▪ Hospitalized with severe‡ COVID-19 and corticosteroids contraindicated	▪ Dexamethasone† vs none, baricitinib + SoC ▪ Tocilizumab + SoC (ie, steroids) vs SoC alone (if tocilizumab not available, use sarilumab) ▪ Remdesivir§ vs no antiviral ▪ Baricitinib vs none ▪ Tofacitinib vs none ▪ Baricitinib + remdesivir vs remdesivir alone

*Mechanical ventilation or ECMO. Includes end organ dysfunction (eg, ARDS). †If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. ‡SpO_2 ≤94% on room air, including those on supplemental oxygen. §5 days suggested.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 8.0.0.

IDSA: Suggestions FOR Treatment of Nonhospitalized Patients With COVID-19

IDSA Guidance	Patient Population	Treatment
Suggests	▪ Exposed to COVID-19 and at high risk of progression to severe COVID-19 ▪ Ambulatory with mild to moderate COVID-19 at high risk for progression to severe disease ▪ Ambulatory with mild to moderate COVID-19 at high risk for progression to severe disease and no other treatment options ▪ Moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine	▪ Postexposure casirivimab/imdevimab* vs none ▪ Bamlanivimab/etesevimab,* casirivimab/imdevimab,* nirmatrelvir + ritonavir,† remdesivir, or sotrovimab rather than none ▪ Molnupiravir rather than none‡ ▪ FDA-qualified high-titer COVID-19 convalescent plasma rather than none§ ▪ Pre-exposure prophylaxis with tixagevimab/cilgavimab rather than none

*Current EUA states therapy is **not** authorized for use in geographic regions where exposure is likely to have been to a non-susceptible SARS-CoV-2 variant
†Must be given within 5 days of symptom onset
‡Must be ≥18 yr and must be initiated within 5 days of symptom onset
§Must be given within 8 days of symptom onset

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 8.0.0.
Casirivimab With Imdevimab. EUA Fact Sheet for Healthcare Providers. Last updated January 24, 2022.
Bamlanivimab and Etesevimab. EUA Fact Sheet for Healthcare Providers. Last updated January 24, 2022.

IDSA: Recommendations AGAINST Treatment of Patients With COVID-19

IDSA Guidance	Patient Population	Treatment
Recommends against	▪ COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with severe COVID-19	▪ (Hydroxy)chloroquine ▪ (Hydroxy)chloroquine + azithromycin ▪ Lopinavir/ritonavir ▪ Bamlanivimab monotherapy ▪ Convalescent plasma
Suggests against	▪ Hospitalized with nonsevere* COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19, receiving invasive ventilation and/or ECMO *or* no need for supplemental oxygen (ie, SpO_2 >94%)	▪ Glucocorticoids ▪ Routine remdesivir
Suggests against outside clinical trial	▪ Hospitalized with severe COVID-19 ▪ Hospitalized with severe COVID-19 or an ambulatory with COVID-19 ▪ Ambulatory with mild to moderate COVID-19	▪ Famotidine ▪ Ivermectin ▪ Inhaled glucocorticoids

*SpO_2 >94%, no supplemental oxygen.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 8.0.0.

NIH Guidelines: Therapeutic Management of Nonhospitalized Adults With COVID-19

Disease Severity	Recommendation
Not requiring hospitalization or supplemental oxygen per ED, in-person, or telehealth visit	▪ ***In order of preference:*** **Nirmatrelvir + ritonavir** **Remdesivir** ▪ **Alternative agents:** **Bebtelovimab** **Molnupiravir** ▪ ***Recommend against*** **dexamethasone** or other glucocorticoids
Discharged from inpatient setting in stable condition, no supplemental oxygen	▪ ***Recommend against*** continuing **baricitinib**, **dexamethasone**, or **remdesivir** after discharge

Disease Severity	Recommendation
Discharged from inpatient setting, supplemental oxygen required	▪ ***Insufficient data*** to recommend for or against continuing **dexamethasone** or **remdesivir** after discharge
Discharged from ED despite new or increasing need for supplemental oxygen	▪ **Dexamethasone** 6 mg PO QD (up to 10 days) during supplemental oxygen therapy ▪ Since **remdesivir** is recommended for patients with similar oxygen needs who are hospitalized, it may be used in this setting

NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated April 8, 2022.

NIH Guidelines: Therapeutic Management of Hospitalized Adults With COVID-19

Disease Severity	Recommendation
Hospitalized but does not require supplemental oxygen	▪ ***Recommend against*** **dexamethasone** or other glucocorticoids ▪ ***Insufficient data*** to recommend for or against **remdesivir**; may be appropriate if high risk of disease progression
Hospitalized and requires supplemental oxygen	***Use 1 of the following:*** ▪ **Remdesivir*** (eg, in case of minimal supplemental oxygen requirement) ▪ **Remdesivir** plus **dexamethasone*** (eg, with increasing need for supplemental oxygen) ▪ **Dexamethasone** (eg, if remdesivir cannot be used or is unavailable) ▪ For patients on dexamethasone with increasing oxygen needs, can add **baricitinib** or **tocilizumab**
Hospitalized and requires high-flow oxygen or noninvasive ventilation	***Use 1 of the following:*** ▪ **Dexamethasone** ▪ **Dexamethasone** + **remdesivir** ▪ Add **baricitinib** or **tocilizumab** if recently hospitalized with increasing oxygen needs and systemic inflammation†‡
Hospitalized and requires invasive mechanical ventilation or ECMO	▪ **Dexamethasone** plus **tocilizumab**‡ if within 24 hr of ICU admission

*If patient progresses to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, complete remdesivir course
†Tofacitinib can be used instead of baricitinib
‡Sarilumab can be used instead of tocilizumab

NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated February 24, 2022.

NIH Guidelines: Investigational COVID-19 Treatments

Antivirals

Guidance	Treatment
Recommends against	▪ (Hydroxy)chloroquine ± azithromycin for hospitalized patients ▪ Lopinavir/ritonavir or other HIV protease inhibitors ▪ Systemic interferon beta for hospitalized patients
Recommends against except in a clinical trial	▪ Ivermectin

NIH COVID-19 Treatment Guidelines. Antiviral drugs that are approved, authorized, or under evaluation for the treatment of COVID-19. Last updated February 24, 2022.
NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated April 8, 2022.

NIH Guidelines: Investigational COVID-19 Treatments

Immune-Based Therapies

Guidance	Treatment
Recommends against	▪ COVID-19 convalescent plasma in hospitalized patients without impaired humoral immunity ▪ Colchicine for hospitalized patients
Insufficient data to recommend for or against	▪ Anakinra ▪ Fluvoxamine ▪ GCSF inhibitors for hospitalized patients ▪ Inhaled corticosteroids ▪ COVID-19 convalescent plasma in nonhospitalized patients with or without impaired humoral immunity and hospitalized patients with impaired humoral immunity
Recommends against except in a clinical trial	▪ Colchicine for nonhospitalized patients ▪ Canakinumab ▪ Siltuximab ▪ Baricitinib + tocilizumab ▪ BTK or JAK inhibitors (not baricitinib or tofacitinib) ▪ Non-SARS-CoV-2–specific IVIG

NIH COVID-19 Treatment Guidelines. Anti-SARS-CoV-2 antibody products. Last updated April 29, 2022.
NIH COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated December 16, 2021.

Ivermectin

- Ivermectin inhibits the replication of SARS-CoV-2 in cell cultures
- Several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have had mixed results
- Most studies had incomplete information and significant methodologic limitations

NIH COVID-19 Treatment Guidelines Panel:

*"…recommends **against** the use of ivermectin for the treatment of COVID-19, except in clinical trials."*

NIH COVID-19 Treatment Guidelines. Ivermectin. Last updated April 29, 2022.

TOGETHER: Day 28 Efficacy Outcomes

- Mean number of days with COVID-19 symptoms was 3.8±1.9 days
- Use of ivermectin did **not** result in lower incidence of hospitalization or ED visit for COVID-19 in high-risk nonhospitalized patients

ITT Population	n	Primary Outcome, n (%)	RR (95% Bayesian Credible Interval)
Ivermectin	679	100 (14.7)	0.9 (0.70-1.16)
Placebo	679	111 (16.3)	Reference
All	1358	211 (15.5)	---

- Subgroup analyses showed **no difference in treatment effect** when stratified by age, sex, BMI, presence of CVD or pulmonary disease, smoking status, or time since symptom onset

Reis. NEJM. 2022;[Epub online ahead of print]

Effect of Monoclonal Antibodies and Antivirals on Hospitalization and/or Death

Agent	Hospitalization or Death While Receiving Treatment, %	Hospitalization or Death While Receiving Placebo, %	Relative Risk Reduction, %	Absolute Risk Reduction, %	Symptom Onset, Days
Monoclonal antibodies[1,2]	1.0-1.3	4.6-7.0	71-85	3.3-6.0	<5 to <7
Oral antivirals[3,4]	1.0-6.8	6.7-9.7	30-85	2.9-5.7	<5
IV antivirals[5]	0.7	5.3	87	4.6	≤7

- Antivirals and antibodies work in preventing disease progression and hospitalization in high-risk patients (ie, aged >50 yr or ≥1 comorbidity), but treatment must be **initiated early**
- All studies to date performed in unvaccinated participants
  - Benefit in vaccinated patients may be lower
- Cost remains an issue for use as a public health intervention given the numbers needed to treat

1. Gupta. NEJM. 2021;385:1941. 2. Weinreich. NEJM. 2021;385:e81. 3. Bernal. NEJM. 2021;[Epub].
4. Pfizer press release. November 5, 2021. Data not peer reviewed. 5. Hill. IDWeek 2021. Abstr LB1.

Kortikosteroidler

Kortikosteroidler

- Kortikosteroidler, inflamasyon bölgelerine giden nötrofil ve monosit trafiğini bozar,
- Makrofajların ve nötrofillerin fagositik ve mikrobisidal fonksiyonunu inhibe eder,
- Bilinen tüm sitokinlerin üretimini inhibe eder,
- Dolaşımdaki dendritik ve T hücrelerinin sayısını keskin bir şekilde azaltır ve antijen sunumunu etkiler,
- Makrofajların ve dendritik hücrelerin efektör işlevlerini bozar.

Kortikosteroidler

- Bağışıklık sistemi üzerindeki etkileri doza bağlıdır.
- Daha düşük dozlarda, t lenfosit sayıları hafifçe azalır (cd4 +> cd8 +)
- Daha yüksek dozlarda lenfosit aktivasyonunun ve b hücreleri tarafından antikor üretiminin baskılanmasına neden olurlar.
- Enfeksiyona yatkınlık doza bağlı
  - Altta yatan hastalıklar ve diğer immünosupresif ajanlarla birlikte uygulanan tedaviler riski artırır

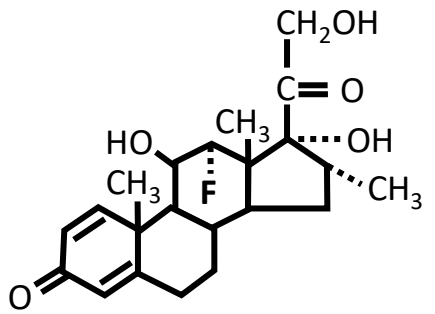
Kortikosteroidler

- COVID-19 hastalarında yapılan son çalışmalar, deksametazonun erken uygulanmasının mekanik ventilasyon süresini ve mortaliteyi azalttığını göstermiştir.

Dexamethasone

- Dexamethasone is a corticosteroid with anti-inflammatory effects that has been used to treat allergies, asthma, dermatitis, rheumatic disorders, MS, other autoimmune disorders, etc
- Can be administered IV or orally
- Contraindicated by FDA in patients with systemic fungal infections
- Pregnancy category C

- **Warnings:** can cause elevation in blood pressure, left ventricular free wall rupture in patients with recent MI, adrenocortical insufficiency, increased susceptibility to infection, and cataracts/glaucoma with possible damage to the optic nerve



Dexamethasone PI. Dexamethasone sodium phosphate PI.

NIH/IDSA: Dexamethasone for COVID-19

NIH[1]*

- For those **not hospitalized (AIII) or hospitalized but not requiring supplemental oxygen (AIIa)**, the Panel **recommends against** the use of **dexamethasone**
- For those **hospitalized and requiring supplemental oxygen**, the Panel **recommends** remdesivir alone (BIIa), remdesivir + **dexamethasone** (BIII), or **dexamethasone** alone (BI)
- For those **hospitalized and requiring high-flow oxygen or noninvasive ventilation**, the Panel **recommends** remdesivir + **dexamethasone** (BIII) or **dexamethasone** alone (AI)
- For those **hospitalized and requiring invasive mechanical ventilation or ECMO**, the Panel **recommends dexamethasone** + tocilizumab (BIIa)
- **Dose**: **Dexamethasone** 6 mg IV or PO for 10 days or until discharge; equivalent corticosteroid dose (eg, prednisone, methylprednisolone, or hydrocortisone) may be used if **dexamethasone** unavailable

IDSA[2]

- For **hospitalized patients with critical[†] COVID-19**, the Panel **recommends dexamethasone** rather than no **dexamethasone** (Strong recommendation, Moderate certainty of evidence)
- For **hospitalized patients with severe[‡] COVID-19**, the Panel **suggests dexamethasone** rather than no **dexamethasone** (Conditional recommendation, Moderate certainty of evidence)
- **Dose**: **Dexamethasone** 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose (eg, methylprednisolone 32 mg, prednisone 40 mg) may be substituted if **dexamethasone** unavailable

*Recommendation rating: A = Strong; B = Moderate; C = Optional. Evidence rating: I = ≥1 randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion. [†]Mechanical ventilation or ECMO. [‡]Patients with SpO_2 ≤94% on room air, including those who require supplemental oxygen.

1. NIH COVID-19 Treatment Guidelines. Therapeutic management of adults with COVID-19. Last updated April 8, 2022.
2. IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 8.0.0.

NIH: Additional Considerations for Dexamethasone

Guidance
▪ Unknown if other corticosteroids will have a similar benefit. Of note: dose equivalencies for dexamethasone 6 mg daily = prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg
▪ The RECOVERY trial included only hospitalized patients
▪ Patients did not receive dexamethasone in the RECOVERY trial if risks deemed too great based on their medical history
▪ It is unclear whether all patients in RECOVERY who received dexamethasone derived benefit from it or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device
▪ Patients should be closely monitored for adverse effects, including hyperglycemia and secondary infections
▪ Systemic corticosteroids may increase risk of reactivation of latent infections (HBV, herpes viruses, TB)
▪ Dexamethasone is a moderate CYP3A4 inducer, which may reduce the concentration and efficacy of some medications; clinicians should review current medications to assess potential interactions
▪ In other coronavirus outbreaks (MERS and SARS), corticosteroid use associated with delayed virus clearance

NIH COVID-19 Treatment Guidelines. Corticosteroids. Last updated December 16, 2021. RECOVERY Collaborative Group. NEJM. 2021;384:693.

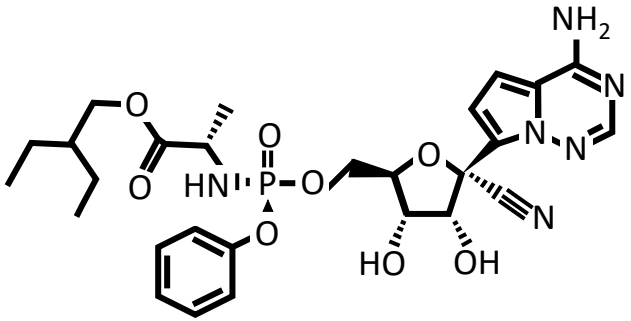
Remdesivir

FDA Approval: Remdesivir for Hospitalized and Nonhospitalized Patients

- Remdesivir is a nucleoside analogue of ATP that inhibits SARS-CoV-2 RNA polymerase by competing with ATP for inclusion into nascent RNA→ delayed chain termination during viral RNA replication

FDA Indication

*Adults and pediatric patients (**≥28 days old and weighing ≥3 kg**) with positive results of SARS-CoV-2 viral testing, who are either **hospitalized**, or **not hospitalized** and have mild to moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death*



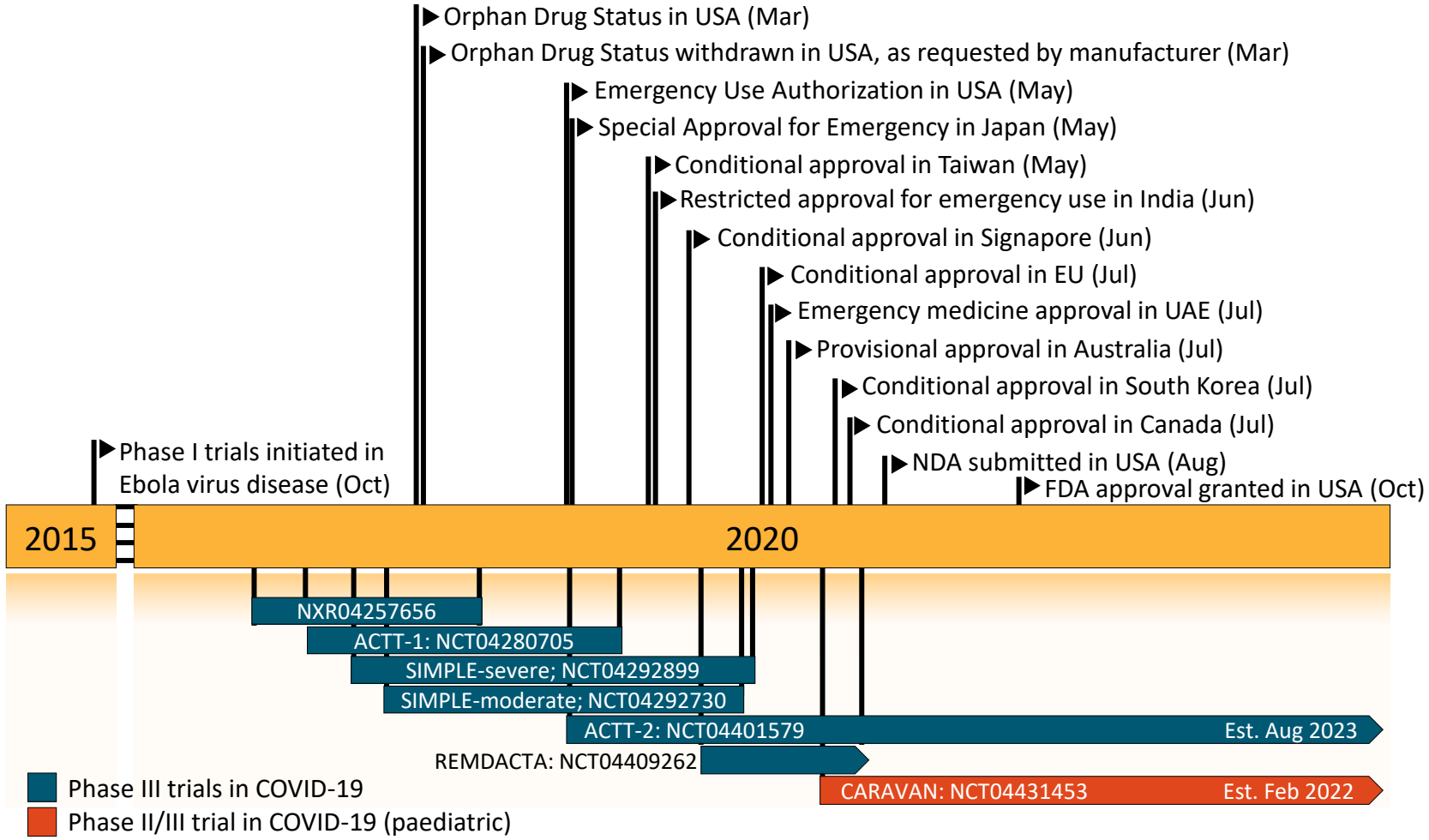
Remdesivir PI. Updated April 2022.

FDA Approval for Remdesivir: Use in Special Populations

Population	Guidance
Pregnancy	Insufficient data to evaluate for drug-associated risks (eg, major birth defects, miscarriage, or adverse maternal or fetal outcomes)
Nursing mothers	No information regarding remdesivir in human milk, effects on breastfed infants, or effects on milk production; in animal studies, remdesivir and metabolites are detected in the nursing pups of mothers given remdesivir, suggesting the presence of remdesivir in milk
Geriatric	Clinical experience has not identified differences in responses between older and younger patients; no dosage adjustment required; should be monitored closely for hepatic, renal, and cardiac function
Renal impairment	Remdesivir PK not evaluated in patients with renal impairment; not recommended for patients with eGFR <30 mL/min
Hepatic impairment	Remdesivir PK not evaluated in patients with hepatic impairment; perform hepatic lab testing prior to starting and while receiving remdesivir as clinically appropriate

Remdesivir PI. Updated April 2022. Remdesivir EUA Fact Sheet for HCPs. Updated April 2022.

Remdesivir: Snapshot on Global Perspectives



"Remdesivir has been approved or authorized for temporary use as a COVID-19 treatment in approximately 50 countries worldwide."

Lamb. Drugs. 2020;80:1355. https://www.gilead.com/news-and-press/press-room/press-releases/2020/10/us-food-and-drug-administration-approves-gileads-antiviral-veklury-remdesivir-for-treatment-of-covid19.

Yeni Oral Antiviraller: Nirmatrelvir + Ritonavir

FDA EUA for Nirmatrelvir + Ritonavir

". . . authorized the emergency use of . . . nirmatrelvir [PF-07321332] tablets and ritonavir tablets . . . for the ***treatment of mild-to-moderate COVID-19 in adults and pediatric patients*** *(12 years of age and older weighing at least 40 kg [88 lbs]) with* ***positive results of direct SARS-CoV-2 viral testing****, and* ***who are at high risk for progression to severe COVID-19****, including hospitalization or death."*

- Nirmatrelvir must be coadministered with ritonavir
- Initiate nirmatrelvir + ritonavir treatment as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset
- **Dosing:**
  - 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days
  - Dose reductions must be made for patients with moderate renal impairment

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-receives-us-fda-emergency-use-authorization-novel
Nirmatrelvir plus Ritonavir. EUA Fact Sheet for Healthcare Providers. Last updated December 22, 2021.

Yeni Oral Antiviraller: Molnupiravir

FDA EUA for Molnupiravir

"…issued an EUA for emergency use of…molnupiravir…for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in ***adults with positive results of direct SARS-CoV-2 viral testing*** *who are at* ***high risk for progressing to severe COVID-19,*** *including hospitalization or death,* ***and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.***"

- Take molnupiravir as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset
- **Dosing:**
  - 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food

Molnupiravir. EUA Fact Sheet for Healthcare Providers. Last updated March 2022.

Oral Antiviral Considerations

Anti–SARS-CoV-2 Therapy	Nirmatrelvir + Ritonavir	Molnupiravir
Mechanism of action	SARS-CoV-2-3CL protease inhibitor	Nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis
Drug interactions	Common - CYP3A	None identified
Timing of use	ASAP within 5 days of symptom onset	
Adverse events	Dysgeusia, diarrhea, hypertension, and myalgia	None greater than placebo
Use in pregnancy	Not studied, RTV safe, NIH panel “would not withhold if benefits >risks”	Avoid use: possible teratogen Childbearing potential: assess if pregnant, contraception recommendations for males and females
Use in renal dysfunction	Adjust eGFR 30-59 mL/min Not recommended if eGFR <30 mL/min	No adjustment needed
Use in liver dysfunction	Do not use if Child-Pugh C	No adjustment needed

covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/
fda.gov/media/155050/download
fda.gov/media/155054/download

Omicron ve Doğrudan Etkili Küçük Molekül Antiviral Ajanlar

Omicron Variant and Direct-Acting Small-Molecule Antiviral Agents

- No biologic plausibility for reduced susceptibility to **molnupiravir, nirmatrelvir,** or **remdesivir**
- **Remdesivir**
  - Genetic analysis of >200 available sequences of omicron isolates revealed **no new mutations** expected to alter the SARS-CoV-2 viral RNA polymerase compared with previous variants
- **Molnupiravir** and **nirmatrelvir + ritonavir**
  - "**Expected to be active** against the omicron VOC, although in vitro and in vivo data are currently limited"

Gilead Press Release. December 1, 2021. Data not peer reviewed.
covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/.

Monoklonal Antikorlar

Mechanisms of Authorized or Approved Monoclonal Antibodies

Monoclonal Antibody	Block Binding of Viral Spike Protein to ACE2	Target Non-RBM Epitopes
Bamlanivimab	X	
Casirivimab	X	
Cilgavimab	X	
Etesevimab	X	
Imdevimab	X	
Regdanvimab	X	
Sotrovimab		X
Tixagevimab	X	

- Combining ACE2-blocking mAbs increases resistance against variants
- mAbs that recognize epitopes conserved among SARS-CoV-2 variants provide protection against viral evolution

Cameroni. Nature. 2022. 604;664.

Temas Sonrası Proflaksi

FDA EUA for Bamlanivimab Plus Etesevimab: Postexposure Prophylaxis

*". . . permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together in **adults and pediatric patients, including neonates**, for **postexposure prophylaxis of COVID-19** in individuals who are at high risk of progression to severe COVID-19, including hospitalization or death . . ."*

- Bamlanivimab and etesevimab must be diluted and **administered together** as a single IV infusion **as soon as possible following exposure** to SARS-CoV-2
- "*Bamlanivimab and etesevimab are **not** authorized for post-exposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a nonsusceptible SARS-CoV-2 variant, based on available information including variant susceptibility to these drugs and regional variant frequency*."

Bamlanivimab and Etesevimab. EUA Fact Sheet for Healthcare Providers. Last updated January 24, 2022.

FDA EUA for Casirivimab With Imdevimab: Postexposure Prophylaxis

" . . . permit the emergency use of the unapproved product, casirivimab with imdevimab, to be administered together, in adult and pediatric individuals (12 yr of age and older weighing at least 40 kg) ***for postexposure prophylaxis of COVID-19*** *in individuals who are at* ***high risk for progression to severe COVID-19, including hospitalization or death.***"

Casirivimab with imdevimab is **not** authorized for postexposure prophylaxis of COVID-19 in geographic regions where exposure is likely to have been to a nonsusceptible SARS-CoV-2 variant, based on available information including variant susceptibility to this drug and regional variant frequency

Casirivimab With Imdevimab. EUA Fact Sheet for Healthcare Providers. Last updated January 24, 2022.

Sotrovimab

- Pan-sarbecovirus neutralizing antibody originally isolated from a patient recovered from SARS-CoV-1
  - Retains activity against major variants, including delta and omicron
  - Fc modified to increase bioavailability in the respiratory mucosa and increase half-life
- Authorized for emergency use for treatment of outpatient mild to moderate COVID-19
- **No data yet for using sotrovimab for pre- or postexposure prophylaxis**
- Recent press release regarding intramuscular administration as noninferior to IV administration in COMET-TAIL trial (COVID-19 treatment)

Gupta. NEJM. 2021;385:1941. gsk.com/en-gb/media/press-releases/primary-endpoint-met-in-comet-tail-phase-iii-trial-evaluating-intramuscular-administration-of-sotrovimab-for-early-treatment-of-covid-19/. Press release; data not peer reviewed .

Temas Öncesi Proflaksi

Tixagevimab + Cilgavimab Emergency Use Authorization

*. . . for **pre-exposure prophylaxis of COVID-19** in patients ≥12 yr of age weighing ≥40 kg who are not currently infected with SARS-CoV-2 and who have moderate to severe immune compromise and/or for whom COVID-19 vaccination is not recommended*

- Updated February 24, 2022, to **double the dose** to 300 mg/300 mg (600 mg total) with the emergence of omicron BA.1 and lower neutralizing activity for this subvariant

Tixagevimab + Cilgavimab Neutralization Data for SARS-CoV-2 Variants

Lineage With Spike Protein Substitution	WHO Nomenclature	Fold Reduction in Susceptibility (Pseudotyped VLPs)	Fold Reduction in Susceptibility (Authentic Virus)
B.1.617.2	Delta	No change	No change
AY.1/AY.2	Delta [+K417N]	No change	No change
BA.1	Omicron (BA.1)	132- to 183-fold	12- to 30-fold
BA.1.1	Omicron (BA.1) [+R346K]	424-fold	176-fold
BA.2	Omicron (BA.2)	No change	5.4-fold

- Omicron BA.1 or BA.1.1 showed **reduced** neutralizing activity
- Omicron BA.2 showed **minimal change** in neutralizing activity

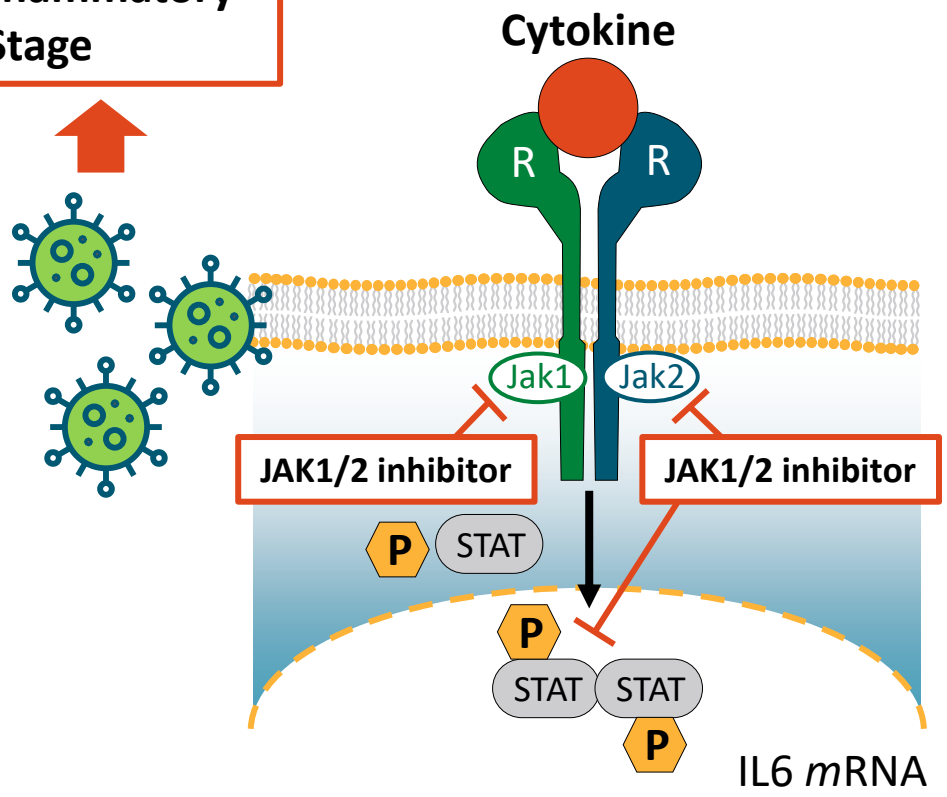
FDA. Fact sheet for healthcare providers: Emergency Use Authorization for tixagevimab co-packaged with cilgavimab.

JAK İnhibitörleri

JAK1/2 Inhibitors

Elevated in blood
IL-1b, IL-2, IL-6, IL-7, IL-8,
IL-9, IL-10, IL-17, G-CSF, GM-CSF,
IFNα, IFNγ, TNF-α, IP10, MCP1,
MIP1A, MIP1B

Hyperinflammatory Stage



Stebbing. EMBO Mol Med. 2020;12:e12697.

Baricitinib

- Janus kinase inhibitor approved as a DMARD for rheumatoid arthritis
- Identified as a therapeutic candidate by artificial intelligence for both immunomodulatory and potential antiviral properties
- Inhibits host proteins (P2-associated kinase 1 AAK1 and the cyclin G–associated kinase GAK)
- May inhibit virus entry into cells and reduce inflammatory responses

Stebbing. Sci Adv. 2021;7:eabe4724.

FDA EUA for Baricitinib

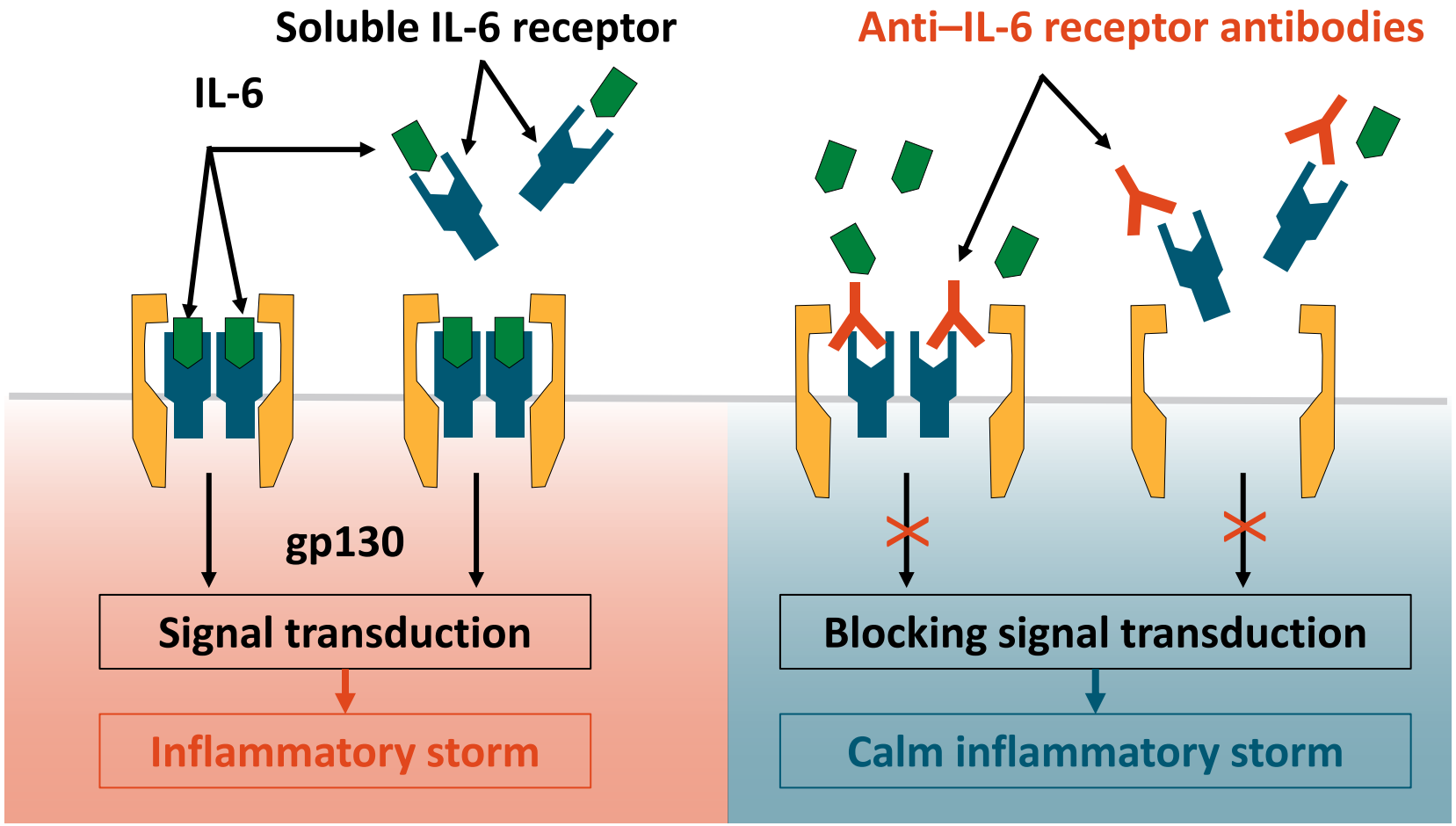
*". . . permit the emergency use of **baricitinib** for treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)."*

- **Recommended dosage under EUA:**
  - Adults and pediatric patients ≥9 yr of age: 4 mg orally once daily
  - Pediatric patients 2 yr to <9 yr of age: 2 mg orally once daily
  - Optimal duration of treatment unknown; 14 days or until hospital discharge (if first) recommended
- eGFR, aminotransferase levels, and CBC with differential must be determined before first dose

Baricitinib. EUA Fact Sheet for Healthcare Providers. Last updated December 2021.

IL-6 inhibitörleri

Anti–IL-6 Receptor Antibodies



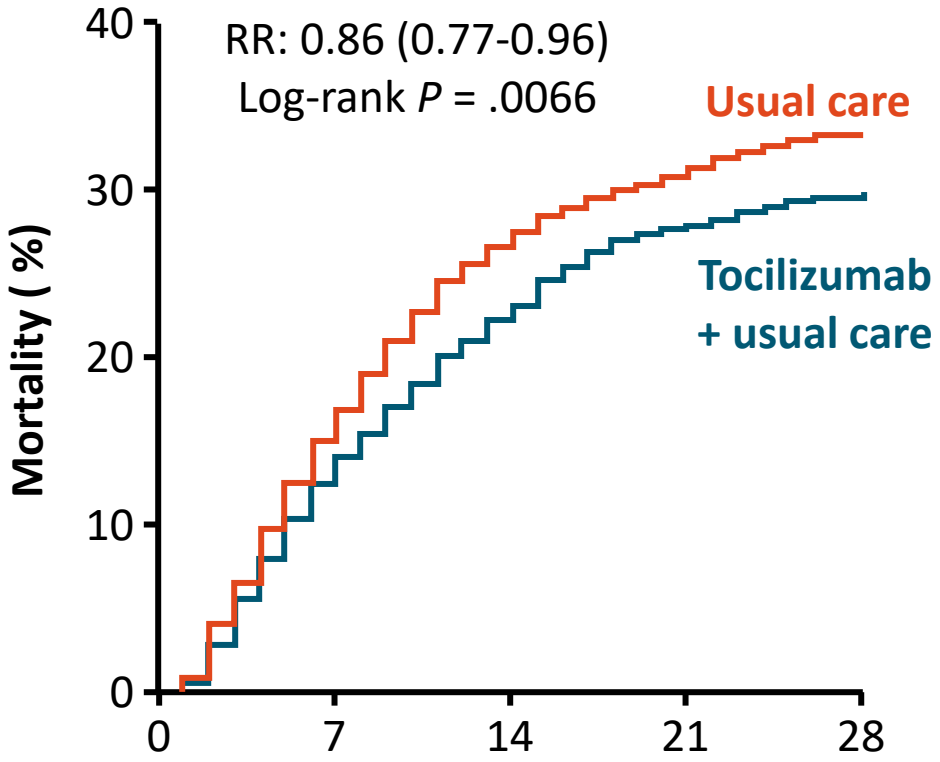
Fu. J Translational Medicine. 2020;18:164.

Select Early RCT Data for IL-6R Inhibitors

Agent	N	Population	Comparator	Primary Outcomes
Tocilizumab[1,2]	130	Moderate or severe pneumonia	Standard care alone	▪ No difference in proportions with WHO-CPS score >5 at Day 4 ▪ Noninvasive ventilation, intubation, or death at Day 14: 24% vs 36% ▪ No mortality difference by Day 28
Sarilumab (200 or 400 mg)[3,4]	457	Severe or critical	Placebo	▪ CRP decline: 77% and 79% vs 21% ▪ IDMC recommended continuing phase III only in critical subgroup with 400 mg sarilumab vs placebo

1. Hermine. JAMA Intern Med. 2021;181:32. 2. NCT04331808. 3. NCT04315298. 4. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive. Press release only, not peer reviewed.

RECOVERY: Results for Tocilizumab + Usual Care vs Usual Care Alone



Patients at Risk, n					
Active	2022	1741	1556	1386	1284
Control	2094	1740	1518	1372	1250

- Secondary endpoint: reduced receipt of mechanical ventilation in patients not receiving ventilation at time of randomization
  - 12% with tocilizumab vs 15% with usual care (RR: 0.81; 95% CI: 0.68-0.95)

Recovery Collaborative Group. Lancet. 2021 May 1;397(10285):1637.

Araştırma Aşamasında olan Diğer Antiviral Ajanlar

Host Targeted Therapies Can Also Reduce Hospitalization

Inhaled budesonide (STOIC Trial)[1]

- **Intervention:** budesonide 400 µg, 2 inhalations twice daily until symptom resolution or usual care
- **Primary endpoint:** COVID-19-related acute care visit
- **Results:** 1% vs 14% met the primary endpoint (*P* = .004)

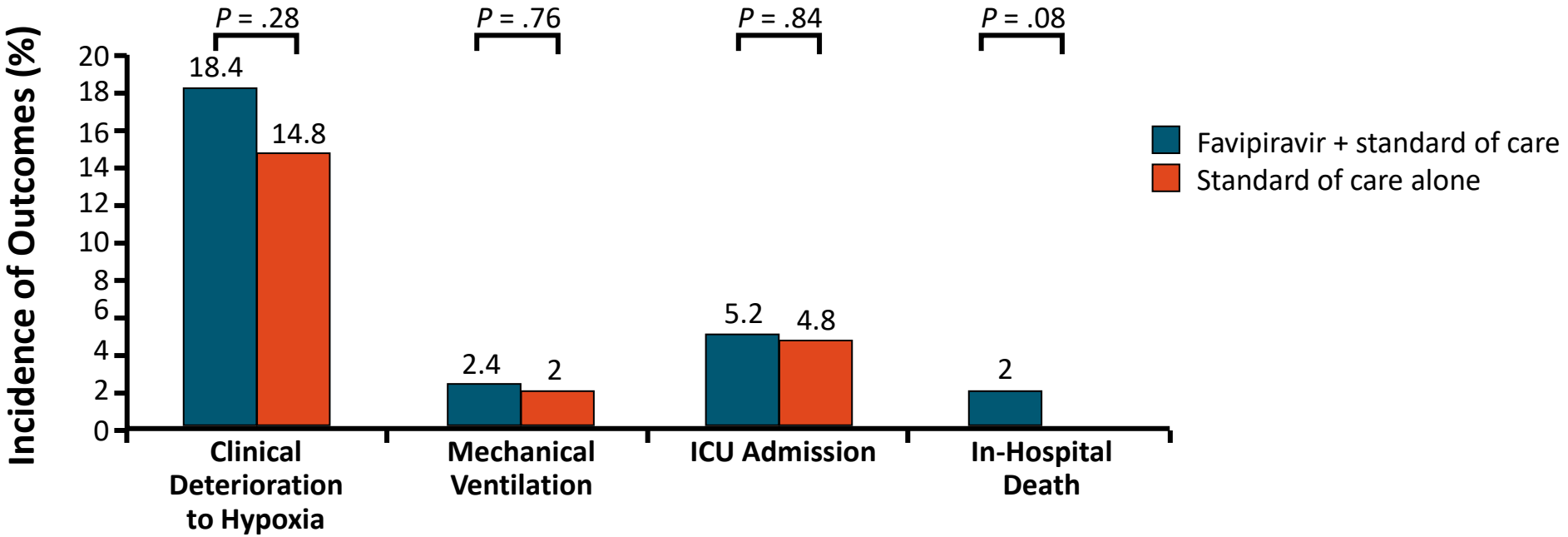
Fluvoxamine (TOGETHER Trial)[2]

- **Intervention:** fluvoxamine 100mg twice daily x 10 days or placebo
- **Primary endpoint:** 28-day hospitalization or transfer to tertiary hospital
- **Results:** 11% vs 16% met the primary endpoint (RR 0.68; 95% CI 0.52-0.88)

1. Ramakrishnan. Lancet Resp Dis. 2021;9:763. 2. Reis. Lancet Global Health. 2021;10:42.

SOF/DCV or SOF/RVD
Novel Oral Antivirals: AT-527
Favipiravir

Favipiravir in Hospitalized Patients



- N = 500, ≥50 yr of age, ≥1 comorbidity
- Favipiravir dose: 1800 mg BID Day 1, then 800 mg BID Days 2-5
- Results: no difference in oxygenation, ICU admission, or mechanical ventilation between favipiravir and placebo groups

Chuah. Clin Infect Dis. 2021;[Epub].

Teşekkürlerimle..