Covid-19 Therapeutics:
Convalescent Plasma and Monoclonal Antibodies

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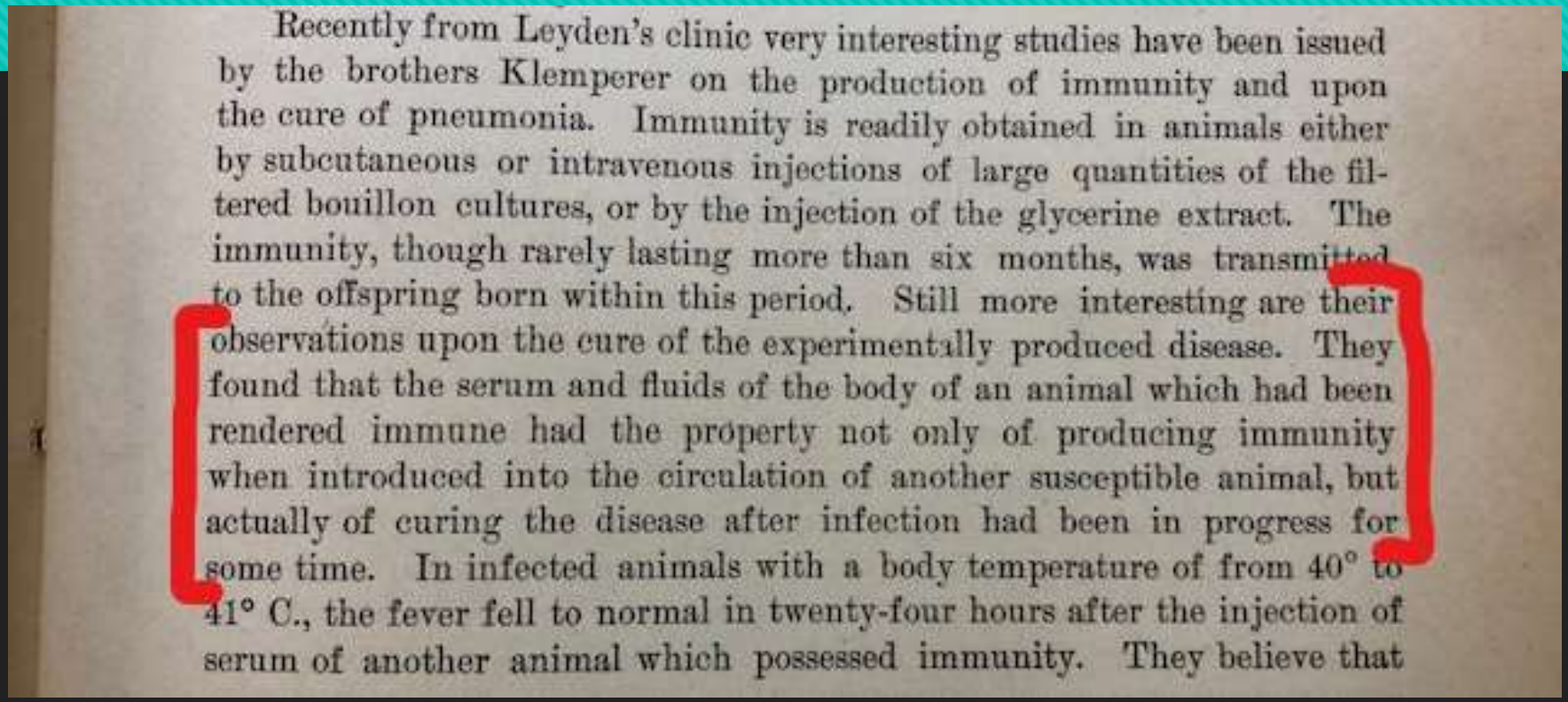
Disclosures

- No financial disclosures
- There will be discussion of therapeutics that do not have full FDA approval and are available only under an EUA

Objectives

- Learn the potential benefits and limitations of convalescent plasma for SARS-CoV-2 infection
- Learn the potential benefits and limitations of monoclonal antibody therapy for SARS-CoV-2 infection

Convalescent Plasma



Recently from Leyden's clinic very interesting studies have been issued by the brothers Klemperer on the production of immunity and upon the cure of pneumonia. Immunity is readily obtained in animals either by subcutaneous or intravenous injections of large quantities of the filtered bouillon cultures, or by the injection of the glycerine extract. The immunity, though rarely lasting more than six months, was transmitted to the offspring born within this period. Still more interesting are their observations upon the cure of the experimentally produced disease. They found that the serum and fluids of the body of an animal which had been rendered immune had the property not only of producing immunity when introduced into the circulation of another susceptible animal, but actually of curing the disease after infection had been in progress for some time. In infected animals with a body temperature of from 40° to 41° C., the fever fell to normal in twenty-four hours after the injection of serum of another animal which possessed immunity. They believe that

Osler, W. The Principles and Practice of Medicine, Second Edition. D Appleton and Company, New York, 1897. p.547

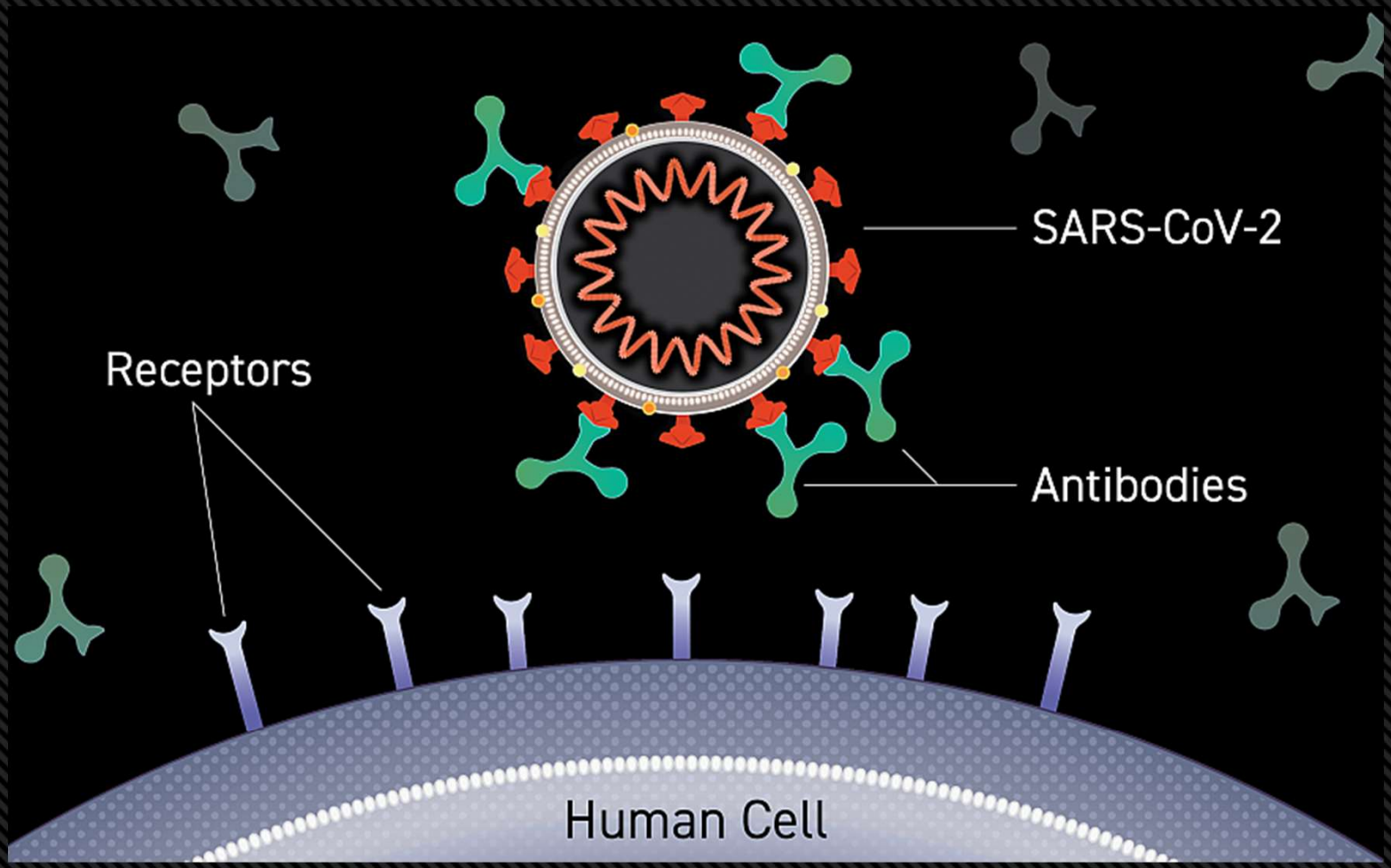


Image of an antibody binding to the surface of a virus, blocking entry into a human cell.*Lisa Donohue, CoVPN,* NIH news release, Monday August 10, 2020. https://www.nih.gov/news-events/news-releases/clinical-trials-monoclonal-antibodies-prevent-covid-19-now-enrolling

Convalescent Plasma

- One randomized study, outpatient administration[1]
  - One unit of high-titer convalescent plasma in high-risk patients
  - Patients within 7 days of symptom onset, stable for outpatient management
  - No difference in progression to severe disease
  - Korley F et al
- One prospective propensity score-matched case-control study of hospitalized inpatients with severe disease[2]
  - Received 1 or 2 units of high-titer convalescent plasma
  - 60-day mortality 6.2% in transfusion recipients, 12.4% in non-recipients (p=0.003)

1. Korley F et al. Early convalescent plasma for high-risk patients with Covid-19. NEJM 2021; 385:1951-60. DOI: 10.1056/NEJMoa2103784

2. Salazar E et al. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. *Am J Pathol*. 2021;191(1):90-107. doi:10.1016/j.ajpath.2020.10.008

Convalescent Plasma

- Where are we today? (as of March 21, 2022)
- IDSA Treatment Guidelines[1]
  - Hospitalized patients: recommend against use
  - Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)
- NIH Treatment Guidelines[2]
  - Recommends against the use in hospitalized patients without defects of humoral immunity
  - Insufficient evidence to recommend for or against use in patients with defects in humoral immunity or ambulatory patients without defects in humoral immunity
- WHO Treatment Guidelines[3]
  - Recommends against the use of convalescent plasma for patients with non-severe, severe, and critical COVID-19, as of 7 December 2021 (unless part of a research trial)

1. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-11

2. https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/convalescent-plasma/

3. https://app.magicapp.org/#/guideline/nBkO1E/section/nJB6MR

Convalescent Plasma: Can you use?

- Most recent FDA EUA (December 28, 2021)
  - "…the scope of this authorization is limited to the use of the authorized COVID-19 convalescent plasma with high titers of antiSARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment, in either the outpatient or inpatient setting."[1]

1.https://www.fda.gov/media/141477/download

Monoclonal Antibodies

- The good:
  - November 9, 2020, EUA issued for bamlanivimab (BAM)
  - November 21, 2020, EUA issued for casirivimab+imdevimab (REGEN-COV)
  - February 9, 2021, EUA issued for bamlanivimab+etesevimab
  - May 26, 2021, EUA issued for sotrovimab
  - December 8, 2021, EUA issued for tixagevimab/cilgavimab (prophylaxis in select patients only)
  - February 11, 2022, EUA issued for bebtelovimab
- The bad
  - April 16, 2021 EUA for bamlanivimab monotherapy revoked
  - December-January 2021, EUA for casirivimab+imdevimab and bamlanivimab+etesevimab revised due to increasing Omicron variant
  - April 5, 2022: Sotrovimab no longer recommended due to BA.2 variant
  - The EUAs for sotrovimab and bebtelovimab included caveat about presence of nonsusceptible variants

Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against SARS-CoV-2 Variants In Vitro.*

Monoclonal Antibody or Antiviral Drug	SARS-CoV-2 Variant					
	SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo (A)	SARS-CoV-2/UT-HP127-1Nf/Human/2021/Tokyo (Alpha/B.1.1.7)	hCoV-19/USA/MD-HP01542/2021 (Beta/B.1.351)	hCoV-19/Japan/TY7-503/2021 (Gamma/P.1)	hCoV-19/USA/WI-UW-5250/2021 (Delta/B.1.617.2)	hCoV-19/Japan/NC928-2N/2021 (Omicron/B.1.1.529)
Neutralization activity of monoclonal antibody — ng/ml†						
LY-CoV016, etesevimab	18.19±9.10	150.38±83.51	>50,000	>50,000	15.37±9.78	>50,000
LY-CoV555, bamlanivimab	4.69±1.43	2.65±1.30	9554.88±926.53	1601.65±896.02	641.73±324.79	>50,000
REGN10987, imdevimab	3.05±0.93	1.87±1.60	2.17±1.30	1.04±0.68	3.95±1.78	>50,000
REGN10933, casirivimab	2.79±1.87	2.74±1.84	757.13±287.91	187.69±128.88	2.89±1.78	14,110.70±1782.13
COV2-2196, tixagevimab	1.92±0.28	1.34±0.67	18.98±1.42	6.56±1.56	4.05±2.60	1299.94±406.58
COV2-2130, cilgavimab	7.70±2.20	3.60±1.62	10.03±3.05	4.00±2.70	12.76±2.93	443.87±167.96
S309, sotrovimab precursor	27.33±3.24	44.91±22.76	100.98±22.27	28.38±1.86	111.43±58.22	373.47±159.49
LY-CoV016 plus LY-CoV555	12.60±1.91	15.26±3.98	>10,000	2545.04±625.72	10.28±3.33	>10,000
REGN10987 plus REGN10933	3.53±0.66	1.55±0.78	5.18±1.45	2.11±0.48	1.91±0.79	>10,000
COV2-2196 plus COV2-2130	3.42±0.92	1.94±0.34	10.30±1.17	1.79±0.87	5.50±2.75	255.86±45.31

Takashita E et al. Efficacy of Antibodies and Antiviral Drugs against Covid-19 Omicron Variant. N Engl J Med. 2022 Mar 10;386(10):995-998. doi: 10.1056/NEJMc2119407. Epub 2022 Jan 26. PMID: 35081300; PMCID: PMC8809508.