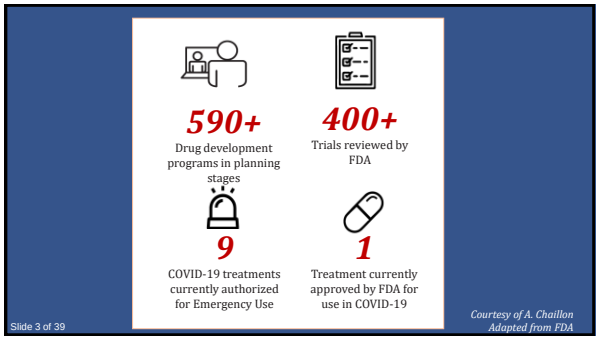
Preventing Severe COVID-19: The Role of Monoclonal Antibodies and Beyond

Davey Smith, MD
Professor of Medicine
University of California San Diego
San Diego, California

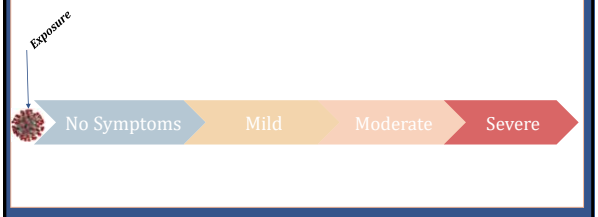
Financial Relationships With Commercial Entities

Dr Smith has served on the board for Linear Therapies and Fluxergy Inc, has served as a consultant for Bayer Pharmaceuticals, Arena Pharmaceuticals, Gilead Sciences, Inc., Merck & Co, Inc., and Medscape, has received payment for the preparation of a manuscript for Kiadis. He has also received grant support paid to his institution from ViiV Healthcare. (Updated 05/17/21)

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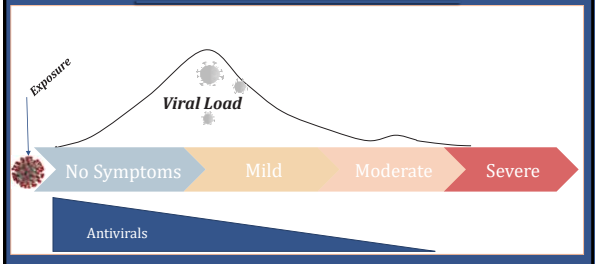
Natural History



Slide 4 of 39

BMJ 2020;371:m3862 - *Courtesy of A. Chaillon*

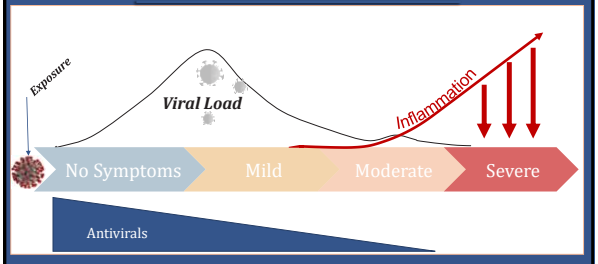
When to treat and what to use



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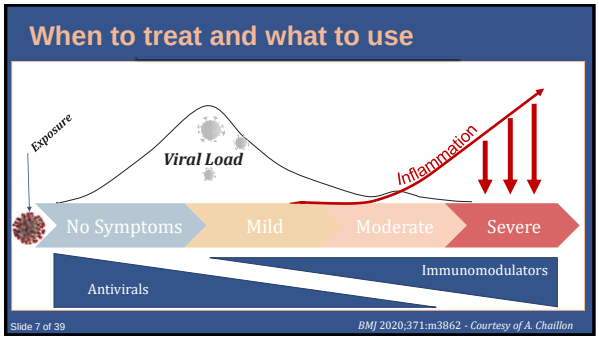
BMJ 2020;371:m3862 - *Courtesy of A. Chaillon*

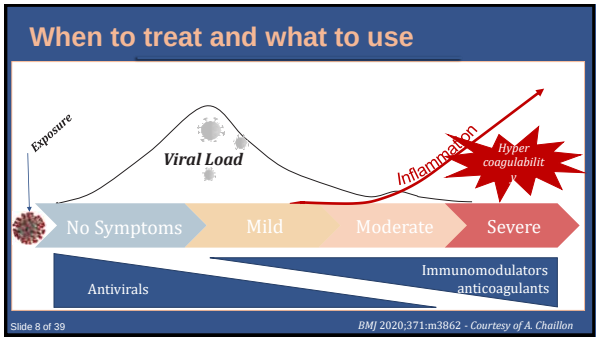
When to treat and what to use

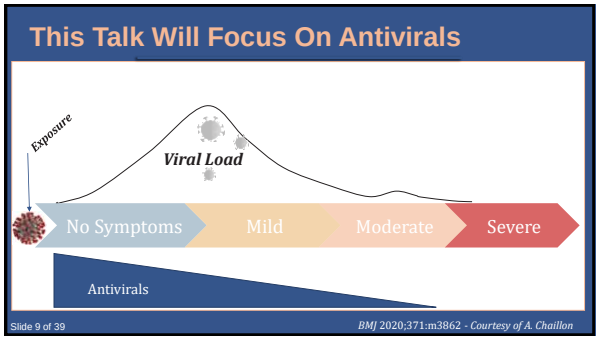


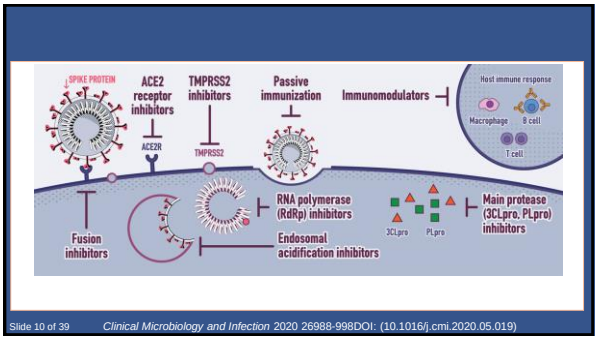
Slide 6 of 39

BMJ 2020;371:m3862 - *Courtesy of A. Chaillon*

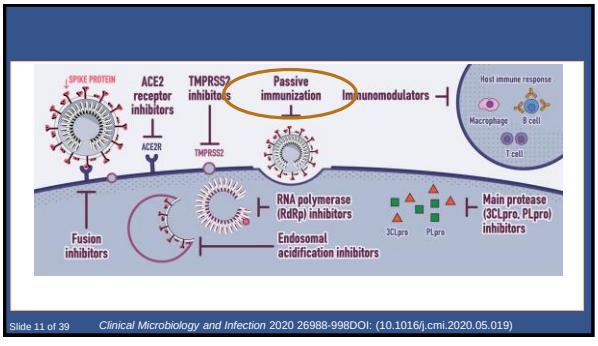

When to treat and what to use
Exposure
Viral Load
Inflammation
No Symptoms
Mild
Moderate
Severe
Immunomodulators
Antivirals
Slide 7 of 39
BMJ 2020;371:m3862 - Courtesy of A. Chaillon


When to treat and what to use
Exposure
Viral Load
Inflammation
Hyper coagulabilit
No Symptoms
Mild
Moderate
Severe
Immunomodulators
anticoagulants
Antivirals
Slide 8 of 39
BMJ 2020;371:m3862 - Courtesy of A. Chaillon


This Talk Will Focus On Antivirals
Exposure
Viral Load
No Symptoms
Mild
Moderate
Severe
Antivirals
Slide 9 of 39
BMJ 2020;371:m3862 - Courtesy of A. Chaillon

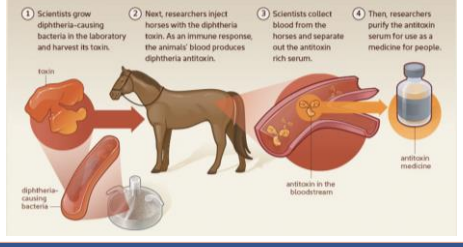


Slide 10 of 39 *Clinical Microbiology and Infection* 2020 26988-998DOI: (10.1016/j.cmi.2020.05.019)



Slide 11 of 39 *Clinical Microbiology and Infection* 2020 26988-998DOI: (10.1016/j.cmi.2020.05.019)

1st Nobel Prize: Diphtheria

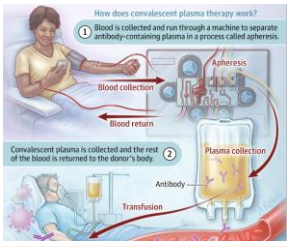




Passive Antibody Infusion Treated Children with Diphtheria

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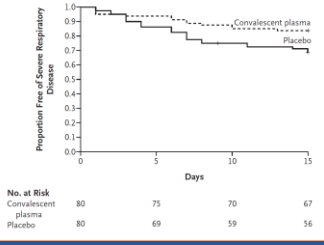
Convalescent plasma



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Convalescent plasma

- Convalescent plasma used w/in 72 hours in 165 elderly persons (+75yo) or 65-74yo with comorbidities with COVID-19
- NNT to avert one episode of severe resp illness was 7.

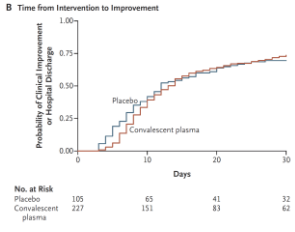


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Libster et al. NEJM. Feb 18, 2021.

Convalescent plasma

- Hospitalized adults with severe COVID-19 pneumonia
  - 228 Conv Plasma
  - 105 Placebo



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Simonovich et al. NEJM. Feb 18, 2021.

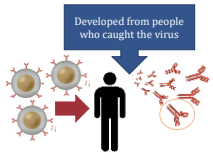
Convalescent plasma

- Multicenter study of CP in hospitalized patients with +PCR
- CP donors had high NAb levels
- Participants also often had high NAb at enrollment
- Stopped after 86 participants for futility.

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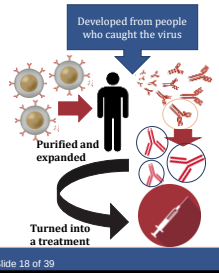
Jordans et al CROI 2021 Late breaker abstract 120.

Monoclonal antibodies



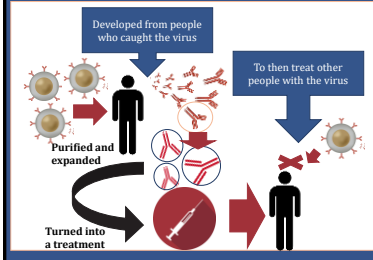
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Monoclonal antibodies



Slide 18 of 39

Monoclonal antibodies



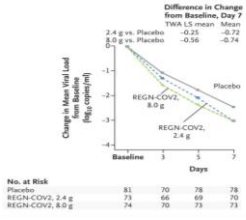
- >25 Companies have made MAbs that are in various stages of clinical testing.

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Casirivimab and imdevimab

- *Viral Load over time in the overall population*

- **Viral Loads**
  - 275 patients randomized 1:1:1 to receive 8 g cocktail (n=90), 2.4 g cocktail (n=92) or placebo (n=93).



Slide 20 of 39 Weinreich et al. NEJM Dec 2020.

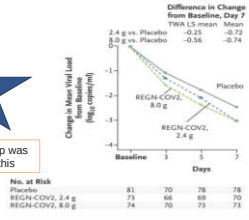
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EUA

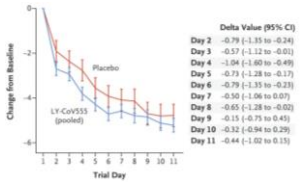
President Trump was treated with this



Slide 21 of 39 Weinreich et al. NEJM Dec 2020.

Bamlanivimab (LY-CoV555)

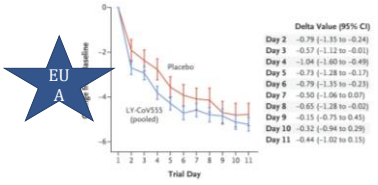
- **Symptom scores**
  - 452 persons received LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo



Chen et al. NEJM Oct 2020.

Bamlanivimab (LY-CoV555)

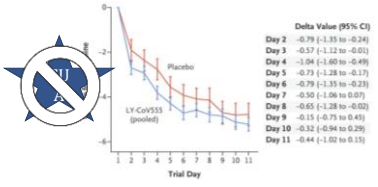
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Chen et al. NEJM Oct 2020.

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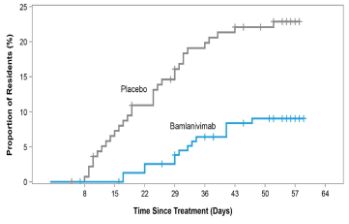
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Chen et al. NEJM Oct 2020.

Bamlanivimab (LY-CoV555)

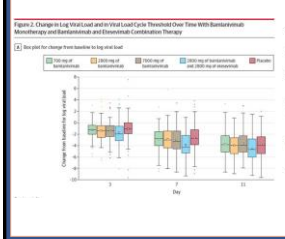
- **Nursing Home BLAZE-2 Prevention Study**



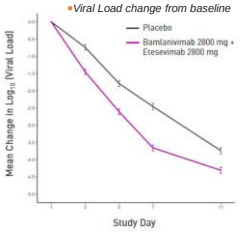
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Cohen et al CROI 2021 Late breaker abstract 121.

Bamlanivimab + Etesevimab



- *Viral Load change from baseline*



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Gottlieb RL, Nirula A, Chen P, et al. *JAMA*. 2021;325(7):632–644. Lily Press Release 2021. CROI 2021 Late breaker, Dougan et al abst 122

Bamlanivimab + Etesevimab

COVID-19 RELATED HOSPITALIZATION OR DEATH BY ANY CAUSE BY DAY 29

	N	Events	Rate	p
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

70% reduction vs. placebo

DEATH BY ANY CAUSE BY DAY 29

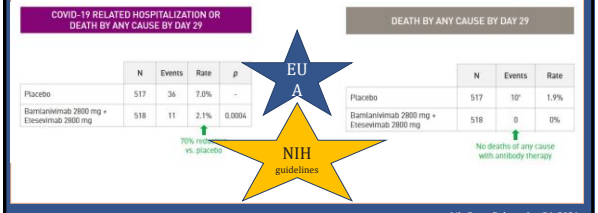
	N	Events	Rate
Placebo	517	10*	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

No deaths of any cause with antibody therapy

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Lily Press Release Jan 26, 2021

Bamlanivimab + Etesevimab



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Lily Press Release Jan 26, 2021

High-Risk Patients Eligible for mAb Treatment

≥ 65 years of age	≥ 55 years of age with any of the following:	≥ 12 years of age with any of the following:	12 years to 17 year of age with any of the following:
• No additional requirements	• CVD • HTN • COPD/other chronic respiratory disease	• BMI ≥ 35 kg/m^2 • CKD • Diabetes • Immunosuppressive disease • Currently receiving immunosuppressive treatment	• BMI ≥ 85th percentile for their age and gender • Sickle cell disease • Congenital or acquired heart disease • Neurodevelopmental disorders (eg, cerebral palsy) • Medical-related technological dependence (eg, tracheostomy, gastrostomy, or positive-pressure ventilation [not related to COVID-19]) • Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control

• FDA. Fact sheet for health care providers Emergency Use Authorization (EUA) of casirivimab and imdevimab; FDA. Fact sheet for health care providers Emergency Use Authorization (EUA) of bamlanivimab; FDA. Fact sheet for health care providers Emergency Use Authorization (EUA) of bamlanivimab and etesevimab.

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Mab Therapy

- *Present*
  - Only for high-risk persons with early COVID-19
  - **Not** for patients:
    - who are **hospitalized** due to COVID-19, OR
    - who **require oxygen** therapy due to COVID-19, or
    - who require an increase in baseline oxygen flow rate due to COVID-19
- *Future*
  - New routes: IM, SQ, Inhaled
- EUA ≠ Approval
- FDA explicitly encouraged more research before approval

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CoV-2 Evolves to its New Home

- Among RNA, coronaviruses have modest mutation rate
- Example D614G in Spike
  - Increased infectivity
  - Increased transmissibility in animal models

614
Virus 1: D R D A V E Y S M I T H
Virus 2: D R G A V E Y S M I T H

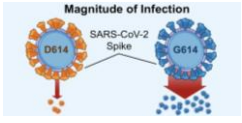
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Korber B, et al. Cell;
Kemp SA, et al. preprint on medRxiv.

CoV-2 Evolves to its New Home

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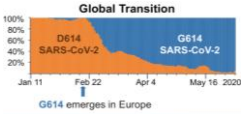
614
Virus 1: D R D A V E Y S M I T H
Virus 2: D R G A V E Y S M I T H



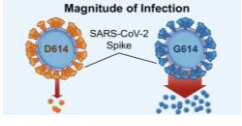
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Korber B, et al. Cell;
Kemp SA, et al. preprint on medRxiv.

CoV-2 Evolves to its New Home



614
Virus 1: D R D A V E Y S M I T H
Virus 2: D R G A V E Y S M I T H

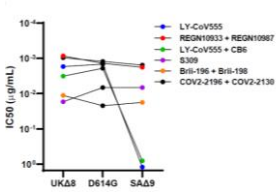


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Korber B, et al. Cell;
Kemp SA, et al. preprint on medRxiv.

Do Variants Impact mAb Treatments?

- Rationale
  - Ab cocktails likely to have better efficacy against new variants.
  - Non-infusion likely will have better uptake



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Cows: polyclonal antibodies



https://www.sciencemag.org/news/2020/06/cow-s-antibodies-could-be-newest-weapon-against-covid-19#

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Summary

- Antivirals are being developed for SARS-CoV-2
- Ab-based therapies are promising and have gotten EUAs
- Currently only available by IV (new versions coming)
- Maybe thwarted by viral evolution
- Check out ACTIV-2 (www.riseabovecovid.org)



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ACKNOWLEDGEMENTS

- ACTIV-2 Participants, Study Team
- US Govt Response to COVID-19
- Antoine Chaillon
- CROI 2021



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Suggested Readings

- Libster R, et al. Fundación INFANT–COVID-19 Group. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021 Feb 18;384(7):610-618. doi: 10.1056/NEJMoa2033700.
- Simonovich V, et al. PlasmAr Study Group. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2021 Feb 18;384(7):619-629. doi: 10.1056/NEJMoa2031304.
- Liu L, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature. 2020 Aug;584(7821):450-456.
- Chen P, et al. BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2021 Jan 21;384(3):229-237.
- Weinreich DM, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021 Jan 21;384(3):238-251.

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Question-and-Answer Session