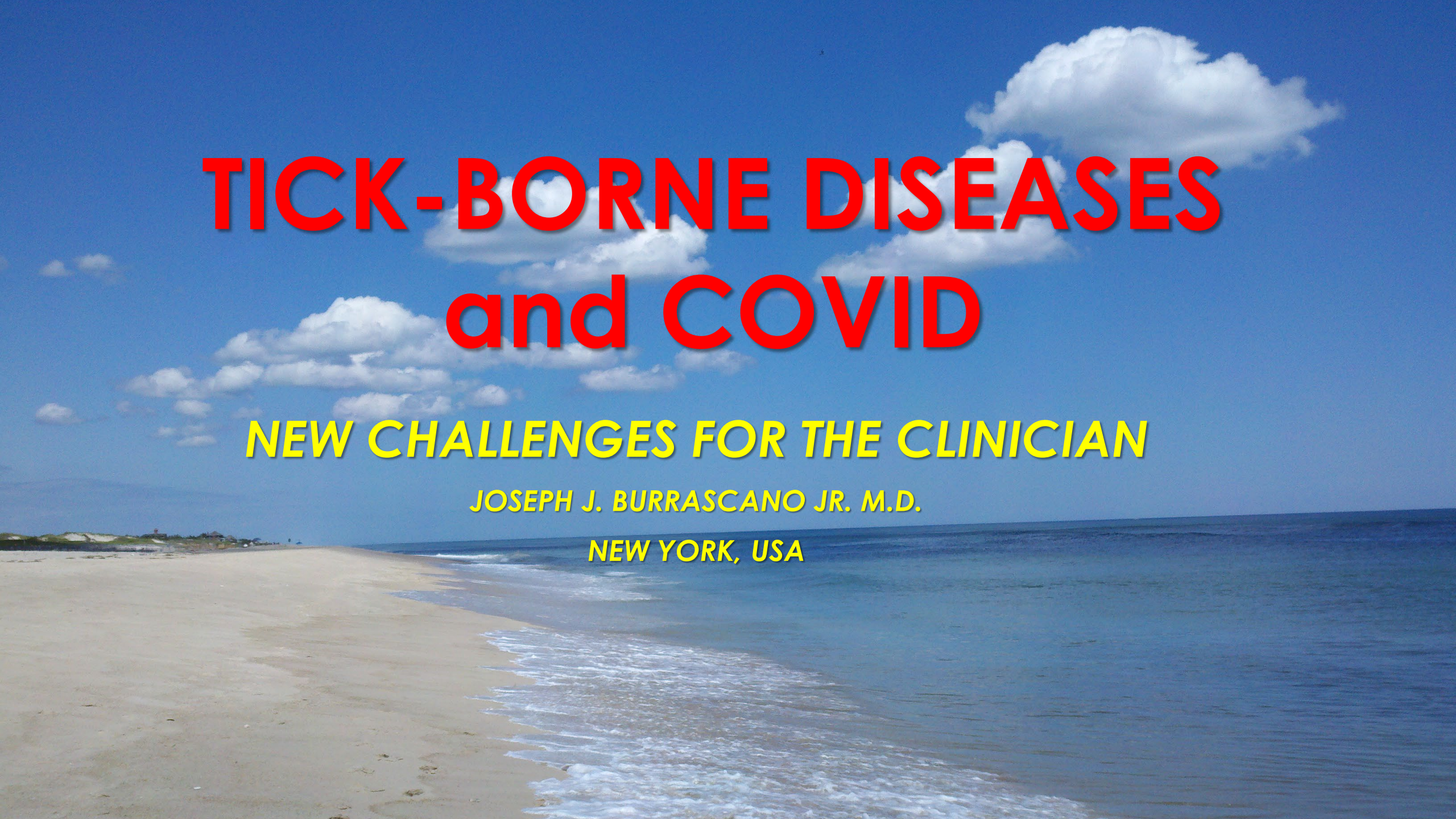

TICK-BORNE DISEASES and COVID

NEW CHALLENGES FOR THE CLINICIAN

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OUTLINE OF PRESENTATION

- Tick-borne diseases and COVID-19
  - Basics and definitions
  - Similarities and differences
- Laboratory testing for COVID-19
- Early infections- how to differentiate between TBDs and COVID-19
- Chronic cases
  - Could “post-COVID” be reactivated TBDs?
- What happens if your TBD patient gets COVID-19
- Vaccines for COVID-19
- Antibody-dependent enhancement
- Recommendations

What is Lyme Disease?

Today we have a broader definition of "Lyme disease"- We include the common tick-borne co-infections- collectively referred to as "tick-borne diseases" (TBDs)

- Borrelia- Lyme Borrelia and TBRF Borrelia
- Babesia species
- Bartonella- MANY species
- Rickettsias- Ehrlichia, Anaplasma, others
- Viruses

They often coexist ("co-infection")

- Co-infections alter and can blur the clinical presentation
- Co-infections worsen the negative impact on the immune system
- Co-infected patients are more ill and are more difficult to treat

Chronic Lyme- immune impairment that worsens over time

- Lyme-induced immune impairment
  - This begins 6 to 12 months into the infection
  - Affects all three cell types- B, T and NK cells. Impairs function and may kill them
  - Earlier onset and more severe if co-infected, especially Borrelia + Babesia
- Lyme infections also activate the inflammatory cascade- mini cytokine storm
  - More severe with later, more active infections
  - More severe when co-infected
  - More severe during Herxheimer reactions

LYME- immune effects

- Signs that Lyme has weakened the immunity
  - Low total WBC counts
  - Low killer cell (NK-cell) counts
  - Decreased immunoglobulin levels (B-cell impairment)
  - Impaired T-cell reactivity
  - Persistent disease that responds poorly to meds that should work
- Signs that Lyme has activated the cytokines
  - Everything!! The malaise, fatigue, aches, cognitive impairment, neuropathy, arthritis…

WHAT IS COVID-19

It is the disease caused by the coronavirus SARS CoV-2

- Highly contagious, but not everybody gets sick
- Initial viral phase- nonspecific viral symptoms- respiratory and gastrointestinal
- Can be followed by a hyperimmune phase- a runaway immune over-reaction resulting in a "cytokine storm"
- Followed by a collapse of T-cell function
- Also associated with significant arterial and venous blood clots, pulmonary fibrosis and decreased oxygen carrying capacity

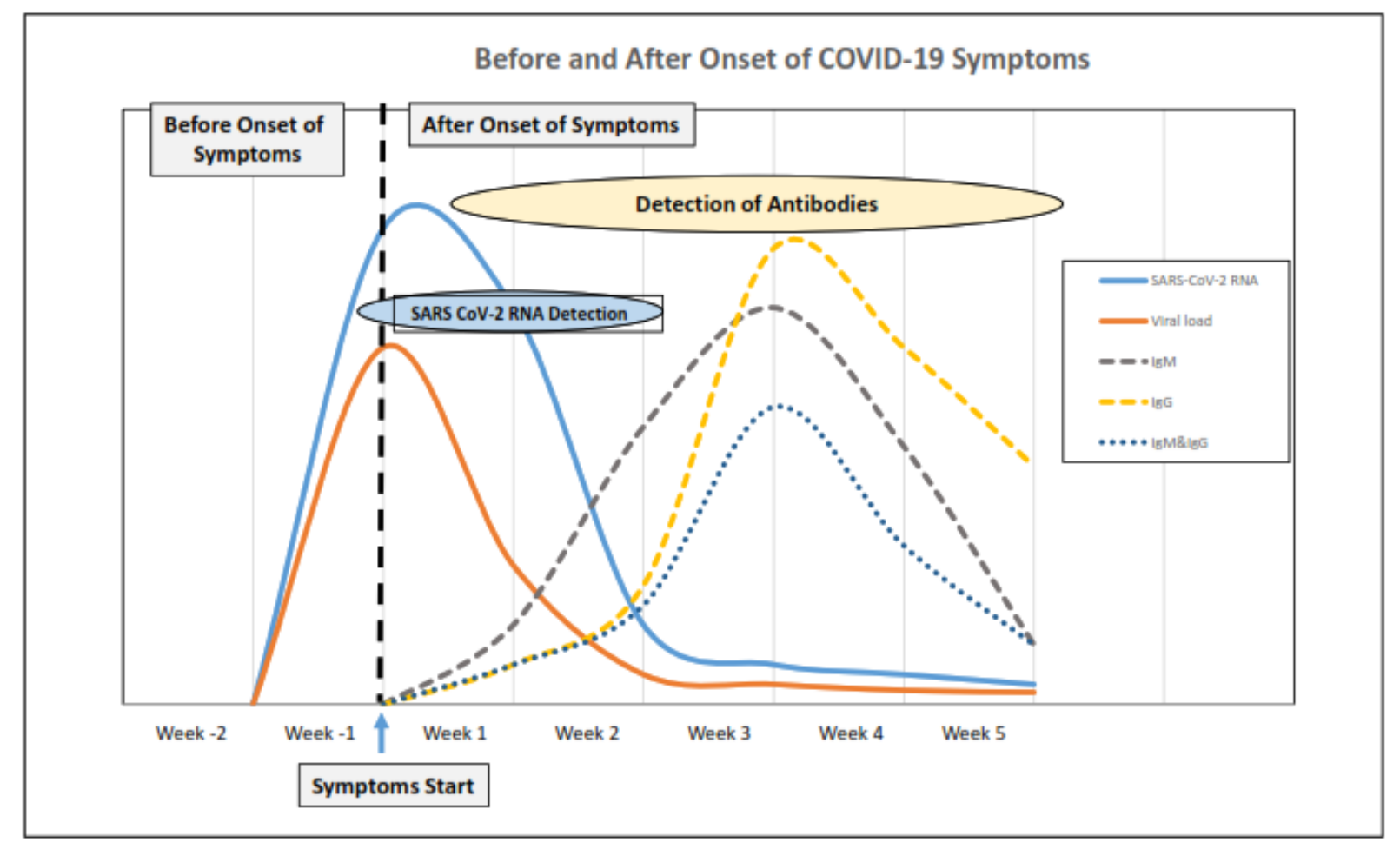
These non-viral effects cause the severe morbidity and mortality

Lyme and COVID- Similarities and differences

Tick-borne diseases	COVID-19
Vector-borne	Airborne and surfaces
Multiple pathogens	Single virus; multiple variants
Blend of infection and inflammation	Viral syndrome can progress to severe cytokine storm
Usually begins with mild disease	Usually begins with mild disease
Mild-moderate immune impairment in late disease	Severe immune impairment is possible in the very ill
Rarely fatal	Wide spectrum from asymptomatic to critical illness and death
Treatable	Treatable
Chronic forms	Chronic forms
No vaccine	Several vaccines

Laboratory testing for COVID-19

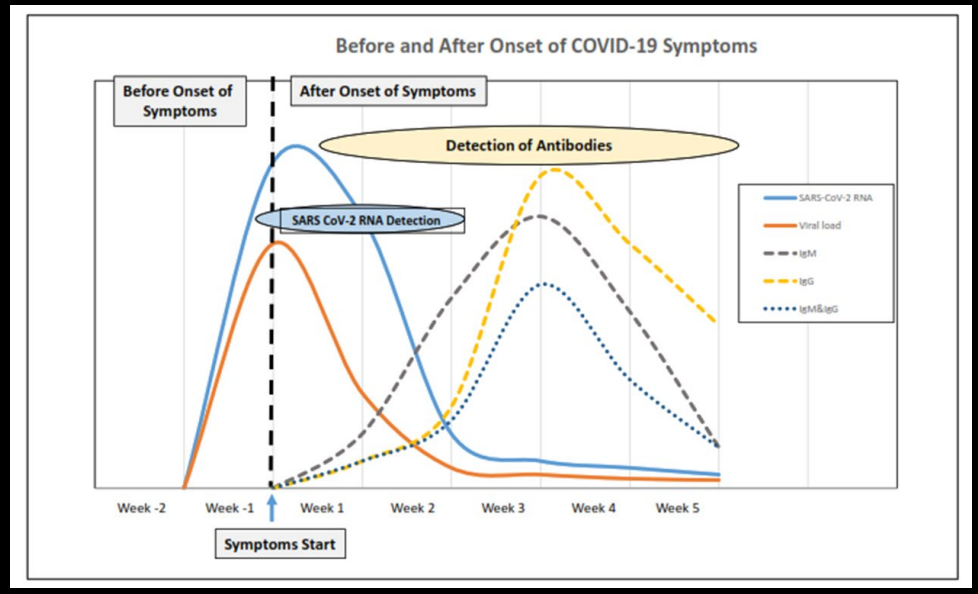
Time course in COVID-19



PCR testing in COVID-19

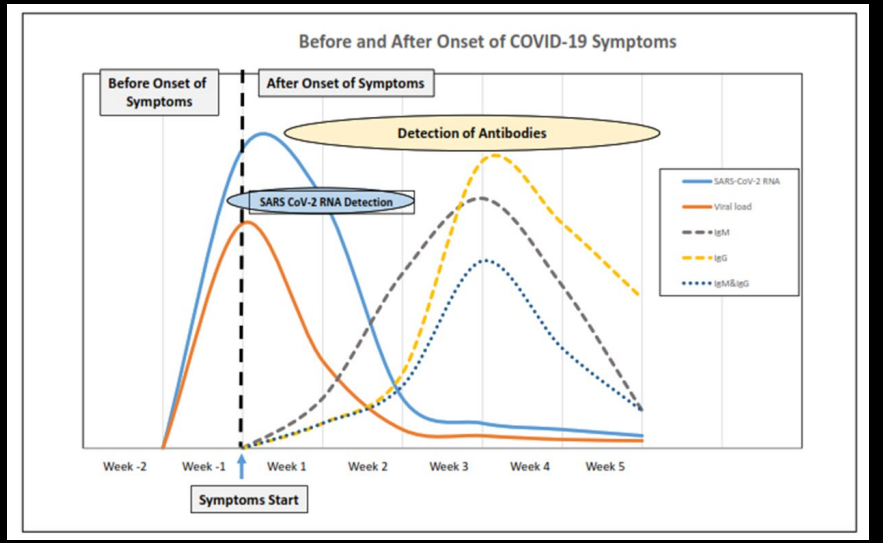
- RT-PCR is highly insensitive and time-dependent
  - 100% false negative on day 1 of infection
  - 67% false negative on day 4 (the day before symptom onset)
  - 38% false negative on day of symptom onset (day 5)
  - 20% false negative on day 8
  - 21% false negative on day 9
  - 66% false negative on day 21
- “If clinical suspicion is high, infection should not be ruled out on the basis of RT-PCR alone”

Ann Intern Med. doi:10.7326/M20-1495; 13 May 2020



Antibody testing in COVID-19

- One week after symptom onset, IgM appears and persists for 6+ weeks
- IgG appears 1 to 2 weeks after IgM and persists for at least 4 months; declines earlier in the elderly
- False positives because almost half of common colds are due to a mild coronavirus- cross reactivity?
- False negatives- need to turn down test sensitivity to decrease these false positives.
- Immunoblotting may be the answer- more sensitive and more specific
  - Sensitivity: IgM 72.2%; IgG 91.7%; Overall 97.2%
  - Specificity: IgM 99.2%; IgG 98.9%; Overall 98.1%



Testing recommendations- COVID-19

- Tests done in infected but asymptomatic people are usually negative
- For early, symptomatic disease, do nasal swab for PCR
- Saliva testing has not been validated for sensitivity and specificity in early disease
- Be aware of high degree of timing-dependent false PCR readings- highest sensitivity is for several days after symptom onset. Positives outside of this window should be suspect
- Serologies can document prior COVID infection but standard tests are inaccurate
- Immunoblotting-
  - more sensitive
  - more specific
  - may be a reasonable alternative to PCR

Differentiating early TBD from early COVID

Early TBDs	Early COVID
Arthropod bite- may be missed	Contagious; may not know source
Early Sx nonspecific: headache, fatigue, body aches. May develop a rash	Early Sx nonspecific: headache, fatigue, body aches. Then anosmia, respiratory Sx and fever; may get diarrhea
Without proper treatment it becomes musculoskeletal, CNS, PNS and cardiac Migratory and cyclic	May resolve May progress to acute cardiopulmonary disease with severe multiorgan involvement
Testing insensitive early in illness	PCR only sensitive during symptoms

CHRONIC CASES

►Post-treatment Lyme disease syndrome
►Post-COVID syndrome ("long haulers")

Many similarities and many differences between chronic Lyme and Post-COVID

- Post-COVID syndrome- many symptoms involving many parts of the body
  - Fatigue, body aches, brain fog; possibly cough, shortness of breath, fever and bowel upset
  - But not all post-COVID patients have respiratory or gastrointestinal symptoms
- Post-COVID pathology can include tissue and organ damage from immune attack, microscopic and macroscopic blood clots, vasculitis and hypoxia
  - However, these are not always seen or may be inapparent

QUESTION: Could some Post-COVID cases in fact reflect reactivated Tick-Borne Diseases?

Symptoms common to both

- Fatigue
- Headache
- Arthralgias
- Cognitive deficits
- Anxiety, depression
- Sleep difficulties
- Chills
- Sweats
- Shortness of breath
- Cough
- Dizzy
- Palpitations, rapid pulse

Signs common to both

These may be seen in some but not every patient….

- Fever
- False positive Anti Nuclear Antibody
- False positive Rheumatoid Factor
- Anti-phospholipid antibodies
- Activated cytokines
- Abnormal brain scans (MRI, SPECT)

Differentiating late TBD from late COVID

- Chronic Lyme
  - Prior history of Lyme or tick exposure
  - Symptoms are migratory and cyclic
  - Positive or suggestive tests for TBDs
- Chronic COVID
  - History of prior COVID
  - Symptoms do not migrate or cycle
  - End-organ damage- renal failure, hypoxia, intravascular clots

Clinical evaluation

TEST FOR CHRONIC TICK-BORNE DISEASES

- Indirect + direct tests because of possible immune dysfunction
  - Serology (immunoblots for Borrelia). Look for positive IgM
  - May also add T-cell reactivity assay
  - PCR, FISH; may add antigen capture assay
- Immune dysfunction is common- Measure immunoglobulin levels (B-cells) and T-cell response assay or skin anergy panel.

TEST FOR COVID AND FOR SPECIFIC DAMAGE ASSOCIATED WITH IT

- COVID serology- immunoblot if available; consider PCR
- Arterial oxygen level, chest x-ray, renal function, ferritin
- Consider pulmonary stress test- look for oxygen desaturation

Summary

- Careful clinical history can help differentiate TBDs from COVID-19
  - Be aware of the high incidence of tick-borne co-infections!
  - If you do not test fully then you can miss an important pathogen
- Testing for COVID worth doing, but PCR may not pick up a late case
  - COVID serology is important, but Immunoblot is preferred to decrease false positives and false negatives
- Test for conditions specific to either one to differentiate them
- Don't exclude the possibility that your patient may have both!

What happens when your Lyme patient gets COVID-19?

Chronic TBDs are associated with depressed immunity

- Concern for worse COVID and reduced vaccine response

However- the paradox-

- Most patients with active Lyme seem to resist getting common colds
- In fact, despite the evidence of immune impairment, there does NOT seem to be an increased susceptibility to other infections except the co-infections
- So will the same be true for resistance to COVID?

COVID-19 in LYME- the Good News

Antibiotics and COVID

- Many antibiotics used in Lyme are also antiviral- tetracyclines, macrolides and azoles
- Most treatments for Babesia are antiviral- those that are based on quinine or artemesia, plus the macrolides that commonly accompany them
- Azole antifungals are also antiviral
- Many complementary treatments used in Lyme are antiviral and/or help the immune system

COVID-19 in LYME-
more Good News

- Survey of several LLMDs all support the finding that COVID is less common in Lyme patients!!
- If they do become infected with COVID, their course tends to be milder
  - However, most LLMDs will prescribe antivirals for these patients: hydroxychloroquine or ivermectin, plus zinc, vitamins C and D and others
- Nevertheless, the usual COVID risk factors still apply
  - Advanced age
  - Concurrent hypertension, diabetes, obesity
  - Clinical immune deficiency- this is possible in very advanced Lyme
  - Immune suppressive treatments

COVID-19 in Lyme- Suggestions

- Avoid strong Herxheimers if exposed to COVID-19. May need to back off
- Most important is mitochondrial support- vital for healthy immune system
  - ATP 360
- Supplemental zinc (antiviral), magnesium and n-acetyl cysteine (dampen cytokine storm); consider artemesia
- Melatonin also for cytokine storm, aspirin to prevent platelet aggregation
- Vitamin C, D and alpha lipoic acid- multiple benefits
- Herbal anti-inflammatories such as quercetin, resveratrol, green tea, sulforaphane, etc.; glutathione for detox and for antioxidant support
  - CytoQuel, Tri-Fortify
- Transfer factors and medicinal mushrooms for NK support
  - Transfer Factor Multi-Immune
- Healthy diet, enforced rest and adequate sleep
- Address fears and anxieties as these can impair immunity
  - Counseling, meditation, exercise, etc.

Should my TBD patient get the COVID vaccine?

- Patients with intact immunity generally do have reactions to the vaccine, especially after dose 2
  - Nearly everyone has some type of reaction
  - Strong reactions in 30%
  - Fever, chills, weakness, fatigue, body aches
- TBD patients currently still symptomatic anecdotally react more strongly to the vaccine
- Likelihood and severity of the reaction may depend on the type of vaccine administered
- In theory, one could get ADE ("antibody-dependent enhancement")- cytokine storm from stimulating an already activated immune system

Vaccine types generally available

- mRNA
  - Induces host cells to create spike protein
- Adenovirus with coronavirus sequences added
  - Adenovirus type 5, 26 or both
  - Chimpanzee adenovirus- concern of development of anti-vaccine antibodies
- Attenuated coronavirus
  - Cultured SARS CoV-2 – Whole virus, attenuated
  - Concern about non-neutralizing antibodies re: ADE
- Peptide vaccine
  - Insert SARS CoV-2 genes into virus that infects lab cells which then produce spike-forming proteins. These proteins are assembled into spikes and are injected along with an adjuvant

VACCINE	EFFIC	TYPE	ANTIGEN	STORAGE	ADJUVANT	DOSES
Moderna	94%	mRNA	Spike	Freezer	No	2
Pfizer	95%	mRNA	Spike	Ultrafreezer	No	2
Sinovac Coronavac	78-91%	Inactivated whole Virus	SARS CoV-2	Refrig	Yes	2
Sinopharm	79%	Inactivated whole virus	SARS CoV-2	Refrig	?	2
Covaxin	?	Inactivated Whole Virus	SARS CoV-2	Freezer	Imidazoquinoline alum	2
AstraZeneca Oxford	70-90%	Genetically modified adenovirus	Chimpanzee adenovirus	Refrig	?	2
Sputnik Gamaleya	91%	Two gen modified adenoviruses	Ad 5 + Ad 26	Freezer	No*	2
J & J Janssen	57-85%	Genetically modified adenovirus	Ad 26	Refrig	No	One, but studying two

Antibody dependent enhancement

ADE is a cytokine storm induced by an extreme immune reaction to antigens that it has previously been sensitized to

- multisystem inflammatory syndrome seen in children (MIS-C) is an example of antibody-mediated enhancement- is due to reinfection with SARS CoV-2
- a severe inflammatory state that includes fever, diarrhea, shock, variable presence of rash, conjunctivitis, peripheral edema, vasculitis, thrombosis, mucosal ulcers
  - in some cases, can lead to multi-organ failure
- the multi-organ failure in MIS-C is manifested by neurologic involvement, hyperferritinemia, and cardiogenic or vasoplegic shock

The potential threat of multisystem inflammatory syndrome in children during the COVID-19 pandemic. Hussin A. Rothan, Siddappa N. Byrareddy. Pediatr. Allergy Immunol. 2021;32:17–22. DOI: 10.1111/pai.13361

Mechanism of ADE in COVID-19

- With infection, neutralizing and non-neutralizing antibodies are formed
- Neutralizing antibodies inhibit the infection and prevent the spike protein from binding to the ACE-2 receptor
- The non-neutralizing antibodies, when complexed with viral antigen, cause binding of immunoglobulin to macrophage receptors and allow viral entry independent of ACE-2 receptors. This initiates an inflammatory cascade
- It is the balance of the two types of antibodies that determine whether ADE will occur.
- It has been proposed that antibodies to non-spike components of SARS CoV-2 are responsible for this (theory, not proven)

Can COVID -19 vaccines cause ADE?

- If the vaccine has predominantly spike protein as the antigen, then it is unlikely that ADE will result (mRNA vaccines)
- Vaccines made from whole, attenuated coronaviruses or from genetically modified adenoviruses may be more of a risk
  - especially with the second dose or if exposed to SARS CoV-2 after vaccine immunity develops
  - More likely if a previous URI resulted in antibodies in common with that of the vaccine
- Vaccines that contain adjuvants are also of concern
- The above are conjecture only. There has not been enough experience with any of these vaccines to know if these are real risks.

TBD patients and COVID vaccination- recommendations

- Consider testing for SARS CoV-2 antibodies prior to vaccination to uncover past infection that may have been missed
- Always try to prepare your patient prior to vaccination
  - Detox regimens, ongoing glutathione, quercetin, vitamin C, D and melatonin (typical regimens used to minimize developing a severe form of COVID infection)
  - Gut health- prebiotics and probiotics (RN CoreBiotic, Multi-Biome)
- Do not vaccinate during a symptom flare
  - May have to hold TBD treatment well before vaccination to calm a Herxheimer
- mRNA vaccines may be safer than adenovirus vector-based vaccines
- With couples, stagger vaccination schedules
- Avoid immunosuppression as it may weaken vaccine-induced immunity
- May need to cancel dose-2 but then must follow SARS CoV-2 antibodies

Conclusions

- Many of us are now dealing with two complex conditions- TBDs and COVID-19
- They may be difficult to differentiate in certain circumstances
- Both pose challenges for patient management
- COVID-19 vaccination, while beneficial, can be difficult to tolerate in the TBD patient and require careful management pre- and post-dose
- There still are more questions than answers
- I urge everyone to keep track of their data and share it so we all can learn from each other
- Please stay safe!


THANK YOU!