To: 5.1.2e)[5.1.2e @minvws.nl]
From: 5.1.2e)
Sent: Fri 4/29/2022 4:55:15 PM
Subject: FW: lockdowns en het langdurig negatief effect op de immuniteit vankinderen; Hepatitis, Adenovirus and SARS-CoV-2
Received: Fri 4/29/2022 4:55:15 PM
image001.jpg
Episode 257 Hepatitis COVID and Adeno.pdf

Hoi 5.1.2e

Dit is wel interessant.

Gr 5.1.2e

5.1.2e 5.1.2e
Ministerie van Volksgezondheid, Welzijn en Sport |
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Van: 5.1.2e 5.1.2e) < 5.1.2e @minvws.nl>
Verzonden: vrijdag 29 april 2022 13:42
Aan: 5.1.2e) < 5.1.2e @minvws.nl>
Onderwerp: lockdowns en het langdurig negatief effect op de immuniteit van kinderen; Hepatitis, Adenovirus and SARS-CoV-2

HA 5.1.2e

Even iets anders: toen wij op het dansfeest spraken, vertelde ik je dat er zorgen zijn over de deuk die de lockdowns mogelijk hebben geslagen in onze immuniteit. In de UK wordt nu voorgesteld dat de golf van hepatitis gevallen bij kinderen hier mogelijk een voorbeeld van is.

Wellicht zouden we moeten laten uitzoeken of het zinvol/mogelijk is om daar het vaccinatieprogramma op aan te passen.

5.1.2e

Van 5.1.2e < 5.1.2e @ext.itg.be>
Verzonden: donderdag 28 april 2022 18:39
Aan 5.1.2e < 5.1.2e @ext.itg.be>
Onderwerp: Episode 257 Hepatitis, Adenovirus and SARS-CoV-2

Dear colleagues,

See papers at https://www.icpcovid.com/en/news/28-april-2022-episode-257-hepatitis-adenovirus-and-sars-cov-2

As we could expect, the UK Health Security Agency has issued a very nice report on the acute hepatitis “of unknown etiology” in children

Ep 257-1: Some highlights in this report:

- Most patients were under 5; most have recovered, but nevertheless 7 received a liver transplant
- Classical hepatitis viruses (A-E) were excluded and most evidence point to **Adenovirus 41f** (40 out of 53 tested). 10/60 were positive for SARS-CoV-2, but that could be "coincidence" in view of the very infectious omicron wave
- Adenovirus DNA levels in blood/serum samples were noted to be approximately 12-fold higher in those who had received a liver transplant versus those who did not

The authors provide the following "working hypotheses (in order of best to worst fit)

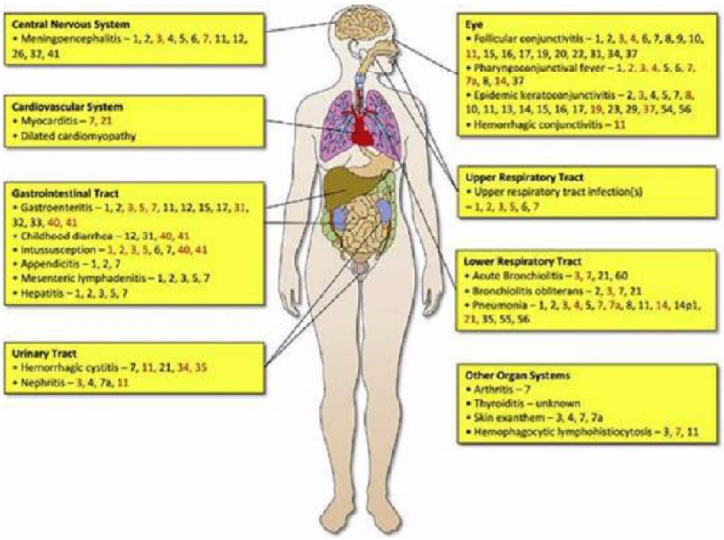
1. A cofactor affecting young children which is rendering normal adenovirus infections more severe or causing them to trigger immunopathology. The cofactor may be:
- susceptibility, for example due to lack of prior exposure during the pandemic
- prior infection with SARS-CoV-2 or another infection, including an Omicron restricted effect
- coinfection with SARS-CoV-2 or another infection
- toxin, drug or environmental exposure

2. A novel variant adenovirus, with or without a contribution from a cofactor as listedabove.
3. A drug, toxin or environmental exposure.
4. A novel pathogen either acting alone or as a coinfection.
5. A new variant of SARS-CoV-2.

Clearly, more information will emerge in the near future.

Par 1 Some background on Adenoviruses and other potential non A-E hepatitis (before the present outbreak)

Ep 257-2: Shieh in 2021 provides a very comprehensive overview of the symptoms by each serotype of Adenoviruses in a pediatric population. In Table 1, Adeno 40 and 41 (type F) are said to cause gastro-enteritis only and in the figure, hepatitis is said to be caused by type 1, 2, 3, 5 and 7 (types B and C).



Ep 257-3: Lynch 2016 also states that hepatitis is a "rare complication" of Adenoviruses.

Ep 257-4: Hong Zhao 2020 provides an overview on non-A to E hepatitis during pregnancy: EBV, CMV, Herpes Simplex, Dengue, Malaria, Leptospirosis, Q fever, Typhoid fever, Varicella-zoster and Yellow Fever are discussed, but Adenoviruses are not mentioned.

Ep 257-5: Saeed Ali in Gastro-enterology Clinics 2021 also discusses "hepatitis by non-hepatotropic agents". The paper is not yet available (I will send it as soon as I have it), but the abstract reads:

*Nonhepatotropic viruses such as **adenovirus**, herpes simplex virus, flaviviruses, filoviruses, and human herpes virus, and bacteria such as Coxiella burnetii, can cause liver injury mimicking acute hepatitis.*

*Most of these organisms cause a **self-limited infection**. However, in immunocompromised patients, they can cause severe hepatitis or in some cases fulminant hepatic failure requiring an urgent liver transplant.*

*Hepatic dysfunction is also commonly seen in patients with **severe acute respiratory syndrome coronavirus-2 infection**. Patients with preexisting liver diseases are likely at risk for severe coronavirus disease 2019 (COVID-19) and may be associated with poor outcomes.*

Based on this recent story, I was wondering what we know today on hepatitis linked to either SARS-CoV-2 infection in adults and children AND/OR on potentially vaccine-induced hepatitis.

Par 2 Association between SARS-COV-2 and hepatitis

2.1 Adults

Ep 257-6 : Harisha Liver dysfunction in **adult** patients in India July-Oct 2020, published in J Family Med and Primary Care

Liver injury in the setting of COVID-19-related illness poses a unique challenge to the physician.

1) Uncertainty whether there is a pre-existing undiagnosed liver disease.
2) Many of the medications used to treat moderate and severe COVID-19 have their liver toxicity profiles
3) In the subset of patients who experience critical illnesses, multiple factors may influence the trajectory of the liver injury.

ACE-2 mainly on cholangiocytes, but also hepatocytes

Retrospective study on 116 patients with rather severe COVID: respiratory rate exceeding 24 cycles per minute and oxygen saturation below 94% without oxygen supplementation

Most patients presented with co-morbidities: kidney dysfunction > diabetes

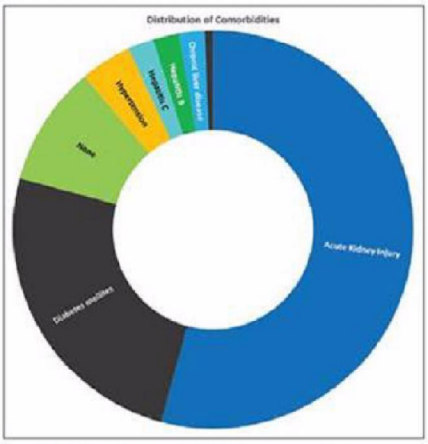


Figure 2: Distribution of comorbidities among the study population

A high proportion showed either kidney (raised urea/creatinine) and/or liver dysfunction (raised ALT/AST, bilirubin, hypo-albumin)

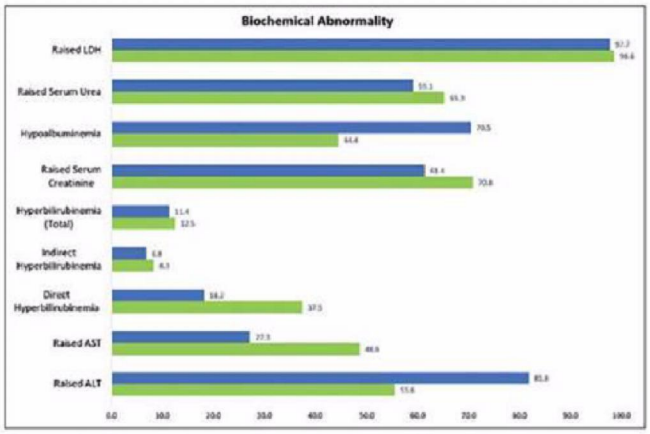


Figure 3: Abnormal biochemistry–males and females

Conclusions:

1) Pre-existing diseases may aggravate the viral hepatic injury

2) Liver toxicity of the drugs for treatment of COVID-19 warrant close monitoring of the liver function.

Ep 257-7: Phipps in Hepatology provides evidence that liver dysfunction is associated with severe COVID in adults

In a large retrospective study in New York area during first wave on > 2000 hospitalized COVID patients**, 45% had mild, 21% moderate, and 6.4% severe liver injury**, defined as peak alanine aminotransferase (ALT) of > 2X upper limit, 2-5 X or > 5X.

In multivariable analysis, severe acute liver injury was significantly associated with **elevated inflammatory markers**, including ferritin (odds ratio [OR], 2.40) and interleukin-6 (OR, 1.45).
These patients had a **more severe clinical course**, including higher rates of intensive care unit admission (69%), intubation (65%), renal replacement therapy (RRT; 33%), and mortality (42%).

Conclusion: Acute liver injury in hospitalized COVID is common, but mostly mild or moderate. Severe hepatitis is associated with poor prognosis. (It is not immediately clear whether severe hepatitis is cause of deterioration or effect of COVID-associated inflammation).

Ep 257-8: Lindholm in ACG CASE REPORTS discusses **cholestatic liver injury** linked to COVID. Maybe not so surprising, since ACE-2 present on cholagiocytes. Nevertheless, only 5 cases have been reported in literature, but it is important to diagnose, because it has been known to cause progressive liver disease requiring transplantation

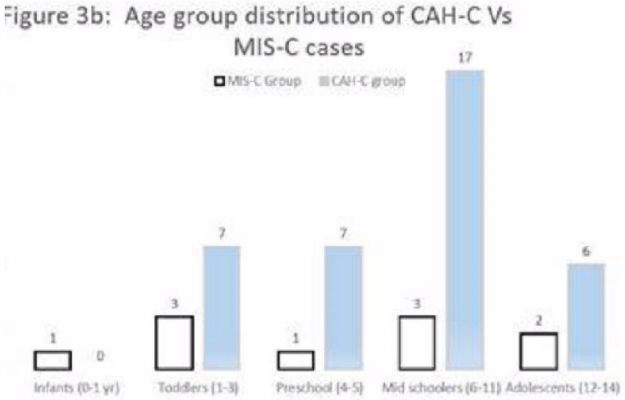
2.2. Children

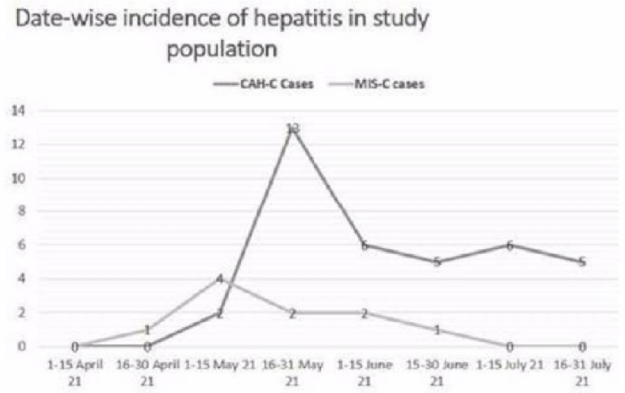
Ep 257-9: Rawat on COVID-associated hepatitis in **children** during second wave (delta April-July 2021) in India. Only published in medRxiv Oct 2021

Retrospective and descriptive study on 47 children out of 475, who presented with clinical features and laboratory findings (elevated transaminases) suggestive of acute hepatitis during post-COVID-19
Two entities can be distinguished:

1) **37 COVID-19 associated hepatitis in children (CAH-C)**: Children with a laboratory evidence of recent COVID-19 presenting with "sudden onset of hepatitis, such as elevated transaminases, non-obstructive jaundice, without history of (a) underlying liver disease (b) other known causes of acute hepatitis or (c) marked inflammatory responses": the majority having unelevated inflammatory markers and uneventful recovery following supportive treatment.
2) **10 MISC associated hepatitis.**

Epidemiological characteristics:





Lab values

Table 2: Laboratory findings of CAC-H Vs MIS-C associated hepatitis cases.

Lab values	CAH-C (n=37)	MIS-C (n=10)	P-value*
	Median (IQR)	Median (IQR)	
CRP, mg/L	4.10 (0.70, 7.90) (n=37)	17.85 (10.82, 28.42) (n=10)	0.0001
IL6, pg/ml	9.70 (4.27, 13.42) (n=37)	134.40 (34.00, 227.52) (n=10)	0.0001
Platelet, /mm^{3}X10^3	2.45 (2.10, 3.06) (n=37)	2.85 (1.35, 3.85) (n=10)	0.894
T Bil, mg/dl	5.4 (2.95, 7.15) (n=37)	0.90 (0.87, 1.37) (n=10)	0.0001
Albumin, gm/dl	3.60 (3.42, 3.67) (n=37)	3.45 (2.70, 3.77) (n=10)	0.394
AST, U/L	942.45 (301.67, 2002.05) (n=37)	85.50 (47.55, 127.90) (n=10)	0.0001
ALT, U/L	1326.25 (492.12, 2124.92) (n=37)	76.00 (44.42, 170.45) (n=10)	0.0001
Alkaline PO4, U/L	311.00 (187.40, 498.20) (n=27)	200.75 (131.12, 312.85) (n=10)	0.097
INR, ratio	1.30 (1.05, 1.52) (n=24)	1.00 (1.00, 1.39) (n=10)	0.174
	*Mann-Whitney U test		
CRP, C-reactive protein; SD, standard deviation; IL-6, interleukin-6; AST, aspartate transaminase; ALT, alanine aminotransferase; TBil, Total bilirubin; INR, international normalized ratio			

Clearly MISC higher inflammatory markers (CRP, IL-6) but lower hepatitis markers and they were more ill on admission.

All CAH-C cases had a recent history of SARS-CoV-2 PCR positivity, but negative by the time of admission with hepatitis symptoms, while none had typical respiratory signs or symptoms of COVID.

All 37 CAHC cases recovered, while 3 out of 7 MISC died.

Ep 257-10: Swati Antala in J Pediatrics describes 4 cases of children with acute severe hepatitis as the predominant feature of SARS-CoV-2 infection, with 3 cases presenting with acute COVID-19 and one with a more subacute presentation. Two patients were less than 1 year, two others were teenagers. The youngest patient (4 months) was found to have complement dysfunction resulting in microangiopathic features and was treated successfully with eculizumab (anti-C5 mAb, known as Soliris).

What was already known:
1. COVID-19 can cause elevated liver enzymes in children.
2. Severe hepatitis in COVID-19 is typically associated with significant respiratory or systemic symptoms.
What is new:
1. COVID-19 in the absence of significant respiratory or other symptoms may be associated with pediatric acute severe hepatitis and even acute liver failure.
2. Complement hyperactivation can be associated with hepatic dysfunction in COVID-19 and may improve with targeted therapy.

Ep 257-11: Perez Risk factors for acute liver injury in a pediatric cohort of 225 patients, of who ¾ were hospitalized, ¼ required intensive care and 8 % had multi-organ failure during first 2020 wave:

- 45 % transaminase (TA) elevation and 12 % severe liver injure (TA > 5 X upper limit)
- Older age and ICU admission were risk factors as well as obesity, pre-existing liver disease, elevated inflammatory markers and multi-organ failure

Ep 257-12: More extensive study on 291 children by the same authors distinguishes two patterns

1) Elevated-ALT in COVID-19 associated with obesity ($P < .001$), immunocompromise ($P = .04$), and chronic liver disease ($P = .01$).
   In the regression models, E-ALT in COVID-19 associated with inflammation: higher c-reactive protein (OR 1.08, $P = .01$)
2) Children with E-ALT + **MIS-C** more often boys ($P = .001$), Hispanic ($P = .04$), or Black ($P < .001$).

1.3 Chronic liver disease

Ep 257-13: Tian-Dan Xiang in WJ Gastroenterology March 2021 reviews the possible interaction between hepatitis B and SARS-CoV-2, but, in fact there is no convincing evidence that Hep B per se worsens the course of COVID, nor that SARS-CoV-2 infection in itself would reactivate Hep B.

Ep 257-14: Praveen Sharma summarizes the broader evidence that chronic liver disease and more particularly the so called metabolic dysfunction-associated fatty liver disease (MAFLD) may constitute an important "co-morbidity" that worsens COVID prognosis.

1) Patients with MAFLD) show a 4–6 fold increase in severity of COVID-19
2) Cirrhosis is an independent predictor of severity of COVID-19 with increased hospitalization and mortality.
3) Also children with end-stage liver disease have increased mortaility.

Immunosuppression should be reduced prophylactically in patients with autoimmune liver disease and post-transplantation with no COVID-19 (as yet).

GENERAL CONCLUSION of Par 2

- Biochemical evidence of hepatitis (increased liver enzymes) is common in adult hospitalized COVID patients, but severe liver dysfunction is rare (6 %). There is a clear association with co-morbidities, increased inflammation and kidney dysfunction. Severe hepatitis is associated with poor outcome.
- There are a few case reports on cholestatic liver injury, which may be dangerous.
- In children, Covid-associated hepatitis is usually mild, but it can also occur in the context of MISC and there are case reports of "acute severe hepatitis", sometimes with underlying disease. In any case, the link with SARS-CoV-2 may not be immediately obvious, as PCR may be negative and respiratory symptoms may be absent.
- Pre-existing chronic liver disease, especially the fatty liver disease, cirrhosis end-stage liver disease as well as immune suppression for auto-immune hepatitis or post-transplant are risk factors for severe COVID.

Par 3: Auto-immune hepatitis (AIH) and mRNA vaccination ?

There is a number of case reports about a temporal association between RNA vaccination and hepatitis with auto-immune characteristics, but it is certainly rare and the causality is often questioned.

Ep 257-15: Shroff A multicenter case study presents **16** patients with hepatitis 5-46 days after the first dose, of whom 12 only presented after the second dose.

- **6** patients had chronic liver disease (4 auto-immune hepatitis; 1 HCV)
- **6** patients had a recent history of taking potentially liver-toxic drugs, but they were not considered as the cause of the hepatitis.
- **Only in 1 case, the lab definition of new AIHI was met**
- **13** showed an hepato-cellular pattern (raised ALT), some cholestatic or mixed. **No acute liver failure,** but 10 hospitalizations with 6 receiving treatment

All in all no evidence of direct liver toxicity of either mRNA or nanoparticles. We know that auto-immune phenomena do occur after other vaccines in predisposed individuals.

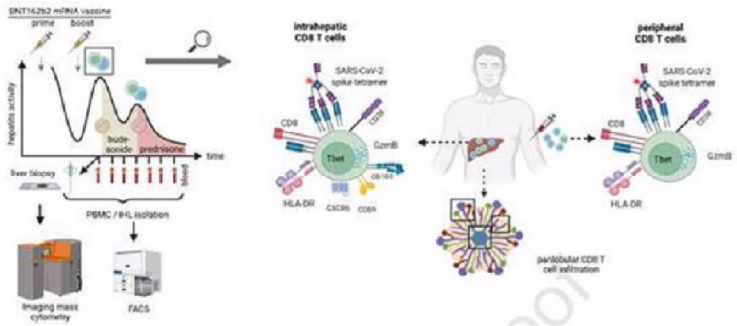
Questions remain:

- Should patients at higher risk of hepatic autoimmunity (e.g., existing AIH, post-liver transplant) undergo pre-emptive laboratory monitoring post-vaccination?
- Will there be safety concerns for these patients for booster doses ?

Ep 257-16: Boetller reports on a post-vaccination hepatitis with CD8 T cell involvement

A 52-year-old male, presenting with bimodal episodes of acute hepatitis, each occurring 2-3 weeks after BNT162b2 mRNA vaccination.
The patient received first oral budesonide, relapsed, but achieved remission under systemic steroids.

Immune findings: liver infiltration of **CD8+ cytotoxic T cells with SARS-CoV-2 Spike specificity**, which correlated with hepatitis severity (while EBV specific T cells did not).



Ep 257-17: Maung in J Hepatology on a possible post-Moderna case of hepatitis. Biochemical and histological evidence of **acute lobular hepatitis with cholestasis.** Importantly, immune histochemistry was positive for Spike and negative for Nucleocapsid. PCR on nasopharyngeal samples remained negative.

Patient was started on ursodeoxycholic acid. Bilirubin remained stable around 200-250 µmol/L for about four weeks and improved with normalization 10 weeks after receiving the vaccination. He subsequently received a full course of Sinovac vaccination with no ill-effects

The authors conclude a possible case *of de-novo liver injury developing post-Moderna vaccine with supportive histology of a possible direct effect from anti-SARS-CoV-2 spike protein antibodies, without features of AIH.*

Ep 257-18: Duengelhoeff presents a large study in United European Gastro-enterology on vaccination in 103 patients with autoimmune hepatitis (AIH) as well as 125 patients with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC).

- Previous SARS-CoV-2 infection was more frequent in AIH than in PBC/PSC (10/112 (9%), versus 4/144 (2.7%), $p = 0.03$).
- **AIH patients demonstrated a reduced humoral response** compared to healthy controls (HC) or patients with cholestatic liver disease.
- Despite a positive serology, **no spike-specific T cell response was detected in half of the patients with AIH,** but in almost all patients with PBC or PSC.
- The impaired vaccination response in AIH was also observed in patients in remission without receiving immunosuppressive drugs.

Along this line, AIH patients seem to have an increased risk to acquire a SARSCoV-2-infection, while – for unknown reasons - patients with PBC/PSC might be protected from infection.
Thus, antibody responses to vaccination in AIH patients need to be monitored and early booster considered in low responders.

Ep 257-19: Mahalingham in Transplant Immunology describes a patient transplanted for **autoimmune hepatitis** who was stable for many years until she had immune-mediated **flares** coinciding with Pfizer-BioNTech mRNA vaccination. Intravenous steroid treatment was required to suppress histologically evident interface hepatitis.

CONCLUSIONS from Par 3

- Rare cases of mRNA vaccine induced hepatitis have been described. Some findings suggest an auto-immune pathogenesis. In a proportion of these patients, there is also a history of pre-existing auto-immune hepatitis or another potential cause of liver damage.
- On the other hand, pre-existing auto-immune hepatitis (but NOT primary biliary cirrhosis or primary sclerosing cholangitis) show a decreased humoral and cellular response to mRNA vaccination.

I hope this was useful to orient yourself !

Best wishes,

5.1.2e