Knowledge Gaps in Our Understanding of Hyperbaric Oxygen Therapy in Post-traumatic Stress Disorder: Current Evidence, Proposed Solutions, and Preliminary Results

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ABSTRACT **Background:** Post-traumatic stress disorder (PTSD) remains a significant and often refractory mental health condition. Hyperbaric oxygen (HBO) therapy has demonstrated promise in alleviating symptoms of PTSD but optimal dosing and treatment duration remain unclear.

Objectives: To evaluate the clinical efficacy and dosing effects of two HBO protocols in patients with PTSD.

Methods: We conducted a randomized controlled trial comparing two HBO protocols: 60 daily sessions of 90 minutes at either 2.0 atmospheres absolute (ATA) or 2.5 ATA (HBO15). Adults with severe PTSD (Clinician Administered PTSD Score [CAPS]-5 ≥ 33) were randomized to treatment arms. CAPS-5 scores were recorded every 2 weeks. Secondary outcomes include measures of depression, sleep, executive function, and safety. Preliminary results are presented for the first nine patients who completed therapy (HBO10: n=5; HBO15: n=4).

Results: Participants in HBO15 were younger (mean age 39 vs. 59 years, P = 0.2). Baseline PTSD severity (CAPS-5) was higher in HBO15 (median 61.5 vs. 48.0, P = 0.4). Other baseline psychological scores were similar between groups. Mean CAPS-5 improvement (ΔCAPS) was greater in HBO15 (-14.0 ± 21.2) vs. HBO10 (-5.3 ± 19.6), although not statistically significant (P = 0.8). Both groups demonstrated the largest symptom reduction by weeks 6–8, with a plateau observed thereafter despite continued treatment through week 12.

Conclusions: Preliminary data suggest both HBO protocols are associated with symptomatic improvement in PTSD, with a trend toward greater effect in the higher-pressure group (2.5 ATA). Improvements appear to peak around 6–8 weeks, potentially indicating a shorter optimal treatment duration.

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KEY WORDS: acute acoustic trauma (AAT), blast injury, hyperbaric oxygen (HBO) therapy, post-traumatic stress disorder (PTSD)

Post-traumatic stress disorder (PTSD) is a significant public health concern [1]. It affects over 6% of the general population. Lifetime prevalence may be as high as 33% in high risk populations such as veterans, combat zone residents, and people living in areas affected by natural disasters [2]. Defined as the administration of breathing oxygen at partial pressures exceeding 1 ATM, hyperbaric oxygen (HBO) therapy has been attempted in various neurological and psychiatric impairments [1,3,4].

HBO THERAPY FOR PTSD

Most prospectively randomized studies were conducted in patients with mild traumatic brain injury (mTBI), in whom PTSD was reported in 30–60% of cases [1]. A recent pooled estimate of four randomized controlled trials (RCT) [4-10] totaling 252 patients found no significant effect of HBO therapy compared with sham (PCL Md of 0.61, 95% confidence interval [95%CI] -7.75–8.96, P = 0.38) [1]. The only trial reporting outcomes over 1 month after HBO therapy termination [5] reported no significant difference between the HBO therapy and the sham control groups at 6 months (PCL Md 4.1, 95%CI -11.9–3.7, P = 0.29). This finding is in stark contrast with the significant improvement observed at the end of the 60 consecutive HBO therapy sessions (PCL Md of 12.3, 95%CI -21.4– -3.1, P = 0.01). At 12 months, PCL scores had worsened in both groups, with mean increases from baseline of 5.8 ± 11.8 in the HBO therapy group and 5.8 ± 13.3 in the sham control group (P = 0.99). Longer (2 and 3 years post-treatment termination) follow-up was conducted in a small subgroup (40% and 14% of the original cohort, respectively). In another study focused on patients with fibromyalgia and childhood sexual assault,

somatization, anxiety, and depression levels reduced by 50% following 60 daily treatments compared to no change in controls receiving psychotherapy alone [3].

To the best of our knowledge, only one RCT focused on PTSD patients with no mTBI until recently [8]. Of 35 patients allocated 1:1 to 60 daily HBO therapy sessions at 2.0 ATA for 90 minutes each, 14/18 completed the HBO therapy (three were removed due to problems equalizing, one opted out after 20 sessions) and 15/17 completed follow-up of no sham control. While Clinician-Administered PTSD Scale (CAPS-5) scores were similar at baseline (46.6 ± 11.5 vs. 49.5 ± 10.7), a significant reduction was observed after 12 weeks of therapy (28.5 ± 17.4 vs. 51.5 ± 8.4, $P < 0.001$). Twenty-two (78.6%) of the original 28 patients completing HBO therapy in that study were re-evaluated a median of 704 ± 230 days after treatment termination. Mean CAPS-5 scores were unchanged compared to those obtained immediately after treatment (26.6 ± 14.4 vs. 28.6 ± 16.7, $P = 0.745$) and both were significantly lower than pre-treatment scores (47.5 ± 13.1, $P < 0.001$) [9].

Last, in the latest sham-controlled RCT by Doenyas-Barak and colleagues [8], 56 male veterans with combat-related PTSD (excluding those with mTBI) were randomized to receive 60 daily sessions of hyperbaric oxygen therapy (HBOT) at 2 ATA versus a sham condition (1.02 ATA with room air). The HBO therapy group saw their mean CAPS-5 score drop significantly from 42.6 to 25.8 post-treatment and remained at 25.1 for an unspecified follow-up interval (all $P < 0.001$). The sham group's scores actually worsened over time (from 42.58 ± 10.73 to 45.37 ± 9.80 immediately following the sham course and 49.22 ± 10.26 at follow-up, $P = 0.011$).

LIMITATIONS OF CURRENT KNOWLEDGE

Isolating the true biological effect of HBO on PTSD has been the cornerstone of the scientific controversy surrounding the role of HBO therapy in psychiatry. Neutralizing participation and placebo effects on the one hand, while providing no increased pressure or PO_2 on the other has been the main limitation of most studies conducted thus far. Sham protocols that involve hyperbaric air exposure result in increased PO_2 (usually < 1.0 ATM) [5,6]. In a single study using hypoxic (10.5% O_2) nitrox at 2.0 ATA [7], there was still exposure to increased ambient pressure. Thus, proponents of HBO explained the lack of effect observed in these studies to be the result of unjustified exposure to hyperbaric conditions in the control group [10]. Conversely, the effect reported in studies opting to avoid any hyperbaric chamber-setting exposure in the control group could be easily attributed to participation and placebo effects [1]. In this approach, neither participants nor observers can be reasonably blinded. Beyond these effects, the intervention group (unlike the passive control group) underwent behavioral changes that may have directly affected PTSD symptoms. These interventions included attending daily treatments, engaging in intense interpersonal interaction during the 2–3 hours of daily treatment (with other patients and the chamber attendant), and completing questionnaires and assessments. Last, the selection of patients able to complete a full HBO course (typically 40–60 daily encounters), not applied in the control group, can be an important source of bias when gauging the effect of HBO in passively controlled PTSD studies. These concerns are further supported by the only RCT examining both sham (1.2 ATA of air) and no hyperbaric intervention controls in patients with mTBI. Improvement was similar in both the HBO and sham groups, both superior to the no hyperbaric intervention group [6].

While a strong attempt to address these concerns has been made recently by Doenyas-Barak and co-authors [8] the relatively small sample size of a single center study warrants corroborative evidence. Previous studies have been very restrictive in including relatively healthy, and overwhelmingly male patients, focusing only on chronic (> 1–4 years duration) PTSD. Measuring PTSD severity only at baseline and post therapy limits our ability to understand the optimal duration of therapy. Most importantly, the optimal dose of HBO therapy for PTSD has not been determined. We aimed to address these issues while independently assessing the comparative effectiveness of various HBO protocols in the treatment of PTSD: during therapy, in the short term, and over 2 years of follow-up.

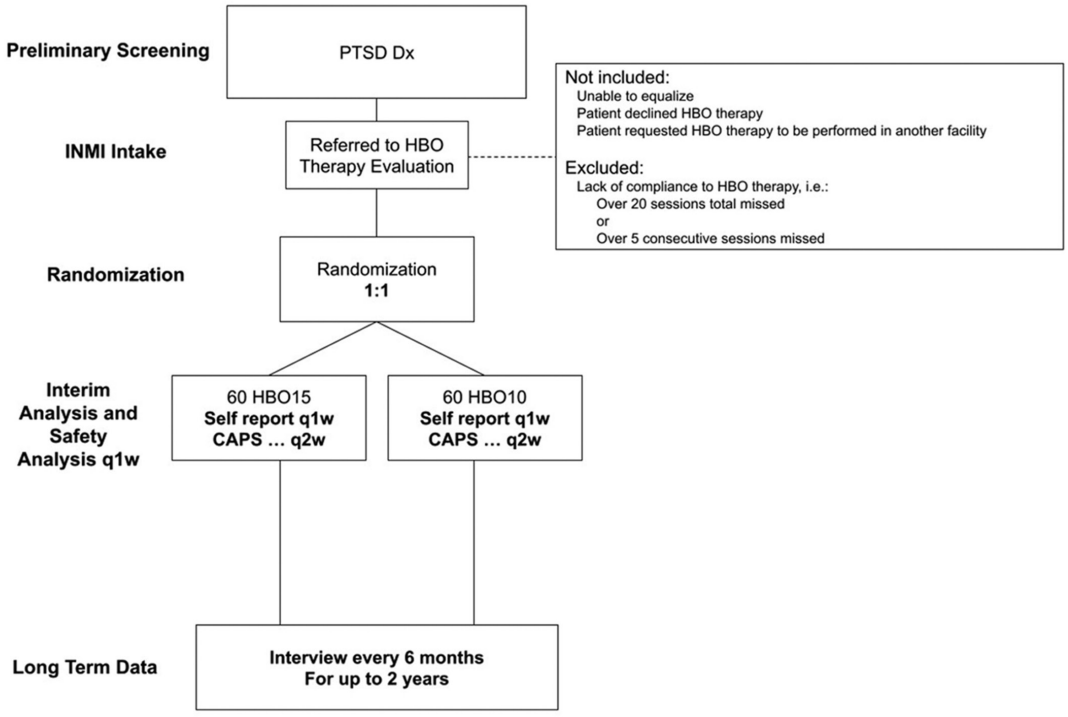
PATIENTS AND METHODS

STUDY DESIGN

We designed a double-blinded, prospectively randomized, pragmatic study. To address previous concerns about the external validity of contemporary clinical HBO research [11], we adopted broad inclusion and exclusion criteria and permitted concurrent real-world treatment practices. These criteria included allowing adjustments to pharmacotherapy and psychotherapy during the trial, as well as permitting cannabis and tobacco use.

Figure 1. Study design

CAPS = clinician administered PTSD scale, Dx = diagnosis, HBO = hyperbaric oxygen, PTSD = post-traumatic stress disorder, q1w = once per week, q2w = once every two weeks



POPULATION AND SETTING

Patients referred by the Combat Reactions Unit or the Rehabilitation Division at the Israeli Ministry of Defense over an estimated period of 2 years were considered for this study. To be included, patients were at least 18 years old and able to provide informed consent with a diagnosis of severe PTSD defined as a CAPS-5 score of at least 33. Since the main goal of this study was to determine the optimal HBO treatment protocol for PTSD, patients with difficulties complying with the treatment protocol were excluded to try to outline the biological effects of different HBO doses. Patients who missed more than five consecutive sessions or over 30 sessions overall were not included. In addition, patients with medical contraindications to HBO [6], current or past psychotic disorders, evidence of active suicidal ideation, or evidence of past or present manic disorder were excluded from this study due to potential harm as a result of HBO exposure.

PRIMARY OUTCOMES

The primary outcome were the change in the CAPS-5 score at the end of the treatment series compared to the baseline score. Changes in Beck's Depression Inventory (BDI), the Pittsburgh Sleep Quality Questionnaire (PSQ), and in the Executive Function Questionnaire (BRIEF-A), as well as accelerometry measured sleep quality and the incidence of HBO related adverse effects (as a safety outcome) served as secondary outcomes.

HBO PROTOCOL

Patients were treated once daily, five days a week, for a total of 60 sessions. Each session began with a pressurization 5–15 minutes to either 2.0 ATA (HBO10) or 2.5 ATA (HBO15). Hyperbaric oxygen was administered by a nonrebreather mask once the target pressure was reached, for a total of 90 minutes in either treatment protocol. This treatment was followed by depressurization [12]. Patients

and providers were blinded to the protocol utilized, as no internal pressure gauges were present inside the HBO chamber and the researcher in charge of assessing the patient was not aware of the treatment protocol utilized.

STATISTICAL ANALYSIS

Mann-Witney U test compared the change in the primary and secondary outcomes between the treatment groups. Both sample size calculations and the estimation of a 95%CI were based on a Monte Carlo bootstrapping approach. We pre-specified two subgroups to be analyzed separately and provided enough participants for each. Due to previous evidence suggesting a potentially distinct biology, patients with concomitant mTBI and patients with very recent (< 6 months) PTSD were excluded. We also identified six major confounders and balanced them during randomization (using the Frane algorithm [7,8] by means of the covariate adaptive randomization (CARAT) in R [7]). These confounders included age, duration of symptoms, initial CAPS-5 score, the presence of additional psychiatric morbidity (including the use of addictive substances), the utilization of acting competing therapies (pharmacotherapy or psychotherapy) and the presence of mTBI. These data were collected before enrollment in the study.

An unplanned interim analysis of the first nine patients was conducted to evaluate early symptom trajectories and safety. As this preliminary evaluation was hypothesis-generating and not designed for early trial termination, formal *P*-value adjustments for multiple looks were not applied. Final efficacy determinations were reserved for the fully powered cohort. Following the decision to conduct this unplanned preliminary analysis, the study's statistical analysis plan was formally amended. To maintain strict control over the cumulative Type I error rate for the ongoing trial, a conservative alpha-spending penalty (Haybittle-Peto boundary) was incorporated into the overall trial design. Because this interim look was not designed for early trial termination, the *P*-values reported for this ad-hoc analysis of the initial nine patients were considered nominal and exploratory and did not cross the stringent threshold required for early statistical significance. Formal efficacy testing, appropriately adjusted for this interim look, was strictly reserved for the final analysis of the fully powered cohort.

SAMPLE SIZE AND POWER

Based on previously published data, we estimated the primary outcome (CAPS-5 score) to have a standard deviation of around 12 points. In view of previously published results and our hypothesis, we did not assume homoscedasticity. Given the lowest effect reported thus far in a positive study was a mean difference of 12 CAPS-5 points [9], and in line with the accepted definition utilized in most previous studies [9], we defined a clinically significant improvement at > 10 CAPS-5 points. To maintain a power of at least 80% to detect such a difference at an alpha of < 0.05 our estimated minimal sample size was calculated at 19 participants in each intervention group.

ETHICS AND OTHER PERMISSIONS

This study was performed in accordance with the Declaration of Helsinki. The human study was approved by our institutional ethics committee (approval #2436-2024).

RESULTS

Nine patients completed the HBO treatment course, of whom four were assigned to receive HBO15, and the remaining five received HBO10. All were veterans of the current Iron Swords war and had been diagnosed with PTSD attributed to combat related stressors. Patients in the HBO15 group tended to be younger (59 ± 5.3 vs. 39 ± 13.4 years, $P = 0.2$). The proportion of tobacco smokers (40% vs. 50%) and cannabis users (20% vs 25%) were comparable in both groups.

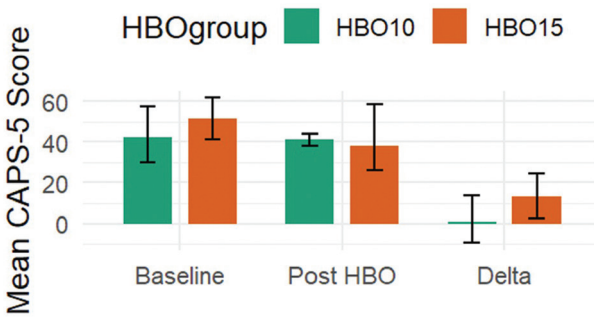
Baseline psychopathology was comparable. Baseline scores for the Childhood Trauma Questionnaire (CTQ) were slightly higher in the HBO10 group (median 34.0, IQR 32.5–35.5) compared to the HBO15 group (median 31.0, IQR 30.0–32.0), but this difference was not statistically significant ($P = 0.4$). Baseline PTSD symptom severity as assessed by the PCL was also similar between groups, with median scores of 57.0 (IQR 51.5–59.0) in the HBO10 group and 53.0 (IQR 50.5–55.5) in the HBO15 group ($P > 0.9$).

At baseline, participants in the HBO15 group exhibited higher CAPS scores (median 61.5, IQR 58.25–64.75) compared to the HBO10 group (median 48.0, IQR 35.0–57.0), reflecting more severe PTSD symptoms, although this difference was not statistically significant ($P = 0.4$). The HBO15 group experienced a more pronounced reduction in symptoms, with a mean ΔCAPS of 14.0 ± 21.21 points compared to a 5.3-point reduction ± 19.60 in the HBO10 group ($P = 0.8$). These results, as well as a bootstrap calculated 95%CI, are presented in Figure 2.

In both groups, the most substantial improvements were observed by weeks 6 to 8. In the HBO10 group, mean CAPS scores declined from 45.3 at baseline to 40.0 by week 8, plateauing thereafter. Similarly, in the

Figure 2. Primary outcomes of two treatment groups

The primary outcome of pre- and post-treatment clinician assessed PTSD severity score (CAPS-5) as well as the change in the mean score because of therapy
HBO10 = 90 minutes of O_2 at 2.0 ATA, HBO15 = 90 minutes of O_2 at 2.5 ATA



HBO15 group, scores declined from a mean of 61.5 at baseline to 49.5 at week 6 and 48.0 at week 8, with minimal further improvement at weeks 10 and post-treatment. This pattern is shown in Figure 3. Because this interim evaluation was not pre-planned for early trial termination, no formal alpha-spending adjustments were applied. These results should be interpreted strictly as hypothesis-generating.

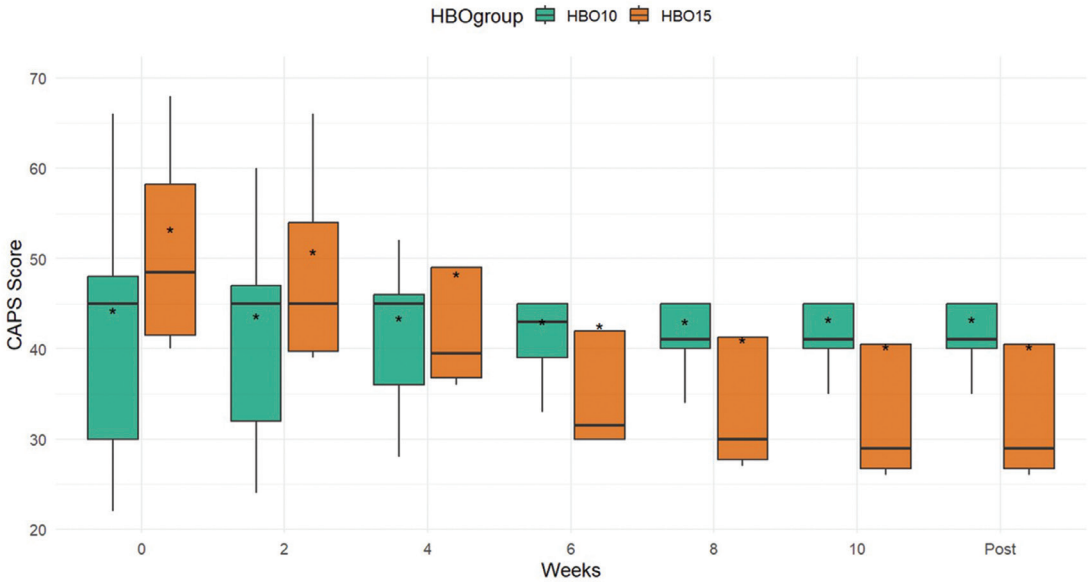
DISCUSSION

In this study, we refined our understanding of HBO in PTSD to ascertain the optimal dosing and duration while providing an independent measurement of the clinical effects of HBO and address some of the caveats raised in previous RCTs. One of our chief stated goals was to include as many females as we could, in an area where practically all empirical data was obtained almost exclusively in males. We were unsuccessful in this pursuit, which was likely due to our recruitment pool being biased toward military veterans, where PTSD diagnosis is highly biased toward males [1].

Our current understanding of the long-term effect of HBO is extremely limited [8]. To the best of our knowledge, this study is the first designed to include a long-term follow-up. Our data were limited by a small sample size, but higher PO_2 seemed to result in somewhat better improvement in the CAPS-5 scores. Despite being severely limited by the small sample size, extracting these early data was prompted by a timely and striking clinical observation: improvements in CAPS-5 scores reached a plateau after as few as 30–40 sessions. These findings must be corroborated in a larger sample, but the economic implications could be stark in view of an overall cost cutting potential of ~30%.

Figure 3. Temporal trends

The mean (asterix), interquartile range (box), and median (bolded line) of the clinician assessed PTSD severity score (CAPS-5) is presented by each measurement (taken each two weeks) during therapy
HBO10 = 90 minutes of O_2 at 2.0 ATA, HBO15 = 90 minutes of O_2 at 2.5 ATA



The preliminary data presented here reflect an unplanned, ad-hoc analysis of the first nine patients. Because this interim look was not formally prespecified in the statistical analysis plan, these findings carry an inherent risk of Type I error and must be considered strictly hypothesis-generating.

Even a slight improvement in our ability to care for PTSD patients could have a profound effect. Co-morbid affective disorders reach a prevalence of over 50%. Over 20% of patients with PTSD have concomitant substance use disorders. Suicidal ideation is reported in as many as 50% of individuals struggling with PTSD. Death by suicide is at least twice as common in individuals with PTSD compared to matched controls. Disability and loss of income affect over 90% of patients [12]. However, the great cost in time and money (over US$7000 per full 60 sessions course) could strain health resources. Determining the optimal dosing of HBO is thus imperative.

While generally safe, the potential complications of HBO therapy can be divided into those originating in pressure shifts and those attributed to increased PO_2. Because of Boyle's law, changing the pressure gradient on a confined gas will result in a proportional change in its volume. Thus, gas pockets that are not fully ventilated may experience volume shifts during the inherent pressure shifts in the hyperbaric chamber. This situation will result in considerable shear forces, often resulting in tissue damage, known as barotrauma. Ear barotrauma is most often reported, at the rate of 1–5%. Sinus barotrauma is reported at 0.5–0.6%, with no serious cases of lung barotrauma or air embolization reported in any of the currently available elective HBO therapy literature [1,13]. The increased PO_2 may result in central nervous system oxygen toxicity (COT), often manifested as myoclonus, visual or other focal neurological impairments, and seizures. Reported incidence associated with elective HBO therapy is estimated below 0.5:10,000 treatments. All these potential adverse events are fully reversible. In our cohort, only one example of middle ear barotrauma, necessitating stopping treatment for 3 days, was recorded.

A safety concern unique to PTSD is the potential to aggravate symptomatology during treatment. Observational data collected [10] suggests surfacing of new trauma related memories is not uncommon, occurring in 35.7% of patients after 30.5 ± 13.2 treatments on average. No increased risk of suicide ideation or behavior was recorded in this study.

CONCLUSIONS

The study of the comparative effectiveness of various HBO treatment protocols, as well as the elucidation of various methodological concerns in its effect on PTSD, are vital to our efforts in trying to improve the care for this important disease and major public health concern. Preliminary data suggest a trend toward greater effectiveness at higher PO_2 exposure and indicate that fewer treatment sessions than the currently used 60-session protocol may be sufficient.

Funding

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Capsule

AI spots immune hubs that matter

Tertiary lymphoid structures (TLSs) form local immune hubs inside tumors, but they are diverse and not all are equally functional. **Cho** et al. built a pancancer atlas and developed an artificial intelligence (AI)-based framework to detect and characterize TLSs in human tumors. TLSs varied in maturation state, spatial location, cellular composition, and organization. Intratumoral TLSs were associated with spatial gradients in tumor-intrinsic signaling. A scalable model was trained to detect and classify TLSs on standard pathology slides, and a composition-based TLS score was designed to stratify patients based on survival outcomes. The study provides insights into TLS biology and may offer a path toward integrating TLS features into future clinical trials.

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Eitan Israeli

Capsule

Defining a catastrophic step in sepsis

Sepsis is a life-threatening condition initiated by an infection that triggers an overwhelming, dysregulated immune response. **Brown** and co-authors used information derived from live imaging of mice to understand the events leading to the formation of clots in the lung vasculature after bacterial infection of the bloodstream. Aggregates between neutrophils and platelets initially contributed to antibacterial responses but developed into detrimental thrombi in steps dependent on the chemoattractant leukotriene B4. Blocking this signal through genetic deletion or treatment with the leukotriene inhibitor zileuton before infection protected mice from sepsis.

Science 2026; 392 (6801): eadv0377
Eitan Israeli

Capsule

Single-cell mapping of peripheral immune dynamics in pregnant women after moderna mRNA COVID-19 vaccination

Pregnant women are at increased risk of severe COVID-19, yet detailed information about their immune responses to mRNA vaccination has remained limited. **Kang** et al. used single-cell RNA sequencing and immune profiling to characterize peripheral blood immune responses in pregnant women following Moderna mRNA COVID-19 vaccination. The study revealed dynamic and coordinated activation of both innate and adaptive immune cells after vaccination. Monocytes, dendritic cells, B cells, and T cells exhibited distinct transcriptional changes associated with antiviral immunity and vaccine-induced immune activation. Importantly, the immune response showed features consistent with effective protection while maintaining the immunologic balance required during pregnancy. The investigators identified specific gene-expression signatures associated with interferon signaling, antigen presentation, and antibody generation. Despite the unique immunological state of pregnancy, vaccinated women generated robust immune responses comparable to those reported in nonpregnant adults.

Genes Immun 2026; 27 (3): 374
Eitan Israeli