

Hepatitis & Rest^{1, 2} (1951-1953)

Purpose

- Primary research question(s):
 - Is enforced bed rest necessary in management of infectious hepatitis?
 - Do patients heal more quickly on a high calorie diet supplemented with vitamins than on an ad lib. diet?
- Primary outcomes:
 - Symptoms, liver tenderness, liver function tests (serum bilirubin and bromosulphalein dye retention)
- Perceived clinical importance:
 - Hepatitis and hepatitis relapse were a significant resource problem during World War II (WWII) and the Korean War. Average hospitalization had doubled (30 > 60 days) due to policies of enforced bed rest instituted after WWII.
 - Early in the Korean War the incidence of hepatitis reached epidemic proportions, the first peak of 31 cases per thousand was reached in November 1950 and then rose to 33 to 35 per thousand during February to April 1951.

Background and Context^{1, 2}

- In WWII, there was a positive association found between relapses and early ambulation. Three controlled studies showed that patients treated with a high-protein diet and prolonged bed rest fared better than those on an ad lib. rest and diet.
- Standard military policy required prolonged bed rest until the patient has no more symptoms or liver function tests return to normal. Hospital lengths of stay rose considerably, reducing troop availability.
- Uncontrolled studies suggested that prolonged bed rest may not be as essential as previously thought, and therefore emphasized the need for a controlled study to determine the safety of a more liberal regimen of rest and less prolonged hospitalization.

Date and Place Conducted:

- Location: United States
 - United States Army Hospital in Kyoto, Japan was designated the "Hepatitis Center" for the Far East

- Recruitment Dates: September 1951 to July 1953.

Principal Investigators:

- 4 civilian physicians including Thomas C. Chalmers, Richard D. Eckhardt, William E. Reynolds and Charles S. Davidson and 4 army doctors including, Joaquin G. Cigarroa, Norman Deane, Robert W. Reifstein, and Clifford W. Smith.

Sponsored by/source of funding:

Surgeon-General, US Army; Armed Forces Epidemiological Board

Size and Design:

- Number of participants: 253
- Inclusion criteria included:
 - male member of armed forces below the grade of warrant officer;
 - clinical jaundice with persistent dark urine and probable diagnosis of infectious hepatitis; duration of symptoms less than 22 days;
 - no evidence of acute malaria, dysentery, pneumonitis, infectious mononucleosis, or any condition requiring surgery;
 - no transfusion of blood or plasma within six months of admission;
 - no previous diagnosis of infectious hepatitis within past year.
- Design: block randomized controlled trial.
 - The four treatment groups included: strict bed rest, ad lib. bed rest, forced high-protein diet, ad lib. diet.

Issues Encountered During the Trial:

- Seven patients removed from the principal analyses- 3 did not have infectious hepatitis; for 4 duration of illness was questionable. In some of the analyses, other patients in the same block were excluded from the analyses to simplify the analyses.

Findings

- Ad lib. rest group had a 10% (3 day) reduction in length of stay compared to enforced rest group (ci: .1% - 19%)
- High protein diet group had a 22% (6 day) reduction in length of stay compared to ad lib. diet (ci: 14% - 30%)

- 17/253 experienced “laboratory relapses” (abnormal bromosuphalein test) independent of treatment
- Various checks performed on analysis:
 - No interaction between diet and rest
 - Significant inter-observer differences in ratings of physical (non-laboratory) findings
 - Chi-square analysis of differences between baseline treatment groups found none
- A follow-up analysis of a random sample of study patients found lost of one or more days “possibly” attributable to hepatitis in 5% of patients, irrespective of treatment. Patients on ad lib. rest had a higher percentage of laboratory abnormalities but these were neither clinically nor statistically significant
- Subsequent to the initial trial, additional studies done of diets with varying caloric intake, and of the effects of hard exercise on reappearance of laboratory and clinical signs of hepatitis
- 10 year follow-up:
 - 460 men enrolled in these studies were followed-up for ten years using Army and Veterans Administration records and questionnaires. A group of 496 enlisted men who served in Korea but were not hospitalized at any time were used as controls.
 - No significant differences were found in mortality rates, cause of death, hospital admission rates, hospital diagnoses and Veterans Administration disability ratings among the various therapeutic regimens.
 - There was no difference in mortality between the hepatitis patients as compared to the group of nonhospitalized men.
 - Hospital admission rates, the proportion of men with at least one change in employment and the proportion of men with complaints related to hepatitis were greater for the hepatitis patients.

Impact ^{1, 6}

- Based on the results of this study, recommendations for the treatment of acute infectious hepatitis were made to the Surgeon General of the Armed Forces. These recommendations included: ad lib. rest after symptoms dissipate, high-calorie protein rich diet, and resumption of vigorous activity after bilirubin levels drop below 1.5 mg/100 mL. It remains unclear whether these recommendations were implemented in military policy. Civilian practice remained unaffected by the study.

- This innovatively designed and analysed study launched the career of "trialist" Tom Chalmers who was a forceful advocate for randomized clinical trials in the second half of the 20th century.

Unresolved issues ¹

- It is not clear why there is a difference between the data from WW2 and this study. The WW2 studies showed a relapse rate of approximately 5%.

Summary

Treatment of acute infectious hepatitis was evaluated in a randomized controlled study. There was no significant difference in duration of illness in patients subjected to prolonged bed rest as compared to patients receiving ad lib. bed rest. High-calorie and high-protein diets were shown to significantly decrease duration of illness when compared with ad lib. diets. Return to vigorous exercise after drop of bilirubin levels did not show clinically significant difference side-effects. Differences were minor and dissipated after 2 weeks of physical conditioning. This study was an example of an early controlled randomized trial that was thoroughly controlled and analyzed. The study is presented in exquisite detail.

The results of this study were used to provide recommendations to the Armed Services which were facing resource constraints because of the former requirement of prolonged bed rest for the treatment of acute infectious hepatitis. Whether the new clinical policies were implemented by the military is not clear.

References

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3. Nefzger, M. D. and T. C. Chalmers (1963). "The Treatment of Acute Infectious Hepatitis. Ten-Year Follow-up Study of the Effects of Diet and Rest." *Am J Med* 35: 299-309.
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6. Chalmers, TC (1974) " The Impact of Controlled Trials on the Practice of Medicine," *Mt. Sinai J. Med* 41: 753-759.

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