Infectious Complications of Blood Transfusion

EDWARD TABOR

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1982

ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers

New York London
Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data

Tabor, Edward.
Infectious complications of blood transfusions.

Includes index.
1. Blood--Transfusion--Complications and sequelae.
2. Infection. I. Title. [DNLM: 1. Blood transfusion--
Adverse effects. 2. Communicable diseases--Transmission.
WC 100 T114i]
RM171.T29 1982 615'.65 82-8850
ISBN 0-12-682140-2 AACR2

PRINTED IN THE UNITED STATES OF AMERICA

82 83 84 85 9 8 7 6 5 4 3 2 1

Preface

This book brings together in a single source all of the important information known today about infectious complications of blood transfusion. Until now, this information has been available only in diverse primary sources, including accessible and inaccessible journals and articles written in languages other than English. It is hoped that this book will be useful to physicians and staffs of blood banks as well as to infectious disease specialists who are evaluating complications of transfusions or responding to enquiries from governments or private individuals concerning such complications. It will also be a useful reference for health departments and government agencies evaluating complications of transfusions and for those who are evaluating the scientific and legal aspects of blood policies.

Infectious complications of blood transfusion are twentieth century diseases caused by, in most cases, historically well-established microorganisms. Without transfusions, most of these diseases would only be transmitted by nonparenteral means or occasionally by "inapparent parenteral" means, such as ritual incisions, shared hygienic articles, ingestion of maternal blood by infants during birth, and insect bites.

The development in the early twentieth century of methods to anticoagulate blood, to classify blood types according to their isoagglutinins, and to substitute for direct donor-to-recipient transfusion the use of stored blood made it possible for physicians in many medical facilities to attempt transfusion. Transfusions were soon attempted in patients who were not terminally ill for whom successful transfusion would mean survival. It was at this point in the history of blood transfusion that infectious complications of blood transfusion became recognized as a significant problem. By World War I, donor infec-

tions which could be transmitted by blood transfusions occurred often enough so that persons with malaria, syphilis, and fevers were excluded from blood donation in some countries. The rapid increase in the number of transfusions in the years during and after World War II led to a sudden awareness of the epidemic proportions which posttransfusion hepatitis can reach. In recent years, partial control of hepatitis B has led to a recognition of non-A, non-B hepatitis, cytomegalovirus, and Epstein–Barr virus as major infectious complications of blood transfusion. Intercontinental jet transportation has maintained malaria as a potential complication of blood transfusion even in temperate regions and has resulted in the potential transmission of other parasites and exotic tropical viruses. Such complications of blood transfusions may not be recognized when they occur. Infections may not be recognized in a seriously ill patient. Only by awareness of such potential complications can they be recognized and treated; only by their careful study can new advances be made.

I would like to acknowledge the kindness of the following researchers who took time to read and criticize the manuscripts: Dr. Harvey J. Alter, Dr. Lewellys F. Barker, Dr. Carter Diggs, Dr. J. Fratantoni, Dr. Robert J. Gerety, Dr. Colin Howard, Dr. Louis Miller, Dr. Theodore Nash, Dr. Charles N. Oster, and Dr. James Shih.

Edward Tabor

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CHAPTER 1

Hepatitis B as a Complication of Blood Transfusion

I. INTRODUCTION

Hepatitis B has continued to receive more attention than any other transfusion-transmitted infection, in part because of the rapid technological developments which have led to a dramatic reduction in the number of posttransfusion cases. Nevertheless, even the availability of sensitive tests for detecting asymptomatic carriers of this virus among blood donors has not led to elimination of the disease. The problems of transmission by blood from donors whose titers of hepatitis B virus (HBV) serologic markers are too low to be detected by available tests and the severe consequences which follow some cases remain with us. The development of a safe, effective vaccine and the cloning of HBV with the potential to produce an inexpensive vaccine substrate are developments which may lead to the control of hepatitis B infections in many parts of the world.

Although infection by HBV following the inoculation of human blood or plasma has been recognized since the late nineteenth century, a means for detect-

ing the agent was not available until 1964 when Blumberg discovered the hepatitis B surface antigen (HBsAg) (Blumberg, 1964). Since then, additional antigens associated with HBV have been identified. Although these antigens and their significance will be discussed in detail later in this chapter, it will be helpful to outline the nomenclature here. *HBsAg* is an antigen found on the surface of the 42-nm HBV and the 22-nm particles of excess virus coat protein found in high concentration in the serum of persons with acute or chronic hepatitis B infections. Antibody to HBsAg, *anti-HBs*, appears in serum during recovery from hepatitis B and usually remains detectable throughout the life of the individual. Hepatitis B core antigen, *HBcAg*, is found in the inner core of HBV and on the 27-nm core particles in the livers of actively infected individuals; it cannot be detected in the serum unless the intact HBV in the serum is modified by treatment with detergent. Antibody to HBcAg, *anti-HBc*, is detected in serum during acute and chronic hepatitis B and remains detectable for many years following recovery. Hepatitis B e antigen, *HBeAg*, believed to originate in the core of the

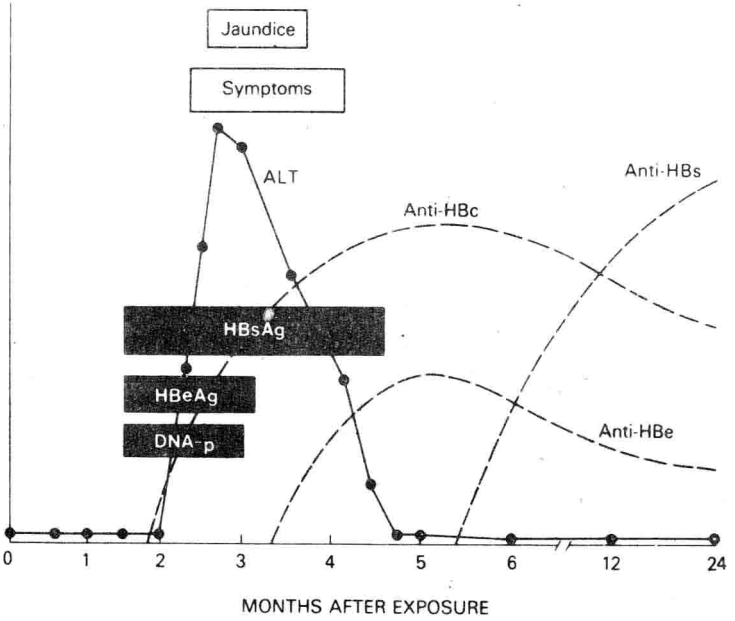

Figure 1.1. Serologic pattern in a typical case of acute HBV infection. (From Hoofnagle, 1980, with permission.)

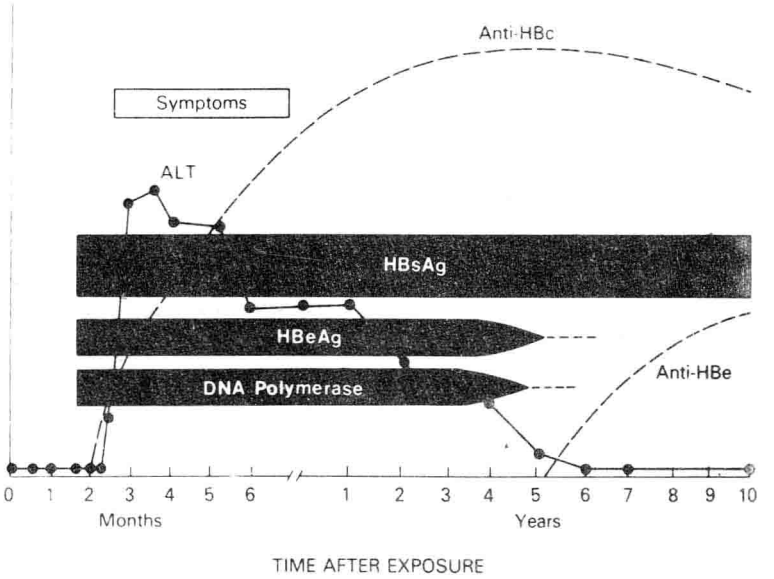

Figure 1.2. Serologic pattern in a typical case of chronic HBV infection. (From Hoofnagle, 1980, with permission.)

HBV, is found free in the serum early in all cases of acute hepatitis B. The persistence of HBeAg for more than 10 weeks indicates a great probability that the patient will develop chronic hepatitis B. HBeAg is associated with greater infectivity of the patient's blood. *Anti-HBe* appears prior to recovery in most cases of hepatitis B but is also associated with asymptomatic chronic hepatitis B infection. It may also be detected for many years following recovery. Typical serologic patterns during acute and chronic hepatitis B are shown in Figs. 1.1 and 1.2. Less common variations of these serologic patterns which may be encountered are discussed later in this chapter.

II. EPIDEMIOLOGY AND BLOOD TRANSFUSION

Prior to the introduction of serologic testing, as many as 60% of post-transfusion hepatitis cases were due to hepatitis B (Alter *et al.*, 1975a). As a result of federal regulatory requirements that donor blood be tested by sensitive techniques in all blood banks in the United States, the prevalence of hepatitis B

has been reduced to 11–13% of cases of posttransfusion hepatitis (Aach *et al.*, 1978; Alter *et al.*, 1975b), occurring in about 1.7% of all blood recipients (Aach *et al.*, 1978).

The remainder of the cases, which make up the majority of posttransfusion hepatitis cases, are caused by the agent or agents of non-A, non-B hepatitis (see Chapter 2). Hepatitis A is almost never responsible for posttransfusion hepatitis (Aach *et al.*, 1978), although one case has been reported (Hollinger *et al.*, 1982). The potential role of cytomegalovirus and Epstein–Barr virus in the etiology of occasional cases of posttransfusion hepatitis is discussed in Chapters 3 and 4.

The reservoir for posttransfusion hepatitis B is the asymptomatic adult who is chronically infected with HBV at a level too low to be detected by screening serum for HBsAg. Although the exact number of such HBsAg-negative, HBV-infected blood donors is not known, their prevalence may be about 0.6%, based on a 3% infection rate of hepatitis B in recipients of 1–5 units of blood (Aach *et al.*, 1978). However, this is an estimate, and the prevalence varies among different cities in the United States (Aach *et al.*, 1978). The greater the number of units transfused, the more likely it is that such an infectious donor's blood will be included.

The characteristics of the HBsAg-negative donors now transmitting hepatitis B may be reflected in the epidemiology of HBsAg-positive individuals. HBsAg is detectable by sensitive assays in approximately 0.3% of healthy United States adults (Barker *et al.*, 1977), ranging from less than 0.1 to 0.5% in different geographic areas of the United States. A number of risk factors affect the prevalence of HBsAg, including lower socioeconomic status, sexual promiscuity, residence in institutions, and employment in certain health care occupations (especially surgeons, dentists, oral surgeons, and ward and laboratory personnel who handle specimens of body fluids). The presence in a household of an HBsAg-positive individual increases the risk that others in the household may also be infected, regardless of the relationships among them (Bernier *et al.*, 1982). Transmission of HBV from HBsAg carriers to susceptible persons may occur by parenteral means, including blood transfusion, parenteral drug abuse with shared needles, or tatooing; in endemic areas of the world it also may be transmitted by hematophagous insects. "Inapparent parenteral" transmission may occur by shared toothbrushes or razors, or the handling of a wound in the presence of cuts on one's hands. Although oral transmission is not believed to play a significant role in the spread of HBV, the finding of HBsAg in a number of body fluids other than blood suggests that spread may sometimes occur by means of infected saliva, urine, breast milk, semen, and vaginal secretions, even

in the absence of detectable blood (Villarejos *et al.*, 1974). Hepatitis B has been experimentally transmitted to gibbons by ingestion of infected saliva (Bancroft *et al.*, 1977) and to chimpanzees by inoculation of semen from human HBsAg carriers (Alter *et al.*, 1977). These factors may explain why the vast majority of individuals with HBV serologic markers have no history of having received a blood transfusion. Inapparent transmission between asymptomatic adults results in a continual entry of infectious persons into the population of potential donors, including donors who have given blood previously without transmitting hepatitis B.

Two other modes of hepatitis B transmission have a major impact on the number of blood donors who may transmit hepatitis B to recipients of their blood. Sexual transmission is believed to occur on the basis of several lines of evidence, although other types of close contact cannot be ruled out as the method of infection. The prevalence of HBV serologic markers is higher among spouses of carriers than among the children of carriers. Prostitutes and male homosexuals have been documented to have higher prevalences of HBV serologic markers. Another mode of transmission occurs from infected mothers to their infants and is responsible for maintaining the reservoir of HBsAg carriers in many parts of the world (Gerety and Schweitzer, 1977). Infections during infancy are more likely to result in a chronic HBsAg carrier state than those infections with a later onset (Gerety *et al.*, 1974).

Since 1978, all blood for transfusion in the United States has been required by federal regulations to be labeled "paid" or "volunteer," according to its source (Federal Register, 1978). This is based on the observation that more than twice as many recipients of HBsAg-negative units of blood from paid donors develop HBV infection compared to those receiving HBsAg-negative blood from volunteer donors (Goldfield *et al.*, 1975). HBsAg-positive paid donors are more likely than HBsAg-positive volunteer donors to have HBeAg detected in their blood at almost every HBsAg titer (Tabor *et al.*, 1980c); the greater prevalence of this marker of infectivity is additional evidence of the HBV risk posed by this group of donors. This risk is believed to reflect the greater likelihood that some paid donors are from population groups with a high risk for HBV, such as parenteral drug abusers and persons of low socioeconomic status. The requirement for labeling "paid" or "volunteer" has not been applied to plasma donations, however, since pooling of plasma units from greater than 1000 donors results in an unavoidable hepatitis risk regardless of the source of the plasma and the majority of pooled plasma is used to manufacture albumin, plasma protein fraction, and immune globulin (IG) which do not transmit hepatitis B. However, with regard to whole blood drawn for transfusion, it was hoped that labeling

according to its source would encourage the use of more volunteer blood for medical and medicolegal reasons.

Certain pooled plasma derivatives, antihemophilic factor (factor VIII, AHF) and factor IX complex (factor IX), have a particularly high risk for the transmission of HBV. The plasma pools used in their manufacture include more than 1000 units of plasma in each pool and therefore have a statistical risk of including a unit of plasma with a level of HBV below the limit of radioimmunoassay (RIA) detectability for HBsAg. They are too labile to withstand heating at 60°C for 10 hours and continue to transmit HBV infections. Such plasma derivatives are administered to thousands of hemophilic patients each year. More than 20% of adult hemophiliacs have a history of having had clinically recognized hepatitis (Peterson *et al.*, 1973), and 60–90% can be shown by serologic tests to have had hepatitis B (Hoofnagle *et al.*, 1975). Patients with newly diagnosed hemophilia who receive AHF or factor IX for the first time are at a particularly high risk for acquiring HBV infection. Factor IX has also been used to prevent bleeding in some patients without a documented deficiency of this clotting factor. Such use is without documented efficacy for most situations and should be avoided because of the high risk of HBV infection.

Some other pooled plasma derivatives have no risk of HBV transmission. Immune globulin (IG, γ-globulin), when properly manufactured by the cold ethanol fractionation method of Cohn using plasma which has been screened for HBsAg, does not transmit HBV. Albumin and plasma protein fraction, which are capable of withstanding treatment by heating at 60°C for 10 hours, are rendered free of any risk of transmitting HBV by the routine application of this procedure to all lots of these two products.

III. THE AGENT

Intact HBV is found in the serum of acutely and chronically infected humans. When serum from an infected individual is observed by electron microscopy, a mixture of "full" and "empty" 42-nm double-shelled particles with cores are seen that are stained so as to be electron-dense or not, respectively. It is presumed that only the full HBV are infectious. The surface of the 42-nm HBV is composed of HBsAg which is immunologically identical to that of the 22-nm particles described below and also contains incorporated host proteins. The surface also contains a viral antigenic determinant distinct from HBsAg and HBcAg (Alberti *et al.*, 1980). An association has been proposed between the absence of

antibodies to this distinct HBV-associated determinant and continuing active virus replication (Alberti *et al.*, 1980), although this relationship has not yet been confirmed.

Vast quantities of excess surface protein are produced during HBV infection and released into the serum in the form of 22-nm HBsAg spheres and tubules. It has been suggested that the tubules are composed of linked spheres, although this has not been documented. The 22-nm spheres, as the least dense of the two forms of free HBsAg, are easiest to separate from intact HBV and thus have provided the antigenic material for most hepatitis B vaccines. The ratio of 22-nm HBsAg particles to intact HBV in serum may range from 10:1 to 1000:1 (Hoofnagle, 1980). These particles are primarily composed of several polypeptides but also contain lipids and carbohydrates. The HBsAg antigenicity of these particles is located primarily on two polypeptides of approximately 23,000 and 28,000 daltons, respectively (Skelly *et al.*, 1979).

Several subtypes of HBsAg exist which are of epidemiologic interest. HBsAg obtained from the serum of a given patient always contains the common **a** subtype determinant and either the **d** or **y** and the **w** or **r** determinants. Thus a particular strain of HBV will be found to have one of the major subtypes of HBsAg, **adw, adr, ayw,** or **ayr.** Rarely, infection by hybrid forms may be responsible for the **adyw** and **adywr** subtypes (Mazzur *et al.*, 1975). Numerous minor subtypes have also been described but are poorly characterized. The HBsAg subtype "breeds true" from one infection to another and may permit a tracing of the source of an infection or confirmation of a point source during an apparent outbreak. In the United States and Western Europe, **adw** is the most common subtype among chronic carriers and hence among blood donors. However, **ayw** is not uncommon among descendants of persons from Mediterranean countries (Sampliner *et al.*, 1981), and **adr** infections may be found among those of Oriental descent and servicemen returning from the Far East. In Eastern Europe and much of Africa, **ayw** is the most common subtype. In northern Japan and northern China, **adr** is common; in southern China, **adw** is the most common. The **adr** subtype is frequently found among persons whose ancestors emigrated from northern China to southern Japan or Taiwan (Yamashita *et al.*, 1975; Sung and Chen, 1978).

A 27-nm nucleocapsid core, HBcAg, is found in the nuclei of liver cells infected with HBV. Although never found free in serum, it may be released from intact HBV obtained from serum by detergent treatment. The core contains circular DNA, of which as much as 85% is double-stranded and the remainder single-stranded, although the percentage is variable (Robinson and Albin, 1980).

The portion which is single-stranded is "made double-stranded" by the presence of a DNA polymerase molecule which is specific for this virus. The core also contains an associated protein kinase activity (Robinson and Albin, 1980). The recent cloning of HBV DNA in prokaryotic cells has permitted partial sequencing of this unusual partially double-stranded DNA.

HBeAg is a soluble antigen associated with HBV. Although completely distinct from the particulate HBcAg, it is believed to originate in the core of the HBV, since it can be released from the core by treatment with Pronase and sodium dodecyl sulfate (Takahashi *et al.*, 1979). HBeAg is associated with two polypeptides of 19,000 and 45,000 daltons, respectively (Takahashi *et al.*, 1979), and three separate antigenic components, HBeAg/1, HBeAg/2, and HBeAg/3 (Murphy *et al.*, 1978).

IV. SYMPTOMS

HBV infection produces a broad spectrum of manifestations ranging from subclinical disease to fulminant disease that is often fatal. Among adults infected with HBV, 55% have no symptoms despite serologic documentation of hepatitis B infection (Hoofnagle *et al.*, 1978a) (Fig. 1.3). This is reflected in the transmission of hepatitis B by blood donors who are infected with this virus but are in apparent good health (Tabor *et al.*, 1979).

In some cases where symptoms are present, they may be so mild as to escape being diagnosed as hepatitis. A slight malaise, fatiguability, or loss of appetite may be the only symptoms. More severe symptoms and signs include severe fatigue, anorexia, nausea, vomiting, jaundice, scleral icterus, and hepatosplenomegaly. A small number of patients have a severe subacute course which may progress to coma and death over as long as 8 weeks.

Fulminant hepatitis develops in 1% of infected adults and is characterized by progressive hepatocellular destruction, encephalopathy, and steadily deepening coma. Death results in approximately 30% of children and 80% of adults with fulminant hepatitis B. An unusual characteristic of fulminant hepatitis B which may be observed is fever, which is not usually part of the signs and symptoms of HBV infection (Tabor *et al.*, 1976a).

Immune complexes formed by the antigens and antibodies associated with HBV have been implicated in the etiology of several HBV-associated syndromes. One of these is a serum sickness-like prodrome in 10–20% of patients with symptomatic hepatitis B, which is characterized by a maculopapular rash,

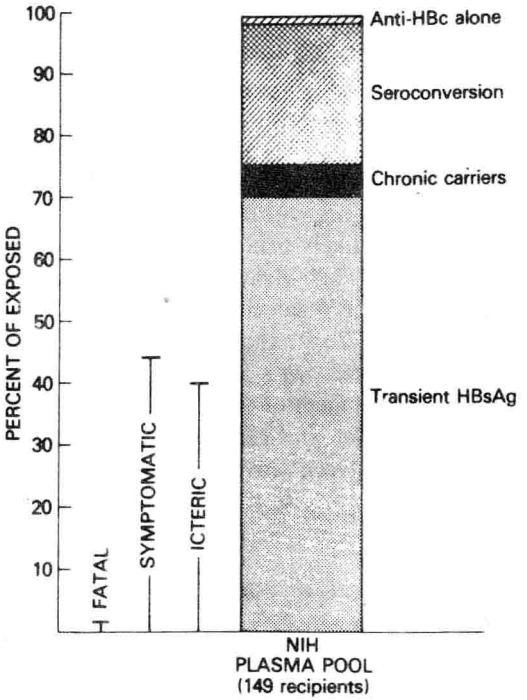

Figure 1.3. Range of symptoms and course in patients acquiring hepatitis B from the inoculation of identical volumes of plasma from a single plasma pool.

pruritic urticaria, and polyarthritis beginning from a few days to 6 weeks prior to the onset of clinical hepatitis. Polyarteritis nodosa, another such syndrome, is associated with chronic HBV, following 1 in 500 cases of symptomatic acute hepatitis B (Redeker, 1975). Both the serum sickness-like prodrome and polyarteritis nodosa have been thought to result from the presence of circulating HBsAg–anti-HBs immune complexes and the deposition of these complexes in the involved tissues. Similar associations have been observed between HBV infection and membranous glomerulonephritis and were initially attributed to HBsAg–anti-HBs immune complexes. A subsequent study, however, implicated immune complexes formed by the soluble HBeAg and its antibody (Takekoshi *et al.*, 1979).

The HBV chronic carrier state, manifested by the persistence of both HBsAg and anti-HBc in the blood for many years, develops in about 10% of infected