The Berkson Bias in Action

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Thirty years ago Berkson recognized that differences in selection rates of different diseases for admission to the hospital will systematically change the frequency with which those diseases co-exist in hospitalized patients from the frequency rate in the general population. Mainland subsequently demonstrated that postmortem studies systematically show a lower co-morbidity rate for any two individually lethal diseases than would be expected from the individual prevalence of these diseases. In studying the concurrence of bacterial endocarditis and cirrhosis, we examined the relationship of these diseases at autopsy where, according to this concept, we would expect a negative association. We found the frequency of bacterial endocarditis to be three times greater in cirrhotic than in non-cirrhotic patients, a statistically significant difference that was even more convincing, since a negative correlation was anticipated. In accord with the Berkson-Mainland hypothesis, however, no such association was seen between bacterial endocarditis and either emphysema or myocardial infarction, two other chronic diseases of different lethality. Similarly, glioblastoma multiforme, a brain tumor with a high mortality rate, showed a negative correlation with cirrhosis, emphysema, and myocardial infarction. A corollary of this bias—that the mean age at death should be lower in patients dying with two lethal diseases than in patients dying of either disease alone—was supported by our study. This investigation provides evidence to validate the Berkson-Mainland hypothesis, and suggests that rather than being always an adverse bias, it may be used beneficially to document the validity of the increased co-existence of diseases at autopsy.

Approximately thirty years ago Joseph Berkson described what has become narrowly known as Berkson's fallacy [1]. His observations were not fallacious, however, and discerning investigators tend to use the more alliterative term, the Berkson bias. Berkson prefers the term “paradox.”

He perceived that for every disease there exists a specific probability that its victims will be selected for admission to the hospital. If the selection rates, i.e., admission rates, differ for different diseases, he reasoned, the ratio of multiple diagnoses to single diagnoses will be different in hospitalized patients from those in the general population. Selection rates may be influenced by factors such as the severity of symptoms, or the reputation of a particular physician or hospital for a particular disease, or these days, by the room rates at the hospital. Berkson showed mathematically that even if the probabilities for admission operated independently in individuals suffering from more than one disease, the coincidence of multiple diseases in...
hospital would differ from, and would tend to occur together more frequently, than in the parent population. Berkson’s original example showed that although diabetes occurs in the same percentage of patients with and without cholecystitis in the general population, different admission rates can result in almost twice the occurrence of diabetes in hospitalized patients with cholecystitis as in patients without cholecystitis [1]. He concluded his paper by stating that “The same results would appear if sampling were applied to randomly distributed cards instead of patients” to show that this phenomenon was mathematical, rather than biological.

Recently, Roberts and Sackett and their associates have, for the first time, presented data that confirm Berkson’s bias in the clinical setting [2].

In addition, calculations about the association of two diseases can be affected by various selective factors after admission to hospital. For example, the avidity with which diagnostic screening tests are used affects the apparent association of different diseases. In a hospital in which the SMA-18, which measures serum glucose and urea among other substances, is routinely used, subclinical elevations of glucose and urea levels will make the association of diabetes and uremia with each of the diseases that precipitated admission higher than in the general population.

Mainland, a few years later, showed that the association of two diseases at autopsy occurs less frequently than one would expect from the individual incidences of the two diseases in the general population [3]. In essence, patients coming to autopsy have been selected by death. Let us, for example, compare the frequency of bacterial endocarditis in patients with cirrhosis and in patients with emphysema according to the theory of competing risks (Table 1).

|                      | Number of Deaths |
|----------------------|------------------|
|                      | Bacterial         |
| Endocarditis         | No Bacterial      |
| Total                |                  |
| Cirrhosis            | 57               |
|                      | 1,386             |
|                      | 1,443             |
| Emphysema            | 52               |
|                      | 396               |
|                      | 448               |

CONCLUSIONS:

Bacterial endocarditis is present in 57 of 1,443 patients who died with cirrhosis (4%).

Bacterial endocarditis is present in 52 of 448 patients who died with emphysema (12%).

This difference is highly significant $p < 0.001$. 

TABLE 1

ASSUMPTIONS:

| There are 10,000 cirrhotic patients and 10,000 patients with emphysema. |
| Bacterial endocarditis occurs in 1% of each group. |
| Emphysema has a mortality rate of 4%. |
| Cirrhosis has a mortality rate of 14%. |
| Bacterial endocarditis has a mortality rate of 50%. |
| These mortality rates are independent of each other. |
43 patients) will die of endocarditis—thus a total of 57 of the cirrhotic patients will have died. (Alternatively one can assume that the two diseases kill simultaneously.) Calculating the other compartments similarly, one finds that endocarditis appears to occur significantly less frequently in cirrhosis (4%) with its higher mortality than in emphysema (12%), which is less lethal. Indeed, the coincidence of two individually lethal diseases will occur at autopsy less frequently together than in the general population. As a corollary, any disease under scrutiny will occur less frequently at autopsy in association with a highly lethal disease than in association with a lowly lethal disease. In the simplest sense, more patients will die of cirrhosis than of emphysema before they have a chance to develop bacterial endocarditis.

Having presented the Berkson hypothesis, let's try it out in practice. Spontaneous bacterial peritonitis is a disease of cirrhotic patients in which it is thought that preexistent ascites becomes infected by blood-borne bacteria. It is believed that the bacteremia in cirrhosis is prolonged because of portal-systemic shunting and that prolonged bacteremia increases the risks of infection of the ascitic fluid. If this proposed, serendipitous pathogenesis is correct, the incidence of bacterial infection of other susceptible sites should also be increased. We assumed the cardiac valves to be such a site, and predicted that if the postulated pathogenesis was correct, bacterial endocarditis would occur more frequently in cirrhotic patients than in non-cirrhotic subjects.

**METHODS**

*Postmortem Study*

Because of the negative concurrence (or antagonism) between lethal diseases at autopsy, we deliberately decided to study the coincidence of cirrhosis and endocarditis from the autopsy files of our hospital. All 4,215 autopsies at the West Haven Veterans Administration Hospital (WHVAH) were reviewed for the presence or absence of bacterial endocarditis and of cirrhosis, and the postmortem diagnosis in each instance was confirmed blindly. The frequency of bacterial endocarditis in patients with cirrhosis was compared with its frequency in non-cirrhotic patients. In addition, we determined the frequency of occurrence of endocarditis in patients with acute myocardial infarction as a highly lethal control disease for cirrhosis, and with pulmonary emphysema as a control disease of lower lethality. We also studied the frequency of association of glioblastoma multiforme as an uncommon but often fatal disease, as a control for bacterial endocarditis. This brain tumor, which is not thought to be pathogenically related to cirrhosis, myocardial infarction, or emphysema, was observed with about the same frequency as bacterial endocarditis.

*Clinical Study*

We also compared the concurrence of bacterial endocarditis in cirrhotic and non-cirrhotic patients based on clinical diagnoses at the WHVAH. It is difficult, however, to determine the precise number of patients admitted to a VA Hospital over any given period. The Veterans Administration record-keeping system registers the number of admissions to the hospital, but does not afford easy access to the number of patients admitted per unit period of time. Furthermore, there is no constant relationship between the number of patients admitted and the total number of admissions. Because no simpler technique was available, the number of patients admitted was estimated by the "yards of cards" method. This estimate is based on the contents of the alphabetical admission file, which contains an index card for every
patient ever admitted to the hospital. Each admission is recorded on the card, and if a patient has been admitted many times, he may have several cards stapled together. After establishing the number of patients per cm of stacked cards, corrected for staples and alphabetical markers, we determined the number of patients from the total height of the stacked index cards. According to this method, 41,151 patients had been admitted during the 20.5 year period of this study.

RESULTS

Postmortem Study

Bacterial endocarditis was seen in 1% of the autopsies, a figure similar to that observed in other series (Table 2). Among the 557 cirrhotic patients, bacterial endocarditis occurred in 1.8%, and among the non-cirrhotic patients in 0.9%. This difference almost, but not quite, achieves statistical significance. The p value is less than 0.06.

No such association was seen between bacterial endocarditis and either emphysema or myocardial infarction or between glioblastoma multiforme and cirrhosis, myocardial infarction, or emphysema (Fig. 1). By contrast, the anticipated antagonism of Mainland at autopsy was observed between glioblastoma and cirrhosis, glioblastoma and myocardial infarction, and glioblastoma and emphysema, and was highly significant in each instance (Fig. 2).

Clinical Study

One-tenth of one percent of the non-cirrhotic patients had bacterial endocarditis compared to 0.34% of the cirrhotic patients. This difference is highly statistically significant ($p < 0.001$) (Table 3).

To be certain that our “yards of cards” estimate of the number of patients admitted did not affect the results, we repeated the calculations assuming that the estimate of admissions was both half and twice the true number. The differences remain highly significantly different ($p < 0.001$).

DISCUSSION

Postmortem Study

Although the positive association between cirrhosis and bacterial endocarditis in the autopsy study did not achieve statistical significance by conventional standards, one might extrapolate, and say that a $p$ value of $< 0.06$ is statistically significant for a positive association when one would have expected a statistically significant negative association. Are statistics available for such calculations? Unless one has for comparison a control disease with the same rate of admission to the hospital and the same

| Group          | Total No. | Bacterial Endocarditis |
|----------------|-----------|------------------------|
| All autopsies  | 4215      | 44                     | 1.0                   |
| Cirrhosis      | 557       | 10                     | 1.8                   |
| No cirrhosis   | 3658      | 34                     | 0.9                   |

TABLE 2

Association of Cirrhosis and Bacterial Endocarditis at the WHVAH (Autopsy Study)
FIG. 1. Postmortem association of bacterial endocarditis with cirrhosis, emphysema and myocardial infarction. The height of the bars represents the percentages of patients in each subgroup. The p value indicates the degree of statistical significance by $X^2$ analysis. Although bacterial endocarditis occurred significantly more commonly in cirrhotic than in non-cirrhotic patients, no such association of endocarditis with emphysema or myocardial infarction was observed.

FIG. 2. Postmortem association of glioblastoma multiforme with cirrhosis, emphysema and myocardial infarction. The p value indicates the degree of statistical significance by $X^2$ analysis. Statistically significant negative associations of glioblastoma multiforme with cirrhosis, with emphysema and with myocardial infarction demonstrate the Berkson-Mainland bias.
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Clinical Study

Since one would expect an increased association between cirrhosis and bacterial endocarditis on the basis of Berkson's bias in the clinical study, it is difficult to know whether this degree of statistical significance ($p < 0.001$) is above and beyond the level expected. Unless one had another disease with exactly the same selection rate as cirrhosis, but had no pathogenic relationship to bacterial endocarditis, this question cannot be answered. In a completely computerized medical record-keeping system it might, perhaps, be possible to compare the frequency of the association of bacterial endocarditis and cirrhosis with that of bacterial endocarditis and a number of other chronic diseases. If none of the others showed a positive association or approached this high degree of togetherness, one might conclude that the absence of such a relationship over a whole spectrum of selection values would support the coincidence of endocarditis and cirrhosis.

We believe that our data support the concept that bacterial endocarditis occurs with increased frequency in cirrhotic patients, and that this fact provides clinical validation for the postulated pathogenesis. Other data from these studies demonstrate that bacterial endocarditis in cirrhotic patients differs from the endocarditis of non-cirrhotic patients in terms of underlying valvular disease and in the species of organisms responsible.

We know that hospital samples are biased samples, i.e., they are not representative of the general population of sick people, which in turn is a biased sample of the parent population. Autopsy samples are doubly biased. It is unlikely that unbiased conclusions can be derived from biased samples.

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