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Infectious endocarditis in patients with cirrhosis of the liver: a model of infection in the frail patient

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Abstract:

To know whether cirrhosis is a predisposing cause of IE and to determine the microbiology, prognosis and the role of cardiac surgery on mortality.

Review of cases of infectious endocarditis in a university-affiliated hospital during 10 years.

Thirty-one(9.8%) patients among 316 cases of infectious endocarditis had hepatic cirrhosis. Valve disorders were present in 62.2% of cirrhotic patients and infection occurred on aortic(48%) and mitral valves(45%).Endocarditis was hospital-acquired in 14(45%) and 11(17.7%) of cirrhotic and controls respectively(OR 3.82;95%CI:1.46-9.99;p 0.005).Staphylococcus aureus was the most common causative microorganism but beta-hemolytic streptococci were most frequently isolated in cirrhotic patients(OR 8.75; 95% CI: 1.7-45.2;p 0.001).Renal failure was more frequent in patients with cirrhosis(OR 8.23;95%CI: 3.06-22.2; p 0.001).Cirrhotic patients had a higher mortality(51% vs 17.7%; OR 4.95;95%CI:1.89-12.91;p 0.001) associated with the severity of liver disease. Valve replacement was performed less frequently in cirrhotic patients(56.2% vs 92%) and the operative mortality was extremely high in patients with stages B and C.

Hepatic cirrhosis is a frequent comorbid condition in patients with endocarditis. Due to the presence severe hepatic dysfunction, cardiac surgery is not undertaken even when indicated and mortality is high in stages B and C. Endocarditis is a serious hazard for hospitalized cirrhotic patients.

Response to Reviewers:

Dear Dr. Van Belkum:

Thank you very much for the opportunity of revising the above mentioned manuscript. In doing the revision, I have taken into account all the suggestions of the reviewer.

Firstly, let me tell you why we chose to perform a case-control study instead of a case-cohort comparison. A case-control study is a simple and very useful investigative tool to identify factors that may contribute to the understanding of many medical conditions. In this case, we compared patients

with cirrhosis of the liver and endocarditis with subjects with endocarditis but without such underlying disease. In short, we looked back to see if there were characteristics of these patients that differ from those who did not have cirrhosis. The main reasons of our choice were:

1. Simplicity.

2. Accuracy. Because patients were seen over a relatively long period -10 years- we tried to bring nearer cases and controls to avoid biases associated with changes in diagnostic techniques (use of TEE, blood cultures), antibiotic usage or surgical team over the time. For this reason we selected two controls for each case: the previous and the consecutive to the index case.

Reviewer:

1. Our patients with cirrhosis of the liver were not on any type of chronic antimicrobial therapy with fluoroquinolones or other agents such as those that are administered for the prevention of primary bacterial peritonitis. We have included a short comment on this in the last paragraph of page 7. This is an interesting comment because such intervention may eventually favour enterococcal infections. Our cases, enterococcal endocarditis mainly occurred as a result of urinary tract instrumentation. Patients with endocarditis caused by beta-hemolytic endocarditis developed the disease in the community and was not associated with a previous use of antibiotics.

2. As suggested, we have included a short summary of our results and a recommendation on the management of cirrhotic patients with endocarditis in the last paragraph of page 11.

In addition, one new quotation (no.13) has been included.

Thank you once more for this opportunity and do not hesitate if further questions are raised.

Looking forward to hearing from you.

Yours sincerely

Manuel L. Fernández Guerrero

Infectious Endocarditis in Patients with Cirrhosis of the Liver: A Model of Infection in the Frail Patient

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Division of Infectious Diseases (Department of Medicine).

Fundación Jiménez Díaz. Universidad Autónoma de Madrid, Spain.

Running title: Infectious endocarditis in patients with hepatic
cirrhosis.

Key words: Infectious endocarditis, liver cirrhosis, nosocomial
endocarditis.

No conflicts of interest declared.

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Abstract

To know whether cirrhosis is a predisposing cause of IE and to determine the microbiology, prognosis and the role of cardiac surgery on mortality.

Review of cases of infectious endocarditis in a university-affiliated hospital during 10 years.

Thirty-one(9.8%) patients among 316 cases of infectious endocarditis had hepatic cirrhosis. Valve disorders were present in 62.2% of cirrhotic patients and infection occurred on aortic(48%) and mitral valves(45%).Endocarditis was hospital-acquired in 14(45%) and 11(17.7%) of cirrhotic and controls respectively(OR 3.82;95%CI:1.46-9.99;p 0.005).*Staphylococcus aureus* was the most common causative microorganism but β eta-hemolytic streptococci were most frequently isolated in cirrhotic patients(OR 8.75; 95% CI: 1.7-45.2;p 0.001).Renal failure was more frequent in patients with cirrhosis(OR 8.23;95%CI: 3.06-22.2; p 0.001).Cirrhotic patients had a higher mortality(51% vs 17.7%; OR 4.95;95%CI:1.89-12.91;p 0.001) associated with the severity of liver disease. Valve replacement was performed less frequently in cirrhotic patients(56.2% vs 92%) and the operative mortality was extremely high in patients with stages B and C.

Hepatic cirrhosis is a frequent comorbid condition in patients with endocarditis. Due to the presence severe hepatic dysfunction, cardiac surgery is not undertaken even when indicated and mortality is high in stages B and C. Endocarditis is a serious hazard for hospitalized cirrhotic patients.

INTRODUCTION.

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Patients with cirrhosis of the liver are prone to develop severe bacterial infections due to the presence of various facilitating mechanisms including changes in the reticuloendothelial system, decreased opsonic activity, leukocyte dysfunction and iatrogenic factors among others [1]. Infections such as primary peritonitis, pneumonia, or tuberculosis are acknowledged causes of morbidity and mortality in patients with cirrhosis of the liver; yet, apart from these particular diseases, other infection issues have not been the subject of in-dept investigation [1].

Infectious endocarditis occurring in patients with hepatic cirrhosis is rarely reported [2]. Anecdotal case reports of endocarditis associated with invasive procedures – TIPS, upper endoscopy, sclerotherapy of esophageal varices or liver biopsy –, and caused by unusual pathogens comprise the majority of the articles [3-7]. However, to the best of our knowledge, studies have not analyzed the impact of liver cirrhosis, a common morbid condition, on the outcome of patients with endocarditis and thus, some important clinical and prognostic factors of endocarditis in patients with cirrhosis are still poorly known.

The aim of this study were: (i) to know whether cirrhosis is in fact a predisposing cause of IE; (ii) to determine the microbial etiology of IE in this population and other clinically relevant features; and (iii) to assess prognostic factors and how frequently cardiac surgery is needed and performed.

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PATIENTS AND METHODS.

Retrospective review of consecutive cases of infectious endocarditis in a tertiary, university affiliated hospital that provides service for a population of 350.000 people in downtown Madrid, during a period of 10 years (1998-2009). A control group composed of 2 patients per case (the previous and the consecutive to the index case) was used for comparison purposes.

Hepatic cirrhosis was diagnosed by clinical and laboratory criteria and in some patients by means of liver biopsy. The severity of liver dysfunction was categorized according to the modified Child-Turcotte-Pugh classification with a scoring system of 5 to 15: scores of 5 and 6 being class A consistent with compensated cirrhosis; scores of 7 to 9 indicating class B characterized by mild ascitis and minimal encephalopathy; and scores of 10 to 15 class C with poorly controlled ascitis and severe hepatic encephalopathy [8]. The risk of postoperative mortality was assessed by the Model for End-stage Liver Damage (MELD) [9] with an on-line tool that used age, type of hepatic disease, the American Society of Anesthesiologists Physical Status Classification (ASA score) and patient's laboratory values for serum bilirubin, serum creatinin and the international normalized ratio for prothrombin time (INR) [10].

IE was diagnosed by the usual modified Duke's criteria [11]. Only patients with a definite diagnosis of endocarditis were included. Hospital-acquired infectious endocarditis was defined as endocarditis developing \geq 72 hours after admission in association

1 with a hospital-based procedure or during another hospitalization
2 within the preceding 8 weeks [7].
3

4 Renal failure was defined as an increase in serum creatinin
5 levels ≥ 1.6 mg/dl persisting ≥ 24 hours despite of the
6 administration of fluids. Central nervous system complications
7 included embolic events and brain hemorrhage and were evaluated
8 by CT-scan and MR-imaging.
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10 Mortality per episode was calculated. All death that occurred
11 during hospitalization as a direct consequence of infection, including
12 operative and perioperative mortality and any death associated with
13 bleeding or acute liver failure occurring during the active phase of
14 infection were considered related with endocarditis.
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16 *Statistics:* SPSS v 11.0 (SPSS Inc., Chicago, IL) was used for the
17 statistical analysis of the data. Continuous variables were expressed
18 as mean (range). Discrete variables were expressed as percentages.
19 Associations were tested by chi-square test or the Fisher exact test
20 when samples were small. The strength of associations was
21 measured by odds ratio (OR) or the Haldane estimator for small
22 sample 2×2 tables, and their 95% confidence interval (CI).
23 Differences in continuous variables were measured by Student t test
24 for independent variables. Differences between groups were
25 considered significant at p value < 0.05 .
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27 RESULTS.

28 Thirty-one (9.8%) patients among 316 cases of infectious
29 endocarditis had cirrhosis of the liver. The mean age of cirrhotic
30 patients was 59.6 years, lower than that in the control group. Most
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1 patients (71%) were males. The etiology of hepatic disease was
2 alcoholic cirrhosis in 16 patients (51.6%), posthepatitis cirrhosis
3 caused by hepatitis C or B viruses in 11 patients (35.4%) or
4 cryptogenic cirrhosis in 4 (13%) and were classified as stages A (12),
5 B (8), C (11) of Child-Turcotte-Pugh.
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11 Table 1 shows some relevant epidemiologic and clinical
12 features of endocarditis in patients with cirrhosis of the liver. An
13 underlying predisposing valve disease was present in 62.2% of
14 cirrhotic patients and infection occurred mainly on aortic (48%) and
15 mitral valves (45%). Infectious endocarditis was hospital-acquired in
16 14 (45%) and 11 (17.7%) of cirrhotic and control patients
17 respectively (OR 3.82;95% CI: 1.46-9.99 ; p 0.005). Central venous
18 catheters (4 cases), urinary tract instrumentation (3 cases),
19 colonoscopy (1 case), total parenteral nutrition (1 case), liver biopsy
20 (1 case), sclerotherapy of esophageal varices (1) and Sengstaken-
21 Blakemore balloon (1 case) were the recognized sources of
22 bacteremia.
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40 No differences were observed among cirrhotic and control
41 patients in the relative frequency of complications such as cardiac
42 failure or central nervous system events. However, renal failure was
43 significantly more frequent in patients with cirrhosis of the liver
44 (OR 8.23; 95% CI: 3.06-22.2; p 0.001).
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52 Table 2 shows the microbial etiology of infectious endocarditis
53 in patients with cirrhosis of the liver. None of these patients were
54 on chronic, low-dose antimicrobial therapy with fluoroquinolones
55 or other drugs for prevention of primary bacterial peritonitis.
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1 *Staphylococcus aureus* was the most common causative microorganism
2 in both cirrhotic and control patients. Beta-hemolytic streptococci,
3 including *S. agalactiae* and *S. pyogenes*, were most frequently isolated in
4 patients with cirrhosis of the liver than in controls (OR 8.75; 95%
5 CI: 1.7-45.2; p 0.001). On the other hand, viridans streptococci
6 were uncommonly found in cirrhotic patients (OR 0.1; 95% CI: 0.01-
7 0.83; p 0.002). *Staphylococcus aureus* (5), enterococci (4), coagulase-
8 negative staphylococci (2), *Escherichia coli* (1), *Candida albicans* (1) and
9 *P aeruginosa* (1) were the microorganisms isolated in cirrhotic patients
10 with nosocomial endocarditis.
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23 Sixteen patients (51%) with cirrhosis of the liver and 11
24 (17.7%) in the control group died during hospitalization for causes
25 associated with endocarditis (OR 4.95;95% CI: 1.89-12.91; p 0.001).
26 Mortality was associated with the severity of liver disease and so,
27 while only 2 of 12 (16.6%) patients in stage A died, 6 out of 8 (75%)
28 in stage B and 8 of 11 (72.7%) in stage C died. Cardiac failure,
29 hepato-renal syndrome with acute renal failure and brain bleeding
30 were the most common causes of death.
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43 Valve replacement was considered in 16 patients with cirrhosis
44 of the liver who developed cardiac failure but was performed in only
45 9 (56.2%) cases in whom it seemed feasible and indicated. Five of
46 these patients survived (4 in stage A, and 1 in stage B) and 4 died (3
47 in stage B and 1 in stage C). The calculated postoperative mortality
48 risk of these last patients ranged from 57% to 80% at 30 days and
49 from 69% to 81% at 1-year. In the rest of the cases, valve
50 replacement was declined due to the presence of end-stage liver
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1 failure (3 in stage B, 4 in stage C). The postoperative mortality risk
2 in this group of patients was retrospectively calculated and ranged
3 from 33% to 85% at 30 days and from 54% to 91% at 1-year. On
4 the other hand, valve replacement was indicated in 24 control
5 patients and was performed in 22 (91.6%) of whom 18 (81.8%)
6 survived the infection.
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13 **DISCUSSION.**

16 Cirrhosis of the liver was a common underlying condition in
17 patients with IE observed in almost 10% of cases. Cirrhotic patients,
18 particularly those with advanced disease exhibit leukocyte
19 dysfunction and phagocytic defects that make them prone to
20 develop focal and systemic bacterial infections. The presence of
21 portosystemic shunts and the common occurrence of cutaneous
22 abrasions in oedematous legs are potential sources of bacteremia
23 from gastrointestinal tract and skin. In addition, patients with
24 hepatic cirrhosis are frequently admitted to hospital where they are
25 the subject of invasive diagnostic and therapeutic procedures with
26 the potential of producing bacteremia and endocarditis.
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43 In this series, endocarditis was a nosocomial infection in 45%
44 of cases, a proportion significantly higher than that found in the
45 control group and much higher than that observed in previous
46 reports on hospital-acquired infectious endocarditis [7,12]. This
47 observation suggests that infectious endocarditis is a serious hazard
48 for hospitalized patients with cirrhosis of the liver. As shown in
49 previous studies, venous catheters and urinary tract instrumentation
50 were the main sources for bacteremia leading to endocarditis in
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cirrhotic patients [13]. However it is interesting to note that other procedures that are commonly undertaken in these patients such as liver biopsy or urgent measures for the control of esophageal bleeding such as sclerotherapy of varices and Sengstaken-Blakemore balloon tamponade may be associated with bacteremia and endocarditis.

While *S aureus* and enterococci were the organisms most frequently found in nosocomial cases, *β -hemolytic streptococci* were common causes of community-acquired endocarditis in patients with cirrhosis. In previous studies, endocarditis caused by *β -hemolytic streptococci* has been associated with chronic underlying diseases such as alcoholism and cirrhosis of the liver [14]. Specifically *S agalactiae*, that in pre- and early antibiotic era was almost exclusively an infection seen in postpartum and postabortal women, is now a microorganism causing severe infections, including bacteremia and endocarditis, in chronically ill patients with cirrhosis of the liver, malignancies and some other conditions [14,15]. As noted before, endocarditis caused by *S agalactiae* followed a complicated course characterized by large vegetations, rapid destruction of cardiac valves and heart failure [15,16]. In addition, chronic liver disease has been recognized as a predisposing factor for *S bovis* bacteremia which may explain the increased frequency of endocarditis caused by these microorganisms in our series [17].

Liver cirrhosis has a significant impact on the mortality of patients with bacteremic infections and high production of proinflammatory cytokines seems to play a role in the worsening of

1 liver function and the development of organ-system failures such as
2 hepato-renal syndrome or hepatic encephalopathy [18,19].
3 Remarkably, renal failure occurred in most of our cases and seemed
4 to contribute to the poor outcome of patients. Besides heart failure,
5 acute renal failure was a major determinant of mortality.
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11 Mortality of cardiac surgery of patients with advanced liver
12 cirrhosis is extremely high [20] and so, the decision to operate on
13 these patients is difficult. In this series, although indicated in most
14 patients with cardiac failure, valve replacement was precluded in
15 many due to the presence of end-stage liver disease and when
16 performed, only patients in good functional state survived. MELD
17 score, which has been recently validated to quantify the risk of
18 mortality postoperatively in patients with cirrhosis, may be a useful
19 tool in the task of deciding whether or not these patients must be
20 sent to the operating room for valve replacement [21].
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In summary, we show herein data that suggest that infectious
endocarditis in patients with cirrhosis of the liver is a severe disease
with unique community-acquired etiologic agents. Besides,
infectious endocarditis is frequently acquired during hospitalization
as a consequence of invasive diagnostic or therapeutic procedures.
When indicated, valve replacement can be successfully performed in
patients with minor or mild hepatic dysfunction. However,
operative mortality of patients with Child stages B and C is
extremely high and probably should be undertaken only in selected
individuals with cardiac failure without renal failure and other
systemic complications.

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Finally, because most of the factors facilitating the development of bacterial infections in cirrhotic patients are unchangeable and many cases occur during hospitalization, prevention should focus on measures to avoid bacteremia and other nosocomial infections. New studies are required to better determine the role of cardiac surgery in the management of infectious endocarditis in cirrhotic patients.

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Table 1. Epidemiologic, Clinical Features and Mortality of Infectious Endocarditis in Patients with Cirrhosis of the Liver.

| | Patients no (%) | | | |
|--------------------------|-----------------|--------------|-----------------|----------|
| | Cirrhosis | Control | OR;95%CI | <i>p</i> |
| Mean age | 59.6 (32-71) | 68.9 (45-86) | | |
| Gender: Male | 22 (70.9) | 41 (66.1) | | |
| Female | 9 (29.19) | 21 (33.8) | | |
| Underlying valve disease | | | | ns |
| Rheumatic disease | 5 (16.1) | 9 (14.5) | | |
| Degenerative | 6 (19.3) | 16 (25.8) | | |
| Prosthetic valve | 4 (12.9) | 10 (16.1) | | |
| Mi valve prolapse | 3 (9.6) | 3 (4.8) | | |
| Other | 1 (3.2) | 7 (11.2) | | |
| Undetermined | 12 (38.7) | 17 (27.4) | | |
| Valve involvement | | | | |
| Mitral valve | 14 (45.1) | 25 (40.3) | | |
| Aortic valve | 15 (48.3) | 23 (37) | | |
| Mi & Ao valves | 2 | 3 | | |
| Tricuspid valve | - | 9 | 0.09;0.01-1.59 | .03 |
| Other* | - | 2 | | |
| Acquisition | | | | |
| Hospital-acquired | 14(45.1) | 11(17.7) | 3.82;1.46-9.99 | .005 |
| Community-acquired | 17 (54.8) | 51 (82.2) | | |
| Complications | | | | |
| Cardiac failure | 16 (51.6) | 25 (40.3) | | |
| Brain emboli | 5 (16) | 10 (16.1) | | |
| Renal failure | 19 (61.2) | 10 (16.1) | 8.23;3.06-22.2 | .001 |
| Mortality | 16 (51.6) | 11 (17.7) | 4.95;1.89-12.91 | .001 |

Table 2. Microbial Etiology of Infectious Endocarditis In Patients with Cirrhosis of the Liver.

| | Patients no (%) | | OR;95%CI | <i>p</i> |
|----------------------------------|---------------------------|------------------|----------------|----------|
| | Hepatic cirrhosis (31) | Controls (62) | | |
| <i>Staphylococcus aureus</i> | 8 (25.8) | 17 (27.4) | | ns |
| <i>Coagulase- staphylococci</i> | 2 (6.4) | 5 (8.6) | | ns |
| <i>Enterococci</i> | 6 (19.3) | 6 (9.6) | | ns |
| β -hemolytic streptococci: | 7 (22.5) | 2 (3.2) | 8.75;1.7-45.2 | .001 |
| <i>S agalactiae</i> | 4 | 1 | | |
| <i>S pyogenes</i> | 3 | - | | |
| Group C streptococci | - | 1 | | |
| <i>Streptococcus bovis</i> | 3 (9.6) | 3 (4.8) | | |
| <i>Streptococcus pneumoniae</i> | 1 | - | | |
| <i>Streptococcus viridans</i> | 1 (3.2) | 15 (24.1) | 0.1; 0.01-0.83 | .002 |
| <i>Listeria monocytogenes</i> | 1 | 1 | | |
| Gram-negative bacteria* | 1 (3.2) | 6 (9.6) | | |
| Fungi | 1 | 1 | | |
| <i>Coxiella burnetii</i> | - | 3 | | |
| Unknown | - | 3 | | |

* HACEK group, Enterobacteriaceae, Pseudomonas.

Ref. EJCMIID-D-10-00196 “Infectious Endocarditis in Patients with Cirrhosis of the Liver:A Model of Infection in the Frail Patient”.

Dear Dr. Van Belkum:

Thank you very much for the opportunity of revising the above mentioned manuscript.

In doing the revision, I have taken into account all the suggestions of the reviewer.

Firstly, let me tell you why we chose to perform a case-control study instead of a case-cohort comparison. A case-control study is a simple and very useful investigative tool to identify factors that may contribute to the understanding of many medical conditions. In this case, we compared patients with cirrhosis of the liver and endocarditis with subjects with endocarditis but without such underlying disease. In short, we looked back to see if there were characteristics of these patients that differ from those who did not have cirrhosis. The main reasons of our choice were:

1. Simplicity.
2. Accuracy. Because patients were seen over a relatively long period -10 years- we tried to bring nearer cases and controls to avoid biases associated with changes in diagnostic techniques (use of TEE, blood cultures), antibiotic usage or surgical team over the time. For this reason we selected two controls for each case: the previous and the consecutive to the index case.

Reviewer:

1. Our patients with cirrhosis of the liver were not on any type of chronic antimicrobial therapy with fluoroquinolones or other agents such as those that are administered for the prevention of primary bacterial peritonitis. We have included a short comment on this in the last paragraph of page 7. This is an interesting comment because such intervention may eventually favour enterococcal infections. Our cases, enterococcal endocarditis mainly occurred as a result of urinary tract instrumentation. Patients with endocarditis caused by beta-hemolytic endocarditis developed the disease in the community and was not associated with a previous use of antibiotics.
2. As suggested, we have included a short summary of our results and a recommendation on the management of cirrhotic patients with endocarditis in the last paragraph of page 11.

In addition, one new quotation (no.13) has been included.

Thank you once more for this opportunity and do not hesitate if further questions are raised.

Looking forward to hearing from you.

Yours sincerely

Manuel L. Fernández Guerrero