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## ORIGINAL ARTICLES



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# Does serum uric acid act as protector in patients with acute ischemic stroke and hyperglycemia? A clinical based evidence

*José C. Arévalo-Lorido[1]*, José P. Miramontes-González[2], Francisco J. Carrasco-Sánchez[3], José M. Fernández-Rodríguez[4], and Juana Carretero-Gómez[1]*

*[1]Internal Medicine Service, Hospital Universitario de Badajoz, Badajoz; [2]Internal Medicine Service, Hospital Universitario de Salamanca, Salamanca; [3]Internal Medicine Service, Hospital Universitario Juan Ramón Jiménez, Huelva; [4]Internal Medicine Service, Hospital Carmen y Severo Ochoa, Cangas de Narcea, Asturias, Spain*

## Abstract

**Introduction and objectives**: To explore if the clinical neurological damage that hyperglycemia could produce may be attenuated by elevated levels of serum uric acid (SUA). **Methods:** Prospective registry that included patients with acute ischemic stroke admitted within 24 h after the event. We divided them into three groups according to their levels of fasting blood glucose (FBG) (FBG < 140 mg/dL, FBG 140-180 mg/dL, and FBG ≥ 180 mg/dL) and subdivided them according to SUA levels (> 6 mg/dL in women and > 7 mg/dL in men). We assessed the worsening of both neurological (based on National Institute of Health Stroke Scale [NIHSS]) and functional damage based on Rankin scale. **Results**: We analyzed 504 patients (53.9% men). Type 2 diabetes mellitus was present in 163 (32.4%) patients and hyperuricemia in 118 (23.4%). The persons belonging to the FBG groups were increasing their neurological (NIHSS) and functional (Rankin) punctuation when their glucose levels raised (p = 0.07). Overall, the groups with hyperuricemia had lower but not significant scores in stroke severity (NIHSS) comparing to the groups without hyperuricemia (p = 0.1). In the logistic regression model, the odds ratio to have a NIHSS score higher than 16 increased as glucose levels were higher and again decreased in the groups with hyperuricemia without reach statistical significance. **Conclusion:** In patients with acute ischemic stroke with hyperglycemia, we found a non-significant tendency between SUA and lower clinical neurological damage. Further studies with larger samples and prospective follow-up are needed to confirm this potential protective role.

**Key words:** Uric acid. Hyperglycemia. Ischemic stroke. Cerebrovascular diseases.

## Introduction

Stroke is a major cause of death and disability around the world. Hyperglycemia in hospitalized patients with and without a history of diabetes mellitus (DM) is reported in up to 40% of critically ill patients and 32% of general medicine and surgery patients[1]. In the case of patients with acute stroke, hyperglycemia is accounted for at least 50% in each subtype, including lacunar strokes[2]. It has been also reported that the presence of hyperglycemia is associated with a worse functional outcome in these patients[3]. Several mechanisms have been postulated for these observations. Among them, it is well known that the blood-brain barrier is

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**Correspondence:**
*José C. Arévalo-Lorido
E-mail: joscarlor@gmail.com

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vulnerable to hyperglycemia, presumably through the liberation of lactic acid and free radicals that could otherwise promote more ischemic injury by intensifying lipid peroxidation and in a vicious circle more free radical formation[4]. In this setting, high serum uric acid (SUA) levels have shown to be beneficial to improve the prognosis of patients with acute ischemic stroke[5], related with its ability to scavenge oxygen radicals, being the central nervous system one of the best sites where uric acid exerts this antioxidant effects[6].

The aim of the study is to explore if the clinical neurological damage that hyperglycemia could produce may be attenuated by elevated levels of SUA. We hypothesize that the antioxidant effect of uric acid in acute ischemic stroke should weaken the deleterious effect in the brain that increasing glycemia has.

## Methods

Patients were enrolled through a stroke registry supported by Zafra County hospital that included consecutive ischemic stroke patients admitted within 24 h after the event and followed up for 1 year. The enrollment began the 1st January 2005-31st January 2012. Patients had to sign out the consent to participate in the registry under an ethics committee-approved protocol. Previous reports from this registry were published formerly[7,8].

The confirmation of stroke was based on the clinical evaluation and computed tomographic scan or magnetic resonance imaging scan of the brain carried out within 24 h of the event. The subtypes of stroke were grouped according to the TOAST classification[9]. We excluded patients with intracerebral hemorrhage, subarachnoid hemorrhage, cerebral venous sinus thrombosis, and late admission (> 24 h after stroke onset). All patients were treated with either antiaggregant or anticoagulant drugs, depending on the etiology, and with antihypertensive agents. Thrombolysis was not performed in any case.

### Data collection

Upon admission, a comprehensive medical history and detailed physical examination were performed. The National Institute of Health stroke scale (NIHSS)[10], Charlson co-morbidity index (CCI)[11], and Rankin score[12] assessed stroke severity, co-morbidity, and disability. Hypertension was defined as blood pressure ≥ 140/90 mmHg and for the use of antihypertensive medications. Subjects with a history of Type 2 DM (T2DM) and those receiving anti-diabetic medications were categorized as having T2DM. Subjects who smoked at least 1 cigarette/day at the time of enrollment were considered as smokers. At last, dyslipidemia was considered when the patient or the caregiver reported a positive history for this condition, and alternatively, we considered diagnostic the chronic usage of statin or ezetimibe or fasting low-density lipoprotein (LDL)-cholesterol levels > 100 mg/dL.

The laboratory data (creatinine, urea, uric acid, glucose, sodium, potassium, hematocrit, total cholesterol, LDL, and high-density lipoprotein (HDL)-cholesterol, triglycerides, and platelets) were recorded at the immediate next day after admission and under fasting condition.

### Patients distribution and outcomes

We have distributed the patients according to their fasting blood glucose (FBG) in three groups: FBG < 140 mg/dL, FBG 140-180 mg/dL, and FBG ≥ 180 mg/dL[13]. In turn, each of these three groups has been subdivided based on the presence or absence of hyperuricemia (SUA > 6 mg/dL in women and > 7 mg/dL in men)[14]. As a result, we have six pre-specified groups (Fig. 1).

The present analysis is referred to the time of admission so to assess the outcome, we have used the value of NIHSS and the Rankin score at admission. We have considered NIHSS as a continuous variable and additionally we have evaluated the pre-specified subgroups according to the clinical neurologic severity score as follows: mild (≤ 8 points), moderate (9-15 points), and severe (≥ 16 points)[15]. In the case of Rankin score, we have considered punctuation lower than 2 as a good prognosis.

### Statistical analysis

According to pre-specified groups, qualitative and categorical data were expressed as absolute number and percentage, and to compare them in univariate analysis, we used the Chi-square test. Quantitative data were expressed as median and interquartile range; to compare them, we used ANOVA test when the distribution of variables was parametric and Kruskal–Wallis test in the remainder. To assess significant differences between the pairs of basal glucose groups (groups 1 and 2, groups 3 and 4, and groups 5 and 6) related to the prognostic variables (NIHSS and Rankin Score), the t test was used when variables were normally distributed and the Wilcoxon test was used in the remainder. Logistic regression analysis was used to investigate whether the pre-specified groups were

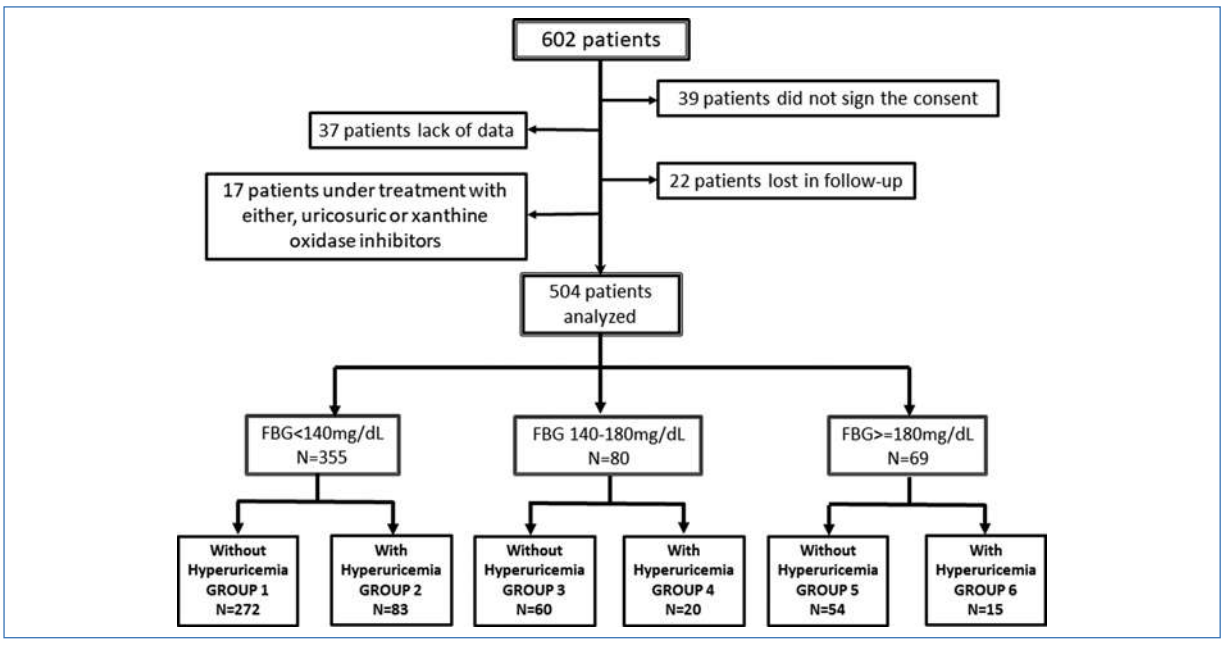



**Figure 1.** Chartflow of the study.

associated with the outcome. We constructed two models. In the first model, a bad prognosis was assessed using an NIHSS score ≥ 16[15]. The following variables were evaluated as potential confounders: age, sex, creatinine, CCI, systolic blood pressure, LDL cholesterol, and triglycerides. In the second model, a good prognosis was assessed using a Rankin score ≤ 2 points. We selected the same variables as previously.

All the statistical analyses were done with R version 3.3.2 (The R Foundation for Statistical Computing c/o Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien Welthandelsplatz 1; 1020 Vienna, Austria). A $p < 0.05$ was considered statistically significant.

## Results

We analyzed 504 patients (272 men, 53.9%) with a mean age of 75 ± 10.5 years. T2DM was present in 163 (32.4%) patients and hyperuricemia in 118 (23.4%). Regarding the three groups based on FBG levels, the first group (FBG < 140 mg/dL) included 355 (70.4%) patients, the second group (FBG 140-180 mg/dL) included 80 (15.9%), and the third group (FBG > 180 mg/dL) included 69 (13.7%) patients. The clinical and laboratory data of these groups, along with those that presented hyperuricemia or not, are shown in table 1. The main differences among the FBG based groups were the prevalence of hypertension, dyslipidemia, and T2DM, which were higher through the groups with higher FBG ($p = 0.004$, $p = 0.003$, and $p = 0.00$, respectively), the greater comorbidity in the groups of higher FBP ($p = 0.00$) and the lower HDL cholesterol levels across the groups of higher FBG ($p = 0.00$). In the setting of patients with or without hyperuricemia, the prevalence of hypertension, dyslipidemia, and T2DM was again higher in patients with hyperuricemia ($p = 0.00$, $p = 0.04$, and $p = 0.01$, respectively). In addition, patients with hyperuricemia had higher comorbidity (CCI = 8 ± 3.6 points, $p = 0.00$) and greater levels of creatinine (1.2 ± 0.6 mg/dL, $p = 0.00$) with more usage of diuretic drugs (43.2% vs. 27.7%, $p = 0.001$).

Regarding the six pre-specified groups, we found significant differences (Table 2) in the age ($p = 0.03$), history of DM ($p = 0.00$), hypertension ($p = 0.00$), and dyslipidemia ($p = 0.00$). The heart rate was significantly increased through the six groups ($p = 0.01$) likewise the HDL cholesterol was lowering ($p = 0.003$). Again, the levels of creatinine were significantly higher in the groups with hyperuricemia, groups 2, 4, and 6 ($p = 0.00$), as well as treatment with diuretics ($p = 0.001$).

### *Outcomes*

#### *NIHSS score*

The patients belonging to the FBG groups were increasing their NIHSS punctuation when their glucose

**Table 1.** Baseline characteristics of patients according to the fasting blood glucose (FBG) and serum uric acid levels

| Variable | Hyperglycemia groups | | | p | Serum uric acid groups | | p |
|---|---|---|---|---|---|---|---|
| | FBG < 140 mg/dL | FBG 140-180 mg/dL | FBG > 180 mg/dL | | Hyperuricemia | Normouricemia | |
| N | 355 | 80 | 69 | | 118 | 386 | |
| Age (years) | 74.3 (10.9) | 78.2 (9) | 76.2 (9.1) | 0.007 | 76.7 (11) | 74.7 (8.4) | 0.3 |
| Sex (Male) | 200 (56.3) | 39 (48.7) | 33 (47.8) | 0.25 | 57 (48.3) | 215 (55.7) | 0.17 |
| Hypertension | 288 (81.1) | 73 (91.2) | 65 (94.2) | 0.004 | 112 (94.9) | 314 (81.3) | 0.0004 |
| Dyslipidemia | 145 (40.8) | 40 (50) | 43 (62.3) | 0.003 | 63 (53.4) | 165 (42.7) | 0.04 |
| T2DM | 60 (16.9) | 43 (53.7) | 60 (86.9) | 0.00 | 49 (41.5) | 114 (29.6) | 0.01 |
| Tobacco | 66 (18.6) | 10 (12.5) | 12 (17.4) | 0.4 | 15 (12.7) | 73 (18.9) | 0.12 |
| SBP (mmHg) | 160.8 (28.4) | 158.5 (26.8) | 159.3 (27.7) | 0.7 | 161 (29.6) | 160 (27.5) | 0.74 |
| DBP (mmHg) | 87.2 (15.8) | 86 (14.5) | 85.5 (17.1) | 0.63 | 87.6 (15.8) | 86.5 (15.7) | 0.5 |
| HR (bpm) | 78 (16.1) | 81.6 (15.6) | 84.2 (17.4) | 0.008 | 81.1 (18.4) | 78.9 (15.7) | 0.2 |
| NIHSS | 8.4 (5.1) | 9.2 (5.6) | 9.9 (5) | 0.07 | 8.4 (5.4) | 8.9 (5.2) | 0.22 |
| Rankin score | 2.9 (1.2) | 3.1 (1.2) | 3.3 (1.3) | 0.07 | 3 (2) | 3 (2) | 0.99 |
| CCI | 7 (2.5) | 7.9 (2.1) | 8.5 (2.5) | 0.00 | 8 (3.6) | 7 (3.4) | 0.00 |
| FBG (mg/dL) | 101.3 (19.5) | 156.4 (11.4) | 240.7 (52.3) | 0.00 | 8 (3.6) | 7 (3.4) | 0.00 |
| Creatinine (mg/dL) | 1.13 (0.6) | 1.1 (0.5) | 1.1 (0.4) | 0.85 | 1.2 (0.6) | 0.9 (0.4) | 0.00 |
| SUA (mg/dL) | 5.4 (1.7) | 5.1 (1.7) | 5.2 (1.5) | 0.3 | 7.2 (1.1) | 4.7 (1.8) | 0.00 |
| Hemoglobin (g/dL) | 13.5 (1.9) | 13.5 (1.9) | 13.4 (1.8) | 0.8 | 13.3 (3.1) | 13.6 (2.4) | 0.1 |
| hsCRP (mg/dL) | 1.7 (2.3) | 2.4 (3.1) | 1.7 (1.8) | 0.06 | 0.8 (1.7) | 0.8 (1.8) | 0.9 |
| HDL-Chol | 44.1 (12.9) | 42.5 (13.5) | 37.8 (9.8) | 0.00 | 41 (13) | 42 (16) | 0.34 |
| LDL-Chol | 117.5 (34.2) | 118.9 (41.8) | 112.1 (34.6) | 0.43 | 112 (40) | 115 (50) | 0.34 |
| TREATMENT | | | | | | | |
| ACEi/ARB | 248 (69.8) | 52 (65) | 53 (76.8) | 0.28 | 82 (69.5) | 271 (70.2) | 0.88 |
| Statins | 221 (62.2) | 54 (67.5) | 48 (69.6) | 0.4 | 71 (60.9) | 252 (65.3) | 0.31 |
| Diuretics | 106 (29.8) | 36 (45) | 16 (23.2) | 0.009 | 51 (43.2) | 107 (27.7) | 0.001 |

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCI: Charlson Comorbidity Index; hsCRP: high sensitivity C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-Chol: HDL cholesterol; HR: heart rate; LDL-Chol: LDL cholesterol; NIHSS: National Institute of Health Stroke Scale; SBP: systolic blood pressure; SUA: serum uric acid levels. T2DM: type 2 diabetes mellitus.

levels raised (p = 0.07) but without reaching statistical significance (Table 1). This NIHSS score was modified downwards in the subgroups having hyperuricemia, again without reaching statistical significance (p = 0.1, Table 2, Fig. 2). In figure 2 may be also observed the sets according to the NIHSS score across the pre-specified groups. Overall, the groups with hyperuricemia (groups 2, 4, and 6) had lower but not significant scores in stroke severity (NIHSS) comparing to the groups without hyperuricemia (groups 1, 3, and 5). Finally, in the logistic regression model (Fig. 3), the odd ratio (OR) of the groups of FBG increased as glucose levels were higher and again, this OR decreased in the groups with hyperuricemia, without statistical significance. Among the covariables included, the age was significantly related to a bad outcome (NIHSS > 16 points) with an OR 1.1, 95%CI 1.04-1.14, p = 0.001.

### *Rankin score*

Regarding Rankin score, again the groups with higher FBG had a greater score in Rankin scale (p = 0.07), and when sub-classified according to the presence-absence of hyperuricemia, the score was lower in the groups with hyperuricemia (p = 0.17), especially in

**Table 2.** Baseline characteristics of patients according to pre-specified groups

| Variable | Group 1 (n = 272) | Group 2 (n = 83) | Group 3 (n = 60) | Group 4 (n = 20) | Group 5 (n = 54) | Group 6 (n = 15) | p |
|---|---|---|---|---|---|---|---|
| Age (years) | 76 (13) | 77 (10) | 79 (12) | 83 (11.5) | 79 (11) | 76 (4) | 0.03 |
| Sex (male) | 161 (59.2) | 39 (46.9) | 31 (51.7) | 8 (40) | 23 (42.6) | 10 (66.7) | 0.07 |
| Hypertension | 210 (77.2) | 78 (93.9) | 54 (90) | 19 (95) | 50 (92.6) | 15 (100) | 0.00 |
| T2DM | 39 (14.4) | 21 (25.3) | 29 (48.3) | 14 (70) | 46 (85.9) | 14 (93.3) | 0.00 |
| Dyslipidemia | 101 (37.1) | 44 (53.1) | 30 (50) | 10 (50) | 34 (62.9) | 9 (60) | 0.002 |
| Tobacco smokers | 55 (20.2) | 11 (13.2) | 8 (13.3) | 2 (10) | 10 (18.5) | 2 (13.3) | 0.52 |
| CCI | 6.4 (3) | 8 (4) | 7.2 (2.3) | 9.2 (3.2) | 8.8 (4.3) | 7.6 (3.4) | 0.00 |
| SBP (mmHg) | 160 (40) | 160 (41) | 160 (37.5) | 156.5 (42) | 155.5 (30) | 160 (50) | 0.94 |
| DBP (mmHg) | 87 (78) | 89 (78) | 81.5 (27.5) | 85 (78.5) | 80 (74) | 87 (70) | 0.81 |
| HR (bpm) | 76 (14) | 78 (20) | 80 (16.5) | 78 (26) | 80 (25) | 80 (19) | 0.01 |
| FBG (mg/dL) | 97 (29) | 106 (30) | 153 (17.5) | 156.5 (27) | 217 (75) | 225 (39) | 0.00 |
| Creatinine (gr/dL) | 0.9 (0.3) | 1.3 (0.7) | 0.9 (0.4) | 1.2 (0.6) | 1 (0.4) | 1.1 (0.7) | 0.00 |
| SUA (mg/dL) | 4.8 (1.7) | 7.2 (1.4) | 4.2 (2.1) | 6.8 (0.6) | 4.7 (1.7) | 7.4 (0.6) | 0.00 |
| Hemoglobin (gr/dL) | 13.6 (2.2) | 13.3 (3.4) | 13.7 (2.5) | 12.4 (3.2) | 13.4 (2.5) | 13.1 (3.6) | 0.52 |
| LDL-Cholesterol (mg/dL) | 115 (49) | 113 (43) | 114 (48) | 117 (58) | 111 (52) | 100 (27) | 0.72 |
| HDL-Cholesterol (mg/dL) | 43 (17.5) | 42 (14) | 41 (14) | 37 (10.5) | 37 (12) | 38 (12) | 0.003 |
| hsCRP (mg/dL) | 0.8 (1.4) | 0.8 (1.6) | 1 (3.1) | 0.6 (1.7) | 0.9 (2) | 1.4 (2) | 0.36 |
| NIHSS | 7 (6) | 7 (7) | 8 (7.5) | 7 (7) | 9 (6) | 10 (8) | 0.1 |
| Rankin score | 3 (2) | 3 (2) | 3 (2) | 3 (2) | 3 (2) | 3 (3) | 0.1 |
| In-hospital mortality | 2 (0.7) | 4 (4.8) | 0 (0) | 0 (0) | 2 (3.7) | 1 (6.7) | 0.6 |
| TOAST | | | | | | | |
| I | 99 (36.4) | 27 (32.5) | 17 (28.3) | 8 (40) | 24 (44.4) | 5 (33.3) | 0.7 |
| II | 73 (26.8) | 25 (30.1) | 19 (31.7) | 6 (30) | 14 (25.9) | 3 (20) | |
| III | 83 (30.5) | 27 (32.5) | 19 (31.7) | 6 (30) | 15 (27.8) | 5 (33.3) | |
| IV | 9 (3.3) | 1 (1.2) | 2 (3.3) | 0 (0) | 0 (0) | 2 (13.3) | |
| V | 8 (2.9) | 3 (3.6) | 3 (5) | 0 (0) | 1 (1.8) | 0 (0) | |
| Treatment | | | | | | | |
| ACEi/ARB | 189 (69.5) | 59 (71.1) | 41 (68.3) | 11 (55) | 41 (75.9) | 12 (80) | 0.5 |
| Statins | 174 (63.9) | 47 (56.6) | 40 (66.7) | 14 (70) | 38 (70.4) | 10 (66.7) | 0.6 |
| Diuretics | 71 (26.1) | 35 (42.2) | 24 (40) | 12 (60) | 12 (22.2) | 4 (26.7) | 0.001 |

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCI: Charlson Comorbidity Index; hsCRP: high sensitivity C-reactive protein; DBP: diastolic blood pressure; FBG: fasting blood glucose; HR: heart rate; NIHSS: National Institute of Health Stroke Scale; SBP: systolic blood pressure; SUA: serum uric acid levels. T2DM: type 2 diabetes mellitus; TOAST: classification of subtype of acute ischemic stroke[9].

those whose FBG was more than 140 mg/dL; however, these differences were not statistically significant (Tables 1 and 2, Fig. 2). In a similar way, the prevalence of patients with Rankin score lower than 2 points was superior but not significant in the groups having hyperuricemia (being this prevalence lower as FBG was higher, Fig. 2).

Finally, no significant differences were found regarding in-hospital mortality (p = 0.6, Table 2).

## Discussion and conclusions

The patients of our cohort showed a worsening in their prognosis (neurological and functional damage) in those groups with higher levels of FBG; however, statistical significance was not reached. These groups had more patients with a history of either hypertension, dyslipidemia, or T2DM, and higher comorbidity what could influence on their prognosis apart from the

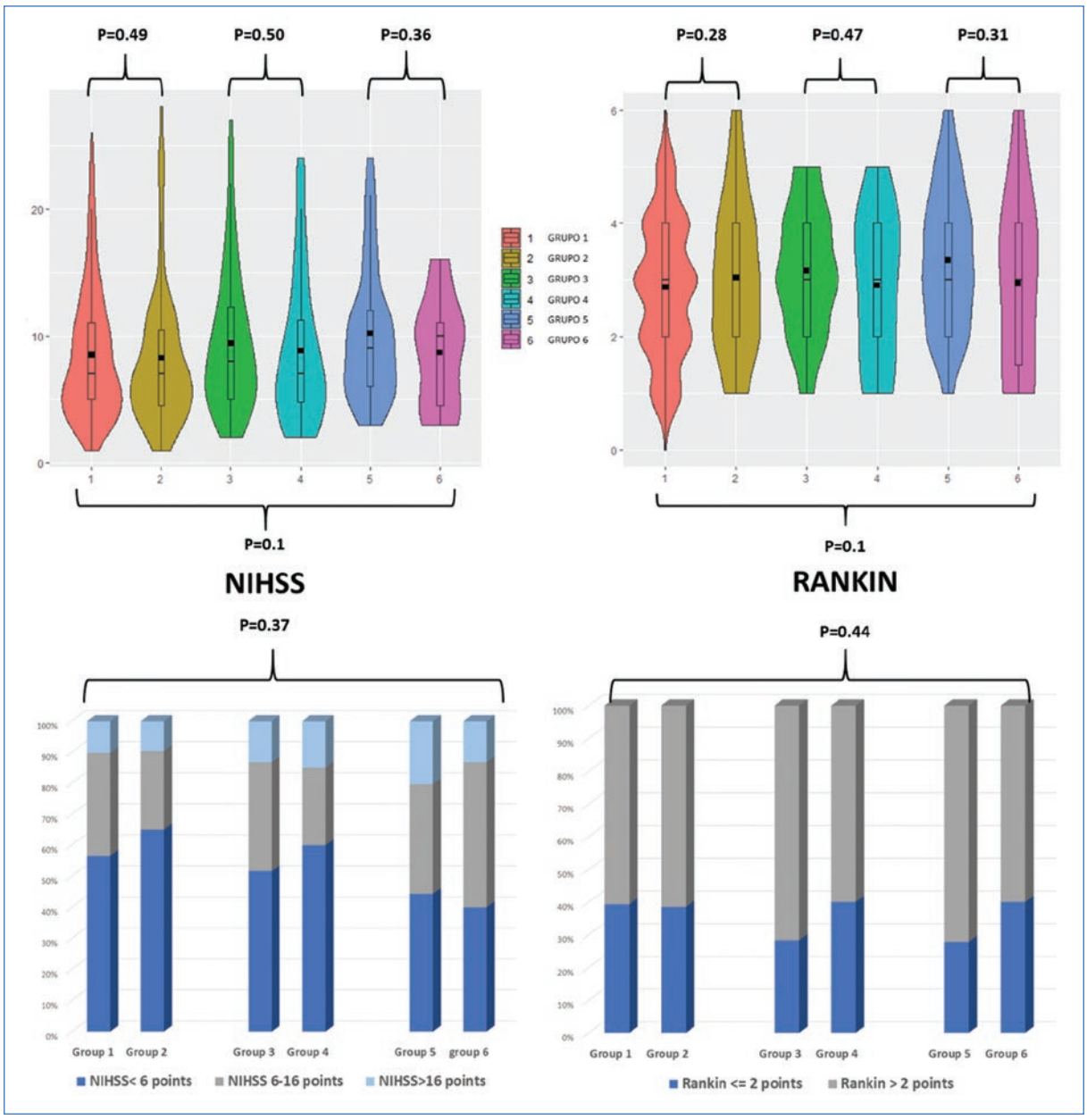
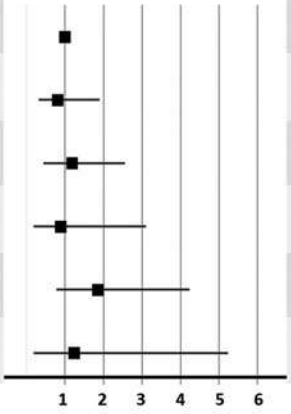



**Figure 2.** Results in neurological (NIHSS score) and functional (Rankin score) outcomes. On the top: comparisons of the pre-specified groups according to their distribution of both NIHSS and Rankin scores. On the bottom: percentage of patients by pre-specified groups according to the established cut-off points for both NIHSS and Rankin scores.

effects of hyperglycemia. In a similar way, the patients with hyperuricemia also had a higher rate of hypertension, dyslipidemia, T2DM, and comorbidities. However, in this setting, their neurological and functional outcomes did hardly differ from the patients without hyperuricemia.

Hyperglycemia has been related to higher mortality and morbidity after acute stroke independently of other adverse prognostic factors[3]. Several explanations may account for this observed association. These patients could undergo more ischemic damage at the time of infarction as a result of wider underlying cerebral vasculopathy associated with T2DM and hypertension. In this regard, hyperglycemia is a well-known determinant of the broad transformations in both small cerebral blood vessels and large extracranial vessels seen in diabetic patients[16]. Hyperglycemia may also disorganize the blood-brain barrier[17] and contribute to hemorrhagic infarct conversion[18]. However, above all, hyperglycemia has been shown to increase inflammation and oxidative

| Group | OR | 95%CI | NIHSS>= 16 points | P |
|---|---|---|---|---|
| Group 1 | Reference | Reference | | - |
| Group 2 | 0.81 | 0.32-1.9 | | 0.64 |
| Group 3 | 1.19 | 0.44-2.55 | | 0.81 |
| Group 4 | 0.89 | 0.19-3.1 | | 0.87 |
| Group 5 | 1.86 | 0.78-4.23 | | 0.14 |
| Group 6 | 1.24 | 0.18-5.23 | | 0.78 |




| Group | OR | 95%CI | Rankin < 2 points | P |
|---|---|---|---|---|
| Group 1 | Reference | Reference | | - |
| Group 2 | 1.11 | 0.64-1.94 | | 0.69 |
| Group 3 | 0.72 | 0.37-1.37 | | 0.33 |
| Group 4 | 1.84 | 0.66-4.95 | | 0.22 |
| Group 5 | 0.75 | 0.36-1.51 | | 0.44 |
| Group 6 | 1.18 | 0.36-3.58 | | 0.77 |

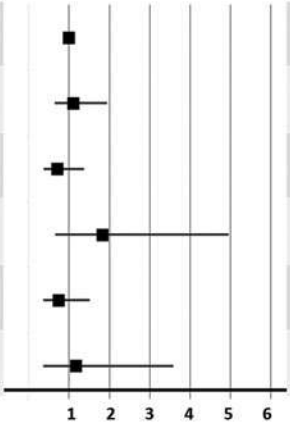



**Figure 3.** Logistic regression by pre-specified groups, regarding NIHSS and Rankin established outcomes.

stress[19]. In fact, increased oxidative stress is claimed to be triggered directly by acute (sudden-onset) hyperglycemia[20]. On the contrary, high levels of SUA have been related to a better functional outcome in patients with acute ischemic stroke[5], and this effect has been associated with its ability to scavenge oxygen radicals and protect the membranes from lipid peroxidation[21].

In spite of the fact that our results were not statistically significant, there was a clear tendency to have a worse prognosis in the case of patients having hyperglycemia (groups 3 to 6) that ameliorated when simultaneously these patients also had hyperuricemia (groups 4 and 6). In the URICO-ICTUS, a randomized clinical trial that compared the administration of uric acid versus placebo in stroke patients treated with alteplase within 4.5 h of onset, the addition of uric acid to thrombolytic therapy did not increase the proportion of patients who achieved good outcome after stroke compared with placebo[22]. However, in a post hoc analysis, uric acid was associated with reduced infarct growth and improved outcome in patients with hyperglycemia during acute stroke[23]. Unlike to this study, uric acid levels in our patients could have been elevated for a longer time before the stroke and, therefore, could also be affected by its deleterious effects related to impair endothelium-mediated relaxation and vascular stiffness[24]. This aspect could explain, on the one hand, the lack of significance on the outcomes in the groups 4 and 6 of our cohort, and on the other hand, the higher prevalence in these groups of either hypertension or T2DM.

Our study has several limitations. First, its data come from a registry, so the sample lacks randomization, and only patients with SUA data and without treatment for hyperuricemia were included, which might cause

selection bias. In addition, other variables not registered could influence on the results. Second, the sample size in the case of groups 4 and 6 might not be sufficiently large to detect a more robust difference between the groups. Finally, thrombolytic treatment was not performed in any case which may result in changes on the prognosis of the patients

In conclusion, in the setting of an acute ischemic stroke with hyperglycemia, we found a non-significant tendency between SUA and lower clinical neurological damage. This potential protective role must be confirmed by further studies with larger samples and prospective follow-up.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

# Prognostic capacity of deformability analysis through speckle tracking by echocardiography in heart failure

*Miguel Martínez-Marín[1]*, Isaac Lacambra-Blasco[2], Ignacio Giménez-López[3], Daniel Grados-Saso[4], Juan M. Salvador-Casabona[2], and Juan I. Pérez-Calvo[3,5]*

*[1]Department of Cardiology, Hospital General de la Defensa en Zaragoza, Zaragoza; [2]Department of Cardiology, Hospital Clínico Universitario "Lozano Blesa," Zaragoza; [3]School of Medicine, Universidad de Zaragoza, Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza; [4]Department of Cardiology, Hospital de Barbastro, Barbastro, Huesca; [5]Department of Internal Medicine, Hospital Clínico Universitario "Lozano Blesa," Zaragoza. Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Zaragoza, Spain*

## Abstract

**Introduction and Objectives:** Bidimensional speckle tracking (ST-2D) enables the quantitative assessment of the left ventricle deformation. This study was aimed to assess discriminative and prognostic value of the left ventricle myocardial deformation analysis (MDA) in patients with heart failure (HF) irrespective ejection fraction. **Methods:** Patients were included during admission for decompensated HF. After clinical stabilization, MDA by 2D-echocardiography was performed. Patients were followed up for 180 days. Differences in MDA profiles were compared between reduced (HF with reduced EF [HFrEF]) and preserved (HF with preserved EF [HFpEF]) EF. An additional prospective follow-up cohort analysis to assess prognostic value of MDA was carried out. End point was a composite of death, non-scheduled emergency visits, and readmissions. **Results:** We included 101 patients, 57 (56.4%) with EF > 50%. Fourteen patients (13.9%) died during follow-up; 31 were readmitted (30.7%); and 17 (16.7%) had unscheduled emergency visits. Global systolic circumferential strain rate (SR) had the highest prognostic value. There was an association between a SR below the median (–1.56 cm/s) and unfavorable development (odds ratio [OR] 2.31, confidence interval at 95% [CI 95%] 1.34-3.96, p = 0.002). In patients with HFrEF, an NT-proBNP above the median and SR below the median the OR for events during follow-up were 2.85 (CI 95% 1.15-9.25, p = 0.042), while in HFpEF were 1,778 (CI 95% 1.13-3.65, p = 0.022). **Conclusions:** In patients with HF, MDA, especially global circumferential SR, is predictive of adverse events during follow-up and combined with NT-proBNP improves risk stratification irrespective of EF phenotype. Furthermore, MDA can be useful for refining classification of patients with HF and intermediate EF range.

**Key words:** Heart failure. Bidimensional speckle tracking. Myocardial deformation analysis. Heart failure prognosis.

## Introduction and objectives

Heart failure (HF) is one of the leading health problems in Western countries. Due to its incidence, prevalence, and morbimortality, it has been considered one of the 21st century epidemics worldwide[1-3].

During cardiac cycle, myocardial fibers change repeatedly their shape and size. These deformations occur in several different directions, namely, longitudinal (from basis to apex), circumferential, and radial. Simultaneously, the heart exerts a twisting shift[4]. Each of these components can be addressed separately.

Visual abstract available at https://spanishjmed.com/frame_esp.php?id=44

**Correspondence:**
*Miguel Martínez-Marín
E-mail: miguelmartinezmarin@hotmail.com

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Cardiac magnetic resonance imaging is the best technique to study myocardial deformation, but 2D-echocardiography (2D-echo) has been used with good results to assess MD analysis (MDA) in normal and abnormal myocardial segments[5]. Through 2D-echo, the degree of deformation quantified as the percentage of change in fibers size (strain) and speed of the change (strain rate [SR]) can be measured in all three main directions (longitudinal, radial, and circumferential)[6,7].

In the previous studies in HF, longitudinal strain of the left ventricle has been found to correlate closely with natriuretic peptides concentrations, irrespective of ejection fraction (EF)[7]. In HF with preserved EF (HFpEF), longitudinal and radial strains are both reduced, while circumferential component stands normal. On the other hand, in patients with HF with reduced EF (HFrEF), all strains, longitudinal, radial, and circumferential, are diminished[8]. It has also been shown that the impairment of longitudinal strain in acute HF has superior prognostic value than EF[9].

The aims of our study were (i) to assess patterns of ventricular deformity according EF phenotype and (ii) prognostic value of the left ventricle MDA in patients with HF with reduced and preserved EF and (iii) whether the combination of MDA with natriuretic peptides improves risk stratification.

## Methods

We prospectively and consecutively included 101 patients admitted for an acute decompensation of HF. Diagnosis of HF was done according to the criteria of the European Society of Cardiology[10]. In addition, a concentration of the aminoterminal fragment of the pro-brain natriuretic peptide (NT-proBNP) adjusted for age[11], measured at admission, was required for inclusion. Patients with recent acute coronary syndrome, significant valvular disease, electronic stimulation devices, constrictive pericarditis, congenital heart diseases, autoimmune, neoplastic diseases, or organ transplant were excluded from the study.

After discharge, patients were followed up for 180 days. End point was a composite of death, non-scheduled emergency ward visits, and readmissions.

The study protocol agrees with the principles of Helsinki Declaration for human experimentation, and it was reviewed and approved by the local ethics committee (Comité de Ética en la Investigación Clínica de Aragón; code number PI13/0142). All patients gave their written and informed consent.

### 2D echocardiographic study

An echocardiograph Acuson SC2000 (Siemens®) with a 4V1c multifrequency probe at 1.25-4.5 MHz was used. The protocol included 2D imaging analysis, M mode, and tissue Doppler imaging. The assessment of myocardial deformation was performed with the software VVI Syngo US WorkStation (Siemens® Medical Solutions). For MDA, clips of 60-100 frames/s were used, obtained from 4, 3, and 2 chambers in apical view and parasternal short axis at papillary muscles level.

All of the parameters for three dimensions of myocardial deformation were assessed (longitudinal, circumferential, and radial planes).

For assessing systolic and diastolic function and structural parameters, we followed recommendations of the European Society of Cardiac Imaging[12].

Echocardiography and MDA were performed soon before discharge with patients in stable condition. The cutoff value of EF for classification into preserved or reduced HF was 50%.

### Laboratory analysis

Blood samples were drawn by peripheral venous puncture and collected into tubes without anticoagulant. NT-proBNP was measured at admission and the day before discharge (Elecsys® proBNP, Roche Diagnostics).

### Statistical analysis

Quantitative variables are shown as mean or median and standard deviation (SD). Dichotomic variables are displayed as absolute or relative frequency.

For contrast analysis, we used Student's t-test and for categorical variables, we performed the Chi-square test.

For survival analysis, that is, the time to the first event, during follow-up, we used survival Kaplan–Meier curves.

The association of prognostic variables with events was calculated by a logistic regression model. The odds ratio (OR) was used as the measure for that association. Calibration of the model was assessed trough Hosmer–Lemeshow analysis.

Sample size estimation was done according to the expected proportion of HFpEF and HFrEF in hospitalized patients for HF[13,14], the rate of events[15], and the frequency of abnormalities in MDA, according to some published results[16]. Software EPIDAT 3.1 (OPS/OMS)

was used for that purpose. Sample size was estimated between 63 and 114 patients for a prevalence of HFpEF between 24 and 55%.

For statistics, we used IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

## Results

We included 101 patients, 55 (54.5%) men and 46 (45.6%) women. Forty-four (43.5%) patients had HFrEF (27 [61.3%] men vs. 17 [38.7%] women) and 57 (56.4%) HFpEF (24 [42.1%] men vs. 33 [57.9%] women).

Baseline clinical and biochemical characteristics and therapy are shown in table 1, and echocardiographic parameters in table 2.

### *Myocardial deformation analysis (MDA)*

As expected, MDA showed significant differences in all dimensions according to EF phenotypes (Table 3).

Global longitudinal strain had the best area under the curve (AUC) of receiver operation curve (ROC) 0.804 (IC 95% 0.675-0.933; p < 0.05) for differentiating HFrEF from HFpEF. For systolic circumferential SR, the AUC was 0.811 (IC 95% 0.687-0.935; p<0.05) (Figure 1).

### *End points during follow-up*

Fourteen patients died (13.9%); 18.8% among HFrEF versus 5.2% in HFpEF (p = 0.02). Mortality was due to cardiac causes in 10 (74.1%) patients, all of them due to pump failure. Non-cardiac death causes (4 patients [25.9%]) were due to infections (3 patients) and digestive hemorrhage (1 patient).

Thirty-one patients (30.7%) were readmitted during follow-up, mostly due to HF, leading to 40 episodes (23 patients had one admission; seven had two; and one was readmitted 3 times). Only four patients were admitted for reasons different form HF (one hip fracture; one digitalis intoxication; one complete atrioventricular blockade; and one for renal insufficiency). Seventeen (16.7%) patients had non-scheduled visits to emergency ward, leading to 21 episodes (four patients went 2 times each). Most of the visits (47.6%) were related with HF. There were not significant differences neither in readmissions (23.2% vs. 21-5; p = 0.58) nor in emergency visits (20.5% vs. 14%; p 0.3) between HFrEF and HFpEF, respectively.

### *Association of MDA and end points during follow-up*

The composite end point (all-cause death, non-scheduled visits to emergency ward, and readmissions) happened in 48 patients (47.5%) over the 180 days follow-up after discharge.

Systolic circumferential SR had the greatest association with events. In the entire cohort, a decrease below the median of this parameter had an OR of 2.31 (CI 95% 1.34-3.96; p = 0.002). Among patients with HFrEF, the OR was even higher (OR 2.51 [IC 95% 1.15-9.2]; p = 0.047) than in HFpEF (OR 1.54 [IC 95 % 1.07-2.8]; p = 0.04), although in both phenotypes, the increase in OR was significant. Neither longitudinal nor radial systolic SR (Table 3) was associated with an impairment in prognosis in the entire cohort or according to LVEF phenotypes.

### *NT-proBNP and events during follow-up*

An increase in NT-proBNP concentration, measured before discharge, above the median was associated with a higher event rate, in the entire cohort and in both HF phenotypes. In the cohort as a whole, an NT-proBNP > 3197 pg/mL had an OR of 1.17 (CI 95% 1.04-1.32; p = 0.009). OR rose 1 unit per each increase of 1000 pg/mL in NT-proBNP levels. In patients with HFrEF, a NT-proBNP increase of > 4315 pg/mL associated with an OR of 1.25 (CI 95% 1.01-1.58; p = 0.003), whereas in HFpEF patients, an increase of NT-proBNP > 2394 pg/mL associated with an OR of 1.07 (CI 95% 1.05-1.26; p = 0.045).

### *Combination of NT-proBNP, MDA, and end points*

We analyzed the prognostic performance of systolic circumferential SR combined with NT-proBNP concentrations. In patients with HFrEF, the combination of a reduction of global circumferential SR with an increased NT-proBNP was associated with a higher event rate during follow-up (OR 2.81 [CI 95% 1.15-9.25]; p = 0.042). In patients with HFpEF, there was also a significant association (OR 1.77 [CI 95% 1.1-3.65]; p = 0.022). Survival curves calculated for different composite NT-proBNP and global circumferential SR levels are shown in figure 2.

## Discussion

Ejection fraction is not a fully reliable measure of systolic function, since this latter can be deeply impaired in

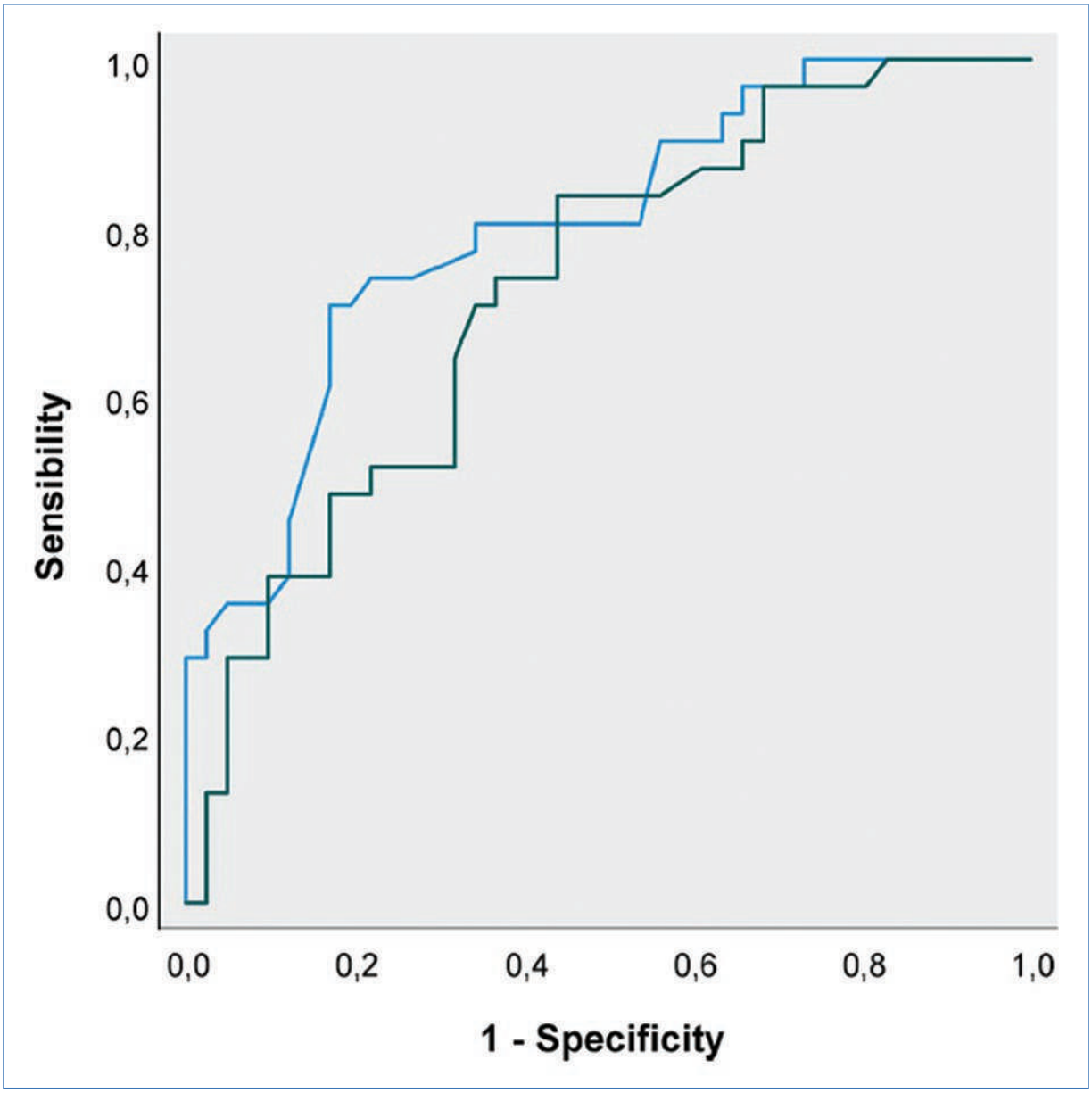


**Figure 1.** Discriminative capacity of myocardial deformation analysis between ejection fraction phenotypes. Area under the curve (AUC) of receiver operation curve (ROC). Green line: global longitudinal strain rate (AUC 0.804 [IC 95% 0.675-0.933]; $p < 0.05$). Blue line: systolic circumferential strain rate (AUC 0.811 [IC 95% 0.687-0.935]; $p < 0.05$).

cases with EF remaining normal[17]. Nonetheless, EF is currently used to categorize HF for its convenience and feasibility. Despite of that, cutoff points for defining reduced versus preserved HF remain arbitrary. In fact, cutoff points to separate both phenotypes[18] are highly variable between studies, ranging from 40 to 50%. This variability likely reflects the heterogeneity of HF physiopathology[19].

In our study, the concept of HF with intermediate ejection fraction intermediate was not used because the latest reports indicate that these patients share characteristics between HFrEF and HfrEF. Mortality or rehospitalizations are similar among the three groups[20].

Our results show that all dimensions of MDA, circumferential, radial, and longitudinal, are significantly different between HFrEF and HFpEF, as expected. Both, strain and SR, are reduced in systole and diastole in patients with HFrEF. Even though simplicity of EF measurement precludes the systematic use of MDA in the clinical setting, its good discriminative value can be useful for refining characterization of patients with HF[21,22].

**Table 1.** Baseline characteristics of the cohort and according to ejection fraction

| | Entire cohort (n = 101) | HFpEF (n = 57) | HFrEF (n = 44) | p value |
|---|---|---|---|---|
| Age (years) | 77.8 (9.3) | 80 (10.2) | 74.9 (8.1) | 0.02 |
| BMI (kg/m$^2$) | 29 (4.4) | 28.9 (4.3) | 29 (4.5) | 0.87 |
| SBP (mmHg) | 142 (32) | 147 (30) | 135 (33) | 0.075 |
| HR (bpm) | 85 (19) | 87 (21) | 83 (18) | 0.31 |
| NYHA* | | | | |
| I | 13.00% | 15.80% | 9.30% | 0.16 |
| II | 49.00% | 47.40% | 51.20% | 0.16 |
| III | 30.00% | 24.60% | 37.20% | 0.16 |
| IV | 8.00% | 12.30% | 2.30% | 0.16 |
| Comorbidities | | | | |
| Diabetes mellitus | 40 (39.60%) | 17 (29.8%) | 23 (52.3%) | 0.02 |
| Arterial hypertension | 86 (85.10%) | 50 (87.7%) | 36 (81.8%) | 0.41 |
| Obesity | 39 (38.6%) | 22 (38.6%) | 17 (38.6%) | 0.99 |
| IHD | 45 (44.6%) | 16 (28.1%) | 29 (65.9%) | < 0.001 |
| Previous admission for HF | 19 (18.8%) | 11 (19.3%) | 8 (18.2%) | 0.89 |
| CKD | 18 (17.8%) | 7 (12.3%) | 11 (25%) | 0.1 |
| Atrial fibrillation | 65 (64.4%) | 39 (68.4%) | 26 (59.1%) | 0.33 |
| COPD | 16 (15.8%) | 6 (10.5%) | 10 (22.7%) | 0.1 |
| Laboratory | | | | |
| Blood urea (mg/dL) | 0.57 (0.26) | 0.57 (0.28) | 0.58 (0.22) | 0.86 |
| Creatinine (mg/dL) | 1.17 (0.37) | 1.12 (0.38) | 1.22 (0.35) | 0.21 |
| eGFR (MDRD-4) (mL/min/1.73 m$^2$) | 60.82 (29.91) | 66.81 (33.27) | 53.05 (23.01) | 0.02 |
| Sodium (mEq/L) | 141.6 (3.3) | 141.6 (3.3) | 141.6 (3.3) | 0.98 |
| Potassium (mEq/L) | 4.03 (0.6) | 4.06 (0.67) | 4 (0.51) | 0.6 |
| Uric acid (mg/dL) | 8 (2.3) | 7.8 (2.2) | 8.2 (2.4) | 0.19 |
| Hemoglobin (g/dL) | 13.5 (2.3) | 12.1 (2.2) | 15.3 (4.4) | 0.25 |
| Admission NT-proBNP | 5182 (692) | 3396.3 (330.9) | 7495.3 (936.3) | 0.008 |
| Pre-discharge NT-proBNP | 3358.7 (424.9) | 2398.6 (240.3) | 4784 (578.6) | 0.03 |
| Treatment | | | | |
| Beta-blockers | 49 (48.5%) | 24 (42.1%) | 25 (56.8%) | 0.14 |
| ACE inhibitors | 42 (41.6%) | 20 (35.1%) | 22 (50%) | 0.13 |
| ARB | 34 (33.7%) | 20 (35.1%) | 14 (31.8%) | 0.73 |
| Loop diuretics | 77 (76.2%) | 40 (70.2%) | 37 (84.1%) | 0.10 |
| Thiazides | 14 (13.9%) | 7 (12,3%) | 7 (15.9%) | 0.60 |
| MRA | 30 (29.7%) | 13 (22.8%) | 17 (38.6%) | 0.08 |
| Calcium channel blockers | 23 (22.8%) | 16 (28.1%) | 7 (15.9%) | 1.15 |
| Ivabradine | 7 (6.9%) | 1 (1.8%) | 6 (13.6%) | 0.02 |
| Nitrates | 26 (25.7%) | 14 (24.6%) | 12 (27.3%) | 0.76 |
| Anticoagulants | 62 (61.4%) | 37 (64.9%) | 25 (56.8%) | 0.41 |
| Antiaggregants | 37 (36.6%) | 16 (28.1%) | 21 (47.7%) | 0.04 |

Values are expressed as units and standard deviation (SD).
*Refers to functional class previous to admission, in stable condition.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; IHD: ischemic heart disease; MDRD: modification diet in renal disease (formula); MRA: mineral corticoid receptor blockers; NYHA: New York Heart Association; NT-proBNP: aminoterminal fragment of the pro-brain natriuretic peptide; SBP: systolic blood pressure.

According to our results, MDA might be useful for prognostic stratification in HF. An impairment of global circumferential SR was strongly associated with unfavorable outcome, even at such a short time as 180 days. Global circumferential SR has a stronger prognostic capacity than the global longitudinal SR, whose results have been demonstrated in previous reports[23].

The decrease of deformation speed in this dimension was associated with poorer prognosis irrespective of EF phenotype. However, the increase of risk in HFrEF patients almost doubled that in HFpEF patients. Nonetheless, in our experience, only global circumferential SR added significant prognostic information, regardless LVEF. Circumferential and radial SR showed a neutral value concerning outcomes.

**Table 2.** Echocardiographic characteristics of the cohort and according to ejection fraction

| | Entire cohort (n = 101) | HFpEF (n = 57) | HFrEF (n = 44) | p value |
|---|---|---|---|---|
| EF | 45 (10) | 57 (6.2) | 34.8 (7.5) | < 0.001 |
| LVEDD (mm) | 57.1 (9.5) | 51.9 (6.5) | 64 (8.3) | < 0.001 |
| LVESD (mm) | 40.7 (11.4) | 33.3 (6.6) | 50.5 (8.6) | < 0.001 |
| LVEDV (mL) | 137.2 (58.3) | 99.8 (26.3) | 163.9 (60.5) | < 0.001 |
| LVESV (mL) | 82.7 (51.5) | 43.5 (16.9) | 110.8 (49.5) | < 0.001 |
| Interventricular septal thickness (mm) | 10.1 (1.8) | 10.3 (2) | 9.9 (1.5) | 0.29 |
| Posterior wall thickness (mm) | 10.1 (1.8) | 10.1 (2.1) | 10 (1.4) | 0.8 |
| LVMI ($g/m^2$) | 113 (32) | 104 (27) | 125 (34) | 0.001 |
| LA diameter (mm) | 48 (8) | 47 (8) | 50 (9) | 0.12 |
| LA indexed volume ($mL/m^2$) | 57.4 (24.7) | 55.3 (19.8) | 60 (29.7) | 0.44 |
| E wave (m/s) | 1.01 (0.34) | 1.08 (0.37) | 0.93 (0.28) | 0.029 |
| A wave (m/s) | 0.7 (0.34) | 0.75 (0.39) | 0.64 (0.29) | 0.29 |
| E/A ratio | 1.74 (1.16) | 1.61 (0.95) | 1.88 (1.37) | 0.45 |
| E/e × ratio | 14.45 (6.89) | 14.16 (7.17) | 14.9 (6.53) | 0.66 |
| TAPSE (mm) | 17 (4) | 18 (3) | 16 (4) | 0.06 |
| PASP (mmHg) | 49 (17) | 51 (17) | 46 (17) | 0.16 |
| Inferior vena cava diameter (mm) | 19 (5) | 18 (5) | 21 (5) | 0.04 |

Values are expressed as units and standard deviation (SD).
EF: ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LA: left atria; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; LVESD: left ventricle end-systolic diameter; LVESV: left ventricle end-systolic volume; LVMI: left ventricle mass index; PASP: pulmonary arterial systolic pressure; TAPSE: tricuspid annular plane systolic excursion.

**Table 3.** Left ventricular myocardial deformation analysis

| | Entire cohort (n = 101) | HFpEF (n = 57) | HFrEF (n = 44) | p value |
|---|---|---|---|---|
| Global longitudinal strain | –11.32 (4.64) | –13.34 (4.52) | –8.71 (3.35) | < 0.001 |
| Global longitudinal systolic SR | –1.36 (0.96) | –1.53 (0.53) | –1.15 (1.3) | 0.047 |
| Global longitudinal early diastolic SR | 1.27 (0.74) | 1.5 (0.84) | 0.97 (0.42) | < 0.001 |
| Global longitudinal late diastolic SR | 0.8 (0.52) | 0.96 (0.61) | 0.6 (0.3) | 0.01 |
| Global circumferential strain | –13 (7.04) | –15.48 (7.7) | –9.8 (4.4) | < 0.001 |
| Global circumferential systolic SR | –1.56 (0.9) | –1.96 (0.85) | –1.05 (0.7) | < 0.001 |
| Global circumferential early diastolic SR | 1.64 (1.1) | 2.12 (1.19) | 1.02 (0.5) | <0.001 |
| Global circumferential late diastolic SR | 0.87 (0.57) | 1.09 (0.65) | 0.61 (0.33) | 0.002 |
| Global radial strain | 18.7 (8.32) | 21.08 (8.5) | 15.62 (7.04) | 0.001 |
| Global radial systolic SR | 2.48 (1.75) | 2.87 (2.01) | 1.96 (1.2) | 0.006 |
| Global radial early diastolic SR | –2.15 (1.78) | –2.56 (2.06) | –1.61 (1.13) | 0.007 |
| Global radial late diastolic SR | –1.08 (1.94) | –1.15 (2.49) | –0.99 (1.02) | 0.76 |

Values are expressed as mean and standard deviation (SD).
HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; SR: strain rate.

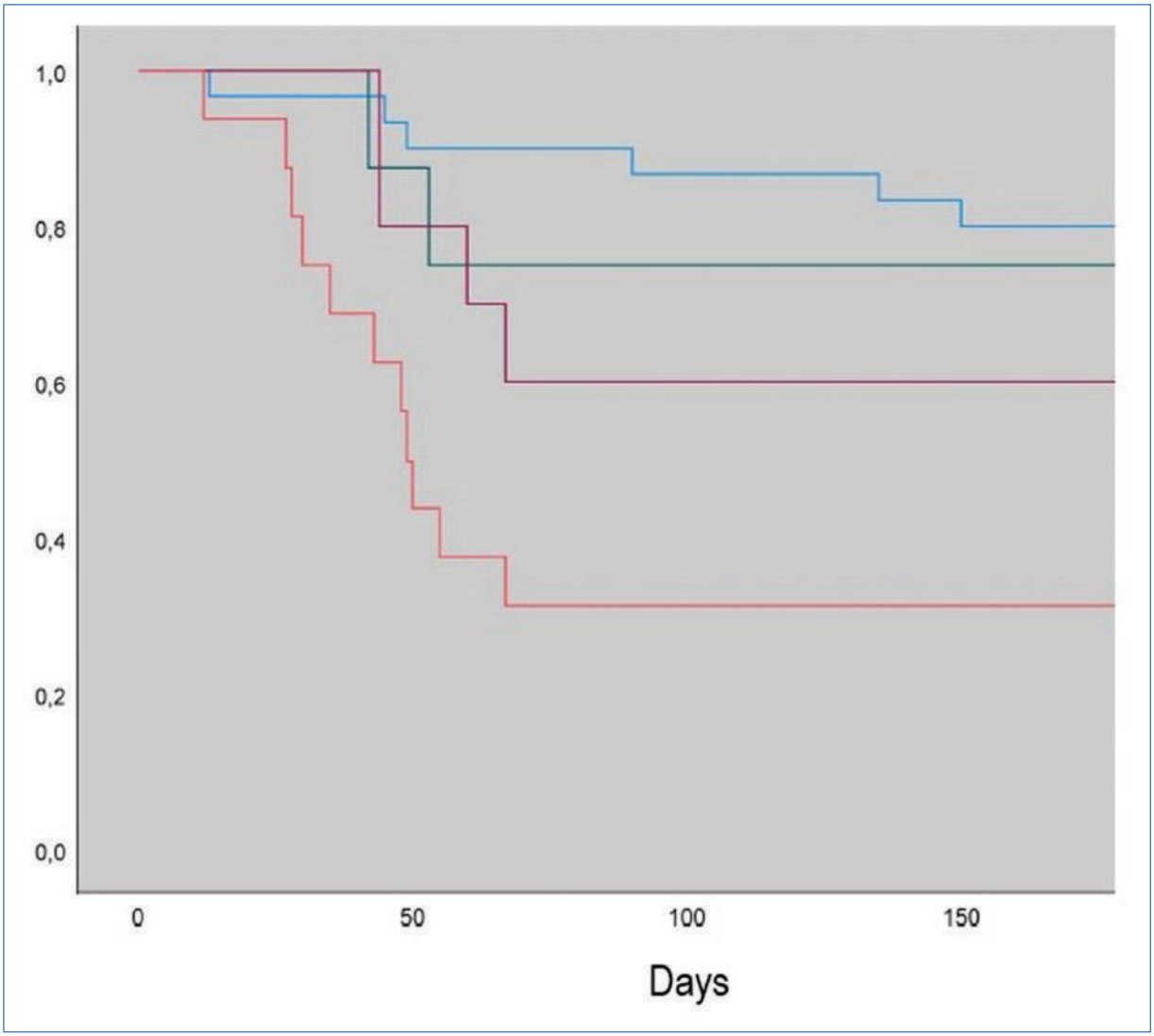


**Figure 2.** Kaplan–Meier survival curves according to NT-proBNP and global circumferential systolic strain rate. Group 1: NT-proBNP below median and systolic circumferential SR above the median. Group 2: NT-proBNP above median and systolic circumferential SR above the median. Group 3: NT-proBNP below median and systolic circumferential SR below the median. Group 4: NT-proBNP above median and systolic circumferential SR below the median. NT-proBNP: aminoterminal fragment of the pro-brain natriuretic peptide; SR: strain rate.

Systolic function of the left ventricle depends on the coordinated contraction of longitudinal, radial, and circumferential fibers. During systole, the main components of myocardial deformation are a shortening of longitudinal fibers along with their radial widening[24]. During systole, deformation of the left ventricle in the three planes reduces its volume. Volumetric techniques – estimation of the left ventricle ejection fraction, assess the global function of myocardial fibers in all three planes at the same time. The information provided is insensitive to the potential isolated impairment of each of these individual components, thus missing subtle deficiencies in systolic function. Accordingly, the fact that patients with HFpEF have an EF > 50% does not mean that their systolic function is entirely normal[17].

It has been previously shown that patients with HFpEF have an impairment in systolic longitudinal and circumferential deformation as compared to healthy controls and patients with hypertensive myocardiopathy[25]. In this study, Kraigher-Krainer et al.[25] showed that patients with HFpEF had a reduction in longitudinal deformation together with an increase in circumferential deformation in comparison to those with hypertensive cardiomyopathy. This phenomenon may happen as a

compensatory reaction to preserve systolic function in HFpEF[26]. It is plausible that early systolic dysfunction initiates with a reduction in longitudinal deformation, compensated by the simultaneous increase in circumferential deformation, to keep left ventricle systolic volume. Consistent with this interpretation, in our study, the impairment in global circumferential SR was the stronger prognostic predictor, associated with higher event rate in follow-up. Global circumferential SR has a stronger prognostic capacity than the global longitudinal SR, whose results have been demonstrated in previous reports[23].

It is tempting to speculate that the impairment of this early compensatory mechanism increases 2-fold the rate of unfavorable events in patients where longitudinal deformation is already decreased, compared to patients able to maintain longitudinal deformation. The impairment of the compensatory mechanism and its association with poorer outcomes in both HFrEF and HFpEF agrees with the interpretation by Borlaug et al.[17] that the limitations of systolic function in HFpEF are an important factor leading to the clinical expression of the HF syndrome.

In our cohort, prognostic information yielded by combined analysis of MDA and NT-proBNP improves risk stratification in both HF phenotypes. The group of patients with a decrease of global circumferential SR and an increase in NT-proBNP levels had the worst prognosis. Within those, in the HFrEF subgroup, the rate of events was 3-fold higher than that of patients with preserved longitudinal deformation and NT-proBNP below the median. In the HFpEF subgroup, the risk of events was almost double and significant as well. This probably reflects the impact of the left ventricle stress as captured by different methods, natriuretic peptide, and MDA, in prognosis. Given the feasibility of both measurements in clinical practice, it is inviting to use both to better stratify patients with HF irrespective of their phenotype.

### *Limitations*

Our study has been carried out in a single center. The sample size is small, although it had been estimated to be enough to give significant results. Existing differences in MDA between workstations and algorithms[27,28] can have a negative impact on the results. However, to minimize them, we used the same software and study protocol in all patients.

## Conclusions

Global circumferential SR is predictive of unfavorable events in patients with HF. When combined with NT-proBNP, MDA improves risk stratification, irrespective of EF.

## Disclosures

Authors declare no conflicts of interest.

## Key points

### *What is known about the topic?*

Myocardial fibers change repeatedly their shape and size during cardiac cycle. These changes occur in different directions, longitudinal (from basis to apex), circumferential, and radial, and simultaneously, the heart exerts a twisting shift. Each of these components can be addressed separately. 2D echocardiography (2D echo) yields good performance to assess deformation analysis in normal myocardium. In addition, the degree of deformation can be quantified as the percentage of change in fibers size (strain) and speed of the change (SR) in all three main directions (longitudinal, radial, and circumferential). Deformation analysis has been shown a good correlation with natriuretic peptides concentrations, irrespective of ejection fraction (EF). The impairment of longitudinal strain in acute HF has superior prognostic value than EF.

### *What does this study add?*

In patients with HF, MDA, especially global circumferential SR, is predictive of adverse events during follow-up, and combined with NT-proBNP improves risk stratification irrespective of ejection fraction. Deformation analysis can also be useful for refining classification of patients with HF and further characterize intermediate ejection fraction range.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

The study was approved by the local ethics committee: (Comité de Ética en la Investigación Clínica de Aragón; code number PI13/0142).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

# Non-criteria manifestations of antiphospholipid syndrome: An overview

*Gilberto Pires-da-Rosa, Gerard Espinosa, and Ricard Cervera**

*Department of Autoimmune Diseases, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universidad de Barcelona, Barcelona, Spain*

## Abstract

While the classification criteria for definite antiphospholipid syndrome (APS) include specific thrombotic and obstetric manifestation, there are numerous clinical features also present in patients with antiphospholipid antibodies (aPL), which are not included in the classification criteria. The term "non-criteria" is currently used to refer to these manifestations. This review intends to provide a summarized, but far-reaching description, of the non-criteria manifestations present in the literature, with special focus on their association with APS and potential impact on the disease course. We analyze the following involvements: cardiac (cardiac microvascular disease and valvular heart disease), dermatological (*livedo reticularis*/*racemosa,* livedoid vasculopathy and skin ulcers), ear, nose, and throat (sensorineural hearing loss), endocrinological (adrenal insufficiency due to hemorrhagic infarction), hematological (hemolytic anemia and thrombocytopenia), musculoskeletal (ischemic bone necrosis), neurological (acute ischemic encephalopathy, chorea, cognitive dysfunction, epilepsy/seizures, migraine, and transverse myelitis), pulmonary (diffuse alveolar hemorrhage and pulmonary hypertension), ophthalmologic (*amaurosis fugax*), renal (APS nephropathy), vascular (superficial vein thrombosis), and obstetric (infertility, *in vitro* fertilization failure, and placenta-mediated complications) manifestations. Although gaining relevance in the current practice, the exact level of association of the different non-criteria manifestations with APS/aPL is still unclear or scarcely characterized in most cases.

**Key words:** Antiphospholipid syndrome. Antiphospholipid antibodies. Non-criteria manifestations.

## Introduction

The 2006 classification criteria for definite antiphospholipid syndrome (APS) include specific manifestations – either thrombotic (arterial, venous, or small-vessel) or obstetric[1]. However, there are several additional manifestations that are also present in patients with antiphospholipid antibodies (aPL), but not included in the classification criteria. The term "non-criteria" manifestations has been gradually and informally adopted throughout the literature to refer to these clinical features, and a rising number of publications discuss their relevance[2,3]. The 2014 report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* suggested the inclusion of some manifestations as part of APS criteria revision[2]. In the initiative for *Development of New International APS Classification Criteria*, currently underway, many of these non-criteria manifestation are analyzed as candidate criteria[4]. A recent article approaches the treatment of some of these manifestations, namely

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**Correspondence:**
*Ricard Cervera
E-mail: rcervera@clinic.cat

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cardiac, pulmonary, hematologic, cutaneous, and neurological involvements[5].

In this review, we intend to cover, in a summarized but far-reaching manner, the existing "non-criteria" manifestations described in the literature (Table 1), focusing on the strength of their association with aPL and their potential impact on the disease course, and allowing for a general view of this subject.

## Cardiac manifestations

### *Cardiac microvascular disease*

There are case reports of APS patients with diffuse cardiomyopathy or evidence of myocardial ischemia with normal coronaries, indicating microvascular disease as a plausible mechanism[6,7]. Histology of these patients may reveal occlusive microthrombosis of small myocardial arterioles and areas of micro-infarction surrounding the affected arterioles, with consequential myocardial necrosis[6]. This situation occurs both in classic and catastrophic APS patients[8]. The absence of vasculitis changes in these patients supports the hypothesis that aPL exert a direct thrombotic effect[6,9]. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including cardiac microvascular disease) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

### *Valvular heart disease*

Valvular disease in APS occurs in the form of valve lesions (thickening or vegetations) and/or valve dysfunction in the absence of rheumatic fever or infective endocarditis[6]. Valve lesions are defined as (i) valve thickness > 3 mm; (ii) localized thickening involving the proximal or middle portion of the leaflets; or (iii) irregular nodules on the atrial face of the mitral valve and/or the vascular face of the aortic valve[2]. The reported frequency in primary APS ranges from 10% to more than 60%[10]. Histopathological findings may include fibrosis, calcification, vascular proliferation, verrucous thrombosis on endocardial valvular surfaces, and thrombosis of intravalvular capillaries[6]. Possible pathogenic mechanisms for these lesions in aPL patients include both thrombotic and inflammatory mechanisms, such as deposition of aPL and complement components or the deposition of fibrin platelet thrombi on the affected valve[10]. Although the role of aPL in heart lesions has not been categorically proven, most studies evaluated in two systematic reviews display an association between the presence of aPL and valvular lesions[11,12]. The risk of valvular heart disease was highest for lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) of the IgG isotype[12]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding valvular heart disease as of "moderate"

**Table 1.** Non-criteria manifestations of the antiphospholipid syndrome

| Affected organ/system | Non-criteria manifestation |
|---|---|
| Cardiac | Cardiac microvascular disease<br>Valvular heart disease |
| Dermatological | *Livedo reticularis/racemosa*<br>Livedoid vasculopathy<br>Skin ulcers<br>Splinter hemorrhages |
| Ear, nose, and throat | Sensorineural hearing loss |
| Endocrinological | Adrenal insufficiency due to hemorrhagic infarction |
| Hematological | Evans syndrome<br>Hemolytic anemia<br>Positive Coombs' test<br>Thrombocytopenia |
| Musculoskeletal | Ischemic bone necrosis |
| Neurological | Acute ischemic encephalopathy<br>Brain MRI white matter lesions<br>Chorea<br>Cognitive dysfunction<br>Epilepsy/seizures<br>Migraine<br>Pseudo-multiple sclerosis<br>Transverse myelitis |
| Pulmonary | Diffuse alveolar hemorrhage<br>Pulmonary hypertension |
| Ophthalmological | *Amaurosis fugax* |
| Renal | APS nephropathy |
| Vascular | Superficial vein thrombosis<br>Raynaud's phenomenon |
| Obstetric | Infertility<br>Late intrauterine growth restriction (after 34 weeks)<br>Late pre-eclampsia (after 34 weeks)<br>*Abruptio placentae*<br>Placental hematoma<br>Preterm birth (> 34-< 37 weeks)<br>Puerperal pre-eclampsia<br>Two or more unexplained IVF failures<br>Two unexplained spontaneous abortion < 10 weeks |

APS: antiphospholipid syndrome; IVF: *in vitro* fertilization; MRI: magnetic resonance imaging.

quality, issuing a "strong recommendation" for this manifestation to be included as part of the APS criteria revision[2]. In the *Phase III of the Development of New International Classification Criteria for APS*, heart valve disease occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Dermatological manifestations

### *Livedo reticularis/racemosa*

*Livedo* is the most frequent dermatologic manifestations of APS (observed in 24.1% of patients of the Euro-phospholipid cohort)[13,14], defined as a persisting violaceous, red, or blue reticular or mottled pattern of the skin, not reversible with rewarming[1]. It can consist of regular unbroken circles (*livedo reticularis*) or irregular-broken circles (*livedo racemosa*)[15]. Several associations have been reported with *livedo*, namely seizures, arterial events (and decreased venous events), cerebral or ocular vascular events, cognitive dysfunction, avascular necrosis, heart valve abnormalities and hypertension[16-20]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding *livedo reticularis* as of "moderate" quality, "recommending" its inclusion as part of the APS criteria revision[2]. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including *livedo racemosa*) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

### *Livedoid vasculopathy and skin ulcers*

Although livedoid vasculopathy is associated with APS, the exact prevalence is unclear[15]. It consists of a non-inflammatory occlusion of the small vessels of the skin due to thrombosis and deposition of fibrin in the vessel walls, mimicking vasculitis[21]. It mostly affects young women and presents as focal purpuric painful lesions that ultimately form irregularly shaped ulcers. These lesions heal slowly and leave porcelain-white, stellate, atrophic scars surrounded by telangiectasia, hemosiderin deposition, and hyperpigmentation (*atrophie blanche*)[15,22].

Skin ulcers in APS can occur due to various etiologies, including APS-related vasculopathy, secondary lesions in the context of prior thrombosis, or ulcerations secondary to warfarin treatment[5].

In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including livedoid vasculopathy) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Ear, nose, and throat (ENT) manifestations

### *Sensorineural hearing loss*

The link between autoimmune diseases and sudden sensorineural hearing loss has been described as early as the 1970s and 1980s[23,24], with various case reports and case series reporting this complication specifically in APS and systemic lupus erythematosus (SLE) patients[25-29]. Among the possible pathogenic mechanisms, microthrombosis of the cochlear vessels associated with aPL is a potential etiology[30]. A recent review found that most of the patients with sensorineural hearing loss and APS were males, with a clinical presentation including vertigo, tinnitus, and headache, and 75% of patients presented bilateral disease[31]. In terms of aPL profile, LA and aCL were found in equal proportions[31]. Regarding treatment, all patients were anticoagulated, and aspirin was added in 25% of the cases, with a complete resolution or improvement of the symptomology observed in 25% of the patients[31].

## Endocrinological manifestations

### *Adrenal insufficiency due to hemorrhagic infarction*

Although rare (0.4% of APS patients)[32], adrenal insufficiency is the most common endocrinologic manifestation of APS and can be its presenting symptom[33]. It has also been frequently observed as part of the multiorgan failure characteristic of catastrophic APS[33]. Data about this manifestation are mostly available from case reports and case series[34-38]. The pathogenesis is unclear, but some mechanisms are proposed: (i) rich adrenal arterial supply with a limited venous drainage predisposing patients to thrombosis, followed by hemorrhagic infarction of the adrenal glands; (ii) development of adrenal hemorrhage following surgery or anticoagulant therapy; and (iii) accumulation in the adrenal cells of late endosomes, which express epitopes recognized by aPL[33]. In a review of cases reported in the literature, the most frequent treatments were steroid replacement therapy (84% of patients), followed by anticoagulation (52%) and aspirin (6%)[38]. In the *Phase III of the Development of New International Classification*

*Criteria for APS*, microvascular disease (including adrenal hemorrhage) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Hematological manifestations

### *Hemolytic anemia*

The Euro-phospholipid cohort reported the presence of autoimmune hemolytic anemia (AIHA) in 9.7% of patients[13], while a study of 308 APS patients found a prevalence of 10.4%[39]. This study also suggested an association between AIHA, arterial thrombosis, heart valve disease, epilepsy or chorea, and *livedo reticularis*[39]. A potential mechanism for AIHA in APS is cross-reactivity between aPL and red cell membrane phospholipids[40]. A recent systematic review and meta-analysis attempting to clarify the relationship between aPL and AIHA found the highest prevalence of AIHA in SLE patients with APS/aPL, low/moderate prevalence in SLE patients without aPL, and a lower prevalence in primary APS[41].

### *Thrombocytopenia*

Thrombocytopenia is one of the most commonly present non-criteria manifestations, with a reported prevalence ranging from 16% to 53% in APS patients[42]. There is limited knowledge on the pathogenesis of thrombocytopenia in APS, but various mechanisms are proposed: (i) increased platelet destruction, either immune-mediated (caused by aPL or associated immune thrombocytopenic purpura), due to thrombotic microangiopathy (as in the case of catastrophic APS), or drug-induced; (ii) decreased platelet production; (iii) increased platelet pooling; and (iv) pseudothrombocytopenia[43]. Thrombocytopenia in APS is usually described as mild (70-120 × $10^9$ platelets/L) and benign[44]; nevertheless, in a study of 51 APS patients with thrombocytopenia, 31% received some form of specific treatment (either corticosteroids, intravenous immunoglobulin or rituximab)[45]. Regarding the disease course, in this same study, the authors observed that if thrombocytopenia was not present at diagnosis, patients had only 2.6% risk to develop it during follow-up[45]. Furthermore, thrombocytopenia was particularly related with a high-risk aPL profile (LA and triple positivity), but the decreased platelet count had no proven impact on the risk of major bleedings[45]. A tempting idea would be the possibility of thrombocytopenia serving as a marker for future development of SLE in APS patients, but different publications could not establish this association[46-48]. However, a study of 138 patients with aPL positivity and thrombocytopenia (i.e., fulfilling laboratory but not clinical criteria of APS) described a 5 times higher risk of future thrombosis in these patients compared with those with normal platelet counts[49]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding thrombocytopenia as of "low" quality, but "recommended" its inclusion as part of the APS criteria revision[2]. In the *Phase III of the Development of New International Classification Criteria for APS*, thrombocytopenia occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Musculoskeletal manifestations

### *Ischemic bone necrosis*

There is an increased incidence of osteonecrosis in primary APS patients in the absence of other predisposing factors, suggesting an association between osteonecrosis and aPL[20]. The reported incidence varies between 0.9% and 20% in primary APS patients[50,51]. Regarding pathogenesis, aPL may play a role in osteonecrosis development by promoting thrombotic vasculopathy in the intraosseous microcirculation[20]. In a prospective study of 30 primary APS patients who had never received corticosteroids, 6 (20%) had evidence of asymptomatic avascular necrosis on magnetic resonance imaging (MRI)[52]. In the same study, avascular necrosis tended to develop more frequently in younger individuals, and *livedo reticularis* was more frequent in patients with avascular necrosis[20].

## Neurological manifestations

### *Acute ischemic encephalopathy*

First described in association with APS in 1989[53], acute ischemic encephalopathy has been observed in several patients with aPL[54-56] and it was present in 1.1% of patients of the Euro-phospholipid cohort[13]. Clinical findings include confusion, asymmetrical quadriparesis, hyperreflexia, and bilateral extensor plantar responses, with imaging exams revealing cortical hypodensities on MRI[57,58]. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including acute ischemic encephalopathy) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Chorea

Chorea is described as a rare complication of APS, with a prevalence of 1.3% in the Euro-phospholipid cohort[13], but constitutes the most common movement disorder associated with the disease. Though still uncertain, the pathophysiology may be related with (i) cerebral infarctions and white matter changes due to a thrombo-occlusive mechanism; or (ii) immune-mediated damage against basal ganglia epitopes[59]. A study of 50 patients with APS and chorea showed a significant percentage of younger women and SLE-associated APS patients and described a possible association with the initiation of oral contraceptives[60,61]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding chorea as of "low" quality, but "recommended" its inclusion as part of the APS criteria revision[2].

## Cognitive dysfunction

The reported frequency of cognitive dysfunction in aPL-positive patients ranges from 19% to 40%, with dementia observed in much lower percentages (0% to 6%)[62]. Cognitive dysfunction is a broad term that encompasses different manifestations, and patients may report difficulty with memory, attention, and concentration, or the dysfunction may be subclinical and apparent only with neuropsychological testing[63]. A study of 60 APS patients found a higher frequency of cognitive impairment in comparison with matched controls, reporting also an increased risk for cognitive dysfunction in patients with *livedo reticularis* and white matter lesions on brain MRI[19]. Another study found cognitive dysfunction to be more common in aPL high-titer patients in comparison with moderate-titer patients[19]. Although it would be tempting to correlate cognitive deficits with cerebral ischemic lesions, while some studies of MRI in APS patients display high frequency of cortical, subcortical, and basal ganglia infarcts, others focusing specifically on cognition failed to demonstrate an increased numbers of infarcts in patients with APS with cognitive deficits compared with controls[60].

## Epilepsy/seizures

The prevalence of epilepsy in APS is reported to range from 3% to 10%, with higher prevalence in SLE-associated APS[5,13,64]. Although the pathogenic mechanism is not clear, possibilities include: (i) occlusion of vessels supplying the nervous tissue and (ii) direct interaction of antibodies with phospholipids of neural cells[65,66]. Regarding clinical presentation, temporal lobe epilepsy is particularly prominent in APS[67]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding seizures as of "very low" quality, recommending against its inclusion as part of the APS criteria revision[2].

## Migraine

In the Euro-phospholipid cohort[13], migraine featured as the most common neurologic manifestation, being present in 20.2% of patients. In the literature, the reported prevalence ranges from 0% to 30%[68]. Nevertheless, the association between aPL and migraine is still not categorical, with conflicting studies regarding this matter[68]. Among possible pathogenic mechanisms, platelet function abnormalities and interaction of LA with neuronal phospholipids such as sphingomyelin have been hypothesized[68,69]. In a review by Hughes[70], the typical clinical picture is migraine (often premenstrual) starting in teenage years, with subsequent improvement and return in the 30s or 40s; additionally, a strong family history of headaches or migraine is reported, and visual or speech disturbance or transient ischemic attacks occur concurrently in some patients[70]. Anticoagulation is still considered the mainstay treatment, with a resolution or improvement of the migraine standing as an additional clue to its relationship with APS[68,71,72]. Nevertheless, the report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding migraine as of "very low" quality, recommending against its inclusion as part of the APS criteria revision[2].

## Transverse myelitis

The prevalence of transverse myelitis in APS is estimated to be around 0.4–4%[59]. Plausible pathophysiological mechanisms of transverse myelitis in patients with aPL include: (i) vasculitis; (ii) arterial thrombosis resulting in ischemic cord necrosis; and (iii) direct interaction between aPL and spinal cord phospholipids[2,73]. Various studies additionally report an association between the presence of aPL and transverse myelitis in SLE patients[74,75]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical*

*Features* classified the evidence regarding longitudinal myelitis as of "low" quality, but "recommended" its inclusion as part of the APS criteria revision[2].

## Pulmonary manifestations

### *Diffuse alveolar hemorrhage*

First described in association with APS in 1991[76], diffuse alveolar hemorrhage is a rare manifestation of APS (0.7% in the Euro-phospholipid cohort together with acute respiratory distress syndrome and pulmonary artery thrombosis)[13], but occurs in 12% of catastrophic APS patients[77]. Possible mechanisms behind this complication in APS include: (i) aPL-induced pulmonary capillaritis; (ii) microvascular thrombosis generating alveoli hemorrhage; (iii) aPL activation of the mTOR kinase leading to endothelium proliferation and consequent vasculopathy; and (iv) complement activation[78]. In a recent review of cases of alveolar hemorrhage associated with APS, this complication was the initial feature of APS in 11% of cases; 65% achieved remission, 55% experienced recurrent disease, and 21% died[78]. Regarding treatment, it should be noted that anticoagulation has not been shown to be beneficial in preventing or treating alveolar hemorrhage in APS patients, with anticoagulation being usually transiently discontinued during the bleeding episode and later restarted depending on the patient's condition[78]. In the *Phase III of the Development of New International Classification Criteria for APS*, microvascular disease (including pulmonary hemorrhage) occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

### *Pulmonary hypertension*

There is growing evidence on the association between pulmonary hypertension and the presence of aPL[79]. Among SLE patients, a meta-analysis found that aPL can identify patients at risk for pulmonary hypertension[80]. There are various pathogenic mechanisms proposed, including: (i) large vessel and small vessel thrombosis; (ii) pro-inflammatory effects of aPL; (iii) Libman-Sacks endocarditis and left-sided valvular disease; and (iv) chronic thromboemboli and associated endothelial remodeling[79,81,82]. The prevalence of this manifestation in the Euro-phospholipid cohort was 2.2%[13], while another European study of 114 APS patients displayed a prevalence of 3.5% in primary APS and 1.8% in APS associated with other autoimmune diseases[83]. The presence of aPL is suggested to be associated with pulmonary hypertension of across all the five WHO groups[81]. A review suggested that the outcome of pulmonary hypertension in aPL-positive patients seemed to be linked with the occurrence of new venous thromboembolic events or left-sided heart abnormalities[79].

## Ophthalmological manifestations

### *Amaurosis fugax*

Ocular changes can be found in 8-88% of APS patients, with manifestations occurring mainly due to thrombotic events in central retinal vessels[84,85]. In the case of *amaurosis fugax*, if binocular, it usually represents central nervous system ischemia[86]. This manifestation was present in 2.2% of patients of the Euro-phospholipid cohort[13]. In a recent study featuring a cohort of 105 primary APS patients, *amaurosis fugax* starred as the most prevalent ophthalmological involvement, being present in 30 (29%) patients, and associated with the presence of *livedo reticularis*, Raynaud's phenomenon, and aCL[87].

## Renal manifestations

### *APS nephropathy*

The first reports of APS nephropathy date back to 1990[88], with the description as a distinct clinical entity occurring in 1999. It comprises renal small vessel vasculopathy with thrombotic microangiopathy, fibrous intimal hyperplasia, arterial and arteriolar recanalizing thrombi, fibrous arterial occlusion, focal cortical atrophy, tubular thyroidization, and absence of vasculitis[89-91]. The clinical presentation includes hypertension, acute or chronic kidney injury, proteinuria (mild to nephrotic), and hematuria[91,92]. The prognosis is variable but includes high prevalence of chronic hypertension in most series, while proteinuria, nephrotic syndrome, chronic renal failure, or end-stage renal disease also occurs[91]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding APS nephropathy as of "moderate" quality, issuing a "strong recommendation" for it to be included as part of the APS criteria revision[2]. In the *Phase III of the Development of New International Classification Criteria for APS*, chronic aPL-related nephropathy occurred with higher frequency in cases categorized as "highly likely" to have an APS diagnosis[4].

## Vascular manifestations

### *Superficial vein thrombosis*

Although common in APS (11.7% of patients in the Euro-phospholipid cohort)[13], the limited evidence regarding the correlation between superficial vein thrombosis and APS/aPL together with the intent to avoid classifying other diseases as APS (e.g., Behçet's disease, where aPL and superficial vein thrombosis can coexist) has determined a maintained exclusion from the classification criteria[2]. Nevertheless, in a prospective cohort study of 92 patients with SLE and/or aPL with a median follow-up of 35 months, superficial vein thrombosis carried a hazard ratio of 7.45 for the occurrence of thromboembolic events, suggesting a possible prognostic significance[93]. The report of the *14th International Congress on aPL Technical Task Force on APS Clinical Features* classified the evidence regarding superficial vein thrombosis as of "low" quality, but "suggested" its inclusion as part of the APS criteria revision[2].

## Obstetric manifestations

### *Infertility*

The concept of a relationship between some infertility cases and APS/aPL, although tempting, is still controversial. Different pathogenic mechanisms could explain this link, namely (i) aPL interfering with oocyte development and uterine decidualization and (ii) neutrophil extracellular traps promoting coagulation[94]. A recent review analyzed 16 studies assessing aPL positivity rates in infertile women and control populations, while 10 studies showed aPL elevation in women with unexplained infertility comparing with healthy controls, six showed no significant differences[94]. The authors concluded that currently there is not enough evidence to support the routine testing of aPL in patients with infertility[94].

### *In vitro fertilization (IVF) failure*

Following the same reasoning as above, aPL have been hypothesized to be related with IVF failures[95]. However, this association is once again controversial. The aforementioned review also analyzed studies evaluating the relevance of aPL in women undergoing IVF. Among 33 studies, 15 showed some contribution of aPL to IVF failure, while 18 failed to show this association[94]. More importantly, the authors noted the presence of an association in some retrospective studies, while it was absent in most of the prospective studies[94].

### *Placenta-mediated complications*

Placenta-mediated complications, such as *abruptio placentae* and hematoma and late pre-eclampsia/intrauterine growth restriction (IUGR), have been reported as complications of APS patients in various case reports and cohorts[96,97]. While pre-eclampsia and IUGR before the 34th week of gestation are included in the revised criteria[1], those occurring afterward are not. It is hypothesized that early pregnancy complications are related to a direct inhibitory effect of aPL on the trophoblast cells, while late manifestations are attributable to placental dysfunction due to thrombotic and inflammatory changes[98]. In the *Summary of the 9th meeting of the European Forum on aPL,* the concept of obstetric morbidity associated with APS (OMAPS) was discussed, including some of these manifestations: two miscarriages, late pre-eclampsia, *abruptio placentae*, late premature birth, and more than two unexplained IVF failures[99]. Nevertheless, a meta-analysis attempting to clarify the association between aPL and some late placenta-mediated complications (i.e., late fetal loss, pre-eclampsia, IUGR, and placental abruption) was unable to establish a categorical relationship due to significant heterogeneity and underpowered studies[100]. The EUROAPS registry has gathered data regarding these obstetric patients with non-criteria manifestations[101,102] and, in a publication with 1000 obstetric APS patients, two spontaneous abortions before 10 weeks of gestation were present in 9.5% of patients, IUGR after 34 weeks of gestation in 4.7%, pre-eclampsia after 34 weeks of gestation in 4.6%, placental hematoma in 1.3%, and *abruptio placentae* in 1%[102]. Nonetheless, the impact of each individual manifestation in APS patient is still unclear.

## Conclusion

From the analysis of the available evidence regarding the different non-criteria manifestations it is notorious that, although relevant, their association with APS/aPL is still unclear or scarcely characterized in most cases. This notion reinforces the need for well-designed studies evaluating specific manifestations in homogeneous APS populations.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

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REVIEW ARTICLE

# Pleural fluid biochemistry: A first step toward an etiological diagnosis of pleural effusions

*José M. Porcel**

*Pleural Medicine Unit, Department of Internal Medicine, Hospital Universitario Arnau de Vilanova, IRBLleida, Universidad de Lleida, Spain*

## Abstract

The analysis of pleural fluid (PF) is the most important diagnostic element in identifying the cause of pleural effusions. PF biochemistries, in particular, are available immediately and offer relevant clinical information. The measurement of proteins and lactate dehydrogenase (LDH) in PF and blood (Light's criteria) establishes the transudative or exudative nature of effusions. Transudates are commonly caused by heart failure (HF), but diuretic therapy may concentrate PF causing higher levels of protein and/or LDH and, therefore, leading to a misclassification as an exudate. In this scenario, a serum-PF albumin gradient > 1.2 g/dL points to a true transudate. Furthermore, elevated concentrations of the natriuretic peptide N-terminal pro-brain natriuretic peptide are virtually pathognomonic of HF as the primary or, at least, secondary diagnosis. In exudates with predominantly polymorphonuclear leukocytes (> 50%), a bacterial infection of the pleural space should be considered, particularly if PF C-reactive protein levels are high. A pleural pH < 7.15 or a glucose < 40 mg/dL in a parapneumonic effusion indicates the need for a drainage tube. When lymphocytes predominate in an exudate, cancer and tuberculosis are the two main diagnoses to consider; an adenosine deaminase activity > 35 U/L strongly supports the diagnosis of tuberculosis. Measuring tumor markers (e.g., carcinoembryonic antigen, CA15-3) under the premise of using 100% specific cutoff points can increase the diagnostic yield for malignancy.

**Key words:** Pleural effusion. Pleural fluid. Tumor markers. Tuberculosis. Empyema.

## Introduction

Under physiological conditions, pleural fluid (PF) is an ultrafiltrate of plasma with an estimated quantity of 0.26 mL/kg in each hemithorax[1]. PF is normally composed of approximately 1-2 g of protein per dL, with levels of lactate dehydrogenase (LDH) < 1/2 of those found in serum. Differential cell count yields a predominance of macrophages (75%) and lymphocytes (20%), with a marginal presence of mesothelial cells, neutrophils, and eosinophils[1]. Through ultrasonography, a minimal film of PF, approximately 3 mm, can be observed in 30% of healthy individuals[2]. Any clinically detectable quantity of PF is considered abnormal. A pleural effusion (PE) may indicate the presence of a pleural, pulmonary or extra-pulmonary disease. Some cases of PE have a clear clinical etiology, but in others there may be more than one etiology or else the cause is uncertain. For example, a bilateral PE in the clinical context of heart failure (HF) is generally secondary to this condition, while a unilateral PE in a patient with a medical history of breast cancer is indicative of

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**Corrrespondence:**
*José M. Porcel
E-mail: jporcelp@yahoo.es

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metastasis until proven otherwise. PEs secondary to multiple etiologies are common, and accounted for 30% of 126 unilateral effusions in one prospective study[3]; HF being a common contributing cause in these cases.

An analysis of PF obtained by thoracentesis allows the physician to establish a definitive or presumptive cause of PE in more than two-thirds of cases and, at minimum, allows for the reliable ruling out of some etiologies[4]. This narrative review focuses on those routine and optional biochemical parameters that can be measured in PF for narrowing the differential diagnosis of PEs.

## Macroscopic appearance of PF

The organoleptic characteristics of PF can provide useful diagnostic information. In the majority of cases, PF can be classified into one of the following color categories: watery (light yellow or transparent), serous (yellowish), blood tinged (reddish), bloody (dark red and similar to blood), purulent (pus), turbid (yellowish, but viscous or opalescent), and milky (whitish and thinner than pus). Approximately half of all bloody PFs are due to neoplasms. However, a malignant PE appears serous in 50% of cases, blood tinged in approximately 30% of cases, and bloody in only 10% of cases[5]. The bloody appearance of malignant PEs does not influence the yield of cytology[6]. Patients with trauma, parapneumonic effusions, post-cardiac injury syndrome, and pulmonary emboli may all exhibit a bloody PF. A watery appearance of PF is indicative of a transudate (see definition below), although the majority are serous (67%) and may even have a blood tinged (11%) or turbid (9%) color[5].

A milky PF is characteristic of chylothorax (though half the cases do not have this appearance) and cholesterol PEs (chyliform PEs or pseudochylothorax). Chylothorax implies a chyle leak that is due to the disruption or blockage of the thoracic duct or its tributaries. Cholesterol PEs have no relationship with lymphatic vessels, but rather are connected with long-standing PEs with or without thickened pleural membranes. The most frequent causes of chylothorax are surgery, lymphoma, and cirrhosis, while cholesterol PEs are usually secondary to tuberculosis and, in fewer instances, to rheumatoid arthritis[7]. The presence of a purulent PF is diagnostic of empyema. Occasionally, the whitish appearance of chylous or chyliform PEs may be difficult to distinguish from the turbidity of empyema. However, after centrifugation, the supernatant in empyema is clear (cells and detritus produce the opalescence), whereas it remains cloudy or milky in chylous or chyliform effusions, due to high lipid content. In addition, chylous PEs are inodorous, while anaerobic empyemas are foul-smelling in over half the cases. The whitish appearance of PF is rarely due to the leakage of an enteral nutrition formula from a central catheter into the pleural space (nutrithorax)[8].

Unusual greenish PFs may be observed if the patient has a biliopleural fistula (bilothorax)[9], while PFs usually appear black if the pleural space is infected by *Aspergillus niger* or *Rhizopus oryzae* or rarely black if the PE is malignant (metastatic melanoma and lung cancer) or there is a pancreaticopleural fistula or a chronic hemothorax[10].

Finally, extremely viscous PFs can be seen in patients with mesothelioma (due to high concentrations of hyaluronic acid) or pleural metastases from mucinous adenocarcinomas.

## Processing of PF

The extraction of 20-40 mL of PF is necessary for a complete analysis, which includes biochemical, cytological, and microbiological studies. PF should be divided into sterile tubes that contain an anticoagulant (heparin or EDTA).

To analyze pH, it has traditionally been taught that fluid should be collected under anaerobic conditions in a heparinized syringe, without being mixed with the local anesthetic used for the thoracentesis. Air falsely elevates pH, whereas local anesthetic falsely lowers the pH. More commonly, the sample is obtained using an unheparinized syringe and then transferred to a heparinized tube; a maneuver which does not cause a clinically relevant increase in pH[11]. The measurement should ideally be obtained with a blood gas machine within 4 h following the extraction of PF, since time delay in processing also falsely elevates pH[12].

PF samples should be transported to the laboratory at room temperature immediately after collection, and processed on receipt. All PF chemistry analytes are stable up to 6 h at room temperature[13]. On storage at –20 °C, stability is maintained for days, with the exception of LDH.

## Routine biochemical analysis of PF

Tests routinely performed on PF include cell count and differential, protein, LDH, glucose, pH, adenosine deaminase (ADA), cytology, and microbiological studies[14]. Some of them should only be ordered when

specific conditions are suspected, such as tuberculosis (ADA), mycobacterial cultures, nucleic acid amplification tests, pleural infection (bacterial cultures), or malignancy (cytology). Many diagnoses can be established by PF analysis in isolation (Table 1).

## Proteins and LDH

The dichotomous classification of PF as a transudate or exudate simplifies diagnostic efforts in determining the cause of PEs. By definition, transudates result from a disequilibrium between the hydrostatic and oncotic forces in the pulmonary or systemic circulation over a structurally intact pleural surface, whereas exudates accumulate because of local factors affecting the pleura, such as increased capillary permeability and/or impaired lymphatic drainage resulting from many inflammatory and malignant causes. If the PE is a transudate, no additional diagnostic procedures are required because they are generally caused by HF (80%) or, to a lesser extent, liver cirrhosis (10%)[15]. In these cases, the administration of diuretics, sometimes in combination with a therapeutic thoracentesis, is sufficient to resolve the PE. In contrast, exudates require a more extensive diagnostic evaluation given that they may have numerous etiologies (Table 2)[15]. Of note, although previously thought to be transudates on occasion, PEs due to pulmonary embolism are invariably exudates when Light's criteria are used as the reference standard[16].

In clinical practice, exudates are separated from transudates through the simultaneous determination of protein and LDH concentrations in blood and PF (Light's criteria)[4] (Table 3). It is accepted that the time interval between collection of PF and blood samples can be up to 24 h instead of necessarily having to be formally paired; a circumstance which does not alter the fluid categorization as exudate or transudate in most cases[17]. The main limitation of Light's criteria is that, despite correctly identifying nearly all exudates (98%), their application misclassifies approximately 30% of PEs secondary to HF and 18% of hepatic hydrothorax as exudates[18]. This misclassification is particularly frequent in patients who have received diuretic treatment or have bloody PFs (> 10,000 erythrocytes/μL)[19]. If a patient presents clinically with HF, but the PF meets Light's criteria as an exudate (generally by a small margin), a calculation of the gradient (difference) between the serum and PF albumin or protein levels is recommended. If the albumin gradient is greater than 1.2 g/dL or the protein gradient surpasses 2.5 g/dL, which occurs in about 80% of patients with these "false exudates," it should be assumed that such a PF is actually a transudate[20]. An alternative for the identification of HF-related PEs is the measurement of natriuretic peptides in PF specimens (see below).

When it is not possible to obtain a blood sample (an unusual circumstance), the combination of PF LDH > 67% of the normal upper limit of serum LDH and PF cholesterol > 55 mg/dL, using an "or" rule (wherein positivity of any of these tests represents a positive result) can be used as an alternative criterion for the

**Table 1.** Diagnoses that can be established by pleural fluid analysis

| Condition | Pleural fluid test |
|---|---|
| Malignancy | Positive cytology |
| Empyema | Pus or positive culture |
| Tuberculosis | Positive acid-fast bacilli, culture or NAAT |
| Fungal or parasite effusion | Positive culture or detection of parasites |
| Hemothorax | Pleural fluid hematocrit divided by serum hematocrit > 0.5 |
| Chylothorax | Triglycerides > 110 mg/dL, chylomicrons present |
| Cholesterol effusion | Cholesterol crystals on polarized light microscopy |
| Pancreatic disease | Elevated amylase (pancreatic isoenzyme) |
| Esophageal rupture | pH < 7 and elevated salivary isoenzyme form of amylase |
| Lupus pleuritis | High levels of anti-dsDNA |
| Rheumatoid pleurisy | Tadpole cells in a background of amorphous debris |
| Peritoneal dialysis | Pleural fluid to serum glucose ratio > 1[a] |
| Bilothorax | Pleural fluid to serum bilirubin ratio > 1 |
| Urinothorax | Pleural fluid to serum creatinine ratio > 1[b] with a pH < 7.30 |
| Glycinothorax[c] | Transudate with a high concentration of glycine |
| Ventriculoperitoneal shunting or duropleural fistula | Presence of beta-2 transferrin |

[a]Analysis for lactate D-isomer that is only found in the dialysate is an alternative diagnostic method.
[b]Diagnostic if ratio > 1.7.
[c]Occurs after urological procedures involving bladder irrigation with glycine-containing solutions.
dsDNA: double-stranded DNA; NAAT: nucleic acid amplification test.

**Table 2.** Causes of pleural effusions

| Transudates | Exudates |
|---|---|
| Common causes (90% overall)<br>Heart failure (80%)<br>Cirrhosis (10%) | Common causes (75% overall)<br>Metastatic malignancy (40%)<br>Parapneumonic (25%)<br>Tuberculosis (10%)<br>Mesothelioma (variable) |
| Less common causes (10% overall)<br>Volume overload/hypervolemia<br>Hypoalbuminemia<br>Nephrotic syndrome<br>Atelectasis<br>Peritoneal dialysis<br>Pulmonary arterial hypertension<br>Trapped lung[a]<br>Constrictive pericarditis<br>Cerebrospinal fluid leak<br>Extravascular migration of CVC<br>Urinothorax[a] | Less common causes (25% overall)<br>Post-surgery (cardiothoracic, abdominal)<br>Pericardial diseases<br>Trauma (hemothorax)<br>Viral pleuritis<br>Pulmonary embolism<br>Drugs<br>Abdominal diseases (e.g., pancreatitis)<br>Autoimmune rheumatic diseases<br>Benign asbestos pleural effusion<br>Chylothorax[b]<br>Uremic pleural effusion<br>Gynecologic (OHS[c], -endometriosis) |

[a]They may also be exudates.
[b]They may also be transudates (e.g., cirrhosis).
[c]A complication of ovulation induction with human chorionic gonadotropin (hCG) in the setting of *in vitro* fertilization.
CVC: central venous catheter; OHS: ovarian hyperstimulation syndrome.

**Table 3.** Light criteria for the differentiation of pleural exudates and transudates

| A pleural effusion is classified as exudative if it meets one or more of the following conditions, while a transudate meets none |
|---|
| – A pleural fluid/serum protein ratio > 0.5<br>– A pleural fluid/serum LDH ratio > 0.6<br>– A pleural fluid LDH concentration > two-thirds (67%) of the normal upper limit for serum LDH |

LDH: lactate dehydrogenase.

identification of exudates (94% sensitivity and 88% specificity)[21-23].

A transudate with a pleural protein concentration < 1 g/dL suggests one of the following diagnoses[24]: (1) extravascular migration of a central venous catheter connected to a saline or glucose infusion system, (2) duropleural fistula, (3) peritoneal dialysis, (4) urinothorax (i.e., urine in the pleural space, usually due to obstructive uropathy), (5) ventriculopleural shunt, or (6) migration of a ventriculoperitoneal shunt to the pleura. At the opposite extreme, 70% of patients with tuberculous PEs exhibit PF protein concentrations > 5 g/dL[25], while 40% of those with multiple myeloma have levels > 7 g/dL[26].

The LDH concentration in PF is not only useful for differentiating exudates from transudates but also for consistently reflecting the degree of pleural inflammation, which is of particular interest in managing pleural infections. In the context of parapneumonic effusions, the finding of a pleural LDH concentration > 2000 U/L (approximately 4 times the upper limit of serum LDH levels) is an indicator of poor clinical outcome that merits consideration for the need of a chest drainage tube (likelihood ratio [LR] positive 3.4)[27]. Moreover, in patients with lymphocytic exudates of unclear etiology, observing a decrease of LDH concentrations in subsequent thoracenteses reduces the probability of a malignant cause[28].

## Leukocyte cell count

While the number of PF leukocytes is of limited value in the differential diagnosis of PE, parapneumonics encompasses more than 80% of counts higher than 10,000/μL[29]. However, only one-third of parapneumonic PEs reach such high counts and, paradoxically, empyemas might exhibit scarce leukocyte cellularity due to neutrophil autolysis. On the other hand, the differential leukocyte count is of interest in all pleural exudates because the predominance of a specific cell type, either neutrophils or lymphocytes, can help to narrow down the differential diagnosis.

## Neutrophilic PE

The delay in performing a thoracentesis from the onset of the pleural lesion determines the predominant type of leukocyte present in the PF. In acute inflammatory processes affecting the pleura, neutrophils predominate (> 50% of the total leukocytes). Although pneumonia is the most frequent cause of neutrophilic PEs, they can also be associated with abdominal diseases (e.g., pancreatitis or subphrenic abscess), pulmonary embolism, acute-phase viral and tuberculous infections, neoplasms, or asbestos exposure (benign asbestos PE). In particular, 10% of tuberculous PEs can be neutrophilic predominant[25], a fact which is associated with a higher yield of mycobacterial cultures of sputum (50% vs. 25%) and PF (50% vs. 10%) as compared to patients whose PF is predominantly lymphocytic[30].

## Lymphocytic PE

In pleural transudates, lymphocyte counts greater than 50% (a finding that occurs in approximately 90% of the cases)[31] have no diagnostic significance. However, pleural lymphocytosis is of great importance in the differential diagnosis of exudates, given that this finding usually indicates a chronic disease. The two main diagnoses to consider for exudates of lymphocytic predominance are cancer and tuberculosis, which together represent more than two-thirds of all cases. Thus, about 90% of tuberculous PEs and 80% of malignant PEs are lymphocytic[31]. Less frequent causes of lymphocyte-predominant exudates are post-cardiac surgery in the late phase, pulmonary embolism, chylothorax, rheumatoid pleuritis (chronic), yellow nail syndrome, sarcoidosis, and acute rejection of a lung transplant, among others. Notably, around 17% of parapneumonic PFs have a predominance of lymphocytes, which is probably influenced by the use of antibiotics before thoracentesis rather than the elapsed time between the start of symptoms and the pleural tap[32].

## Eosinophilic PE

PF eosinophilia is defined as having greater than 10% of eosinophils in the total PF cell count. In a recent systematic review that included 687 cases of eosinophilic PEs, the most frequent causes were neoplasms (26%), idiopathic (25%), parapneumonic (13%), blood or air in the pleural cavity (13%), tuberculosis (7%), and transudates (7%), among a variety of additional causes[33]. As the percentage of eosinophils in the PF increases (e.g., > 30%), the probability of a neoplasm decreases while the probability of idiopathic causes increases[33,34]. For instance, neoplasms only explained 7% of the PEs with eosinophil counts > 32% in the aforementioned systematic review[33].

Conventionally, eosinophilic PEs are thought to be the result of air or blood in the pleural cavity (e.g., hemothorax, pneumothorax, or repeated thoracentesis). Yet, in some reports only 5% of PEs became eosinophilic after a second thoracentesis was performed[35].

## Erythrocyte count

A concentration of 5000-10,000 erythrocytes/μL is required for PF to have a reddish appearance. Only 1 mL of blood in a moderate-sized PE is needed to produce a blood-tinged PF. The diagnostic value of reddish PEs is limited, as this appearance is present in about 15% of transudates and one-third of exudates[31]. A PF erythrocyte concentration greater than 10,000/μL is observed in > 75% of post-traumatic PEs, 56% of PEs secondary to pulmonary embolism, 40% of malignant PEs, and more than one-third of parapneumonic PEs[31].

Of greater interest is the finding of a bloody PE, which corresponds to PF erythrocyte counts greater than 100,000/μL. A PE with these characteristics is suggestive of three possible diagnoses: cancer, trauma, or pulmonary embolism. These high red blood cell counts characterize, however, only around 10% of PEs secondary to cancer or pulmonary embolism[16,31]. It has been traditionally thought that PF hematocrit should be determined for all purely bloody PEs. If it exceeds 50% of that in the peripheral blood, a hemothorax is present, the majority of which are caused by trauma. Nevertheless, a confident approximation of the PF hematocrit level can be obtained by dividing the erythrocyte count in the PE by 100,000.

## pH

Under physiological conditions, PF pH is alkaline (7.60-7.66) due to the accumulation of bicarbonate in the pleural cavity. Pleural transudates have a pH that tends to vary between 7.40 and 7.55, while it ranges between 7.30 and 7.45 in the majority of exudates[36]. However, a group of exudative PEs does exhibit pH values < 7.30, which represent a substantial accumulation of hydrogen ions in the pleural space. The etiology of these PEs, which tend to be associated with a low PF glucose content (< 60 mg/dL), includes[24]: (1)

complicated parapneumonic PEs and empyemas, which are the most frequent cause of pleural acidosis, (2) malignant PEs, (3) tuberculous PEs, (4) chronic rheumatoid PEs, and (5) esophageal rupture (anaerobic empyema). Marked pleural acidosis (pH < 7.20) has been described in around 60%, 6%, 9%, 70%, and 100% of these etiologies, respectively[25,27,31]. The only transudative PE (although this condition may also meet exudative criteria) presenting with a pH < 7.30 is urinothorax, which results from the migration of acidic urine from the capsule of an obstructed kidney to the pleural space through ipsilateral diaphragmatic defects[37].

PF pH is valuable for the management of patients with parapneumonic PEs. By definition, an uncomplicated parapneumonic PE resolves with antibiotic treatment alone. In contrast, a complicated parapneumonic PE requires a tube thoracostomy for resolution. Empyema, characterized by the presence of pus in the pleural cavity, is a type of complicated parapneumonic PE. The challenge for the clinician is to identify those parapneumonic PEs with a non-purulent appearance that requires a drainage tube. The pleural acidosis that can develop in this type of PEs results from an increase in metabolic activity in the pleural space (neutrophilic phagocytosis and bacterial metabolism) and the accumulation of products derived from glucose, $CO_2$, and lactic acid. A parapneumonic non-purulent PE with a pH < 7.15 is unlikely to resolve without the insertion of a chest tube (LR = 6.2)[27]. However, pH alone is not sensitive enough (66%) to identify complicated parapneumonic PEs[27], and about 10% of parapneumonic PEs with marked PF acidosis may even resolve with antibiotics alone[27,38]. In a retrospective study of 641 parapneumonic PEs, findings increasing the probability of chest tube usage the most were[27]: PEs occupying half or more of the hemithorax on a chest radiograph (LR = 13.5), PF pH ≤ 7.15 (LR = 6.2), PF glucose ≤ 40 mg/dL (LR = 5.6), pus (LR = 4.8), positive PF cultures (LR = 3.6), and PF LDH > 2000 U/L (LR = 3.4). It should be noted that in a multiloculated parapneumonic PE, different locules of fluid can have different pH measurements[39]. The measurement of pH or any assay, other than a Gram stain and culture, for a purulent PE is of no value and should not be conducted as empyemas virtually always require a tube thoracostomy or, if small, maximal aspiration when technically feasible.

PF acidosis in malignant PEs results from an extensive tumor infiltration of the pleura that inhibits the flow of glucose products from the pleural space. Thus, a low pH is typically found in advanced malignant PEs and is associated with poorer response to pleurodesis[40] and survival[41], and increased probability of requiring a definitive therapy for the pleural space (i.e., pleurodesis or indwelling pleural catheters)[42].

## Glucose

The significance of low PF glucose is similar to that of low pH and, at a cutoff point of < 40-60 mg/dL, it is a good substitute for pH to predict the need for pleural drainage in parapneumonic PEs (LR = 5.6)[27,43]. Extremely low glucose levels are characteristic of complicated parapneumonic PEs, empyemas, paragonimiasis, and rheumatoid PEs (80% of rheumatoid PEs have this characteristic)[44]. In pleural infections, there is an increased utilization of glucose by neutrophils and bacteria of PF, whereas in rheumatoid pleurisy the underlying mechanism is a decreased diffusion of glucose from blood to PF as a result of thickened pleural membranes. Approximately, 9% of malignant PEs[31] and 25% of tuberculous pleuritis[25] also exhibit PF glucose levels lower than 60 mg/dL. On the other hand, when glucose values in PF exceed those in serum, two potential diagnoses should be considered[24]: (1) extravascular migration of a central venous catheter through which a glucose solution is being instilled, and (2) migration of peritoneal dialysate fluid from the peritoneal space to the pleural cavity.

## ADA

In geographical areas where tuberculosis has a moderate or high incidence, the determination of ADA levels in PF is routine for diagnosing a tuberculous PE and has replaced pleural needle biopsy[45]. In areas with low disease burden, ADA is still of value in that a low PF level almost entirely rules out tuberculosis. According to recently published meta-analyses, pleural ADA values greater than 35-40 U/L have an approximate sensitivity of 92%, a specificity of 90%, a positive LR of 9, and a negative LR of 0.09 for establishing the tuberculous origin of a PE[46,47]. Perhaps lower thresholds should be considered in older patients, since ADA concentrations decrease with age[48]. The majority of false-positive ADA results have been attributed to parapneumonic PEs and empyemas that, in contrast to the majority of tuberculous PEs, predominantly contain neutrophils. ADA activity still remains elevated in tuberculous PEs with neutrophilic predominance[30]. Approximately 16% of non-complicated parapneumonic PEs, 44% of complicated non-purulent parapneumonic PEs, 70% of

empyemas, and 10% of malignant PEs (a percentage that increases to 35% in diffuse large B-cell lymphomas) exhibit high pleural ADA values[49,50]. When ADA concentrations are extremely elevated (> 250 U/L), an empyema (easily diagnosed due to the purulent appearance of the PF) or lymphoma, rather than tuberculosis, should be a strong consideration[49]. Measurement of the isoenzyme ADA2 is not standardized and adds little to total ADA measurement in the majority of cases[30].

## Optional analysis of PF

### *Natriuretic peptides*

Natriuretic peptides, in particular brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), are hormones synthesized by cardiomyocytes in response to parietal stress secondary to volume or pressure overload. In a meta-analysis of 12 studies that included 599 PEs due to HF and 1055 non-cardiac PEs, NT-proBNP levels in PF had a sensitivity of 94%, a specificity of 91%, a positive LR of 10.9, and a negative LR of 0.07 in identifying PEs with a cardiac origin[51]. Respective figures for blood NT-proBNP extracted from four studies were 92%, 88%, 7.8, and 0.10[51]. The most widely used cutoff point is 1500 pg/mL[52,53], though with the advent of more sensitive new generation tests this threshold needs to be reevaluated. NT-proBNP is a more useful biomarker of HF than BNP when measured in PF[53]. In addition, NT-proBNP concentrations allow clinicians to correctly identify > 80% of those cardiac PEs misclassified as exudates by Light's criteria[53]. Furthermore, natriuretic peptides are optimal for differentiating between cardiac and hepatic (cirrhosis) transudates, as the pathophysiological mechanisms underlying PF formation differ in the two processes. Detection of elevated PF levels of NT-proBNP in patients with established non-cardiac causes of PE (e.g., pneumonia, cancer, and pericardial disease) is currently a frequent situation which may reflect some degree of underlying decompensated cardiac disease contributing partially to PF development.

### *Tumor markers*

A number of soluble-protein biomarkers have been studied in PF for the diagnosis of malignancy. For tumor markers to be diagnostically useful, they must be 100% specific (i.e., threshold levels should not be exceeded by any benign PEs) which inevitably results in low diagnostic sensitivity. For example, one study evaluated the diagnostic accuracy of PF carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) in 1575 patients with non-purulent exudates[54]. Using cutoff values with 100% specificity, it was found that 41%, 40%, and 60% of malignant PEs had PF levels of CEA > 45 ng/mL, CA 15-3 > 77 IU/L, or either, respectively. More importantly, more than one-third of cytology-negative malignant PEs could be identified by at least one marker[54]. However, the use of tumor markers does not eliminate the need for obtaining a definitive cytohistological diagnosis.

There is great interest in the discovery of biomarkers for malignant mesothelioma, a tumor which is difficult to diagnose. Soluble mesothelin is the most widely accepted biomarker. A meta-analysis on the diagnostic value of PF soluble mesothelin in 3359 patients (including 759 mesothelioma cases) estimated sensitivity, specificity, LR positive and LR negative at 68%, 91%, 7.8, and 0.35, respectively[55]. The threshold value commonly employed is 20 nmoL/L. Although measuring PF mesothelin levels doubles the yield of conventional cytology to diagnose mesothelioma, the histological confirmation of this neoplasm is mandatory.

### *C-reactive protein (CRP)*

The presence of a PF with a predominance of polymorphonuclear leukocytes and a CRP concentration > 45 mg/L strongly suggests that the cause of the PE is a bacterial infection[56]. In a recent meta-analysis of 18 publications, the diagnostic performance of PF CRP for the identification of parapneumonic PEs was as follows: sensitivity 80%, specificity 82%, LR positive 4.51, and LR negative 0.25[57]. Moreover, the diagnostic indexes of PF CRP in differentiating complicated from uncomplicated parapneumonic PEs, using a cutoff of around 100 mg/dL, were: sensitivity 65%, specificity 85%, LR positive 4.26, and LR negative 0.41[57].

### *Lipids*

The PF analysis of a chylothorax shows an exudate in 85% of the cases, mostly by the protein but not the LDH criterion (referred to as protein-discordant exudate). A transudative chylothorax (15%) should lead to a suspicion of cirrhosis[7]. Lymphocytes are predominant in 80% of the cases, and PF triglyceride concentrations are greater than 110 mg/dL in 85%[58]. A PF triglyceride concentration that is lower than 50 mg/dL strongly argues against the diagnosis of chylothorax (< 3% of cases). If pleural

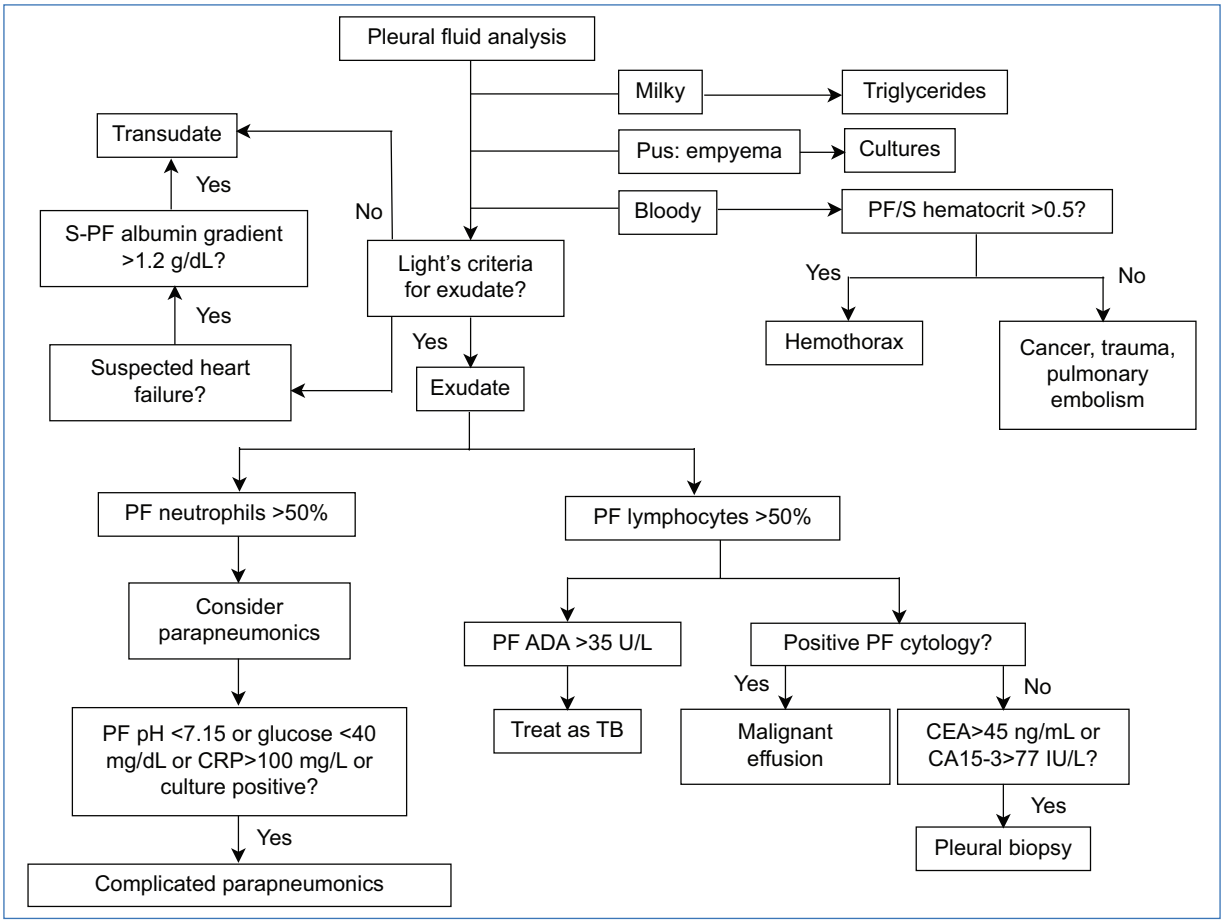


**Figure 1.** A proposed algorithm for diagnosing pleural effusions based on pleural fluid analyses. Modified from Porcel 2010[68], with permission. ADA: adenosine deaminase; CRP: C-reactive protein; PF: pleural fluid; PF/S: pleural fluid to serum ratio; S-PF: gradient (difference) between the serum and pleural fluid; TB: tuberculosis.

triglyceride values are intermediate (50-110 mg/dL) and there are doubts regarding the existence of a chylothorax, the finding of chylomicrons in PF is definitive. However, if a lipoprotein analysis is not available and there are still concerns about the diagnosis, the administration of a high-fat meal will result in a dramatic change in the appearance and triglyceride content of the PF.

In contrast, cholesterol PEs are exudates, often lymphocyte-predominant (60%), with a PF cholesterol/triglyceride ratio > 1 (97%), cholesterol crystals visible under a polarized light microscope (90%), PF cholesterol concentrations > 200 mg/dL (75%), and the absence of chylomicrons[59].

## *Antinuclear antibodies (ANAs)*

PEs can present clinically in one-third of patients with systemic lupus erythematosus (SLE). However, PEs in this population may be caused not only by lupus pleuritis, but also by infections, pulmonary embolism, nephrotic syndrome, HF, or neoplasms. All patients with lupus pleuritis have positive serum ANAs, which raises questions about the need to measure their levels in PF for diagnostic purposes. However, the presence or absence of ANAs in PF may be of interest in the diagnosis of individuals with known SLE and a PE of uncertain etiology. Specifically, the absence of PF ANAs is a strong argument against lupus pleuritis and should motivate the search for alternative diagnoses[60]. Conversely, the presence of ANAs (titers ≥ 1/160), anti-dsDNA, or anti-ENA antibodies in PF strongly supports the diagnosis of lupus pleuritis (LR = 17)[60]. Approximately 6% of SLE-unrelated PEs, primarily malignant PEs, show significant ANA titers in PF[60,61].

### *Amylase*

The most frequent causes of increased PF amylase levels (values greater than the upper limits of normal for serum amylase) are malignancy (55%) and tuberculosis (13%)[62,63]. This enzyme is elevated in approximately 15% and 10% of patients with malignant (more commonly in lung cancer) and tuberculous PEs, respectively. However, only when an acute or chronic (pancreatic pseudocyst) pancreatic disease or esophageal rupture is suspected is it justified to request a PF amylase measurement. PF amylase is of the salivary type in neoplasms and esophageal rupture, while the pancreatic isoenzyme predominates in pancreatic diseases.

### *Unstimulated interferon-γ and interleukin-27 (IL-27)*

PF unstimulated interferon-γ and IL-27, both measured by enzyme-linked immunosorbent assays, have an accuracy similar to ADA for identifying tuberculous PEs. However, the latter is simpler, cheaper, and less time-consuming.

A meta-analysis of 67 publications, comprising 2657 tuberculous and 4496 non-tuberculous PEs, yielded summary estimates of sensitivity (93%), specificity (96%), LR positive (22.8), and LR negative (0.07) for PF interferon-γ in diagnosing tuberculosis[64]. Discriminative threshold values have ranged from < 2 IU/mL to > 5 IU/mL. As is the case for ADA, empyemas and lymphomas can cause "false elevations" in the level of this cytokine.

In contrast to unstimulated IFN-γ, interferon-γ release assays (IGRA), which quantify IFN-γ released by T lymphocytes in response to stimulation by specific mycobacterial antigens, are generally thought to be of little value for diagnostic purposes[65]. It has been suggested, however, that IGRA (e.g., T-SPOT) might be diagnostically helpful in patients with tuberculous PE whose ADA is lower than 40 U/L[66].

In a meta-analysis of 11 studies with 502 tuberculous and 952 non-tuberculous PEs, the pooled sensitivity, specificity, positive LR, and negative LR of PF IL-27 assays for tuberculosis were 95%, 91%, 13.9, and 0.07, respectively[67]. Optimal cutoff values, however, need to be determined.

## Conclusions

The routine biochemical analysis of PF obtained by thoracentesis should include total and differential cell counts, protein, LDH, glucose, pH, and ADA. The differentiation of transudates and exudates using Light's criteria is the first diagnostic step for all PEs. If the PE is a transudate, HF is usually the cause and diuretics should be instituted. Not infrequently, however, diuretics remove more water than protein and LDH from the pleural space, resulting in a misclassification of the PE as an exudate. In these circumstances, a serum-effusion albumin (or protein) gradient should be obtained as a simple strategy to reveal the true transudative nature of the PE.

If the PE is an exudate, different analytical tests can narrow down the differential diagnosis. Specifically, an ADA concentration > 35 U/L generally indicates tuberculosis in PFs with a lymphocytic predominance, while a pH < 7.15 or a glucose concentration < 40 mg/dL allows for the identification of complicated parapneumonic PEs. Other PF assays are optional and facilitate the diagnosis of PEs which have uncertain etiologies. For example, natriuretic peptides (NT-proBNP) are good biomarkers of HF, triglycerides, and cholesterol facilitate the identification of lipid-rich PEs, elevated PF concentrations of CEA and/or CA 15-3 strongly suggest a diagnosis of malignancy, and a PF CRP concentration > 100 mg/L indicates a parapneumonic PE that will most likely require drainage. Figure 1 provides an algorithm for diagnosing PEs based on PF analysis[68].

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

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REVIEW ARTICLE

# To DAIR or not to DAIR: Decision-making in the management of acute prosthetic joint infection – A narrative review

*Jaime Lora-Tamayo*, Mikel Mancheño-Losa, and Carlos Lumbreras*

*Department of Internal Medicine, Hospital Universitario 12 de Octubre, Instituto de Investigación "i+12" Hospital 12 de Octubre, Madrid, Spain*

## Abstract

Prosthetic joint infections are much-feared complications of joint arthroplasty that require complex multidisciplinary treatment. Although prosthesis removal is usually needed, the performance of debridement, antibiotics, and implant retention (DAIR) is an attractive alternative in well-selected patients with acute infection. Whether or not to indicate DAIR in a given situation is not a straightforward decision, despite validated algorithms and published guidelines. The odds of eradicating the infection and retaining an arthroplasty that is functional and painless are influenced by multiple variables regarding not only type of infection but also causative microorganism, antimicrobial treatment, surgical procedure, and the patient's condition and baseline characteristics. In this narrative review, we go over current recommendations, and algorithms, along with reported rates of success and risk factors of failure, and we will balance the decision to perform DAIR against other alternatives.

**Key words:** Debridement. Irrigation. Functional outcome. Foreign body infection. Arthroplasty.

## Clinical case

An 81-year-old male with hypertension and a left total knee prosthesis needed a cemented arthroplasty due to a left hip fracture some years ago. The patient has no cognitive impairment and is independent in routine activities. The patient recently fell and presented with periprosthetic hip fracture. A revision procedure was performed, in which the femoral component of the prosthesis was replaced by a new device with a longer cemented stem. Six weeks after that surgery, the patient presented in the emergency room with 10 days of fever (38.0 °C), along with tenderness and signs of inflammation over the surgical wound. No sinus tract was observed. C-reactive protein (CRP) was 12.5 mg/dL (normal range < 0.5 mg/dL). Until the symptoms started, the prosthesis seemed to perform well, and X-rays showed no signs of loosening or infection. How should this patient be managed?

## Introduction

The most feared complication of joint arthroplasty is prosthetic joint infection (PJI). While infrequent in relative terms, the absolute number of episodes is rising in parallel with the life expectancy of the population and the increasing number of devices placed[1,2]. As with foreign body infection, an infected prosthetic device is characterized by the presence of bacterial biofilm, in which microorganisms undergo phenotypic and metabolic change, become tolerant to antibiotics, and are able to evade the host's immune system[3]. The management of PJI, therefore, is complex and commonly

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**Corrrespondence:**
*Jaime Lora-Tamayo
E-mail: jaime@lora-tamayo.es

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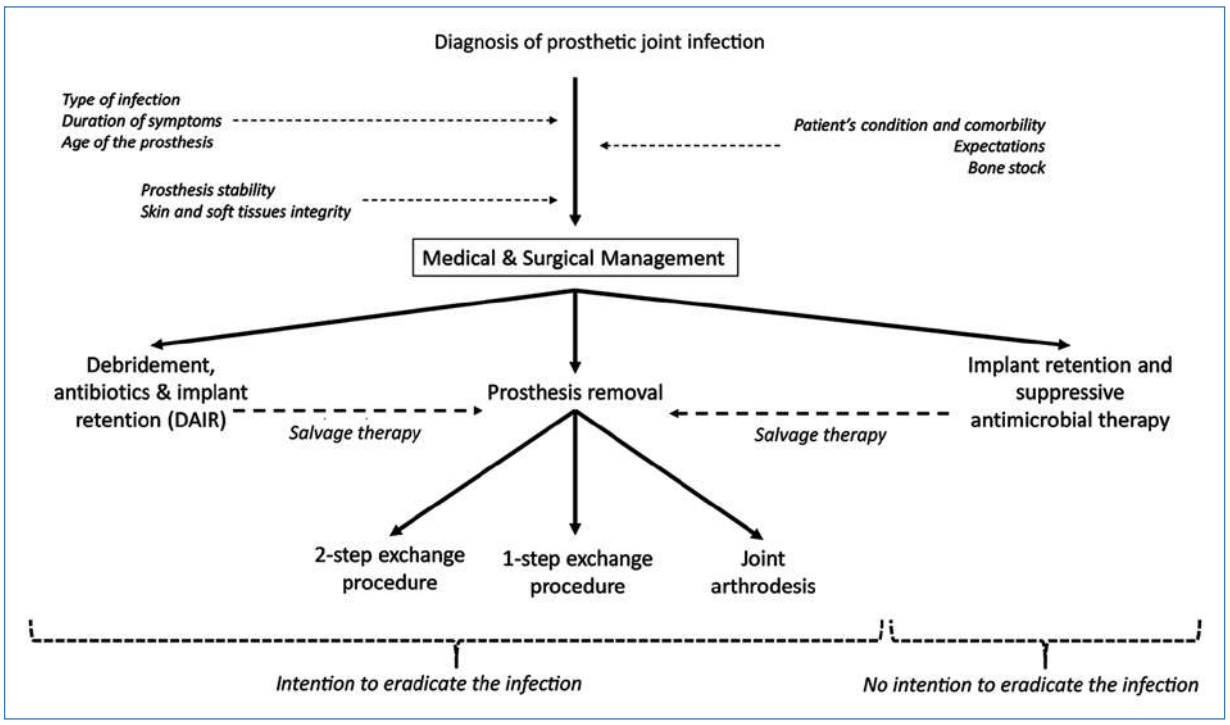


**Figure 1.** Surgical and medical options for prosthetic joint infection (adapted from Ariza et al.[10]).

requires aggressive surgery and optimized antimicrobial treatment, posing a significant economic burden for the health-care system and a considerable psychological stress for the patient[4-8].

Decision-making in PJI is not straightforward and should be made on an interdisciplinary basis, with the involvement of orthopedic surgeons, microbiologists, and clinicians with experience in the management of bone and joint infections. The patient's condition, expectations, and personal preferences should also form part of the final decision. The goals of treatment are to eradicate infection and maintain painless joint function[2,9]. While multiple surgical and clinical variables should be taken into account, there are basically three main options, two of them with an eradicative intention and a third, non-eradicative one (Fig. 1)[10].

Among the options for microbial eradication, prosthesis removal is the reference treatment, as is the rule with the infections associated with other medical devices such as pacemakers, intravenous catheters, and cerebrospinal shunt devices[11]. Whether prosthesis extraction is followed by definite arthrodesis, one-step revision, or two-step exchange procedure, the common denominator of this strategy is to remove the foreign body and the bacterial biofilm, which significantly facilitates the healing of the infection[12-14]. The two-stage revision is considered to be the gold standard procedure, with high rates of success (11%, range 0-25%)[15], although comparable results have been reported in single-stage revisions in well-selected patients[16].

However, several drawbacks of removing the prosthesis should also be considered. First, it is not easy to remove a soundly fixed cemented prosthesis and commonly requires a longitudinal osteotomy during long operations. This type of surgery may be too aggressive for frail elderly patients such as the one described in the clinical case, especially if infection presents with sepsis and a significant worsening of the patient's condition. Second, prosthesis exchange depletes bone stock, which is an important issue in elderly patients with a revision prosthesis, but also in younger patients with many years ahead of them who may require further revisions[17,18]. The patient depicted here had a revision hip prosthesis and a knee prosthesis on the same limb, leaving little space for anchoring a new revision device. Third, implant removal followed by replacement with a new prosthesis is not always guaranteed, and some patients may be left with joint arthrodesis and a poor functional situation. Furthermore, amputation may be needed in the most dramatic

scenarios. Finally, the two-step exchange procedure needs at least two surgeries, with impaired function between procedures.

Debridement, antibiotics, and implant retention (DAIR) provides an alternative curative treatment[10,13,19]. When applied to well-selected patients, it can cure infection, avoid the disadvantages mentioned above, and achieve good results in terms of functional outcome and patient satisfaction[17,20]. Notwithstanding, the real odds of curing the infection when DAIR is attempted may be very different when it comes to specific episodes of PJI, even when the basic conditions for indicating this strategy are met. Performance of DAIR is discouraged when the pre-operative risk of failure is unacceptably high[21]. In this context, several studies have identified risk factors for failure that can significantly reduce the likelihood of success[22-49] and there are also published risk scores that set out to quantify this probability[50,51].

In line with the multidisciplinary nature of decision-making in the PJI setting, multiple variables and questions need to be considered when deciding whether to remove a prosthesis or attempt DAIR. In this narrative review, our aim is to go over the relevant evidence and the key factors involved in this decision. Here, we review the current recommendations and decision algorithms, together with the reported rates of success and risk factors for failure, and evaluate the decision to perform DAIR against other alternatives.

## Search strategy

We searched the PubMed database for publications addressing the variables that influence the outcome of DAIR, combining the search terms "DAIR," "debridement," "irrigation," "guidelines," "review," "salvage therapy," "PJI," and "arthroplasty." Abstracts were reviewed and relevant full-length papers were read, as appropriate. We also went through the references in these articles to select previous original papers of relevance. Articles focused on the management of PJIs other than DAIR (i.e., one-step exchange procedure, staged revision, and suppressive antimicrobial therapy) were discarded. Our search was restricted to articles written in English, French, and Spanish.

## Current recommendations for performing DAIR: the paradigm and its fissures

The choice of suitable candidates for DAIR is paramount to its success. Zimmerli's algorithm[19] is the basis of the current guidelines and is generally accepted in everyday practice and by many scientific societies (Table 1)[10,21,52,53]. According to these recommendations, the infection should be acute (either early post-surgical or hematogenous) and the duration of symptoms short (i.e., less than 21 days), the infected prosthesis should be soundly fixed (i.e., not loose), and the surrounding skin and soft tissues in good condition. Ideally, the causative microorganism should be susceptible to antimicrobials with good activity against biofilm-embedded bacteria, although this information may not be available at the moment of making the decision[19,21]. These conditions aim to select infections where the biofilm is not too mature and is, therefore, more susceptible to surgical debridement and antimicrobial therapy[9,54]. These criteria also stress the need to select devices that are worth the effort of performing DAIR, since there would be no point attempting to retain a loose or exposed prosthesis. Zimmerli's algorithm is simple and consistent, and various observational studies have shown that the prognosis for patients undergoing DAIR who meet these conditions is significantly better than for those who do not[55-57].

Nevertheless, implementing Zimmerli's rules in any given situation involve reconciling two different aspects of the same problem. On the one hand, a substantial number of patients could benefit from the DAIR strategy even if they do not meet all the conditions of the algorithm, and on the other, a significant percentage of patients fail after DAIR despite meeting those conditions. In this context, the rates of failure after DAIR reported in published series vary widely, ranging from 8% to 82%[22-49]. While this surely reflects heterogeneity across studies, and also in the application of the algorithm, it also suggests that there are other important variables with a significant influence on prognosis.

With respect to the first issue, the definition of *acute infection* can be somewhat variable. It is based, as mentioned, on two chronological criteria involving the type of PJI (early post-operative and hematogenous infections) and duration of infection. Early post-surgical PJIs are those whose symptoms begin a few weeks after prosthesis placement, although the specific cut-off has changed over time. In 1996, Tsukayama et al. set the limit at 1 month[38]. In Zimmerli's pivotal randomized clinical trial of 1998, patients with post-operative infection underwent DAIR if the orthopedic hardware had been in place for 2 months or less[58]. Later, in a reference review, early infections were those that presented within the first 3 months after the index surgery[19]. Finally, the current IDSA guidelines once again set the cut-off at 1 month[52].

**Table 1.** Conditions needed for indicating DAIR

| Reference | Type of infection | | | Short duration of symptoms | Skin and soft tissues in good condition | Prosthesis stability | Microorganisms to avoid |
|---|---|---|---|---|---|---|---|
| | Hematogenous | Early post-operative | Late/chronic post-operative | | | | |
| Zimmerli et al., 2004[19] | Yes | Yes (< 3 months) | No (> 3 month) | < 21 days | Required. No sinus tract | Required | Non-susceptible to biofilm-active antibiotics |
| Del Pozo and Patel, 2009[2] | Yes | Yes (< 3 months) | No (> 3 months) | < 21 days | Required. No abscess or sinus tract | Required | MDR, SCV *S. aureus*, enterococci, fungus, quinolone-resistant *P. aeruginosa* |
| Osmon et al., 2013[52] (IDSA) | Yes | Yes (< 1 month, approximately) | No (> 1 month) | < 21 days | Required. No sinus tract | Required | Non-susceptible to biofilm-active antibiotics |
| SPILF, 2014[53] | Yes | Yes (< 1 month)* | No (> 1 month) | < 10-21 days | Required | Required | - |
| Ariza et al., 2017[10] (SEIMC) | Yes | Yes (< 3 months) | No (> 3 months) | < 21 days | Required | Required | Caution when there is impossibility of using rifampin/ fluoroquinolones |
| ICM, 2019[21] | Yes | Yes (not specified) | Discouraged | < 28 days | Required | Required | - |

*In a document from 2010, SPILF recommended a prosthesis age < 2 weeks for considering DAIR[82].
IDSA: Infectious Diseases Society of America; SPILF: Société de Pathologie Infectieuse de Langue Française; ICM: International Consensus Meeting (Philadelphia, USA); SEIMC: *Sociedad de Enfermedades Infecciosas y Microbiología Clínica* (Spain); MDR: multidrug resistant; SCV: small colony variant.

While there is little debate about discouraging DAIR in patients whose symptoms begin subacutely after the 3rd month following the index surgery (i.e., chronic post-operative infections), there continues to be some discussion about those whose symptoms begin between 1 and 3 months afterward. A recent analysis of DAIR involving 769 episodes of post-operative PJI with symptom onset until day 90 after prosthesis placement observed no differences in prognosis based on the specific week where symptoms appeared[59]. Others have also observed a similar prognosis in patients whose symptoms start between the first 30 and 90 days and those with symptom onset within the first 30 days[33,55,56]. These findings challenge the use of 4 weeks after prosthesis placement to select suitable candidates for DAIR as being too strict, which could then be extended to 3 months[10].

Duration of symptoms is the second chronological criterion. In post-operative infections, this variable is difficult to measure, since many signs and symptoms of inflammation overlap with those that are expected in the post-operative period, such as pain or local warmth. In contrast, it is a helpful measure for hematogenous infections that present suddenly with inflammatory signs on prosthetic joints that had been placed some months or years previously[19,38].

The 21-day limit of symptom duration comes from the Zimmerli's trial[58], in which none of the patients recruited presented with symptom duration of more than 3 weeks before surgical debridement. However, this does not necessarily mean that patients could not benefit from DAIR even if symptom duration was longer than 21 days. While it seems clear that the sooner the patient undergoes debridement, the better, no consistent reproducible time limit has been found across several studies[22,23,35,47,55,56,60-62]. Indeed, from a retrospective point of view, a very short time interval between patient symptoms and undergoing debridement may be a surrogate marker of poor prognosis, since patients with more severe PJIs (those with sepsis, high levels of CRP, or bacteremia) would be prioritized in the operating theater. This consideration represents an added difficulty to the search for a reliable time limit beyond which DAIR is not worth the effort.

In addition, it is possible that the chronology of infection, including both the age of the prosthesis and

duration of symptoms, may have a differential influence on outcome, depending on the specific etiology, and furthermore on the specific bacterial strain, its virulence factors, and ability to form a mature biofilm[63]. Other variables, such as the activity of the antimicrobial treatment used, could also modify the importance of time. While Brandt et al. found that delaying debridement by more than 2 days was enough to worsen the prognosis of patients with staphylococcal PJI, mostly treated with β-lactams[60], other series, mainly using rifampin-based combinations, raised this time limit to 10 days[55].

## Failure despite following the rules: variables beyond the algorithms

Treatment failure despite meeting Zimmerli's criteria is controversial. While some series have shown very good results with DAIR in very well-selected patients[37], multiple observational studies have reported significant failure rates among patients who fulfilled the terms of the algorithm. In this respect, a number of risk factors for failure have been identified across these studies including variables related to the host's baseline condition, clinical presentation, and surgical and clinical management (Table 2). The bottom line of these studies is that the selection of candidates for DAIR should go beyond the standard recommendations and take some of these variables into account, along with PJI etiology when available.

To help with this decision, an interesting risk score was proposed by Tornero et al.[51] based on a cohort of 222 patients with early post-surgical infection (defined according to the 90-day limit after prosthesis placement) who received DAIR within 21 days of symptom onset. The primary endpoint was failure in the first 60 days after DAIR. The KLICC score included five variables (kidney – chronic renal failure [2 points]; liver cirrhosis [1.5 points]; index surgery due to femoral neck fracture [1.5 points]; cemented prosthesis [2 points]; and CRP > 11.5 mg/dL [2.5 points]) and showed good discriminatory power (area under the curve 0.839). At scores > 3.5, the sensitivity and specificity of predicting failure were 74% and 86%, respectively[51]. This score was retrospectively validated by other investigators and showed a slightly lower sensitivity and specificity at the 3.5 limit[64,65]. An alternative risk score, CRIME80, has also been published for hematogenous infections (i.e., late acute infections) (COPD, CRP > 150 mg/L, rheumatoid arthritis, fracture as indication of prosthesis, male sex, exchange of removable components, and age > 80 years)[50].

As was stated above, the etiology is commonly unknown when the decision is made, which is a significant limitation of algorithms and risk scores. Microbial etiology and the use of antibiotics with good activity against biofilm-embedded bacteria are certainly key factors for determining a given patient's prognosis. The benefits of using rifampin-based combinations to treat *Staphylococcus aureus* when the prosthesis is retained are well established in pre-clinical and clinical research, including a randomized clinical trial and several observational studies[55,58,66-69]. Likewise, a dramatic improvement in prognosis has been shown using fluoroquinolones for infections caused by Gram-negative bacilli (GNB)[70-73]. The largest published study of PJI caused by GNB managed with DAIR included 173 cases and showed that 79% of patients treated with ciprofloxacin were cured as compared with 41% who were not (p = 0.01), and the same benefit applied to specific types of bacteria such as *Pseudomonas aeruginosa* (88% vs. 45%, p = 0.01; n = 42) and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (100% vs. 46%, p = 0.47; n = 15)[72]. Ciprofloxacin is so important for treating these infections that it has still to be determined whether or not infections caused by multidrug-resistant (MDR) GNB imply a worse prognosis than those caused by GNB that are only resistant to fluoroquinolones. In a large study of cases of MDR PJI, the failure rate among cases managed with DAIR was 52%[74].

Unless the patient has a positive blood culture, knowing the etiology of PJI before DAIR requires a joint aspirate sample (feasible in knee prostheses, more complex in hip prostheses) and waiting for the bacteria to grow. Obtaining the antibiotic susceptibility profile takes extra time. Since the success of DAIR is time sensitive, the debate about whether to wait for pre-operative microbiological results or perform surgery as soon as possible remains open. At the recent Philadelphia International Consensus meeting, it was agreed that it was desirable to identify the microorganism but that this should not delay the performance of DAIR[21].

Furthermore, even if we have the information on etiology beforehand, there is still controversy about the specific microorganisms that should discourage the performance of DAIR. While fungal infection clearly has a poor prognosis when managed with DAIR[75], the odds of success for other microorganisms are variable (Table 3). From an overall perspective, a reasonably good outcome is expected against coagulase-negative staphylococci and fluoroquinolone-susceptible GNB[46,61,72]. While the prognosis of streptococcal PJI was thought to be favorable, a large case series

**Table 2.** Risk factors for failure after attempting DAIR

| Risk factor | References |
|---|---|
| **Baseline conditions** | |
| – Age | 40,50 |
| – Male sex | 50 |
| – Rheumatoid arthritis | 28,50,56 |
| – Smoking | 83 |
| – Chronic renal failure | 51 |
| – Liver cirrhosis | 51 |
| – High ASA score | 44 |
| – Obesity | 36,48 |
| – Immunosuppression | 32 |
| – Anemia | 34 |
| **Prosthesis features** | |
| – Cemented prosthesis | 38,51 |
| – Revision prosthesis | 46 |
| – Femoral head fracture as indication of prosthesis | 45,50,51 |
| – Other indications | 32 |
| **Clinical presentation** | |
| – Prosthesis age > 4 weeks | 24 |
| – Duration of symptoms | 22,23,28,29,35,36,60-62 |
| – Radiological signs of infection | 23 |
| – Hematogenous infections* | 26,28,32,38,42,84,85 |
| – Bacteremia | 32,54,55 |
| – Sinus tract | 29 |
| – High levels of C-reactive protein or ESR | 27,28,32,48,50,51,55,86,87 |
| – Not meeting criteria for DAIR | 55,56,89,90 |
| – Macroscopic purulence surrounding the prosthesis | 44 |
| **Microbiology** | |
| – *Staphylococcus aureus* | 12,22,26,34,46,47,50 |
| – Methicillin-resistant *Staphylococcus aureus* | 30,32,36,61 |
| – Staphylococci | 27,44 |
| – *Enterococcus* spp. | 30 |
| – Fluoroquinolone-resistant Gram-negative bacilli | 72,86 |
| – Microorganisms other than Gram-negative bacilli | 72,90 |
| – Non-susceptible microorganisms | 23,30 |
| – Polymicrobial infection | 32,55,92 |

*(Continues)*

**Table 2.** Risk factors for failure after attempting DAIR (*Continued*)

| Risk factor | References |
|---|---|
| **Management** | |
| – Arthroscopy (instead of arthrotomy) | 47 |
| – Need for an unplanned second debridement | 27,55,87 |
| – Not exchanging prosthetic removable components | 12,25,32,55,56 |
| – Using gentamicin-loaded cement beads | 48 |
| – Not using Rifampin (staphylococci) | 55,58,67,69,83 |
| – Not using Fluoroquinolones (Gram-negative bacilli) | 72,92 |

*Some authors have found a worse prognosis for late acute or hematogenous infection when the cause was *Staphylococcus aureus* but not other etiologies[85].
ASA: American Society of Anesthesiologists; ESR: erythorcyte sedimentation rate; DAIR: debridement, antibiotics, and implant retention.

challenged this and placed this infection in a mid-term outcome, similar to or slightly better than that of *S. aureus*[56]. The prognosis of methicillin-resistant *S. aureus* (MRSA) has also traditionally been regarded as poor[76], but in a case series including a large number of episodes caused by MRSA, the outcome was similar to methicillin-susceptible strains as long as rifampin was used[55]. The outcomes for fluoroquinolone-resistant GNB and enterococci are poor[72,77].

All in all, the etiology of the infection and the antimicrobial treatment are crucial for establishing the prognosis of a given infection. In some patients, the existence of risk failures that reduce the odds of success could be appeased by the use antibiotics with good activity against biofilm-embedded bacteria.

## The penalty for failure: one shot, one opportunity?

Patients who fail DAIR treatment are usually rescued by a two-step exchange procedure. The need for salvage therapy is always disappointing, for the patient and the attending medical team, as well as time and resource consuming. Every effort should be made to achieve a satisfactory outcome at the first attempt, and the choice of curative treatment should, therefore, be made carefully (Fig. 1).

As discussed above, the available algorithms and tools are useful for making decisions, but may at the same time lack specificity. A patient such as the one in the clinical case would have a KLICC score of over 3.5 (cemented prosthesis, indication for neck fracture, and high levels of CRP), which would theoretically preclude the possibility of DAIR. While this is the type of patient that nobody wants to operate on more often than is necessary, it is not altogether clear that prosthesis removal is really the best approach. The physiological stress involved in surgical debridement (prosthesis retention) or a longitudinal osteotomy (prosthesis removal) is not the same. In a cost-effectiveness analysis, Fisman et al. suggested that DAIR was a preferable option for elderly patients with stable prostheses[13]. In an interesting study of patients with infected knee prostheses, Djaza et al. also showed that functional outcome was better in patients with a successful DAIR than those who directly underwent a staged revision and similar to control patients with no infection[17]. On the other hand, the need for salvage therapy and repeated surgeries over a prosthetic joint may jeopardize the integrity of soft tissues, increase the odds of post-surgical joint stiffness, and eventually lead to poor functional results[78].

Underlying these considerations is the question of whether or not patients who fail at the first attempt have a worse prognosis when they undergo salvage therapy; in other words, is the likelihood of being cured and having a good functional outcome in patients who go directly to the two-step exchange procedure the same when they receive it as salvage therapy after a failed DAIR? Is there just one shot, one opportunity? Otherwise, if the prognosis of salvage therapy is similar to a direct staged revision and the odds of success with DAIR are not too bad, trying DAIR would be an attractive choice.

Table 4 summarizes the studies that address this clinical question. Sherrel et al. observed a higher than

**Table 3.** Success rates of PJI managed by DAIR according to specific etiologies

| Microorganism | Reference | Success – n/N (%) | |
|---|---|---|---|
| ***Staphylococcus aureus*** | | | 564/913 (62%) |
| | Brandt et al., 1997[60] | 12/33 (36%) | (Range 13-91%) |
| | Marculescu et al., 2006[29] | 4/32 (13%) | |
| | Barberán et al., 2006[61] | 13/21 (62%) | |
| | Aboltins et al., 2007[93] | 17/19 (89%) | |
| | Byren et al., 2009[46] | 34/47 (72%) | |
| | Bradbury et al., 2009[76] | 3/19 (16%) | |
| | Vilchez et al., 2011[87] | 40/53 (75%) | |
| | Senneville et al., 2011[67] | 32/41 (78%) | |
| | Lora-Tamayo et al., 2013[55] | 182/328 (55%) | |
| | Betz et al., 2015[94] | 22/29 (76%) | |
| | Lora-Tamayo et al., 2016*[95] | 31/34 (91%) | |
| | Lesens et al., 2018[83] | 104/137 (76%) | |
| | Muñoz-Gallego et al., 2020[63] | 29/55 (53%) | |
| | Becker et al., 2020[68] | 41/65 (63%) | |
| **Coagulase-negative staphylococci** | | | 86/114 (75%) |
| | Marculescu et al., 2006[29] | 14/23 (61%) | (Range 61-100%) |
| | Barberán et al., 2006[61] | 26/39 (67%) | |
| | Byren et al., 2009[46] | 21/26 (81%) | |
| | Lora-Tamayo et al., 2016[a,95] | 10/10 (100%) | |
| | Becker et al., 2020[68] | 15/16 (94%) | |
| ***Streptococcus* spp.** | | | 379/609 (62%) |
| | Meehan et al., 2003[96] | 17/19 (89%) | (Range 50-100%) |
| | Zeller et al., 2009[97] | 4/6 (66%) | |
| | Sendi et al., 2011[89] | 13/20 (65%) | |
| | Corverc et al., 2011[98] | 3/3 (100%)[3] | |
| | Bertz et al., 2015[94] | 9/9 (100%) | |
| | Lora-Tamayo et al., 2017[56] | 257/444 (58%) | |
| | Akgün et al., 2017[99] | 4/6 (67%) | |
| | Lam et al., 2018[100] | 53/64 (82%) | |
| | Mahieu et al., 2019[101] | 19/38 (50%) | |
| ***Enterococcus* spp.** | | | 119/222 (54%) |
| | Raymond et al., 1995[102] | 1/2 (50%) | (Range 39-72%) |
| | Marculescu et al., 2006[29] | 2/3 (66%) | |
| | Rasouli et al., 2012[103] | 4/10 (40%) | |
| | Tornero et al., 2014[77] | 44/94 (47%) | |
| | Duijf et al., 2015[104] | 29/44 (66%) | |
| | Kheir et al., 2017[105] | 13/33 (39%) | |
| | Thompson et al., 2019[106] | 26/36 (72%) | |

*(Continues)*

**Table 3.** Success rates of PJI managed by DAIR according to specific etiologies (*Continued*)

| Microorganism | Reference | Success – n/N (%) | |
|---|---|---|---|
| **Gram-negative bacilli** | | | 225/361 (62%)[d] |
| | Marculescu et al., 2006[29] | 4/6 (66%) | (Range 26-88%) |
| | Hsieh et al., 2009[62] | 7/27 (26%) | |
| | Martínez-Pastor et al., 2009[86] | 35/47 (74%) | |
| | Aboltins et al., 2011[70] | 15/17 (88%) | |
| | Zmistowsky et al., 2011[90] | 7/10 (70%) | |
| | Rodríguez-Pardo et al., 2014[72] | 118/174 (68%) | |
| | Bouige et al., 2019[b,71] | 7/13 (54%) | |
| | Papadopoulos et al., 2019[c,74] | 32/67 (48%) | |

[a]Data from the per-protocol analysis[95].
[b]Series including only PJI caused by *Enterobacter* spp. (55% ESBL producers)[71].
[c]Series including only PJI caused by multidrug resistant and extremely drug-resistant Gram-negative bacilli[74].
[d]After excluding case series focused on resistant microorganisms (Bouige et al.[71], Papadopoulos et al.[74]), the rate of success is 186/281 (66%). Important differences may be observed for patients with a PJI caused by Gram-negative bacilli depending on whether they have been treated with fluoroquinolones or not[70-72].

expected frequency of failure, and Rajgopal et al. observed worse functional and microbiological results in patients undergoing prosthesis removal after DAIR[15,78]. However, Rajgopal's groups were unbalanced and included a higher proportion of difficult-to-treat microorganisms in patients with previous DAIR, and when these patients were excluded from the analysis the prognosis for both groups was similar[78]. These results have been contested by other researchers, who observed similar functional results and microbiological eradication for direct and salvage two-step prosthetic exchange[17,18,79-81]. Overall, the question remains open: more studies are needed, with more patients, including hip prostheses and using a common outcome definition.

The observed heterogeneity across studies addressing the efficacy of DAIR also underlines the importance of focusing on adjustable risk factors, such as optimization of the patient's baseline conditions before and after DAIR treatment, using biofilm-active antimicrobials when possible, and thorough performance of surgical debridement. Several studies in this respect observed a better prognosis when the removable components of the prosthesis were exchanged during debridement[12,25,32,50,55,56].

## The decision

Saving an infected foreign body is difficult. Optimizing management involves selecting the correct patient, the right infection, and the most appropriate surgical and medical treatment. Current guidelines provide a helpful approach to decision making. Expertise, knowledge, and multidisciplinary consensus will put any given patient with a specific infection in the relevant context.

The clinical case described herein is a common example of real-life clinical practice. When considering DAIR for this patient, we should note that duration of symptoms was less than 21 days. Importantly, the prosthesis appeared to be well fixed, and the skin and periprosthetic soft tissues were in good condition. However, the patient had a post-operative infection that a number of guidelines would define as chronic[21,52,53]. We have no information about the causative microorganism so that we cannot be sure of the availability of antibiotics with good activity against biofilm-embedded bacteria. Finally, this patient would have a KLICC score of 6 points, well beyond the proposed cut-off of 3.5[51].

Nevertheless, other authors would consider the same infection as early post-operative and with the same odds of success as those with symptoms beginning in the first 4 weeks[55,56,59]. Of importance, this patient has a revision hip and a knee prosthesis on the same limb and so has little remaining bone stock, which would make prosthesis exchange difficult and completion of the procedure could not be guaranteed. Finally, although we cannot exclude an infection caused by a MDR microorganism, this was the first episode and there was no previous antibiotic exposure so that the microorganism may well be sensitive. Better functional results may be obtained with DAIR than with a direct attempt at staged revision[17]. In case of failure, some authors would argue that a two-step salvage exchange procedure could be undertaken with a reasonable guarantee of good results[18,80,81].

**Table 4.** Studies addressing the prognosis of patients undergoing prosthesis removal as salvage therapy after DAIR

| Reference | Type of prosthesis | Number of patients | | Etiology | Microbiological results | Functional results |
|---|---|---|---|---|---|---|
| | | Direct 2SEP | Salvage 2SEP | | | |
| Sherrel et al., 2011[15] | Knees | (Historical controls) | 83 | Various | Failure 34% (Historical controls: 11%) | - |
| Kubista et al., 2012[79] | Knees | 314 | 54 | Various | Overall failure of 2SEP 15% Risk of failure for salvage 2SEP: HR 1.46; P = 0.16. | - |
| Dzaja et al., 2015[a,17] | Knees | 91 | 33 | Various | - | Similar functional results |
| Brimmo et al., 2016[18] | Knees | 693 | 57 | Various | Failure at 4 years: Direct 2SEP – 17.5% Salvage 2SEP – 8.7% (p = 0.131) | - |
| Herman et al., 2017[a,80] | Hips | 68 | 28 | Various | - | Similar functional results |
| Nodzo et al., 2017[81] | Knees | 132 | 45 | Various | Failure 17.5% direct 2SEP Failure 17.8% salvage 2SEP | - |
| Raigopal et al., 2018[78] | Knees | 96 | 88 | Various | Failure 15.6% direct 2SEP Failure 23.9% salvage 2SEP[b,c] | Range of motion 96.4° direct 2SEP Range of motion 88.4° salvage 2SEP[b] |

[a]From the London Health Science Center (London, Ontario, Canada).
[b]Statistically significant difference.
[c]A higher proportion of MRSA was observed among patients in the salvage 2SEP group; when MRSA, *P. aeruginosa*, and methicillin-resistant *S. epidermidis* were excluded, no significant differences in microbiological outcome were observed.
2SEP: 2-step exchange procedure; MRSA: methicillin-resistant *S. aureus*; HR: hazard ratio.

To sum up, we would discuss this case with our colleagues, orthopedists, and microbiologists, and present the pros and cons to the patient and his family. If there is agreement, we would advocate DAIR as soon as possible, including the exchange of removable components, if feasible. Finally, we would optimize the patient's perioperative condition and comorbidity, and ensure the best antimicrobial treatment. In case of failure, we would favor a two-step exchange procedure.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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