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ORIGINAL CONTRIBUTION

Randomized Clinical Trial: A Normocaloric Low-Fiber Diet the Day Before Colonoscopy Is the Most Effective Approach to Bowel Preparation in Colorectal Cancer Screening Colonoscopy

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BACKGROUND: Clinical guidelines recommend either a clear-liquid diet or a low-fiber diet for colonoscopy preparation. Participants in a screening program are usually motivated healthy individuals in which a good tolerability is important to improve adherence to potential surveillance colonoscopies.

OBJECTIVE: Our aim was to assess whether or not a normocaloric low-fiber diet followed the day before a screening colonoscopy compromises the efficacy of bowel cleansing and may improve the tolerability of bowel preparation.

DESIGN: This is a randomized, endoscopist-blinded, noninferiority clinical trial.

SETTINGS: The study was conducted at a tertiary care center.

PATIENTS: A total of 276 consecutive participants of the Barcelona colorectal cancer screening program were included.

INTERVENTION: Participants were randomly assigned to a clear-liquid diet or a normocaloric low-fiber diet the day before the colonoscopy. Both groups received 4 L of polyethylene glycol in a split-dose regimen.

MAIN OUTCOME MEASURES: Primary outcome was the adequate bowel preparation rate measured with the Boston bowel preparation scale. Secondary outcomes included tolerability, fluid-intake perception, hunger, side effects, and acceptability.

RESULTS: Participants in both groups were similar in baseline characteristics. Adequate bowel preparation was achieved in 89.1% vs 95.7% in clear-liquid diet and low-fiber diet groups, showing not only noninferiority, but also superiority ($p = 0.04$). Low-fiber diet participants reported less fluid-intake perception ($p = 0.04$) and less hunger ($p = 0.006$), with no differences in bloating or nausea.

LIMITATIONS: The single-center design of the study could limit the external validity of the results. The present findings may not be comparable to other clinical settings.

CONCLUSION: A normocaloric low-fiber diet the day before a screening colonoscopy achieved better results than a clear-liquid diet in terms of adequate colon preparation. Moreover, it also improved the perception of hunger and excessive fluid intake. Registered at clinicaltrials.gov: NCT02401802. See **Video Abstract** at http://links.lww.com/DCR/A829.

Funding/Support: None reported.

Financial Disclosure: None reported.

*Members of the PROCOLON research group are listed in the Acknowledgments.

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Dis Colon Rectum 2019; 62: 491–497
DOI: 10.1097/DCR.0000000000001305

KEY WORDS: Bowel preparation; Colonoscopy; Colorectal cancer screening.

Bowel preparation is essential for the success of colonoscopy; however, it is usually perceived as an extremely unpleasant part of the procedure and one of the major drawbacks for repeating the colonoscopy.[1] Furthermore, a patient-perceived negative experience with bowel preparation is a predictor of both lower-quality bowel preparation and a lower rate of polyp detection.[2] General population acceptance of a screening colonoscopy depends on perception of its relative risks and benefits. Colorectal cancer (CRC) screening programs have raised the quality standards on bowel preparation, demanding not only a high-quality bowel cleansing, but also a good tolerability. The wide implementation of these programs has increased the expectations of participants who are healthy and asymptomatic; therefore, achieving optimum tolerability in the bowel preparation process is mandatory to increase adherence to follow-up colonoscopies and to promote general population uptake of the CRC screening program. Current guidelines are very challenging in their recommendations for the rate of adequate bowel preparations in screening colonoscopy, suggesting rates of at least 90%. Nevertheless, the optimum diet recommendation for achieving this high standard in bowel preparation efficacy is not yet established.[3]

Traditionally, bowel preparation included a low-residue diet for several days, followed by a clear-liquid diet (CLD) the day before colonoscopy. Several recent randomized clinical trials (RCTs) showed that a low-residue diet the day before the procedure may be as effective as a CLD, with slightly better tolerance.[4–12]

However, there were 2 main limitations in the proposed intervention in those RCTs. First, the amount of fiber included in the proposed "low-residue diet" was either not specified or inadequate. Second, the dietary recommendations given were usually hypocaloric and none included a 5-meal balanced diet.

Our study aimed to ascertain whether or not a normocaloric, well-defined low-fiber diet (LFD) taken the day before a screening colonoscopy compromises the efficacy of bowel cleansing and may improve the tolerability of bowel preparation.

PATIENTS AND METHODS

Study Design

A randomized, single-blind, parallel group, noninferiority-controlled trial was conducted to compare the efficacy of a normocaloric LFD with a CLD the day before CRC screening colonoscopy. The study protocol followed the Declaration of Helsinki ethical guidelines and was approved on January 12, 2015 by the local ethics committee of the Hospital del Mar, Barcelona (4870/l). It was registered on March 17, 2015 at clinicaltrials.gov (NCT02401802)

Study Population

The study was performed at the Hospital del Mar, Barcelona. Consecutive participants of the Barcelona CRC screening program with a positive fecal blood immunochemical test attending a protocol study appointment were invited to participate. Detailed data on the Barcelona CRC screening program and the screening process has been described elsewhere.[13] Exclusion criteria were: unwillingness to participate, inability to follow instructions, incomplete colonoscopies for technical reasons or contraindicated by the endoscopist, and IBD.

Treatment Allocation and Masking

The allocation sequence was obtained by using a computer-generated block randomization table with a 1:1 allocation rate. A research nurse randomly assigned consenting patients to CLD or LFD, according to a randomization table, assigned the bowel preparation diet, and facilitated self-administered questionnaires. At the time of the appointed colonoscopy, a researcher collected the questionnaires and interviewed the participants. Five skilled endoscopists (>10,000 colonoscopies each) performed the colonoscopies blinded to randomization. Endoscopists underwent a calibration exercise before the study in the use of the Boston bowel preparation scale (BBPS) to improve consensus.

Interventions

All participants were instructed by nurses on the importance of bowel preparation and received verbal and written instructions on diet recommendations and laxative intake. All participants were given a dietary plan with a normocaloric LFD, developed by an endocrinologist and a nutritionist, to be started 4 days before the colonoscopy. In that period they were also required to stop all fiber-based laxatives, allowing them to take other sorts of laxatives. The LFD was calculated to provide up to 2000 kcal/day with a mean dietary fiber content <10 g (Table 1). The LFD group received instructions on continuing the LFD plan the day before the colonoscopy and were allowed to eat 5 meals, including breakfast, midmorning snack, lunch, midafternoon snack, and dinner (Table 1), whereas CLD subjects received instructions on following a strict CLD 24 hours before the procedure.

All study participants received 4 L of polyethylene glycol solution in a split-dose fashion: 2 L in the evening of the day before colonoscopy and 2 L in the morning starting 5 hours before the procedure. All colonoscopies were performed during the morning.

TABLE 1. Barcelona diet plan for the day before colonoscopy: low-fiber diet group

Meal	*Carbohydrate*	*Protein*	*Dairy products*
Breakfast	80 g of white bread or refined cereals (60 g) or 3 slices of white toast	Turkey breast (120 g) or ham (120 g) or cheese (60 g)	1 glass (250 mL) milk or 2 full-fat yogurts (coffee at will is allowed)
Snack			1 glass (250 mL) milk or 2 full-fat yogurts
Lunch	White rice (130 g) or plain white pasta (200 g) or peeled potatoes (fried, baked, or boiled) (300 g)	Lean meat: beef (100 g) or pork or poultry (160 g) or fish (200 g) or eggs (2 units)	1 full-fat yogurt
Snack			1 glass (250 mL) milk or 2 full-fat yogurts
Dinner (6 P.M.)	White rice (130 g) or plain white pasta (200 g) or peeled potatoes (fried, baked, or boiled) (300 g)	Lean meat: beef (100 g) or pork or poultry (160 g) or fish (200 g) or eggs (2 units)	1 full-fat yogurt

Choose 1 item of each group. (The maximum allowed quantity is indicated.) In each meal, 2 tablespoons of vegetable oil or an equivalent amount of butter are allowed.

Outcome Measures

Our primary outcome was the rate of adequate bowel preparation measured with the BBPS.[14] Adequacy was defined as a colonoscopy with a score of 2 or 3 points in all colon segments.[15]

Secondary outcomes were the adequate bowel preparation rate in the different segments of the BBPS (right, left, and transverse colon) and other colonoscopy quality variables, tolerability, acceptability, and compliance with the laxative intake. Other indicators of colonoscopy quality included cecal intubation rate, and whole, proximal, and distal colon polyp and adenoma detection rate in the whole, proximal, or distal colon (related to the splenic flexure). Tolerability of the bowel preparation was measured rating hunger and patient volume perception, which were quantified using a 1 to 10 visual analogue scale (1 = excellent and 10 = unbearable), and also with self-reported nausea or vomiting and bloating. We defined acceptability as the patient´s willingness to use the same bowel preparation protocol in a hypothetical new procedure. Compliance was evaluated as mean laxative intake in liters and also as the proportion of patients imbibing at least 3 L (75%) of laxative.

Data Collection

Information on age, sex, history of constipation (according to Rome III criteria), Charlson Comorbidity Index,[16] and the endoscopist who performed the procedure were gathered in a personal interview and from medical charts. The participants completed self-administered questionnaires on hunger, volume perception, nausea, vomiting, and bloating during the bowel preparation process, and acceptability and compliance with laxative intake.

Statistical Analysis

The sample size was calculated for a noninferiority test. Estimating 96% of adequate bowel preparation with CLD was based on our previous data with our current CLD bowel preparation protocol (unpublished data). A noninferiority margin of 6% was established to maintain adequate bowel preparation with an LFD over 90%, as recommended in the clinical guidelines.[3] The sample size resulted in 138 subjects per arm, with an α-risk of 0.05, 80% power, and an expected loss to follow-up of 5%. This sample size calculation was estimated to provide noninferiority of LFD to CLD while achieving the recommended minimum of 90% of adequate preparations for a screening colonoscopy.

All randomly assigned patients were included in the intention-to-treat (ITT) analysis. Missing efficacy data were imputed as failures. Patients who fulfilled the bowel preparation protocol and underwent the colonoscopy were included in the per protocol (PP) analysis.

For the primary outcome, a noninferiority test was performed. It was proven if the 1-sided 95% lower confidence limit for the difference between treatments was ≥–6%. If noninferiority was met, a superiority test was performed.

As for the secondary outcomes, the qualitative variables were compared between groups by the Pearson χ^2 test or Fisher test when appropriate. Quantitative variables were compared using the Student *t* test for independent samples. Two-tailed *p* values of <0.05 were considered statistically significant. A research statistician performed the analysis using Stata software version 13 (StataCorp, College Station, TX).

RESULTS

The study was conducted between March 17 and June 30, 2015. Figure 1 shows the flow diagram of patient recruitment. All 276 eligible candidates were randomly assigned and included in the ITT analysis for efficacy. For the PP analysis, 9 participants (3%) were excluded after randomization: 6 in the CLD group and 3 in the LFD group, all for nonappearance at the colonoscopy appointment. Self-administered questionnaires were collected in 249 cases (90%). Both groups had comparable baseline character-

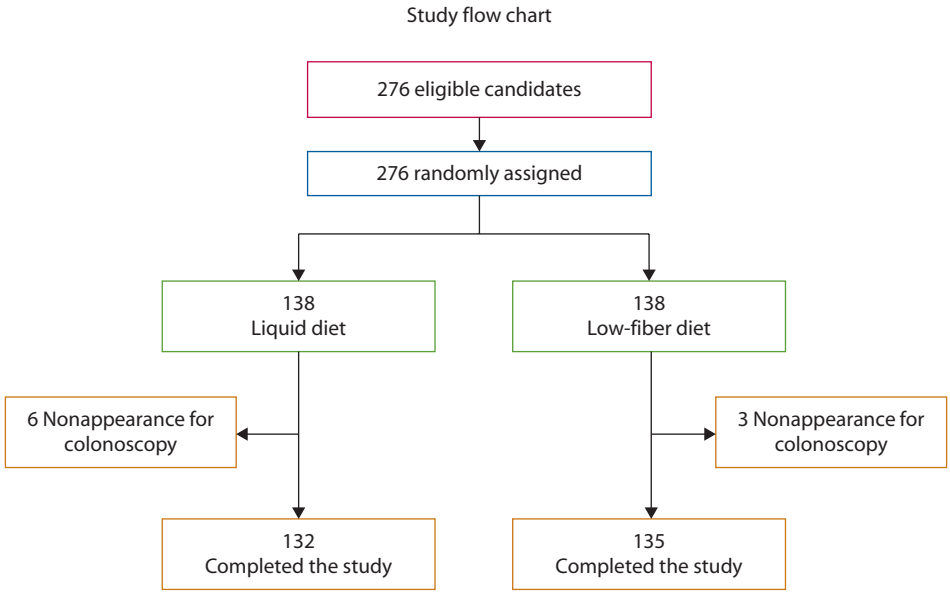

FIGURE 1. Consolidated Standards of Reporting Trials flow diagram.

istics and patients were equally distributed among endoscopists. Men accounted for 52% of participants (48% in CLD and 56% in LFD, $p = 0.19$) with a mean age of 59.9 years (60.1 in the CLD group and 59.9 in the LFD group, $p = 0.83$). The mean Charlson Comorbidity Index was 2.4 (2.4 in CLD and 2.4 in LFD groups, $p = 0.87$), and 5.5% had a history of chronic constipation (6% in CLD and 5% LFD, $p = 0.8$).

Primary Outcome

In the ITT analysis, the adequate bowel preparation rate was 89.1% (95% CI, 82.8–93.3) in the CLD group and 95.7% (95% CI, 90.8–98) in the LFD group (Table 2). The lower CI limit for adequate bowel preparation was >90% in the LFD group but not in the CLD group. The risk difference between groups was 6.5% (95% CI, 0.2%–13.2%). Noninferiority was demonstrated for LFD since the lower confidence limit of the risk difference was 0.2%, which was over the –6% considered for noninferiority. Furthermore, the rate of adequate bowel preparation with LFD also attained statistical superiority, $p = 0.04$.

In the PP analysis, the rate of adequate bowel preparation in the CLD group was 93.2% (95% CI, 87.5%–96.4%) and 97.8% (95% CI, 93.7%–99.2%) in LFD participants. The risk difference was 4.6% (CI 95%, –0.6% to 10.4%). Noninferiority was proven as the lower confidence limit of the risk difference (–0.6%) that was over the –6% considered for noninferiority. The superiority test for LFD in the PP analysis was not proven ($p = 0.07$).

There were no statistically significant differences in the adequacy scoring between endoscopists (Fisher exact test, $p = 0.393$).

Secondary Outcomes

Both ITT and PP analyses showed no statistical differences in adequate bowel preparation in the different segments

TABLE 2. Primary and secondary efficacy outcome measures: intention-to-treat analysis

Variable	*CLD group n = 138*	*LFD group n = 138*	*Risk difference % (95% CI)*	*p*
Adequate bowel preparation, n (%)	123 (89)	132 (96)	6.5 (0.2 to 13.2)	**0.041**
BBPS ≥2, n (%)				
Right colon	126 (91)	132 (96)	4.3 (–1.6 to 10.7)	0.144
Transverse colon	131 (95)	133 (96)	1.4 (–4 to 6.9)	0.56
Left colon	126 (91)	133 (96)	5.1 (–0.8 to 11.3)	0.08
Cecal intubation rate, n (%)	131 (95)	133 (96)	1.4 (–3.8 to 6.9)	0.56
Whole-polyp detection rate, n (%)	86 (62)	100 (72)	10.1 (–0.9 to 20.9)	0.07
Proximal colon polyp detection rate, n (%)	60 (43)	65 (47)	3.6 (–8 to 15.3)	0.545
Distal colon polyp detection rate, n (%)	58 (42)	72 (52)	10.1 (–1.6 to 21.5)	0.091
Overall adenoma detection rate, n (%)	69 (50)	82 (59)	9.4 (–2.3 to 20.8)	0.116
Proximal adenoma detection rate, n (%)	49 (36)	49 (36)	0 (–11.1 to 11.1)	1
Distal adenoma detection rate, n (%)	43 (31)	58 (42)	10.9 (–0.5 to 21.8)	0.061

CLD = clear-liquid diet; LFD = low-fiber diet; BBPS = Boston bowel preparation scale. Bolded values are statistical significant.

TABLE 3. Tolerability, acceptability, and compliance

Variable	*CLD group n = 138*	*LFD group n = 138*	*p*
Hunger, VAS, mean (95% CI)	4.5 (4.1–5)	3.5 (3.1–4)	**0.003**
Excessive volume perception, VAS, mean (95% CI)	6.9 (6.5–7.3)	6.2 (5.7–6.7)	**0.03**
Bloating, VAS, mean (95% CI)	3.3 (2.9–3.8)	3.3 (2.8–3.7)	0.8
Nausea or vomiting, VAS, mean (95% CI)	2.3 (1.9–2.7)	1.6 (1.2–2)	**0.02**
Acceptability, n (%)	106 (86)	112 (89)	0.5
Laxative intake, liters, mean (95% CI)	3.2 (3.1–3.4)	3.4 (3.3–3.6)	0.07
Laxative intake ≥3 L, n (%)	96 (78)	110 (88)	**0.037**

CLD = clear-liquid diet; LFD: = low-fiber diet; BBPS = Boston bowel preparation scale; VAS = visual analogue scale (1 = excellent, 10 = unbearable). Bolded values are statistical significant.

of the BBPS, cecal intubation rate, adenoma detection rate (ADR), and polyp detection rate in the whole, proximal, and distal colon. Table 2 shows the results of the ITT analysis.

Hunger, volume perception, and nausea/vomiting scores were significantly lower in the LFD group. No differences were found in bloating or acceptability. Regarding compliance, a slight increase was observed in mean laxative intake in the LFD group, but without achieving statistical significance ($p = 0.07$); however, the number of patients completing at least 3 L (75%) of laxative was higher in the LFD group than in the CLD group ($p = 0.04$) (Table 3).

DISCUSSION

In a randomized trial conducted within an organized CRC screening program, a normocaloric LFD the day before colonoscopy achieved not only noninferior efficacy, but also superiority for adequate bowel preparation compared with a CLD. In addition, our dietary intervention associated improved tolerability with less hunger and volume perception. No differences were found in other quality parameters of colonoscopy, such as cecal intubation rate, polyp detection rate, or ADR in whole colon or right-sided colon.

A normocaloric LFD the day before colonoscopy achieved a higher quality of bowel preparation than a CLD. The efficacy of an LFD versus a CLD the day before colonoscopy has been evaluated in previous studies, but their results were dissimilar. In this respect, 8 RCTs found no significant differences in terms of efficacy,[4–6,8–12] whereas 1 RCT reported better efficacy with LFD.[7] Nevertheless, that study had an unacceptably low rate of adequate bowel preparation in the CLD group (52%).

Those RCTs had several limitations that should be mentioned. On the one hand, the definition of LFD varied across studies. Most referred to a low-residue diet instead of a LFD. Recently, the term low-residue diet has been removed from nutritional clinical guidelines given the lack of consensus in its quantitative definition.[17] Because the only component of fecal residue present in the diet is dietary fiber, it has been proposed to substitute the term low-residue diet with LFD and to quantitatively define a maximum of 10 g fiber/day for an LFD.[18] In 8 of the 9 published RCTs, the amount of fiber in the recommended diet was not specified.[4,5,7–12] Only 1 RCT indicated the amount of fiber included in the diet; however, the quantity is 32 g/day, well above the 10-g limit recommendation.[6] It should be pointed out that the fiber content in our proposed diet plan was <10 g/day.

On the other hand, all the proposed diets were hypocaloric, ranging from 1000 to 1200 kcal/day. The recommended caloric intake for a middle-aged adult varied between 1800 and 2100 kcal/day, as calculated with the Harris-Benedict formula.[19] In the present study, a full diet with a mean caloric intake of up to 2000 kcal/day was included. A normocaloric diet could facilitate patient adherence to the recommendations.

Another significant flaw of most of the published RCTs is the lack of information on what truly defines "adequacy." Guidelines define adequate bowel preparation if the endoscopist is able to identify polyps >5 mm.[20] A study by Clark et al[15] aimed at quantifying adequate bowel cleansing for surveillance or screening colonoscopy concluded that those with BBPS scores ≥2 for every colon segment have adequate bowel preparation. Six of the studies did not use the BBPS, which is the most rigorously validated bowel preparation scale.[4–8,11] Furthermore, the 3 RCTs that used the BBPS either did not report a minimum score for the definition of adequate preparation,[9] or used an overall score without establishing a minimum score for each colon segment.[10,12]

Finally, the use of a split-dose protocol was systematically used in only 4 studies.[4,9,10,12] The split-dose regimen is the only intervention that has been demonstrated to improve both bowel preparation quality and ADR.[21]

Another salient aspect of the present study was the recruited population. Earlier RCTs focused on a mixed population of symptomatic, screening, and surveillance colonoscopies. The analysis of 8 previous studies of an unselected population[4,5,7–12] shows that 87% (629/723) of participants in the LFD group had an adequate bowel preparation, compared with 83% (586/704) of participants in the CLD group. Although there may be a slight trend toward a better efficacy in the LFD group, in the pooled analysis there were no statistically significant differences in

efficacy between both groups.[22] Our study included only participants in an organized colorectal screening program based on fecal immunochemical testing (FIT). The randomized setting, coupled with the highly controlled and homogeneous population included, also brought the initial findings on such an association shown in previous studies to a higher level of evidence. Moreover, in a CRC screening program, the need for a high standard of bowel cleanliness is crucial because the findings of the index colonoscopy will determine the interval for the follow-up colonoscopy.

It should be pointed out that a previous study demonstrated that an LFD adapted to diabetic patients, together with an educational intervention before colonoscopy, improved bowel cleanliness.[23]

Fecal residue is composed from nonabsorbable fiber as well as dead cells, mucus, and bacteria. During the bowel preparation process, all that matter has to be removed from the colon. There are some explanations that may justify why patients on a LFD the day before the colonoscopy achieve better cleansing.

First, a strict CLD is difficult to follow and compliance may be suboptimal; nevertheless, we did not measure patient´s compliance in study groups and we cannot confirm this hypothesis. Second, a strict CLD may impair bowel peristalsis, resulting in ineffective evacuation of fecal residue. In fact, because an LFD adds little fecal residue, another possible complementary explanation is that the total balance of fecal evacuation is improved with this diet.

Although efficacy is the leading factor in bowel preparation, patient tolerability is also important. Participants in the LFD group reported less hunger, perception of excessive volume intake, and nausea or vomiting, and better compliance with the laxative intake. In the setting of a screening colonoscopy, tolerability is a major concern because participants are asymptomatic, relatively young, and apparently healthy, and patient experience is important for both general uptake of the program and compliance with future follow-up colonoscopies.

We found no differences in other colonoscopy quality parameters, such as ADR and the cecal intubation rate, although a tendency toward a higher polyp detection rate, in particular, for distal polyps and adenomas, was observed. Note the high yield of ADR in our population, which is in accordance with other FIT-positive average screening population studies.[24] Several studies with a large sample size found that bowel cleanliness increased ADR, although the present study was underpowered to detect differences in ADR.[25,26]

To our knowledge, this is the largest clinical trial evaluating a well-structured dietary intervention in bowel preparation for colonoscopy. Moreover, it is also the only clinical trial including a very homogeneous population from an organized CRC screening program.

Our study was not limitation-free. First, the single-center design of the study could limit the external validity of the results. Nevertheless, the selection criteria for this trial were not restrictive and the results may thus apply to any FIT-based screening program population. Furthermore, the present findings may not be generalizable to other clinical settings. We did not measure participant's compliance with the proposed diet. Finally, we used a non-validated questionnaire for symptoms, a common limitation in most studies on bowel preparation.

CONCLUSIONS

This trial showed that a normocaloric LFD the day before a screening colonoscopy achieves better results in terms of adequate colon preparation and tolerability than a CLD. We conclude that a LFD the day before colonoscopy should be considered the most effective approach to bowel preparation in CRC screening colonoscopy.

ACKNOWLEDGMENTS

We thank as contributors all the registered nurses who participated in the study: Gemma Casals, Montserrat Bonilla and Ines Ibañez. We also thank as contributor Dr Agnés Fernández-Clotet who was involved in critical revision for intellectual content of the manuscript. We thank Christine O'Hara for review of the English version of the manuscript.

PROCOLON is a group of investigators conducting research in the frame of the Barcelona colorectal cancer screening program, and includes the following members: Rafael Abós-Herrándiz, Jaume Grau, Eva Abril, Marta Aldea, Cristina Álvarez, Marco Antonio Alvarez-Gonzalez, Montserrat Andreu, Isis Araujo, Josep M. Augé, Anna Aymar, Guillermo Bagaria, Francesc Balaguer, Xavier Bessa, Montserrat Bonilla, Andrea Burón, Sabela Carballal, Xavier Castells, Antoni Castells, Rosa Costa, Míriam Cuatrecasas, Maria Pellisé, Mercè Comas, Josep M. Dedeu, Imma Garrell, Maria Estrada, Jordi Gordillo, Rafael Guayta, Mar Iglesias, Leticia Moreira, Cristina Hernández, Laura Llovet, María López-Cerón, Francesc Macià, Lorena Moreno, Gemma Navarro, Teresa Ocaña, Mercè Pintanell, Àngels Pozo, Cristina Rodríguez, Teresa Puig, Faust Riu, Liseth Rivero-Sánchez, Maria Sala, Ariadna Sánchez, M. Francisca Murciano, Antoni Trilla, Agustín Seoane, Judit Sivilla, Anna Serradesanferm, Isabel Torà.

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