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Conflict of Interest Disclosures: None reported.

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In Reply We agree with Dr Talan that goals of treatment and individual preferences are decisive factors that will guide modern care of acute appendicitis. However, for appendicitis treated with antibiotics, we would like to clarify the meaning of treatment failure, which is scientific terminology describing lack of symptom improvement within 24 to 48 hours after initiation of antibiotics.[1] In our Review,[1] we based our recommendations for the management of acute uncomplicated appendicitis on a critical evaluation of currently available data about the potential of success of each treatment modality. That said, patients with appendicoliths and signs of systemic inflammatory response (such as high fever and leukocytosis)[2] may choose to pursue antibiotic treatment and accept the chance of a higher "failure" rate, hoping to achieve the other benefits of nonoperative therapy noted by Talan. We believe that the management of acute appendicitis is changing. Now, patients have a reasonable therapeutic option other than surgery that should be presented to them in detail. For patients who want a choice, our responsibility is to adequately inform them of the long-term outcome of the antibiotics-first approach to appendicitis before proceeding with nonoperative therapy, especially since long-term data have shown that almost 50% of patients initially treated with antibiotics alone for acute appendicitis require appendectomy within 3 to 4 years.[3]

We also agree with Dr Huerta's concerns about the applicability of our proposed therapeutic algorithm for patients with acute appendicitis in LMICs. It is true that the approach recommended in our Review[1] was adjusted to health care typically provided in high-income countries. We recognize that routine use of imaging (especially computed tomography) is the standard of care in the US but not in other parts of the world; thus, the management of appendicitis must be modified based on the resources and experience at the site of care. For example, data from Europe support the routine use of ultrasound as the imaging modality of choice for patients with suspected appendicitis to assess for the presence of appendicoliths or perforation.[4] Regarding the surgical approach, the focus of our article was not to discuss the role of open vs laparoscopic appendectomy in the management of acute uncomplicated appendicitis but to identify which patients could benefit from an antibiotics-first approach compared with surgery, based on recent relevant trials.

Thus, we provided in-depth data about these trials to guide physicians, surgeons, and patients in weighing the pros and cons of each treatment option, to allow for planning of appropriate care and improvement in the quality of informed consent. In the setting of a disease that can be easily cured with routine surgery, patients should be aware of the high rates of long-term treatment failure of appendicitis with antibiotics. We believe that the definitive management of appendicitis continues to be appendectomy for most patients. However, we can envision an era of shared decision-making in which many patients with acute appendicitis could avoid emergent surgery by being successfully treated with antibiotics and then undergoing appendectomy on an outpatient elective basis.

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Conflict of Interest Disclosures: Dr Pappas reported serving as a paid consultant for TransEnterix. No other disclosures were reported.

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Intra-articular Platelet-Rich Plasma vs Placebo Injection and Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis

To the Editor A recent study[1] found that intra-articular injection of platelet-rich plasma (PRP) did not significantly improve symptoms or joint structure at 12 months in patients with mild to moderate knee osteoarthritis (OA) compared with placebo injection. However, we have some concerns about this study's methodology and nomenclature that should be discussed so that the results and conclusions are put into proper context.

First, the authors reported that the PRP used in their study had platelets concentrated 1.2 times over baseline. Other studies demonstrated that this same concentration system

produced a solution with platelets concentrated 1.6 times.[2] Furthermore, the standard deviation of platelet counts reported in these studies[2] demonstrates that some preparations have platelets reduced below baseline. Therefore, the injections used in this study[1] cannot be referred to as PRP because they do not meet the necessary minimum concentration of PRP.[3] The experimental group of the study used red blood cell– and white blood cell–reduced plasma, but this is not PRP. While an accurate conclusion of this trial is that plasma is not superior to placebo for knee OA, this is still valuable information because plasma contains anabolic proteins, such as insulin-like growth factor 1, that have been suggested as potential therapeutics for knee OA.[4] Despite the presence of such growth factors, the work by Dr Bennell and colleagues demonstrates that plasma alone has no significant benefit for knee OA patients.

Second, a dose-response relationship for PRP in knee OA has been shown in double-blind, randomized, placebo-controlled trials,[5] demonstrating that platelet concentration matters. Given the low platelet doses used, it is possible that the PRP used in this study[1] failed to meet the therapeutic threshold.

Third, we believe that in the performance of rigorous clinical trials, definitions and titles of studies need to accurately convey the intervention being studied. While Bennell and colleagues have completed an excellent study on the use of plasma for knee OA, the current title does not accurately represent the intervention.

The field of PRP needs studies with the rigorous design presented in this study,[1] but we want to ensure that the PRP product used meets the standard definition and that premature conclusions are not drawn from the present work.

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Conflict of Interest Disclosures: Dr Baria reported receipt of compensation as an educational instructor from Arthrex. Dr Flanigan reported receipt of consulting, travel and lodging, and education payments from Linvatec Corp; consulting payments, travel and lodging, and honoraria from Vericel; payment for services other than consulting from Smith & Nephew, Karl Storz Endoscopy, and Pacira Pharmaceuticals; and consulting payments from Zimmer Biomet, Medical Device Business Services, and DePuy Synthes.

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To the Editor As representatives of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO), the Groupe de Recherche International Sur Les Injections de Plaquettes (GRIIP), and the Société Française de Traumatologie du Sport (SFTS), which include groups of physicians and researchers interested in regenerative medicine, we have some possible explanations for the negative results of the recent study investigating the effect of PRP injections on knee OA.[1]

First, the sample size was calculated to detect a 40% difference between groups, whereas saline injection is known to have a substantial placebo effect. Second, the authors chose a structural assessment as a co-primary end point although cartilage regeneration by PRP remains unclear. Third, the study included a large percentage of patients with joint effusion (43.8% in the PRP group and 36.8% in the saline group), which may decrease the potential efficacy of PRP.[2] Fourth, no data were reported between 2 and 12 months, preventing any midterm conclusions. Fifth, the MRI Osteoarthritis Knee Score (MOAKS), which assesses the evolution of OA, does not measure cartilage volume as mentioned in the title.

In addition, although the authors provided the Minimum Information for Studies Evaluating Biologics in Orthopaedics, further analysis reveals that this study did not perform systematic quality control of the injected PRP. The biological variability of the PRP used in this trial has been previously described.[3] Moreover, analysis of growth factors and cytokines contained in the injected PRP used in this study reveals an extremely high concentration of transforming growth factor (TGF) β compared with their healthy reference controls, which is concerning because a significant correlation has been shown between TGF-β and worsening of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score.[4]

From a more general perspective, it is essential to consider that a recent meta-analysis (which included more than 20 randomized clinical trials) demonstrated benefits of PRP for knee OA compared with other injectable treatments.[5] In addition, Marx's pioneering study from 20 years ago provided the most precise details of his procedure regarding harvesting and preparation steps, a systematic quality control for each patient, and use of an objective assessment of efficacy reminding that randomized clinical trials published in this field should have the rigor of what Marx did.

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To the Editor We would like to draw attention to 3 concerns about the recent study[1] of intra-articular PRP injection for knee OA. First, participants were asked to discontinue nonsteroidal anti-inflammatory drugs and other analgesics for knee pain (except acetaminophen rescue pain relief); however, more than 68% of participants in the PRP group and more than 60% of participants in the placebo group used pain medications, including nonrescue pain medication in more than 50% in the PRP group and almost 37% in the placebo group. This nonadherence to the study protocol may have had an important effect on the comparisons. Therefore, we believe that both intention-to-treat and per-protocol analyses should have been performed and presented.

Second, previous studies have shown that knee effusions are independently associated with knee pain,[2] and a recent clinical trial used the change in effusion size as its primary outcome.[3] The current study[1] found no significant benefit of PRP treatment on knee effusion. Moreover, the presence of knee effusion did not moderate the effects of PRP on the 2 primary outcomes at 12-month follow-up. The study[1] stated that "if an effusion was present and amendable to aspiration, this was performed using a separate syringe via the suprapatellar burse." This may have contributed to the negative study findings, so it would be helpful to have information about the number of participants who underwent aspiration of a knee effusion in both groups.

Third, the saline placebo treatment group exceeded the minimum clinically important difference for decreased pain score, indicating a significant placebo effect. According to the medical literature, about 75% of pain relief may be attributed to placebo effect or context of therapy in OA trials. Moreover, invasive treatments have a greater placebo effect than noninvasive treatments.[4] While injections can cause local bleeding and change the pressure-volume relationship in an anatomical space, the needle effects could mimic acupuncture, which has been used to treat OA.[5]

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To the Editor We believe there are 3 issues worth considering about the study by Dr Bennell and colleagues.[1] First, individuals diagnosed with unilateral or bilateral knee OA were included in this trial, and only the most symptomatic knee received the intervention. However, pain assessments are prone to being influenced by the severity of pain in the contralateral knee.[2] Therefore, the number of patients with bilateral knee OA and the severity in the less symptomatic knee may affect the conclusion and should be provided.

Second, because the sample size was determined based on the level of reduction in medial tibial cartilage volume loss, which could delay knee replacement, the incidence of knee replacement of the index knee during follow-up should be reported. Third, prior studies have shown that hip problems can play a role in knee pain and function.[3] In this study,[1] more patients in the PRP group (41/144) had problems in hip joints than in the placebo group (32/144), although the difference was not statistically significant—a finding that warrants further investigation.

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Conflict of Interest Disclosures: None reported.

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In Reply Drs Baria and Flanigan consider the platelet concentration used in our study[1] too low to be PRP, claiming it was 1.2 times baseline. It appears they miscalculated this using the *participant* baseline whole blood platelet count and the *manufacturer* PRP mean platelet volume.[1] We were unable to assess our participants' PRP platelet count, but data from the manufacturer and an independent study[2] report a concentration of 1.6 times baseline, which exceeds the US Food and Drug Administration's minimum platelet concentration for PRP[3] and meets Marx's definition.[4] To our knowledge, no study has directly shown greater clinical efficacy with higher platelet concentrations; one found no relationship,[5] while a systematic review found that high concentrations might be less effective.[6] The study by Görmeli et al cited by Baria and Flanigan did not assess associations of platelet concentration and pain but found that 3 injections (the same number used in our study) were more effective than 1.

Dr Magalon and colleagues suggest that the high TGF-β concentration in the PRP used in our trial could have been detrimental based on a small study (n = 22) in which higher TGF-β concentration was associated with worse outcome.[5] However, the TGF-β concentrations in our PRP were consistent with other systems, and we found no significant relationship between TGF-β concentration and 12-month change in pain in a subsample of our PRP group (P = .12; n = 54).

Drs Zhu and Ding and Dr Lei and colleagues express concern about whether participant factors might explain the null findings of our study. We included individuals with bilateral knee OA and hip pain because these are common clinical presentations. Additional analyses adjusting the primary outcomes for these did not show significant between-group differences (pain: P = .17 to P = .18; cartilage volume: P = .78 to P = .81).

Forty percent of our participants had magnetic resonance imaging–detected knee effusion, which Magalon and colleagues and Zhu and Ding believe could reduce PRP benefits, a contention based on expert consensus given a lack of evidence. Our finding that the presence of knee effusion did not moderate outcomes (eTable 13 in the article's Supplement 2)[1] suggests the inclusion of these participants did not dilute PRP effects. Sensitivity analyses (eTable 12)[1] adjusting for between-group differences in aspiration also did not alter primary outcomes.

Zhu and Ding question whether use of pain medications influenced outcomes. This is unlikely given similar proportions across groups. They request a per-protocol analysis excluding those who used pain medication. However, this would render the randomized group comparison invalid because medication use was a postrandomization variable.

In addition to pain, we chose a co-primary structural outcome of cartilage volume because of the hypothetical potential effects yet limited data to allow definitive conclusions. Cartilage volume was measured quantitatively using a well-accepted protocol, not the semiquantitative MOAKS score, which was used for secondary structural outcomes. We did also measure the primary pain outcome at midterm time points for potential health economic purposes, and improvements with PRP were not significantly better than saline (6-month mean difference, −0.2 [95% CI, −0.8 to 0.4; P = .53]; 9-month mean difference, −0.3 [95% CI, −0.8 to 0.3; P = .38]).

Lei and colleagues ask for information about knee replacements during follow-up. Due to the small numbers (0 in the PRP group and 3 in the placebo group), no conclusions can be drawn about PRP effects on knee replacement. Substantial placebo effects of injection therapies, including saline, are well documented. We believe we did not overestimate potential PRP effects as we powered our study to find clinically relevant between-group differences in our 2 primary outcomes.

We tested 1 commercial PRP system and encourage additional rigorous trials with other PRP systems. Pending those results, guidelines will likely continue not to recommend PRP for knee OA.

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