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COMMENT & RESPONSE

Revised Meta-analysis of Vitamin K and Fractures

To the Editor Torgerson and colleagues are to be congratulated in addressing the effect on their meta-analysis of trials of vitamin K and fractures following the recognition that 3 of 7 contributing trials are problematic.[1] However, we are concerned that the conclusions of the updated article are no longer consistent with the results of the updated analysis presented in their Figure 4.

After removing the trials reported by Sato et al, fracture data are available for only 440 participants (221 control, 291 vitamin K) in 4 small trials, none of which was placebo controlled. In the updated pooled analysis there are only 78 morphometric vertebral fractures (54 control, 24 vitamin K), 9 nonvertebral fractures (8 control, 1 vitamin K), and 3 hip fractures (3 control, 0 vitamin K).

In the original publication,[2] the authors were concerned about the high rate of hip fractures in the trials of Sato et al and therefore conducted a sensitivity analysis excluding these trials. This concern also applies to vertebral fractures in each of the remaining trials, in which the incidence in the control groups ranged from 10% to 13% per year, 2- to 3-fold higher than that in control groups in large, double-blind placebo-controlled osteoporosis trials, including those in Japan.[3,4] Thus, the results for vertebral fracture may not be generalizable beyond these trial cohorts with very high vertebral fracture rates.

Consequently, the data in the updated analysis do not justify statements in the study abstract that the effect of vitamin K on hip fracture is "still a large effect" when analyses are based on only 3 hip fractures, or that there is a "strong effect on incident fractures among Japanese patients" when there are few events and the results are of questionable external validity. It is difficult when the much later retraction of contributing trials substantially changes the results of a meta-analysis. However, clarity is important, because this meta-analysis has been cited 187 times, including 4 citations already in 2018 and in the executive summary of the 2011 Japanese guidelines for prevention and treatment of osteoporosis.[5]

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In Reply I thank the authors for their considered response to our note of caution about our vitamin K review,[1,2] with respect to problems of including trials by Sato et al. In our original review, the phrase we used of there being a large effect (odds ratio, 0.30) is technically correct, because this kind of treatment effect is rarely seen in trials of treatments for osteoporosis. Nevertheless, Grey and colleagues are right to be concerned that this effect is based on a tiny number of events and is not statistically significant. Consequently, the findings from our review should, at best, be used to inform future research studies that could confirm or refute the suggestion that there might be a clinically important difference in fracture rates using vitamin K supplements rather than informing current clinical practice. Similarly, their concerns about generalizability are also well founded given that the populations where an effect was noted had unusually high event rates.

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Good Clinical Practice in Diagnosis of Vulvovaginal Symptoms

To the Editor We read with great interest the recent report by Mitchell and colleagues regarding the efficacy of topical low-dose vaginal estrogen vs topical vaginal moisturizer or placebo for treating postmenopausal vulvovaginal symptoms.[1(p681)] We are concerned with the authors' conclusion that "...neither prescribed vaginal estradiol tablet nor over-the-counter vaginal moisturizer provides additional benefit over placebo vaginal tablet and gel in reducing postmenopausal vulvovaginal symptoms."[1]

Choosing "symptoms" as the inclusion criteria and not a confirmed diagnosis of vaginal atrophy caused by estrogen deficiency as the cause of the symptoms is, in our opinion, the

main limitation of the study. Postmenopausal women are prone to have various conditions other than vaginal atrophy, including vulvodynia, desquamative inflammatory vaginitis, lichen sclerosus, contact dermatitis, and more.[2] All of these conditions cause symptoms of itching, pain, irritation, dryness, or dyspareunia. In addition, it is common for women to have 2 genital conditions simultaneously.[3] For instance, a woman can have vaginal atrophy and lichen sclerosus or contact dermatitis, and topical vaginal estrogen will treat only the atrophy but will not treat the other entity. In such case, the woman will continue to be symptomatic, and one can mistakenly conclude that vaginal estrogen is only as good as placebo. We fear that this is the case in the current study by Mitchell and colleagues. The objective data available in the study regarding vaginal atrophy are reflected in the vaginal maturation index and, as presented, only the arm treated with estrogen had an improved vaginal maturation index, increase in superficial cells (57% [45] vs 11% [8]), and a pH lower than 5.0 (46% [36] vs 12% [10]) following treatment. Our clinical experience supports the assumption that if measured physiologic improvement in vaginal mucosa is not reflected in improved symptoms, there are other reasons for symptoms aside from atrophy.

We are concerned that the authors' conclusion will be adopted by others, as it appeared in the *New England Journal of Medicine* bulletin Journal Watch 1 day after publication:[4] "...postmenopausal women experiencing vulvovaginal symptoms should choose the cheapest moisturizer or lubricant available over the counter...."[4] No doubt that a study that deals with such a common universal problem as postmenopausal vulvovaginal symptom has the potential to influence clinical management. We believe that whenever possible, good clinical practice should always be based on confirmed diagnosis followed by specific treatment and not on "symptomatic" diagnosis that is nonspecific and does not clarify which of the various entities potentially contributing to symptoms need be treated.

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In Reply We appreciate the comments of Drs Reichman and Sobel in regard to our recent report of efficacy of hormonal and nonhormonal treatments for postmenopausal vaginal discomfort.[1] They express concern that we enrolled participants based on symptoms rather than objective physical findings of vulvovaginal atrophy. We opted to use an outcome that is relevant to patients—symptom severity—in a 12-week trial, the standard duration for studying interventions for genitourinary syndrome of menopause. Trials of longer duration have not shown greater benefit.[2,3] Our study was powered to detect a difference of half a standard deviation between treatment arms in the change from baseline of most bothersome vulvovaginal symptom severity (approximately 0.5 on a 0- to 3-point scale; mean baseline score, 2.5). Smaller differences, arguably, would not reflect a clinically relevant benefit. As to objective endpoints, several studies show that physician assessment of the appearance of vulvovaginal atrophy does not correlate with patient report of symptoms,[4,5] which is why we chose symptoms as our inclusion criteria and primary outcome. That said, the majority of our participants did meet the objective criteria for atrophy, with vaginal maturation index less than 5% superficial cells and a pH greater than 5 (81%).

With regard to the concern that we might have enrolled women who had symptoms due to another condition such as lichen sclerosus, all participants underwent an in-person screening visit, which included a pelvic exam and examination of a vaginal wet mount, to exclude the conditions mentioned by Drs Reichman and Sobel. In addition, women who reported premenopausal vulvovaginal pain of more than 3 months' duration were excluded, thus excluding women with chronic vulvodynia.

Finally, Drs Reichman and Sobel imply that we reported that estradiol was not beneficial for postmenopausal vulvovaginal symptoms. Far from it. Estradiol plus placebo gel worked very well (70% [67] of women experienced at least 50% reduction in symptom severity), but dual placebo worked equally as well (65% [62] of women experienced at least 50% reduction in severity). Even in the absence of "objective" improvement, women subjectively improved; more than half of the women from each treatment group with no improvement in vaginal maturation index or pH had reduction in symptom severity of more than 50% (estradiol, 57%; vaginal moisturizer, 55%; dual placebo 66%). To us, this suggests that estrogen repletion is sufficient to improve genitourinary symptoms after menopause in many women but is not always necessary for symptom improvement. We hope that the results of our study encourage patients and physicians to appreciate the complexity of this highly burdensome problem and to discuss all options for symptom management, choosing the one that best meets the patient's medical and financial needs.

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Acute Kidney Injury Due to Concomitant Vancomycin and Piperacillin-Tazobactam

To the Editor Bergstrom and colleagues present a very important case that highlights the dangers of medical overuse and specifically brings to light an increasingly recognized adverse event of acute kidney injury due to concomitant vancomycin and piperacillin-tazobactam.[1] The Infectious Diseases Society of America guidelines do not routinely recommend empirical vancomycin use, and, as the authors highlight, this patient was low risk and did not have an indication for additional gram-positive coverage with intravenous vancomycin.[2] This is especially important given the emerging data that concomitant use of vancomycin with piperacillin-tazobactam independently puts patients at risk of acute kidney injury. A 2017 systematic review and meta-analysis of 14 observational studies involving 3549 patients found a more than 3-fold increased risk of acute kidney injury with vancomycin and piperacillin-tazobactam when compared with vancomycin alone or in combination with another β-lactam (including cefipime or carbapenem).[3] Following this, a more recent systematic review and meta-analysis in 2018 involving more than 24 000 patients found that the rate of acute kidney injury was 22.2% for vancomycin and piperacillin-tazobactam vs 12.9% for comparators (eg, vancomycin plus cefipime, vancomycin plus carbapenem, monotherapy with vancomycin or piperacillin-tazobactam), yielding a number needed to harm of 11.[4]

Acute kidney injury secondary to vancomycin and piperacillin-tazobactam is a relatively new entity that may not be immediately appreciated and further supports appropriate antimicrobial use, especially in cases such as this where no clear indication for vancomycin was present. In situations where combination therapy is warranted, close monitoring of renal function is prudent. We agree with the authors that this case likely could have been safely managed as an outpatient procedure with oral antibiotics and close follow-up, and furthermore, even with an admission, judicious antibiotic use and avoidance of vancomycin use may very well have prevented the acute kidney injury and prolonged hospitalization.

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In Reply We concur with and thank Wu and Leong for emphasizing the risk of acute kidney injury with concomitant vancomycin and piperacillin-tazobactam therapy. This is especially relevant in low-risk patients with febrile neutropenia who do not have an indication for empirical vancomycin as in the patient described.[1] In 1 large retrospective study conducted at an academic medical center, combination vancomycin and piperacillin-tazobactam therapy was associated with twice the odds of developing acute kidney injury compared with combination vancomycin and cefepime.[2] Compared with cefepime, piperacillin-tazobactam is also associated with greater risk of developing thrombocytopenia, which is often already present in cancer patients with febrile neutropenia due to myelosuppression.[3] Thus, cefepime alone is a reasonable first-line drug for most cases of neutropenic fever. However, ultimately it requires thoughtful clinical judgment that considers the likely source of infection, severity of illness, the hospital or unit antibiograms, prior antibiotic exposure, and prior infections or colonization with multidrug resistant pathogens to determine when to choose an alternative antipseudomonal β-lactam or to add vancomycin.

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