MAJOR ARTICLE

Bacterial Vaginosis and Anaerobic Bacteria Are Associated with Endometritis

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Background. *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* account for approximately one-third to one-half of pelvic inflammatory disease (PID) cases. Thus, up to 70% of cases have an unknown, nongonococcal/nonchlamydial microbial etiology.

Methods. We investigated the associations of *N. gonorrhoeae, C. trachomatis,* bacterial vaginosis, anaerobic bacteria, facultative bacteria, and lactobacilli with endometritis among 278 women with complete endometrial histology and culture from the PID Evaluation and Clinical Health Study.

Results. Women with acute endometritis were less likely to have H_2O_2-producing *Lactobacillus* species (odds ratio [OR], 0.1; 95% confidence interval [CI], 0.01–0.8) and more likely to be infected with *C. trachomatis* (OR, 16.2; 95% CI, 4.6–56.6), *N. gonorrhoeae* (OR, 11.6; 95% CI, 4.5–29.9), diphtheroids (OR, 5.0; 95% CI, 2.1–12.2), black-pigmented gram-negative rods (OR, 3.1; 95% CI, 1.4–7.0), and anaerobic gram-positive cocci (OR, 2.1; 95% CI, 1.0–4.3) and to have bacterial vaginosis (OR, 2.4; 95% CI, 1.3–4.3).

Conclusions. We conclude that bacterial vaginosis–associated organisms are frequent among women with PID. Because these organisms were strongly associated with endometritis, we recommend that all women with PID be treated with regimens that include metronidazole.

Pelvic inflammatory disease (PID), the infection and inflammation of a woman's fallopian tubes (salpingitis) and uterine lining (endometritis), is a frequent and morbid condition among young women. In a 1995 national survey, 8% of all women and 11% of African American women reported that they had received treatment for PID [1]. More than 1 million American women seek treatment for PID annually [2, 3]. Major reproductive and gynecologic sequelae result from PID including infertility, ectopic pregnancy, recurrent PID, and chronic pelvic pain [4, 5].

PID has a multimicrobial etiology. *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* account for approximately one-third to one-half of PID cases [6–23]. Thus, up to 70% of cases of PID have a nongonococcal/nonchlamydial etiology. Anaerobic gram-negative rods and mycoplasmal bacteria, including *Mycoplasma hominis* and *Ureaplasma urealyticum,* have been isolated from the upper genital tract in women with endometritis and salpingitis [8, 10–14, 16–28]. Bacterial vaginosis diagnosed by the criteria of Nugent et al. [29] has been associated with clinically suspected and subclinical PID [21, 23–26, 28, 30, 31]. However, the upper genital tract microbiology among women with nongonococcal/nonchlamydial PID has not been comprehensively described. Most studies have been conducted in small samples of women and few have compared the upper genital tract frequency of nongonococcal/nonchlamydial microorganisms between women with and those without endometritis or salpingitis. Furthermore, coinfection of anaerobic or facultative bacteria with *N. gonorrhoeae* and *C. trachomatis* is common [11, 14, 16, 19, 20], and few studies have examined the independent role of nongonococcal/nonchlamydial pathogens in PID.

We tested the hypotheses that bacterial vaginosis and bacterial vaginosis–associated microorganisms are independently associated with endometritis in the PID Evaluation and Clinical Health (PEACH) Study, a multicenter randomized clinical trial designed to compare

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the effectiveness of inpatient and outpatient treatment for mild to moderate PID.

PATIENTS AND METHODS

Patient selection. The methods of participant recruitment, data collection, and follow-up have been described in detail elsewhere [32]. In brief, women aged 14–37 years were recruited from emergency departments, obstetrics and gynecology clinics, sexually transmitted disease clinics, and private practices at 13 clinical sites located throughout the eastern, southern, and central regions of the United States during the period of March 1996 through February 1999. Women with clinically suspected PID who gave informed consent were eligible for the PEACH study. Specifically, all women had a history of pelvic discomfort for ⩽30 days, findings of pelvic organ tenderness (uterine or adnexal) on bimanual examination, and leukorrhea and/or mucopurulent cervicitis and/or untreated (but documented) gonococcal or chlamydial cervicitis. Eight hundred thirty-one women met all of the inclusion criteria and were enrolled onto the PEACH study. Six hundred fifty-four women consented to undergo endometrial biopsies. Cultures for anaerobic and facultative aerobic pathogens were an unfunded component of the protocol. Three hundred forty-eight women from 4 of the 13 clinical sites (Charleston, SC; Philadelphia, PA; Pittsburgh, PA; and Providence, RI) participated in this elective substudy by separate fee arrangement. These women were not more or less likely to have endometritis at baseline. Two hundred seventy-eight women with complete endometrial histologic and culture data at baseline were included in these analyses. These women were not found to differ by age, marital status, occupational status, or education, compared with women who were not included. Those who were included in the analyses were less likely to be nonwhite (76.4% vs. 87.8%; $P < .01$).

Microbiologic studies and endometrial histology. Vaginal smears were Gram stained for bacterial vaginosis in a central laboratory by means of the standardized method as described by Nugent et al. [29]. An endometrial biopsy was performed, and samples were obtained for histologic examination, chlamydial PCR (Roche Diagnostics), gonococcal culture, and, in some women, facultative and anaerobic isolate culture. PCR and cultures were performed at the laboratory of one of the authors (S.L.H.).

Endometrial biopsy tissue specimens were examined for *Lactobacillus* species, anaerobic gram-negative rods, *Gardnerella vaginalis,* group B streptococcus, *Enterococcus* species, *Escherichia coli, Candida* species, *Mycoplasma hominis,* and *Ureaplasma urealyticum* . One sample was used to inoculate a human blood bilayer Tween agar for detection of *G. vaginalis* and a Columbia blood agar for detection of group B streptococcus, *Enterococcus* species, *E. coli* , and *Candida* species. A second swab sample was used to inoculate a Rogosa agar for recovery of lactobacilli, a *Brucella* agar for recovery of anaerobic bacteria, and broth media for recovery of *M. hominis* and *U. urealyticum.*

Lactobacilli were identified to the genus level on the basis of Gram stain morphology and production of lactic acid. All lactobacilli were tested for production of H_2O_2 by means of a qualitative assay on a tetramethylbenzidine agar plate, as described elsewhere [33]. Anaerobic gram-negative rods were identified on the basis of lack of capacity to grow in oxygen and on the basis of Gram stain characteristics [34]. Group B streptococci, *E. coli,* and yeast were identified by standard methods. Mycoplasma were identified by their characteristic morphology on the agar plate after subculture from the selective broths [34].

Endometrial histology was determined on the basis of hematoxylin and eosin–stained and methyl green pyronine–stained endometrial biopsy tissue specimens, which were examined separately by 2 reference pathologists who reviewed the slide together to reach consensus upon disagreement. Methyl green pyronine was used to facilitate the identification of plasma cells. By means of the criteria proposed by Kiviat et al. [9], we classified acute endometritis upon finding at least 5 neutrophils per ×400 field in the endometrial surface epithelium in the absence of menstrual endometrium and one or more plasma cells per ×120 field in the endometrial stroma. Chronic endometritis was defined by the presence of plasma cells in the endometrial stroma, absent of neutrophils.

Statistical analysis. We computed the frequencies of all organisms identified in the endometrium. Frequencies of *C. trachomatis , N. gonorrhoeae,* H_2O_2-producing *Lactobacillus* species, bacterial vaginosis diagnosed by vaginal Gram stain, and facultative and anaerobic isolates previously identified among women with PID [10–14, 16–18, 20, 27] or bacterial vaginosis [34, 35] were compared among women with no endometritis, chronic endometritis, and acute endometritis by the χ^2 test for proportions. To determine the relationships of facultative and anaerobic isolates and H_2O_2-producing *Lactobacillus* species with acute endometritis independent of chlamydia and gonorrhea, microorganism comparisons were repeated in a subset of women without endometrial *C. trachomatis* or *N. gonorrhoeae* infection. Because bacterial vaginosis has been associated with *C. trachomatis* and *N. gonorrhoeae* [36], and because an endometrial culture positive for bacterial vaginosis–associated organisms may result from cervical contamination during sampling, microorganism frequencies were also compared in a subset of women without bacterial vaginosis. For all comparisons, unadjusted ORs and 95% CIs were calculated directly from logistic regression coefficients.

We have a power of 85% to detect a 3-fold difference in microorganism rates, assuming frequencies of 30% among women with acute endometritis and 10% among women with

no endometritis. All analyses were conducted using SPSS, version 11.5 for Windows (SPSS).

RESULTS

Table 1 lists the microorganisms we isolated. *C. trachomatis* was present in the endometrium of 10% and *N. gonorrhoeae* was isolated in the endometrium of 13% of women. Of women with both complete chlamydial PCR and gonococcal culture data, 22% were positive for either species in the endometrium. A larger percentage (41%) were infected with *N. gonorrhoeae* and/or *C. trachomatis* in either the cervix or the endometrium. The majority of women (61%) had growth of facultative or anaerobic bacteria. Most (56%) had >1 organism identified in the endometrium. More than 50% of women were classified as having bacterial vaginosis by vaginal Gram stain, and <8% had H_2O_2-producing *Lactobacillus* species present.

Women with acute endometritis were 16 times more likely to have *C. trachomatis* (OR, 16.2; 95% CI, 4.6–56.6) and 12 times more likely to have *N. gonorrhoeae* (OR, 11.6; 95% CI, 4.5–29.9) identified in the endometrium (table 2). Acute endometritis was also significantly associated with endometrial diphtheroids, black-pigmented gram-negative rods, anaerobic gram-positive cocci, and bacterial vaginosis, with ORs of 2.0–5.0. Endometritis cases were 90% less likely to have H_2O_2-producing lactobacilli. Women with acute endometritis were no more likely than those without endometritis to have *M. hominis* or *U. urealyticum* present. There were no significant differences in the rates of any microbial isolates between women with chronic endometritis and women with no endometritis. Results were similar when rerun among a sample of women without bacterial vaginosis.

After excluding women with endometrial *C. trachomatis* and/or *N. gonorrhoeae* infection, acute endometritis remained significantly associated with black-pigmented gram-negative rods, anaerobic gram-positive cocci, and bacterial vaginosis by Gram stain. H_2O_2-producing lactobacilli were significantly and negatively associated with acute endometritis (table 3).

Table 1. Frequency of microorganisms isolated from the endometrium of women with clinically diagnosed pelvic inflammatory disease.

Microorganism	Percentage of women
Chlamydia trachomatis	9.9
Neisseria gonorrhoeae	13.4
Mycoplasma hominis	6.8
Ureaplasma urealyticum	6.8
H_2O_2-producing *Lactobacillus* species	7.6
Non–H_2O_2-producing *Lactobacillus* H_2O_2 species	8.6
Diphtheroids	11.2
Gardnerella vaginalis	30.9
Group B *S treptococcus* species	8.3
Enterococcus species	3.6
Viridans streptococci	12.9
Coagulase-negative *Staphylococcus* species	6.8
Escherichia coli	2.5
Any anaerobic gram-negative rod[a]	21.9
Black-pigmented gram-negative rod	10.8
Nonpigmented gram-negative rod	15.1
Bacteroides fragilis[b]	0.7
Fusobacterium species[c]	0.7
Any anaerobic gram-positive cocci[d]	15.8
Anaerobic *S treptococcus* species	4.7
Bacterial vaginosis[e]	53.5

[a] Selected gram-negative anaerobes include *Prevotella bivia, Prevotella disiens, Prevotella oralis/veroralis, Prevotella oulora/veroralis, Prevotella buccalis/oralis, Prevotella oris/buccae, Preveotella* species, *Bacteroides ureolyticus,* anaerobic nonpigmented gram-negative rods, black anaerobic negative rod, *Prevotella intermedia, Prevotella corporis, Prevotella denticola/loeschii, Prevotella denticola/melaninogenica, Porphyromonas asaccharolytica, Porphyromonas endodontails/asaccharolytica, Bactercides levii, Bacteroides fragilis, Bacteroides thetaiotaormicron, Bacteroides distasonis, Bacteroides ovatus, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus, Bacteroides merdae, Bacteroides* species, *Fusobacterium nucleatum, Fusobacterium* species, and *Veillonella* species.

[b] Selected anaerobes include *B . fragilis, B. thetaiotaomicron, B . distasonis, B. ovatus, B. caccae, B. uniformis, B. vulgatus, B. merdae,* and *Bacteroides* species.

[c] Selected anaerobes include *F. nucleatum, Fusobacterium* species, and *Veillonella* species.

[d] Selected anaerobic gram-positive cocci include: *Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus/micros, Peptostreptococcus prevotii, Peptostreptococcus tetradius, Peptococcus niger, Peptostreptococcus* species, and unspeciated anaerobic gram-positive cocci.

[e] Bacterial vaginosis was determined using vaginal Gram stain.

DISCUSSION

We found that acute but not chronic endometritis was associated with *N. gonorrhoeae*, *C. trachomatis*, diphtheroids, black-pigmented gram-negative rods, anaerobic gram-positive cocci, and bacterial vaginosis. H_2O_2-producing *Lactobacillus* in the endometrium was negatively associated with acute, but not chronic, endometritis. Little is known about the clinical significance of plasma cells without concomitant neutrophils. Our findings suggest that plasma cell endometritis is not associated with the presence of upper genital tract pathogens.

Bacterial vaginosis is characterized by a shift from a lactobacilli predominant vaginal flora to one with high concentrations of aerobic and anaerobic pathogens. H_2O_2-producing lactobacilli control the overgrowth of catalase-negative organisms and are associated with a lower prevalence of bacterial vaginosis [34, 37, 38]. Our findings are consistent with previous studies associating bacterial vaginosis with asymptomatic and symptomatic PID [25, 28, 30, 31]. To our knowledge, this is the first study to show this association to be independent of gonococcal or chlamydial infection. In agreement with previous reports [8, 28], we demonstrated associations between anaerobic gram-negative rods and gram-positive cocci, microorganisms common among women with bacterial vaginosis, and

Table 2. Associations between endometrial microorganisms and histologic endometritis.

Microorganism	No. of subjects	Percentage of subjects with no endometritis (n = 151)	Chronic endometritis, plasma cell (n = 82)		Acute endometritis, plasma cell and neutrophil (n = 45)	
			Percentage of subjects	OR (95% CI)	Percentage of subjects	OR (95% CI)
Chlamydia trachomatis	26	2.1	7.3	3.7 (0.7–19.1)	25.6	16.2 (4.6–56.6)
Neisseria gonorrhoeae	34	4.2	8.1	2.0 (0.5–8.4)	33.8	11.6 (4.5–29.9)
Mycoplasma hominis	19	7.9	2.2	0.3 (0.03–2.1)	7.3	0.9 (0.3–2.5)
Ureaplasma urealyticum	19	6.6	6.7	1.0 (0.3–3.8)	7.3	1.1 (0.4–3.2)
H_2O_2-producing *Lactobacillus* species	21	10.6	8.9	0.8 (0.3–2.6)	1.2	0.1 (0.01–0.8)
Diphtheroids	31	5.3	11.1	2.2 (0.7–7.2)	22.0	5.0 (2.1–12.2)
Gardnerella vaginalis	81	31.1	31.1	1.0 (0.5–2.1)	30.5	1.0 (0.5–1.7)
Any anaerobic gram-negative rod[a]	61	18.5	15.6	0.8 (0.3–2.0)	31.7	2.0 (1.1–3.8)
Black-pigmented gram-negative rod	30	7.3	6.7	0.9 (0.2–3.4)	19.5	3.1 (1.4–7.0)
Nonpigmented gram-negative rod	42	13.9	11.1	0.8 (0.3–2.2)	19.5	1.5 (0.7–3.1)
Any anaerobic gram-positive cocci[b]	44	11.9	17.8	1.6 (0.6–4.0)	22.0	2.1 (1.0–4.3)
Bacterial vaginosis[c]	137	46.9	51.3	1.2 (0.6–2.4)	67.6	2.4 (1.3–4.3)

[a] Selected gram-negative anaerobes include *Prevotella bivia, Prevotella disiens, Prevotella oralis/veroralis, Prevotella oulora/veroralis, Prevotella buccalis/oralis, Prevotella oris/buccae, Preveotella* species, *Bacteroides ureolyticus,* anaerobic nonpigmented gram-negative rod, black anaerobic negative rod, *Prevotella intermedia, Prevotella corporis, Prevotella denticola/loeschii, Prevotella denticola/melaninogenica, Porphyromonas asaccharolytica, Porphyromonas endodontails/asaccharolytica, Bactercides levii, Bacteroides fragilis, Bacteroides thetaiotaormicron, Bacteroides distasonis, Bacteroides ovatus, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus, Bacteroides merdae, Bacteroides, Fusobacterium nucleatum, Fusobacterium* species, and *Veillonella* species.

[b] Selected anaerobic gram-positive cocci include *P. anaerobius, P. asaccharolyticus, P. magnus/micros, P. prevottii, P. tetradius, Peptococcus niger, Peptostreptococcus* species, and unspeciated anaerobic gram-positive cocci.

[c] Bacterial vaginosis was determined by a vaginal Gram stain.

acute endometritis. We confirmed the gonococcal/chlamydial independent association between anaerobic gram-negative rods and endometritis, as shown by Hillier et al. [8]. In addition, to our knowledge, this is the first report to show an association between anaerobic gram-positive cocci and endometritis, independent of *N. gonorrhoeae* or *C. trachomatis* infection. Furthermore, we demonstrated that women with acute endometritis were more likely to have diphtheroids and less likely to have H_2O_2-producing lactobacilli present. The protective effect of lactobacilli for endometritis may be mediated through a decreased prevalence of bacterial vaginosis and anaerobic and facultative bacteria.

Our results suggest that vaginal microorganisms frequent among women with bacterial vaginosis ascend to the endometrium, resulting in upper genital tract infection. Alternatively, transcervical sampling of the endometrium may have resulted in contamination of endometrial biopsy specimens by vaginal or cervical microorganisms. In fact, the high prevalence of endometrial microorganisms suggests that some contamination may have occurred during sampling. Several lines of evidence suggest that contamination does not account for the relationships between bacterial vaginosis–associated microorganisms and acute endometritis. First, anaerobic gram-negative bacteria remained significantly associated with acute endometritis, in analyses conducted among a group of women without bacterial vaginosis. Furthermore, anaerobic gram-negative rods and anaerobic gram-positive cocci, but not other organisms common among women with bacterial vaginosis (i.e., *G. vaginalis* and *M. hominis*), were associated with acute endometritis.

Although in a previous analysis of PEACH data, no microorganisms were associated with infertility, chronic pelvic pain, or recurrent PID when compared with the lack of each respective microorganism, women with nongonococcal bacteria identified in the endometrium were generally more likely to experience reproductive morbidity than were women with endometrial gonococcal infection (infertility rates were 13% for *N. gonorrhoeae,* 19% for *C. trachomatis,* 22% for anaerobic bacteria, 27% for *U. urealyticum,* and 17% for *M. hominis;* chronic pelvic pain rates were 27% for *N. gonorrhoeae,* 21% for *C. trachomatis,* 33% for anaerobic bacteria, 41% for *U. urealyticum,* and 54% for *M. hominis*) [39]. Similarly, in a study of 50 women with laparoscopically confirmed salpingitis by Brunham et al. [17], 54% of women with nongonococcal infections experienced future adverse reproductive outcomes, compared with none of the women with gonococcal infections. Collectively, the PEACH study and the study by Brunham et al. [17] suggest that nongonococcal endometritis and salpingitis are indicative of adverse reproductive morbidity.

C. trachomatis and/or *N. gonorrhoeae* account for only one-third to one-half of cases of PID [6–23]. Consistent with previous studies, we identified gonorrhea and chlamydia in the cervix or endometrium of 41% of women. Thus, the majority of PID cases have a nongonococcal/nonchlamydial etiology. We found that bacterial vaginosis–associated organisms of the en-

Table 3. Associations between endometrial microorganisms and histologic endometritis among women without endometrial *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection.

Microorganism	No. of women	Percentage of subjects with no endometritis (n = 130)	Acute endometritis, plasma cell and neutrophil (n = 34)	
			Percentage of subjects	OR (95% CI)
Mycoplasma hominis	9	5.4	8.8	1.7 (0.4–7.0)
Ureaplasma urealyticum	12	6.2	5.9	1.0 (0.2–4.7)
H_2O_2-producing *Lactobacillus* species	14	10.0	0.0	0.8 (0.7–0.8)
Diphtheroids	12	6.2	11.8	2.0 (0.6–7.2)
Gardnerella vaginalis	51	30.8	35.3	1.3 (0.6–2.7)
Any anaerobic gram-negative rod[a]	34	15.4	26.5	2.0 (0.8–4.9)
Black-pigmented gram-negative rod	13	4.6	17.6	4.4 (1.3–14.8)
Nonpigmented gram-negative rod	39	13.1	17.6	1.4 (0.5–3.9)
Any anaerobic gram-positive cocci[b]	22	10.0	26.5	3.2 (1.2–8.4)
Bacterial vaginosis[c]	78	46.0	70.0	2.7 (1.2–6.5)

NOTE. Women with positive chlamydial PCR results, positive gonococcal culture results, or incomplete data for either test were excluded from these analyses.

[a] Selected gram-negative anaerobes include *Prevotella bivia, Prevotella disiens, Prevotella oralis/veroralis, Prevotella oulora/veroralis, Prevotella buccalis/oralis, Prevotella oris/buccae, Preveotella* species, *Bacteroides ureolyticus*, anaerobic nonpigmented gram-negative rod, black anaerobic negative rod, *Prevotella intermedia, Prevotella corporis, Prevotella denticola/loeschii, Prevotella denticola/melaninogenica, Porphyromonas asaccharolytica, Porphyromonas endodontails/asaccharolytica, Bactercides levii, Bacteroides fragilis, Bacteroides thetaiotaormicron, Bacteroides distasonis, Bacteroides ovatus, Bacteroides caccae, Bacteroides uniformis, Bacteroides vulgatus, Bacteroides merdae, Bacteroides* species, *Fusobacterium nucleatum, Fusobacterium* species, and *Veillonella* species.

[b] Selected anaerobic gram-positive cocci include *P. anaerobius, P. asaccharolyticus, P. magnus/micros, P. prevottii, P. tetradius, Peptococcus niger, Peptostreptococcus* species, and unspeciated anaerobic gram-positive cocci.

[c] Bacterial vaginosis was determined using vaginal Gram stain.

dogenous vaginal flora were also significantly associated with endometritis. Current CDC guidelines recommend treatment of PID with ofloxacin, levofloxacin, ceftriaxone plus doxycycline, or cefoxitin plus doxycycline, all with or without the addition of metronidazole for full coverage against anaerobes and bacterial vaginosis [40]. Because we frequently isolated bacterial vaginosis–associated organisms in our cohort of women with clinically suspected PID, and because these organisms were strongly associated with endometritis, we recommend that all women with PID be treated with regimens that include metronidazole. A recent proof of principle study of twice-daily oral dosages of cefixime (400 mg), azithromycin (1 g), and metronidazole (500 mg) for 7 days among women with histologic endometritis but without clinical evidence of PID reported a 50% reduction in rates of bacterial vaginosis and an overall reduction of endometrial isolates (from 28% to 11%) [41]. Further studies of broad-spectrum treatment among women with signs and symptoms of PID are needed.

PID is a common disease among American women that results in frequent, serious reproductive morbidity. Most women with PID are treated with antibiotics directed toward *N. gonorrhoeae* and/or *C. trachomatis,* despite the fact that these bacterial pathogens account for only one-third to one-half of cases of PID. Because we found that bacterial vaginosis–associated organisms were strongly associated with endometritis, we recommend the addition of metronidazole to all regimens of PID therapy to improve anaerobic coverage and potentially reduce the frequency of infertility, chronic pelvic pain, recurrent PID, and ectopic pregnancy after treatment.

STUDY GROUP MEMBERS

The principal investigators of the PEACH Study include Antonio Amortegui, Susan L. Hendrix, Sharon L. Hillier, Robert L. Holley, Deborah B. Nelson, Roberta B. Ness, John Nichols, Jr., Jeffrey Peipert, Hugh Randall, Diane Schubeck, Steven J. Sondheimer, David E. Soper, Richard L. Sweet, Wayne Trout, Guiliana Trucco, Harold C. Wiesenfeld, and Tamer Yalcinkaya.

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