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Vancomycin plus Gentamicin and Cotrimoxazole for Prevention of Infections in Neutropenic Cancer Patients (a Comparative, Placebo-controlled Pilot Study)

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Abstract—*Vancomycin and gentamicin, cotrimoxazole, or vancomycin and gentamicin plus cotrimoxazole were administered respectively to* 21, 22 *and* 20 *cancer patients with neutropenia in order to prevent infection. The administration of cotrimoxazole was associated with less infections than that of vancomycin plus gentamicin. The administration of vancomycin and gentamicin plus cotrimoxazole was associated with no Gram-negative bacillary infections at all, but the tolerance to this latter regimen was less good and was associated with a* 40% *rate of discontinuation of the prophylactic therapy because of adverse effects, namely nausea and diarrhea. Cotrimoxazole administration was associated with less complete microbial suppression of the aerobic Gram-negative bacilli in the digestive tract than vancomycin plus gentamicin. In addition, in cotrimoxazole-treated patients a high incidence* (66%) *of cotrimoxazole-resistant Gram-negative aerobic bacilli was found, whereas it was much lower in the two other study groups. It is concluded that the use of cotrimoxazole in addition to vancomycin and gentamicin to prevent infection in neutropenic cancer patients might have some advantages and should be evaluated in more extensive studies.*

INTRODUCTION

MOST infections in neutropenic cancer patients are related to the organisms which colonize the alimentary canal. Many of these organisms have been acquired in hospitals, with acquisition occurring most frequently during periods of reduced colonization resistance due to antimicrobial therapy. In this patient population, one of the proposed techniques for reducing the incidence of infection has been to suppress the aerobic microflora of the alimentary canal with oral non-absorbable antibiotics [1]. Suppression of the microbial flora with non-absorbable oral antibiotics in neutropenic patients has been related, in some studies, to significantly decreased numbers of bacteremic episodes and infections [1–4]. Antibiotic regimens used today include GVN (gentamicin, vancomycin, nystatin) [1–5], FRACON (framycetin, colistin, nystatin) or other similar combinations. However, these treatment programs have been associated with nausea, vomiting, diarrhea and abdominal cramps when administered at four-hourly intervals. Compliance of the patients has not always been very satisfactory. In addition, these methods have been associated with further suppression of colonization resistance, leading to acquisition and ultimate colonization with antibiotic-resistant Gram-negative bacilli.

The use of newer approaches for suppression of the aerobic Gram-negative flora of the alimentary canal are thus indicated in the management of these high risk patients.

Reports that oral cotrimoxazole could reduce or eliminate intestinal Enterobacteriaceae [6–8] prompted investigations of its use in granulocytopenic patients. In a study in which granulocytopenic patients were randomly allocated prospectively to oral cotrimoxazole or to no prophylactic antibiotics, Gurwith *et al.* [9] found that the number of days with fever, the number of days during which patients received intravenous antibiotics and the frequency of bacteremia and urinary tract infection were all significantly decreased in the cotrimoxazole group compared to controls.

Side-effects were limited to allergic skin rashes in 5 patients and there was no increase in fungal infections.

At the same time, Hughes *et al.* [4] reported a

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prophylactic trial for *P. carinii* pneumonia of cotrimoxazole and placebo in 160 children with acute leukemia and other cancer. Pneumocystis pneumonia was completely prevented in patients receiving cotrimoxazole. In addition, the investigators reported a significant reduction in bacterial colonization by enterobacteriaceae in cotrimoxazole recipients compared to placebo controls. Cotrimoxazole recipients had significantly fewer episodes of pneumonia, sinusitis, cellulitis and bacteremia than the placebo-treated patients.

We have therefore decided to investigate the efficacy of cotrimoxazole to prevent infections in neutropenic patients in a comparative study, using the standard VGN regimen as a control group. In addition, we were interested in investigating, at the same time, the efficacy of a combined regimen using cotrimoxazole and VGN.

Since nystatin has been an integral part of the VGN protocol, and because of the high incidence of candidiasis in the gastrointestinal tract of granulocytopenic patients, it was felt that nystatin should also be administered to all patients in the present study, although its efficacy for prevention of invasive fungal infections remains unproven.

MATERIALS AND METHODS

Patient population

Adult patients receiving chemotherapy for leukemia, lymphoma or solid tumors and one patient with aplastic anemia of unknown origin were randomly allocated to receive either vancomycin and gentamicin, cotrimoxazole, or vancomycin and gentamicin plus cotrimoxazole. Informed consent was obtained before randomization. As indicated in Table 1, 63 adult patients were studied. Twenty-one received vancomycin and gentamicin, 22 received cotrimoxazole and 20 were treated with vancomycin and gentamicin plus cotrimoxazole. The distribution of acute leukemias, lymphomas and solid tumors was similar in the three study groups. The proportion of male to female patients was also similar. The mean age was not significantly different in the three groups. As far as the duration of prophylaxis is concerned, no significant difference existed between the patients treated with vancomycin and gentamicin and those receiving cotrimoxazole: the median duration of prophylaxis was 14.0 and 13.5 days in these two groups. On the other hand, the median duration of prophylaxis among the patients receiving vancomycin and gentamicin plus cotrimoxazole was only 8.0 days; this shorter duration of prophylaxis in the patients receiving vancomycin and gentamicin plus cotrimoxazole can probably be explained by a higher incidence of side-effects in the latter group of patients.

On-study time was defined as beginning with antibiotic prophylaxis institution and continuing until death, or the occurrence of excessive side-effects requiring discontinuation of prophylaxis or the return of the granulocyte count to normal.

Patients were eligible for the present study if their leucocytes count was lower than 1000 per cubic millimeter. In addition, to be eligible, the patients had to be free from infection at the time of randomization and thus not be receiving any antibiotics at that time.

The expected duration of the neutropenic period was at least 7 days in the patients who were included in the present study and those patients who received the prophylactic regimens for less than 4 days were not considered for evaluation. Patients who were unable to take oral medication and those who were known or suspected to be allergic to cotrimoxazole were also excluded from the present study.

Most patients were hospitalized in single rooms, some were treated on general wards of

Table 1. *Characteristics of the patients*

Type of prophylaxis*	VG	Co	VG + Co
Total numbers of patients	21	22	20
Acute leukemia	12	11	9
Lymphomas	3	2	5
Solid tumors	5	9	6
Aplastic anemia	1	0	0
Ratio males/females	14/7	16/6	11/9
Mean age (years)	48	43	43
Mean and median duration of prophylaxis (days)	15.9/14.0	18.9/13.5	13.6/8.0

*VG = vancomycin + gentamicin; Co = cotrimoxazole.

a medical oncology service. No special program of isolation was used here; visitors and staff did not utilize any special precautions while taking care of the patients, and no special low microbial-content diets were utilized.

Oral non-absorbable antibiotics

The VGN (vancomycin–gentamicin–nystatin) regimen utilized in the present study consisted of gentamicin (160 mg; Schering Laboratories) diluted in sterile water, vancomycin (500 mg; Eli Lilly and Co) prepared in sterile water, and nystatin suspension (2×10^6 units; Lederle Laboratories) administered every 8 hr around the clock. Cotrimoxazole tablets consisted of 400 mg of sulfamethoxazole and 80 mg of tri methoprim each; 2 tablets were given twice daily. The hospital pharmacy provided when indicated for each drug a suitable placebo, e.g., placebo tablets identical to the cotrimoxazole tablets for the patients in the vancomycin–gentamicin group and placebo suspensions identical to the real suspensions of vancomycin and gentamicin for the patients in the cotrimoxazole group. The regimens were allocated at random to the patients and all evaluations were made prior to breaking the code. The patients were visited by an infection control nurse every day for the study period to determine antibiotic ingestion and tolerance (palatability and incidence of nausea and vomiting). Compliance (the actual ingestion of the prescribed dose) was determined by reviewing drug administration records.

Microbiological studies

All patients had swabs on their pharynx and stools taken at the time of randomization and twice weekly thereafter. No special effort had been made to culture these specimens anaerobically. Microbiological identification of all morphologically distinct isolates was performed. Antibiotic susceptibility tests to gentamicin, vancomycin and cotrimoxazole (Kirby–Bauer disc technique) were performed on all Gram-negative aerobic isolates obtained during the decontamination procedure. Colony quantitation in cultures from the rectum was determined by using the broad designation of one plus, two plus, three plus and four plus growth.

Infections

Diagnostic evaluation of possibly infected patients included, at a minimum, (1) three blood cultures, (2) urinalysis and culture of urine, (3) cultures of stools and pharynx and (4) chest X-rays. Viral cultures, serology and invasive procedures, such as trans-tracheal or percutaneous aspiration of bronchopulmonary infiltrates, biopsies and cultures of liver, bone marrow and skin, were performed in some patients when indicated and feasible.

Clinical and microbiological data

Infections were classified as one of the following: microbiologically documented (site and pathogen defined with and without bacteremia) or clinically documented (site defined but pathogen not isolated). Equivocal infections were disregarded for this evaluation. Suspected infectious episodes were treated empirically with carbenicillin, cefazolin and amikacin; transfusions of granulocytes were given when indicated.

RESULTS

The frequency of systemic treatment with antibiotics for demonstrated or suspected infections is indicated in Table 2. It can be seen that about 50% of the patients in the groups receiving vancomycin and gentamicin or cotrimoxazole were treated with systemic antimicrobial agents during the period of neutropenia; on the other hand, only 6 out of 20 patients (30%) receiving vancomycin and gentamicin plus cotrimoxazole received systemic antibiotics. Clinically documented infections were more frequent among the patients receiving cotrimoxazole. As far as microbiologically documented infections are concerned, 8 (38.9%) were found in patients receiving vancomycin and gentamicin, 2 (9.8%) were observed among the patients who received cotrimoxazole alone and 3 (15%) were documented in the group of patients receiving vancomycin and gentamicin plus cotrimoxazole.

Gram-positive pathogens were encountered with a similar frequency in all three study groups; fungal infections were observed in one patient receiving vancomycin and gentamicin (*Aspergillus* pneumonia) and in one patient receiving vancomycin and gentamicin plus cotrimoxazole (*Candida* fungemia).

The comparison of the frequency of Gram-negative infections is of particular interest here: Gram-negative infections occurred in 5 out of 21 patients receiving vancomycin and gentamicin, in one out of 22 patients receiving cotrimoxazole alone and in none of the patients receiving vancomycin and gentamicin plus cotrimoxazole. Although the number of patients in the three study groups are relatively small, the difference, as far as Gram-negative infection is concerned, is statistically significant ($P = 0.025$) (exact Fisher's test).

Table 2. Number of systemic treatments for documented infection

Type of prophylaxis*	VG	Co	VG + Co
Total number of patients	21	22	20
Patients days (PD)† on study	335	416	272
Number of patients treated with systemic antimicrobials	11(52%)	11(50%)	6(30%)
Episodes of systemic antimicrobial therapy	13(62%)‡	11(50%)	7(35%)§
Clinically documented infection	5	9	4
Microbiologically documented infections	7(33%)	2(10%)	2(10%)
Total Gram-positive infections	2	1	2
Gram-positive infections/100 PD	0.59	0.24	0.73
Total Gram-negative infections	5	1	0
Gram-negative infections/100 PD	1.49	0.24	0

*VG = vancomycin + gentamicin; Co = cotrimoxazole.
†PD = days spent with less than 1000 leucocytes/cu mm on study.
‡One patient had *Klebsiella* sp. septicemia and *Ps. aeruginosa* pneumonia and one patient had *Staph. aureus* septicemia and meningitis.
§Same patient had *Staph. epidermidis* septicemia and *Candida albicans* fungermia.

The microbiological characteristics of the microbiologically documented infections in the present series are indicated in Table 3. It should be observed, however, that the patients who received cotrimoxazole in addition to vancomycin and gentamicin spent less days at risk than those in the other groups. Among the patients receiving vancomycin and gentamicin plus cotrimoxazole, 1 patient developed *Staph. epidermidis* and *Candida albicans* septicemia, probably related to the presence of an intravenous catheter. In another patient, *Staph. epidermidis* meningitis developed, associated with the presence of an intraventricular reservoir for the treatment of neoplastic meningitis. Among the 22 patients who were treated pro-

Table 3. Microbiological characteristics of microbiologically documented infections

Type of prophylaxis*	VG	Co	VG + Co
Total number of patients	21	22	20
Number of microbiologically documented infections†	8	2	3
Septicemia	*Staph. epidermidis* (S, S)	*E. coli* (R, S)	*Staph. epidermidis* (S, S)
	Staph. aureus (S, S)‡		
	Klebsiella sp. (S, R)§		
Pneumonia	*Ps. aeruginosa* (R, S)§	*Pneumococcus* (S, R)	
Urinary tract infection	*E. coli* (R, S)		
	Klebsiella sp. (S, S)		
	E. coli (S, S)		
Meningitis	*Staph. aureus* (S, S)		*Staph. epidermidis* (S, S)

*VG = vancomycin + gentamicin; Co = cotrimoxazole.
†In brackets: resistance (R) or sensitivity (S) to Co and G.
‡Same patient had *Staph. aureus* bacteremia and meningitis.
§Same patient had *Klebsiella* sp. bacteremia and *Ps. aeruginosa* pneumonia.

phylactically with cotrimoxazole alone, two developed microbiologically documented infections: one patient developed septicemia caused by *E. coli* which was resistant to cotrimoxazole; the source of the septicemia was not documented. This infection was diagnosed on the 5th day after onset of cotrimoxazole prophylaxis. Another patient developed pneumococcal pneumonia; the microorganism was sensitive to cotrimoxazole. The largest number of infections was seen among the 21 patients receiving vancomycin and gentamicin. Among 8 such microbiologically documented infections, 3 were septicemias: one patient developed *Staph. epidermidis* bacteremia associated with an indwelling intravenous catheter; another developed *Staph. aureus* septicemia associated with *Staph. aureus* meningitis and, in this case, the pathogen was sensitive to both vancomycin and gentamicin; a third patient developed bacteremia caused by *Klebsiella* sp. which was sensitive to cotrimoxazole but resistant to gentamicin. Pulmonary infection was documented in two patients: one developed *Pseudomonas aeruginosa* pneumonia with an organism sensitive to gentamicin; the same patient had presented earlier a *Klebsiella* septicemia. In addition, another patient presented an *Aspergillus* pneumonia.

Urinary tract infection was documented in three patients: *E. coli* was responsible for two of them and *Klebsiella* sp. for one; all these microorganisms were sensitive to gentamicin.

In the present study, only aerobic microbiological techniques were used. The results of the stool cultures are indicated in Table 4. Not all the patients who were evaluated from the clinical point of view have been evaluated from the point of view of surveillance cultures. It can be seen that patients who were receiving vancomycin and gentamicin, or vancomycin and gentamicin plus cotrimoxazole, had a higher rate of persistently negative stool cultures (no aerobic growth) than the patients who were treated with cotrimoxazole alone. Eight out of 15 (50%) patients receiving vancomycin and gentamicin and 9 out of 12 (75%) patients receiving vancomycin and gentamicin plus cotrimoxazole had persistently negative stool cultures; on the other hand, only 3 out of 15 (20%) patients receiving cotrimoxazole alone demonstrated persistent negative stool cultures for aerobic Gram-negative bacteria.

It appears, therefore, that the use of vancomycin and gentamicin plus cotrimoxazole was associated, in the present study, with a better efficacy, as far as suppression of aerobic Gram-negative organisms in the stools is concerned, than the two other regimens.

In the patients treated with cotrimoxazole alone, we observed the highest frequency of positive stool cultures (75%); two thirds of these positive cultures contained cotrimoxazole-resistant bacteria and 25% contained gentamicin-resistant bacteria. In most cases, only one antibiotic-resistant organism could be identified in a stool specimen and, usually, once it had appeared it persisted in subsequent cultures. The frequency of positive stool cultures in the patients treated with vancomycin and gentamicin or vancomycin and gentamicin plus cotrimoxazole was much lower: 19 and 25% respectively. Cotrimoxazole-resistant bacteria were isolated in 16 and 11% of the stool cultures in these two groups respectively; gentamicin-resistant bacteria were isolated in 19 and 11% of the stool cultures in these two groups of patients.

In all 3 study groups, *E. coli*, *Enterobacter* sp., *Klebsiella* sp. and enterococci represented the

Table 4. Results of cultures (aerobic) of stools

Type of prophylaxis*	VG	Co	VG + Co
Total number of patients	21	22	20
Evaluable patients	16	15	12
Number of patients with stool cultures consistently negative†	8(50%)	3(20%)	9(75%)
Number of patients with positive stool cultures†	8(50%)	12(80%)	3(25%)
Total number of survey cultures	85	60	62
% of positive cultures†	19.4	75.0	24.8
% of cultures with Co–R bacteria‡	16.4	66.6	11.0
% of cultures with G–R bacteria‡	18.8	25.0	11.0

*VG = vancomycin and gentamicin; Co = cotrimoxazole.
†For aerobic microorganisms.
‡Co–R = cotrimoxazole-resistant; G–R = gentamicin-resistant.

Table 5. Untoward effects

Type of prophylaxis*	VG	Co	VG + Co
Total number of patients	21	22	20
Nausea and/or vomiting	9(43%)	9(41%)	9(45%)
Diarrhea	3(14%)	0	4(20%)
Discontinuation of prophylaxis because of adverse effects	6(29%)	6(27%)	8(40%)
Fungal infections	1†		1‡

*VG = cancomycin and gentamicin; Co = cotrimoxazole.
†*Aspergillus* sp. pneumonia.
‡*Candida albicans* fungemia (occurred in a patient who also presented *Staph. albus* bacteramia).

most frequently isolated resistant organisms. *P. aeruginosa, Serratia marscens, P. mirabilis* and *Citrobacter* sp., resistant to gentamicin and/or to cotrimoxazole, have been isolated only occasionally.

Untoward effects

It can be seen in Table 5 that the untoward effects of the prophylactic regimens used in the present study were more frequent among the patients who were treated with vancomycin and gentamicin plus cotrimoxazole than in the two other groups. In fact, the prophylactic regimen had to be discontinued in 8 out of 20 (40%) of the patients receiving the vancomycin and gentamicin plus cotrimoxazole regimen, while discontinuation was necessary in only 6 out of 21 (28.5%) of the patients receiving vancomycin and gentamicin and in 6 out of 22 (27%) of the patients receiving cotrimoxazole alone. The higher frequency of adverse effects in the vancomycin and gentamicin plus cotrimoxazole group may explain why the mean and median duration of prophylaxis were lower among these patients than in the two other treatment groups. Adverse effects consisted mainly of nausea and/or vomiting; this type of adverse reaction occurred with a similar frequency in all three study groups. Diarrhea was seen only among the patients who received vancomycin and gentamicin. The combination of these two adverse effects was severe enough to cause discontinuation of therapy in 6 out of 21 patients in the vancomycin and gentamicin group, and in 6 out of 22 patients in the cotrimoxazole group.

DISCUSSION

The use of oral non-absorbable antibiotics as a means of infection prevention in granulocytopenic leukemia patients who are not treated in a protective environment is controversial [10]. Several trials have shown its efficacy, but others have not. At the Institut Jules Bordet, a controlled trial has shown that the combination of protective environment and gastrointestinal decontamination, or decontamination alone, were both superior to standard ward care in preventing severe infections in neutropenic patients [3]. A subsequent trial showed that protective environment plus decontamination was, in fact, superior to oral antibiotics given alone [11]. A similar experience has been published by Schimpff and his co-workers, at the Baltimore Cancer Research Center [1]. These authors have presented data suggesting that decontamination in neutropenic patients, especially if combined with other preventive techniques, is feasible and tolerable and is associated with a low order of life-threatening infections [12].

The optimal antimicrobial regimen to be used for gut decontamination remains still to be defined. The classical oral non-absorbable antibiotic regimen consists of vancomycin and gentamicin. It seems likely that gentamicin is a necessary component in this type of antimicrobial regimen, since Gram-negative rods are the major pathogens to be eradicated from the stools or reduced in number. Recently, Bender and his associates studied the role of vancomycin as a component of oral non-absorbable antibiotics for microbial suppression in leukemic patients [13]; colonization by newly acquired Gram-negative bacilli was significantly less in the group of patients receiving gentamicin without vancomycin, suggesting that omission of vancomycin preserves to some extent the 'resistance to colonization'. Vancomycin is believed to have a substantial capability of suppressing the Gram-positive anaerobic alimentary tract flora. Evidence from animal studies conducted by van der Waaij and associates [14, 15] suggests that the presence of anaerobic organisms in the alimentary tract exerts a protection against colonization by

newly acquired organisms, such as aerobic Gram-negative bacilli. Their study suggests that the total suppression of intestinal flora might not be the best prevention for infection. Hughes *et al.* [4] and Gurwith *et al.* [9] reported favorable results with cotrimoxazole as a preventive regimen for infections in neutropenic patients. These authors specifically found no increased incidence of megaloblastic anemia, bone marrow suppression, thrombocytopenia or bacterial overgrowth in the cotrimoxazole groups. They found that the colonic anaerobes were slightly reduced, but much less so than the enteric aerobes. They found no cotrimoxazole resistance development, an observation which is consistent with an earlier study on long-term administration of cotrimoxazole [8].

Although the number of observations reported in the present study is limited, it is quite clear that Gram-negative infections occurred less frequently in the patients who were treated with cotrimoxazole with vancomycin and gentamicin.

Cotrimoxazole might also have prevented some infections caused by Gram-positive microorganisms not originating from the gastro-intestinal tract. One might wonder whether cotrimoxazole is not exerting some of its beneficial effects through its systemic action, in addition to its effect on aerobic Gram-negative bacteria in the digestive tract, since the drug is readily absorbed. In fact, Rodriguez *et al.* [16] found systemic antibiotics as effective as non-absorbable antibiotics in preventing infections in neutropenic patients.

In the present study, cotrimoxazole also prevented urinary tract infection, a common source for Gram-negative sepsis. The efficacy of cotrimoxazole in urinary tract infection, as a therapeutic or preventive means, is well established [6]; in the studies reported by Gurwith [9], it was already clear that cotrimoxazole exerted some of its beneficial effects, at least, by effectively preventing urinary tract infections.

As far as the eradication of aerobic microorganism from the stools is concerned, in our series cotrimoxazole was definitely less effective than the regimens containing vancomycin and gentamicin, with or without cotrimoxazole: 75% of the stool cultures taken from cotrimoxazole-treated patients were positive for aerobic Gram-negative bacilli, while only 20 and 25% of the stool cultures were positive in the vancomycin and gentamicin-treated patients and in those receiving vancomycin and gentamicin plus cotrimoxazole respectively. We also found a higher number of aerobic Gram-negative bacilli to be resistant to cotrimoxazole in patients who were receiving cotrimoxazole as the only prophylactic regimen; on the other hand, cotrimoxazole-resistant bacteria were found only in 16 and 11% in the two other groups. Resistance to gentamicin was seen in 19% of the patients receiving vancomycin and gentamicin, 25% of the patients receiving cotrimoxazole and 11% of those receiving vancomycin and gentamicin plus cotrimoxazole.

Thus, in this series, cotrimoxazole might have selected, in stools, a high number of cotrimoxazole-resistant strains. This latter observation might be related to the fairly extensive use of cotrimoxazole in this country for many years and development of resistance; the percentage of cotrimoxazole-resistant enterobacteriacae isolated from blood cultures at the Institut Bordet has increased from 25% in 1975 to 43% in 1980.

Nystatin was given to all the patients in the three study groups in the present series. Such a measure might be useful for preventing systemic fungal disease, although this question has not been adequately settled yet. That some antifungal prophylaxis might be needed in these patients is suggested by the recent observations by Ezdinli and co-workers [17], who showed, in a controlled trial in patients with hematologic malignant neoplasms who received antibiotics, that the concomitant oral administration of amphotericin was effective in the decreasing incidence of systemic candidal infection.

The present study suggests that preventive administration of cotrimoxazole and vancomycin plus gentamicin to granulocytopenic patients with cancer decreases the frequency of Gram-negative bacillary infections in these patients.

Cotrimoxazole alone was less effective than vancomycin and gentamicin in eradicating aerobic potential Gram-negative pathogens from the bowel, and was associated with the isolation of large numbers of cotrimoxazole-resistant Gram-negative bacilli from these stools.

Only a large study including many patients would be able to evaluate fully the respective merits of the various available decontaminating regimens including that of cotrimoxazole. Until such studies are available (a large cooperative study on this question is now under way by the EORTC Antimicrobial Therapy Project Group), we feel that the decontamination in neutropenic cancer patients with cotrimoxazole alone should be considered as an investigational procedure.

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