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Fatal mycobacterium bovis bacille Calmette-Guerin infection caused by contamination of chemotherapeutic agents and not by endogenous reactivation: Correction of a previous conclusion (letter)

Vos, M.C.; van Deutekom, H.; de Haas, P.E.W.; van Soolingen, D.

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Correspondence

Multiple Blood Cultures for Diagnosing Bacteremia

SIR—The model used by Lamy et al. [1] to assess the relevance of obtaining multiple blood cultures used as the criterion for test positivity “any positive sample,” regardless of bacterial species and clinical syndrome. This leaves uncertain the relevance to clinical practice of the investigators’ conclusion that obtaining a single blood sample is preferable to obtaining multiple samples. Clinicians commonly use the number of bottles (or sets) that produce positive results to assess the significance of cultures that yield coagulase-negative staphylococci. This is because, with intravascular device infections or endocarditis (i.e., syndromes in which such organisms may be true pathogens), sustained bacteremia is expected.

Although each additional venipuncture increases the likelihood that at least 1 bottle or set will produce a false-positive result, it decreases the likelihood that a single false-positive result will lead to a false conclusion of bacteremia, provided that a “majority rule” is applied to the results. For example, if 3 samples are collected and the background false-positive rate is 25%, the probability of having at least 1 false-positive result is 58%. Clearly, this percentage is unacceptably high, and it is much greater than the 25% false-positive rate for the single-sample model advocated by Lamy et al. [1]. However, the probability of ≥ 2 samples having false-positive results is only 15.6%, and the probability of all 3 samples having false-positive results is 1.6%.

By using clinical judgment as to what criterion should be used to define a positive test result for a given patient, the clinician can take advantage of multiple sampling to avoid false conclusions based on contaminants. The analysis by Lamy et al.

[1] does not adequately address this issue, and, therefore, does not provide a persuasive rationale for abandoning the practice of performing multiple cultures with blood samples obtained from different sites in patients with suspected bacteremia.

James R. Johnson

Veterans Affairs Medical Center and Department of Medicine, University of Minnesota, Minneapolis

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Reprints or correspondence: Dr. James R. Johnson, Infectious Diseases, 111F, Minneapolis Veterans Affairs Medical Center, 1 Veterans Dr., Minneapolis, MN 55417 (johns007@umn.edu).

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Quinolones and Arrhythmia

SIR—I read with interest the brief report by Nicholson et al. [1] on bradycardic syncope in patients receiving gatifloxacin. Such arrhythmic effects have been described in patients receiving all quinolones, and such effects were to be expected. Infectious disease experts seem to have forgotten that, in 1993, flosequinan—a quinolone—was registered and marketed as a vasodilator for use in treating heart failure [2]. Soon after, in April of the same year, it was withdrawn from the market, most probably because of arrhythmogenesis. All quinolones should be used with caution in patients at risk for arrhythmia.

Pramod M. Shah

Zentrum der Innere Medizin, Schwerpunkt Infektiologie, Klinikum der J.W. Goethe Universitaet, Frankfurt am Main, Germany

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Reprints or correspondence: Dr. Pramod M. Shah, Zentrum der Innere Medizin, Schwerpunkt Infektiologie, Klinikum der J.W. Goethe Universitaet, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany (shah@em.uni-frankfurt.de).

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Fatal *Mycobacterium bovis* Bacille Calmette-Guérin Infection Caused by Contamination of Chemotherapeutic Agents and Not by Endogenous Reactivation: Correction of a Previous Conclusion

SIR—Live attenuated *Mycobacterium bovis* bacille Calmette-Guérin (BCG) OncotICE bacteria are used for bladder instillation in patients with bladder carcinoma. Iatrogenic transmission can happen by contamination of the medication prepared in hoods that have been contaminated with BCG bacteria. In The Netherlands, we recently identified 5 immunocompromised patients in 3 different hospitals who had nosocomial, disseminated *M. bovis* BCG infections [1]. All patients had received chemotherapeutic agents prepared in biological safety cabinets that had also been used to prepare BCG bladder instillation preparations. One of these patients was earlier described as having fatal meningitis caused by late endogenous reactivation of BCG vaccine bacteria [2]. The respective *M. bovis* BCG isolate was

recently further analyzed by restriction fragment-length polymorphism typing, using the B9 probe for hybridization. The latter probe detected a sequence present in the genome of BCG OncoTICE bacteria but absent from the DNA of the BCG Pasteur strain, which strain was used until 1997 in The Netherlands for vaccination [3]. It appeared that the isolate obtained from the patient who had fatal meningitis reacted with the B9 probe, and, thus, proved to be an OncoTICE strain instead of the supposed Pasteur bacteria. Therefore, this molecular analysis made it highly likely that the fatal infection was contracted nosocomially and not by endogenous reactivation of BCG bacteria introduced by vaccination 12 years prior to the manifestation of the infection. Therefore, we have to retract the conclusions drawn earlier [2].

Further typing of BCG isolates to subspecies level is very important in order to determine the route and source of transmission and, thus, to prevent other cases. These findings question previous critical reports on the safety aspects of BCG vaccination in immunocompromised individuals.

Margreet C. Vos,¹ Henk van Deutekom,² Petra de Haas,³ and Dick van Soolingen³

¹Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, ²Department of Tuberculosis Control, Municipal Health Service, Amsterdam, and ³Diagnostic Laboratory for Infectious Diseases and Perinatal Screening, National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands

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Reprints or correspondence: Dr. M. C. Vos, Dept. of Medical Microbiology and Infectious Diseases, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands (m.vos@erasmusmc.nl).

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Human Immunodeficiency Virus and Hepatitis C Virus: Which Is the Cart, and Which Is the Horse?

STR—The interesting findings by Martinez-Sierra et al. [1] are subject to alternative interpretations that challenge some of the authors' underlying suppositions. The authors' observation of more-prevalent cirrhosis among patients with CD4⁺ cell counts ≤ 200 cells/mm³ than among patients with CD4⁺ cell counts > 200 cells/mm³ at the time of diagnosis of HIV infection was interpreted as evidence that HIV-induced immunosuppression accelerated hepatitis C virus (HCV) disease. Alternatively, the severity of HCV-induced liver disease could have been the cause, rather than the result, of the accelerated decrease in CD4⁺ cell counts. The possibility that HCV infection contributed to CD4⁺ cell count decreases in parallel with the severity of liver disease should not be excluded, given that the analysis by Martinez-Sierra et al. [1] did not take into account factors known to be associated with lower CD4⁺ cell counts, such as the duration of HIV infection and virus load. The observation in the Swiss HIV Cohort Study [2] that increases in CD4⁺ cell counts were smaller among HCV-infected patients in whom HIV loads were sustained at undetectable levels by HAART than among HCV-uninfected patients with the same response to treatment is compatible with the premise that liver disease adversely affects CD4⁺ cell count.

It may be that no demonstrable improvement in the fibrosis progression rate (FPR; expressed as the ratio of fibrosis units to the duration of infection) attributable to HAART was seen in the study by Martinez-Sierra et al. [1] because FPR is too insensitive a measure to reflect changes occurring over a relatively short

period. The number of fibrosis units used to calculate FPR can only be an integer between 0 and 4. Thirty-six months, the study period, may have been insufficient to accomplish a 1-unit change in fibrosis score that could be reflected as a change in FPR. Furthermore, although an increase in CD4⁺ cell count was not independently associated with a lower prevalence of cirrhosis after adjustment for baseline CD4⁺ cell count, the possibility that a relationship exists between the robustness of the increase in CD4⁺ cell count induced by HAART and the severity of liver disease was not explored. In addition, the authors' demonstration that the duration of HCV infection (≤ 20 vs. > 20 years) strongly correlated with FPR both for HIV-negative patients (0.082 vs. 0.139; $P = .01$) and for HIV-positive patients (0.132 vs. 0.165; $P = .01$) contradicts the implicit premise on which the prognostic value of the FPR is based—namely, that liver fibrosis progress is linear over time.

Large cohort studies, stratified by factors affecting HIV and HCV disease progression, likely will shed greater light on the reciprocal interactions between HIV and HCV and the role of HAART in mitigating the consequences of HCV infection for HIV-infected individuals.

Elizabeth R. Jenny-Avital

AIDS Consultation Service, Jacobi Medical Center, Bronx, New York

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Reprints or correspondence: Dr. Elizabeth R. Jenny-Avital, AIDS Consultation Service, Jacobi Medical Center, Bldg. 5, Rm. 607, 1400 Pelham Pkwy. S, Bronx, NY 10461 (jennyavita@aol.com).

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Reply

SIR—Our study demonstrates that the evolution of liver disease in HIV-infected patients is influenced by the baseline CD4⁺ cell count and the hepatitis C virus (HCV) load [1]. Immune reconstitution induced by therapy was not an independent factor associated with a higher fibrosis progression rate (FPR). In a letter written in response to our article [2], 2 questions about the methods refer to the FPR as the measure of evolution of liver disease. The first question relates to the differences in FPR as a function of the period of evolution of HCV infection. We believe that the influence of other covariables putatively implicated in FPR (e.g., age at infection, alcohol consumption, and HCV load) cannot be excluded with confidence without a multivariate analysis, as was performed in our study. Second, it could certainly be argued that, as a test, FPR is not sufficiently sensitive to reflect changes occurring over a relatively short period (36 months); however, it was sensitive enough to prove that immune reconstitution induced by HAART was associated with a lower prevalence of liver cirrhosis, although (again, using multiple linear regression) that immune recovery has an independent effect could be discounted. Both aspects are related to the research design; our study was cross-sectional and lacked the perspective gained by use of a large cohort.

The main point for discussion is the relative importance of the effect of CD4⁺ cell count on FPR and the effect of HCV-induced liver disease on CD4⁺ cell count evolution. Our study was not designed to analyze the differences in CD4⁺ T cell count evolution as a function of the presence of HCV coinfection, and, thus, our results cannot identify definitively whether HIV is the horse or the cart. Greub et al. [3] have presented data supporting the view that HCV infection may blunt immune recovery. However, our patients showed a notable recovery of CD4⁺ cell count after a follow-up period of 36 months, with a median increase of 225

cells/ μ L. In addition, we have now calculated an index for measuring the increase in CD4⁺ cell count to analyze the relationship between the robustness of the CD4⁺ cell count increase induced by HAART and the severity of the liver disease: $100 \times [(CD4^+ \text{ cell count at liver biopsy} - CD4^+ \text{ cell count at HIV diagnosis}) / CD4^+ \text{ cell count at HIV diagnosis}]$. When patients are classified into 2 groups, those with fibrosis of stages 0 or 1 and those with fibrosis of stage 2 or higher, this index is similar in both groups: the mean index (\pm SD) is $424\% \pm 328\%$ for the first group and $406\% \pm 116\%$ for the second group ($P = 1.000$). On the other hand, the index of CD4⁺ cell count increase is significantly higher among patients with HIV load suppression ($n = 32$) than among those without HIV virological response to treatment ($n = 9$) (mean index [\pm SD], $448\% \pm 179\%$ vs. $25\% \pm 15\%$, respectively; $P = .026$). Thus, our results differ from those of the Swiss cohort [3] and are similar to those of Sulkowski et al. [4], Chung et al. [5], and Tebaldi et al. [6], who did not detect evidence that HCV infection substantially alters the probability that a patient will respond immunologically to HAART, after accounting for differences in its administration and effectiveness.

José A. Girón-González,¹ Carmen Martínez-Sierra,² Ana Arizcorreta,¹ and Fernando Díaz²

¹Infectious Diseases Unit and ²Gastroenterology Department, Hospital Universitario Puerta del Mar, Cadiz, Spain

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Reprints or correspondence: Dr. J. A. Girón-González, Servicio de Medicina Interna, Hospital Universitario Puerta del Mar, Ave. Ana de Viya 21, 11009 Cádiz, Spain (joseantonio.giron@uca.es).

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Infection of Transjugular Intrahepatic Portosystemic Shunt Devices

SIR—I read with great interest the article by Armstrong and MacLeod [1] that described 3 patients with presumed infection of transjugular intrahepatic portosystemic shunt (TIPS) devices and reviewed the medical literature on this infection. TIPS is now a routine procedure performed for complications of portal hypertension that are unresponsive to medical therapy or sclerotherapy [2]. Infections of TIPS devices are infrequent and have been reported in the literature mainly in case reports or reports from single-center, retrospective studies. Thus, this recent summary is both timely and relevant.

As Armstrong and MacLeod [1] correctly point out, one major problem in determining the incidence of TIPS infection is that there is no standardized case definition for this entity. Although pathologic and microbiologic sampling of the stent itself might serve as a “gold standard” for identifying infection of these devices, such examination can only occur either after liver transplantation or during autopsy. Because the stent is placed as a conduit between the portal and the systemic circulatory system, comparison with other endovascular infections, such as infective endocarditis, is reasonable. Indeed, when my colleagues and I [3] evaluated the 99

TIPS procedures performed at our institution, our case definition was modeled after that for infective endocarditis. We evaluated patients with TIPS devices in place who developed sustained bacteremia; the criteria for sustained bacteremia were the same as those used for sustained bacteremia associated with infective endocarditis [4, 5]. Certainly, other potential sources of sustained bacteremia, such as infective endocarditis, must be definitively excluded before TIPS infection is suspected.

The 3 patients with presumptive TIPS infection described by Armstrong and MacLeod [1] developed sustained and prolonged bacteremia due to *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. In an attempt to create a more specific standardized definition of TIPS infection, and on the basis of the very prolonged bacteremia that these 3 patients experienced, the authors proposed an alternative definition of sustained bacteremia. They proposed that sustained bacteremia should be defined as ≥ 2 blood cultures positive for the same organism, the first and last being separated by ≥ 7 days.

I disagree with this proposed definition. The definition of sustained bacteremia due to endovascular infection should not differ according to the site of infection. Infection of the endovascular system is defined by continuous bacteremia over time. Once continuous bacteremia is documented, there is no reason to apply an arbitrary duration of bacteremia, such as 7 days. It may be noteworthy that the 3 patients described in this report were bacteremic for several days, but this could be explained by the virulence of these 3 organisms or the antimicrobial therapy used. MRSA, *P. aeruginosa*, and *E. coli* may be more difficult to eradicate than some of the other organisms that have been implicated in TIPS infection. For example, resolution of TIPS-associated bacteremia due to *Streptococcus sanguis* or *Lactobacillus acidophilus* may occur more quickly than that due to MRSA. Furthermore, it has been sug-

gested that resolution of bacteremia due to MRSA may be slower with vancomycin therapy than with β -lactam antibiotic therapy [6].

Another factor that may contribute to the duration of bacteremia associated with TIPS infection is the underlying immune status of the patient. Bacteremia is a known complication of cirrhosis, and underlying cirrhosis may affect response to antimicrobial therapy [7]. In our analysis, we classified each patient by underlying etiology of cirrhosis and by Child-Pugh class to identify whether these factors affected the duration of TIPS infection. Armstrong and MacLeod [1] do not provide the Child-Pugh classification for the patients described in their article. Although the effect of these factors on TIPS infection is unknown, the level of underlying immunodeficiency associated with cirrhosis may explain why these 3 patients remained bacteremic for a prolonged period.

In summary, I think this recent review of TIPS infection is clinically important and well written. However, I think that it is premature to state that a minimum of 7 days of continuous bacteremia is necessary before identifying a TIPS infection. As stated above, documentation of sustained bacteremia without evidence of infection elsewhere in the endovascular system should be adequate to identify TIPS infection.

Joseph A. DeSimone, Jr.

Division of Infectious Disease, Thomas Jefferson University, Philadelphia, Pennsylvania

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Reprints or correspondence: Dr. Joseph A. DeSimone, Jr., Div. of Infectious Disease, Thomas Jefferson University, 1015 Chestnut St., Ste. 610, Philadelphia, PA 19107 (joseph.desimone@mail.tju.edu).

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Resumption of Linezolid Therapy after Myelotoxicity

SIR—Linezolid is associated with hematologic toxicity, including anemia, thrombocytopenia, and pancytopenia [1, 2]. This toxicity is rapidly reversible with withdrawal of the drug from the therapeutic regimen, but no information exists about the risk of resuming linezolid therapy. I recently had the occasion to re-administer linezolid therapy at a reduced dose in the treatment of relapsing methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and no recurrence of hematologic toxicity was seen.

In January 2002, a 69-year-old man presented with MRSA bacteremia related to an infected axillofemoral-femoral bypass graft. Despite removal of the vascular prosthesis and administration of antibiotic therapy with various regimens involving vancomycin, rifampin, and trimethoprim-sulfamethoxazole, bacteremia persisted. Linezolid therapy (600 mg b.i.d.) was started on 2 April 2002, with clearance of the bacteremia. The hemoglobin level was 11.3 g/dL, and the platelet count was 315,000 platelets/ μ L when linezolid was initiated.

On 4 June 2002, the patient was readmitted to the hospital with weakness. His hemoglobin level was 6.7 g/dL, and

his platelet count was 123,000 platelets/ μ L. There was no evidence of bleeding, and the results of hemocult tests of stool samples were negative. Reticulocytes were absent on a blood smear. Thyroid-stimulating hormone, vitamin B12, and folate levels were normal. Six blood cultures were sterile. The iron level was 218 μ g/dL, and the total iron-binding capacity value was 269 μ L/dL. The serum creatinine level was 1.6 mg/dL. Other medications received included simvastatin, carvedilol, oxybutynin chloride, aspirin, and iron sulfate.

Linezolid was discontinued, and, although the nadir platelet count was 82,000 platelets/ μ L, the patient's hematologic presentation gradually improved. He was discharged with no antibiotic therapy. On 20 June 2002, the patient was readmitted to the hospital with fever. Multiple blood cultures grew MRSA. The hemoglobin level was 9.8 g/dL, and the platelet count was 523,000 platelets/ μ L. Linezolid therapy was resumed at a dosage of 600 mg/day. His fever quickly resolved, and his blood cultures became sterile. The patient has subsequently received 9 months of linezolid therapy and remained clinically well. Multiple blood cultures were sterile. His hemoglobin level gradually improved; in March 2003, it was 13.7 g/dL, and the platelet count was 242,000 platelets/ μ L.

This case demonstrates that the hematologic toxicity of linezolid appears to be dose related and may be managed with dose reduction. Prolonged therapy at a lower dose was well tolerated in this case. Also important is the excellent efficacy that reduced-dose linezolid therapy demonstrated in this case. The relapse of MRSA bacteremia \leq 2 weeks after the initial discontinuation of linezolid therapy indicates the severity of the infection in this patient, although reduced-dose linezolid therapy effectively controlled his infection. Evidence of the clinical effectiveness of low-dose linezolid is conflicting. Linezolid at 200 mg twice per day has been shown to be clinically efficacious for vancomycin-resistant enterococcal infections,

although the rate of microbiologic success was lower at the lower dose [3]. However, clinical failure to treat MRSA bacteremia was recently reported [4]; it was attributed to low linezolid levels, despite use of typical doses. My case demonstrates the prolonged clinical efficacy of low-dose linezolid therapy. However, whether this approach is acceptable requires additional study.

William B. McNamee, Jr.

Department of Medicine, Division of Infectious Diseases, Mercy Fitzgerald Hospital, Darby, Pennsylvania

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Reprints or correspondence: Dr. William B. McNamee, Jr., 1503 Lansdowne Ave., Ste. 3010, Darby, PA 19023 (Mcnamees@erols.com).

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Concurrent Antibiotic Review Programs—A Role for Infectious Diseases Specialists at Small Community Hospitals

SIR—The recent article by Petrak et al. [1] cites examples of antibiotic-utilization programs developed by infectious diseases (ID) specialists at either academic [2] or large urban medical centers [3]. We developed a concurrent antibiotic review program, similar to that reported by Fraser et al. [4], which resulted in significant cost savings and improved antibiotic utilization at our 120-bed community hospital.

Our antibiotic support team (AST), which consisted of an ID specialist, a clinical pharmacist, and representatives from the infection-control department and mi-

crobiology laboratory at Glenwood Regional Medical Center (West Monroe, LA), performed concurrent chart reviews 3 days per week that targeted patients receiving multiple, prolonged, or high-cost antibiotic therapy. Data collected included diagnosis and indications for antibiotics currently received; age; weight; allergies; renal, hepatic, and gastrointestinal function; and microbiology reports. Recommendations were communicated to managing physicians via a confidential form that was temporarily placed in the chart but did not become part of the official medical record. Telephone calls were made if urgent communication was warranted. Physicians were not obligated to follow the AST's advice but were encouraged to request formal ID consultation if a conflict arose.

The medical staff was initially apprehensive about this program, which was due somewhat to a perceived loss of prescriptive autonomy but more so to concerns of legal liability, especially if physicians chose to reject AST recommendations. However, as a subcommittee of the hospital's pharmacy and therapeutics committee, and because its work involved quality assurance and utilization review activities, the AST's records were kept separate from patient medical records and, therefore, were not subject to legal discovery. We also realized the limitations of clinical decisions based solely on chart-review data, and we were careful to make recommendations only in well-defined clinical scenarios. No suggestions were made if data were insufficient to allow a comfortable decision. In essence, we aimed at harvesting the "low-hanging fruit," rather than delving into complicated management issues. After several months, the program had met with wide approval, and some physicians regularly requested review of their patients' charts.

From January through December 2000, we made 488 recommendations. Three hundred and thirty-six (69%) were accepted and implemented; 126 (26%) were rejected; and 26 (5%) were cancelled be-

cause of patient discharge. Thirty-eight percent of recommendations were to discontinue 1 or more antibiotics, because of duplicate coverage, inappropriate use, or excessive duration; 33% were to change from intravenous to oral administration; 23% were to substitute or add an antibiotic to the regimen; and 6% were to change dosage. Antibiotic costs for the year 2000 averaged \$14.77 per patient-day, compared with \$18.21 per patient-day in 1999—a cost reduction of 19% and a total estimated savings of \$177,000. Although we did not track clinical outcomes, no adverse events were reported in connection with this program. The AST required ~8–12 h per week of the ID specialist's time.

In addition to the financial and clinical benefits, concurrent antibiotic utilization programs can help smaller hospitals attract ID specialists to settings where lower patient volumes may not support traditional consultative practices. The Infectious Diseases Society of America, pharmacists, and hospital administrators should work together to promote further study and development of and financial support for these programs.

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Anthony LaRocco, Jr.

Department of Internal Medicine, Glenwood Regional Medical Center, West Monroe, Louisiana

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Reprints or correspondence: Dr. Anthony LaRocco, Jr., Div. of Infectious Diseases, Dept. of Internal Medicine, Eastern Virginia Medical School, 825 Fairfax Ave., Norfolk, Virginia 23507 (larocca@evms.edu).

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