Received:
19 October 2013

Revised:
20 January 2014

Accepted:
11 February 2014

doi: 10.1259/bjr.20130667

Cite this article as:

Yau TY, Alkandari LAA, Haaland B, Low W, Tan CH. Is intravenous contrast necessary for detection of clinically significant extracolonic findings in patients undergoing CT colonography?. *Br J Radiol* 2014;87:20130667.

FULL PAPER

Is intravenous contrast necessary for detection of clinically significant extracolonic findings in patients undergoing CT colonography?

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Objective: To determine whether intravenous contrast (IVC) is necessary for detection of extracolonic findings (ECFs) in patients undergoing CT colonography (CTC).

Methods: We performed a retrospective review of CT findings in 179 cases of CTC studies performed over 18 months where both pre-contrast (NECT) and post-contrast (CECT) scans were performed in the prone and supine positions, respectively, in the same patients. All ECFs were recorded on a per patient basis and graded according to the colonography reporting and data system classification.

Results: There was no significant change in E grade for the cohort ($p = 0.171$) between the NECT and CECT scans. On the CECT scans, additional findings were detected in

49.1% of patients. Overall, there were 27/179 (15.1%) patients graded E3 and 18/179 (10.1%) patients graded E4 on the CECT study. Compared with the NECT study, there was a decrease of 12.9% of patients graded E3 and no change in the number of patients graded E4.

Conclusion: With IVC administration, additional ECFs are detected in nearly half of all patients. However, there was no increase in the number of patients with clinically significant lesions. The risk-benefit ratio of routine IVC administration for CTC in symptomatic patients thus requires further evaluation.

Advances in knowledge: This study reviews the utility of IVC in CTC and is thus relevant to current clinical practice at many institutions.

CT colonography (CTC) has emerged as an acceptable diagnostic tool for detection of colonic polyps and cancers. Numerous studies have corroborated the high sensitivity and specificity rates (>90%) in screening for large polyps.¹ Fewer studies have specifically examined the role of CTC for detection of extracolonic findings (ECFs) and the effect of these findings on subsequent patient treatment and cost.²⁻⁸

A distinct advantage of CTC over other diagnostic tests for colorectal abnormalities is the additional information provided by concomitant imaging of the extracolonic organs in the abdomen and pelvis, and, to a certain extent, the lower thorax. For example, early detection of extracolonic malignancies or metastases may make a difference to patient management and outcomes. The study by Veerappan et al³ showed that screening CTC without intravenous contrast (IVC) administration itself increased the odds of detection of high-risk lesions by 78%, half of which were ECFs. ECFs of at least moderate importance are seen in

between 7% and 11% of patients.^{2,4-8} Detection of these abnormalities, such as extracolonic cancers (e.g. renal cell carcinoma) and aortic aneurysms, can sometimes be beneficial.⁹

The administration of IVC increases soft-tissue contrast and theoretically increases detection of ECFs. However, it has not been shown in a single patient cohort whether IVC increases detection of clinically significant ECFs in the setting of CTC. This is an important question because routine administration of IVC is not without adverse effects. These include increased cost and potential adverse events resulting from unnecessary subsequent work-up of incidentally detected ECFs. Hence, the purpose of our study was to determine whether IVC is necessary for the detection of clinically significant ECFs in patients undergoing CTC. The hypothesis of this study is that routine IVC in symptomatic patients undergoing CTC is not necessary for the detection of clinically significant ECFs.

METHODS AND MATERIALS

Data collection

A retrospective review of cases was performed following approval by the local institutional review board. Consecutive patients who were referred for conventional CTC during 2009 and 2010 at a tertiary care diagnostic radiology department and who had scans both with and without IVC administration were included. This included patients with symptoms related to the gastrointestinal tract as well as patients with non-specific symptoms who were referred to exclude malignancy. Symptoms which were considered to be related to the gastrointestinal tract included constipation, change in bowel habits and rectal bleeding, whereas symptoms that were non-specific included anaemia and weight loss. Patients who did not have IVC administered during the study (*e.g.* those referred for screening and renal impairment) were excluded.

All patient demographic and clinical data were retrieved from the electronic records of the hospital. Patient age and gender, reason for examination, the absence or presence of follow-up imaging and laboratory tests were reviewed. The surgical or interventional radiology procedures directly related to the ECFs of the CTC examination (including histopathology) were also reviewed where available. Correlation with optical colonoscopy for colonic findings was not performed as this was deemed to be beyond the scope of the present study.

There are few published data on the change of E gradings in patients with pre-contrast (NECT) and post-contrast (CECT) CTC studies; hence, the power analysis was made using an anecdotal figure of 5% for clinically significant upgrades and 15% for clinically significant downgrades (taking into account that IVC allows better characterization of indeterminate lesions on the unenhanced study). In this way, it was estimated that a sample size of >155 would provide a study power of >0.8.

Bowel preparation

All patients underwent routine bowel preparation. At our institution, a standard low-residue diet and adequate hydration, 2–3 days before the examination, is encouraged in all patients. The laxative regime includes 240 ml of dilute magnesium sulfate syrup (35% magnesium sulfate in 5 ml, two doses given the day before the examination) and two bisacodyl tablets (5 mg, Dulcolax®; Boehringer, Ingelheim, Germany) 1 day before imaging (at 2 pm and at 9 pm) and bisacodyl suppository at 7 am on the day of the examination.

Faecal tagging with a commercially prepared barium sulfate suspension (Tagitol™; E-Z-EM, Bicester, UK; 60 ml of barium sulfate suspension 40% w/v) was administered in three divided doses 1 day before the procedure. A single 325-ml dose of dilute 3% Gastrografin® (Bayer Schering Pharma, Berlin, Germany) was routinely given for fluid tagging 2 hours before the procedure.

Scanning technique

The standard technique at our institution is as follows: 20 mg of intravenous antispasmodic agent, hyoscine butylbromide (Buscopan®; Boehringer), was administered on the table prior to initiation of the scan. A thin-calibre flexible catheter was inserted into the rectum and the colon insufflated with room temperature air by the CT technician. The insufflation of air is done first in the right decubitus position followed by the supine and the left decubitus positions. The volume of air administered is empirically between 2 and 3 litres and limited by the reported patient discomfort.

A CT scout of the patient is used before the scans to determine whether further insufflation of air is needed. The procedure is then performed in a single breath hold. All scans were performed on one of three multidetector row CT scanners (16 slice or 64 slice, Somatom® Definition AS; Siemens Healthcare, Erlangen, Germany). CT scanning was performed in the prone followed by supine positions. Full coverage of the abdomen and pelvis from above the diaphragm to below the symphysis pubis was ensured for both scans. Prone images were first acquired at a collimation of 0.625 mm at 120 kVp, 50 mAs, slice thickness of 1 mm, position increment of 0.8 mm and a pitch of 0.9. Scanning parameters were the same for the supine position, albeit at a higher dose (150 mAs). A standard in-built dose reduction technique (tube current modulation) was applied in all cases. A single bolus of 90 ml of intravenous low-osmolar agent, iohexol (Ominipaque™ 350; GE Healthcare, Waukesha, MI), was administered in all patients, at a fixed rate of 2 ml s⁻¹, before the acquisition of the supine scan. CECT images are routinely acquired in the portal venous phase, approximately 60 s following initiation of contrast administration.

Image analysis

For this study, two-dimensional images in NECT and CECT scans were reviewed in the axial planes. All ECFs for this study were assessed using the local picture archiving and communication system (Centricity™, GE Healthcare, London, UK).

Table 1. Number of patients classified under the respective E grades according to the colonography reporting and data system classification in the pre-contrast (NECT) and post-contrast (CECT) scans

NECT (<i>x</i> -axis)/CECT (<i>y</i> -axis)	E1	E2	E3	E4	Total
E1	16	0	0	0	16
E2	18	93	7	0	118
E3	1	2	23	1	27
E4	0	0	1	17	18
Total	35	95	31	18	179

Table 2. Total number of patients classified under the respective E grades in the pre-contrast (NECT) and post-contrast (CECT) scans and differences in number

Scan	E1	E2	E3	E4	Total
NECT	35 (19.5)	95 (53.1)	31 (17.3)	18 (10.1)	179
CECT	16 (8.9)	118 (65.9)	27 (15.1)	18 (10.1)	179
Difference (CECT – NECT)/NECT	–19 (–54.2)	+23 (+24.2)	–4 (–12.9)	0 (0)	

Percentages are given in parentheses.

The patient's NECT and CECT scans were reviewed separately by two radiologists (TCH and LAAA) with 9 and 6 years' radiology experience, respectively, without reference to the issued CTC reports or to the patients' underlying medical records. The differences in findings were then reviewed together and a consensus read was obtained.

The NECT and the CECT images were reviewed at time intervals of at least 2 weeks apart (mean, 18 days) to reduce recall bias. The cases were presented in random order to each observer and reshuffled before being represented for CECT reading. The NECT images were not made available to the observers during CECT reading, as our purpose was to separately assess the value of IVC for detection of lesions. For all cases, the NECT was evaluated first for standardization and ease of reading. All abnormal ECFs were recorded. Subsequently, the CECT scans were reviewed 2 weeks later. All ECFs were assigned a grade based on the colonography reporting and data system (C-RADS) classification proposed by Zalis et al¹⁰ (E0 = compromised by artefact, evaluation of extracolonic soft tissues is severely limited; E1 = no extracolonic abnormalities visible, includes anatomical variant such as retroaortic left renal vein; E2 = clinically unimportant finding that does not require work-up, e.g. renal and hepatic cysts, cholelithiasis without cholecystitis and vertebral haemangioma; E3 = likely unimportant finding, incompletely characterized, work-up may be indicated subject to local practice and patient preference, e.g. minimal complex or homogeneously hyperattenuating renal cyst; E4 = potentially important finding that requires communication to referring physician as per accepted practice guidelines, e.g. solid renal mass, lymphadenopathy, aortic aneurysm, non-uniformly calcified pulmonary parenchymal nodule >1 cm in size). The highest E grade in each patient was recorded and used for comparison analysis. The presence of additional findings on the CECT scan, if any, was also recorded.

Statistical analysis

A comparison between the findings in the NECT and CECT scans was performed. The McNemar–Bowker test was used to compare the two groups (NECT and CECT) for significant differences in the prevalence of the findings in each risk category. Subgroup analyses of patients based on age (<50 vs ≥50 years) and symptoms (gastrointestinal symptoms vs non-gastrointestinal symptoms) were additionally performed. A clinically significant upgrade was defined as a grade of E3 or E4 on the CECT, when the NECT was E2 and below. A clinically significant downgrade was conversely defined as a grade of E2

and below on the CECT, when the NECT was graded E3 or E4. Data analyses were performed using SPSS® v. 18.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 181 cases of CTC with contrast performed at our institution between January 2009 and June 2010 were evaluated. Of

Figure 1. (a) Axial post-contrast image shows subcentimetre hypodensity in the interpolar region of a right kidney consistent with the cyst. (b) Retrospective review of the axial pre-contrast image that shows subtle hypodensity in the same region that was missed at first interpretation (E1). This finding, however, is not of clinical significance (E2).

(a)

(b)

Table 3. Conditions in patients who were graded E3 on the post-contrast scan

Condition	Number of patients
Liver/kidneys	
Complicated renal cyst	3
Renal angiomyolipoma	1
Biliary ductal dilatation	3
Complicated liver cyst	3*
Complicated liver cyst, breast implant intracapsular rupture	1*
Pelvic	
Prostate enlargement	1
Rim calcified ovarian cyst	1
Left ovarian mass	1
Bladder polyp	1
Other abdominal organs	
Chronic calcific pancreatitis	1
Adrenal hyperplasia	1
Left subphrenic collection	1
Ventral abdominal hernia	1
Left groin foreign body	1
Mesenteric lymph nodes	1
Ascites	1
Pulmonary	
Lung nodules	1
Pulmonary tuberculosis	1
Bronchiectasis	1
Others	
Varices	1
Left iliac bony lesion	1
Total	27

All of these findings were picked up on the non-contrast CT, except for two septated liver cysts and one breast by intracapsular rupture indicated implant an asterisk (*). No further work-up was done for these.

these, 86 (47.5%) were males and 95 (52.5%) were females. 60 (33.1%) patients had non-specific symptoms and were referred to exclude malignancy, whereas the remaining 121 (66.9%) patients had symptoms related to the gastrointestinal tract. The mean age of the patients was 62.9 years (range, 21–96 years).

In our study, two of the cases which were graded E0 were excluded from our retrospective analysis. A summary of the number of patients classified under the different C-RADS headings in the NECT and CECT scans is listed in [Tables 1](#) and [2](#). Of note, there was a significant decrease in the number of patients classified as E1 and E3 on the CECT scans (−54.2% and −12.9%, respectively), while there was an increase in the number of patients graded E2 (+24.2%).

35 (19.5%) patients were classified as E1 on the NECT scan. The E grades for 18 of these patients (51.4%) were upgraded to E2 on the CECT scan, 16 of which were attributed to tiny hypodensities that most likely represent cysts, in either the liver or kidneys or ovaries ([Figure 1](#)). Two patients were upgraded to E2, one for lung atelectasis and one for liver haemangioma. One patient was upgraded to E3 for an indeterminate liver lesion, which was subsequently shown on MRI to represent a cyst.

Of 95 (53.1%) patients who were graded E2 based on the NECT scan, two were re-graded (to E3). This was related to a septated left kidney cyst and breast implant intracapsular rupture.

Of 31 (17.3%) patients who were graded E3 on the NECT scan, 7 patients were re-graded as E2, the majority of whom were

shown to represent either hepatic haemangiomas or renal cysts that demonstrated benign features. One patient was upgraded from E3 to E4 on the CECT scan (hepatocellular carcinoma). The conditions for the patients graded E3 on the CECT scan in whom further evaluation was deemed necessary are detailed in Table 3.

18 (10.1%) patients were graded E4 on the NECT scan. One, a Bosniak category 2F cyst, was deemed E3 based on the CECT images (Figure 2). The rest of the patients did not show a change in E grade following IVC administration. Underlying conditions for the patients in whom the ECFs were considered to be clinically important and which had to be conveyed to the clinicians are detailed in Table 4.

Figure 2. (a) Axial pre-contrast image demonstrates a heterogeneous low-density 2.5-cm lesion in the upper pole of the left kidney. Faint rim calcifications are present. The lesion was classified E4 given the possibility of malignancy. (b) Axial post-contrast image shows the lesion to be predominantly cystic with thin internal septations that do not show measurable enhancement (Bosniak Type 2F). This was deemed E3 and observed at follow-up.

(a)

(b)

Overall, there were 163 additional extracolonic lesions found on the CECT study (400 on the CECT compared with 237 on the NECT), representing an increase of 68.7%. 49.1% of patients had additional lesions; however, there was a significant upgrade in E grade in only three patients (Table 5). There were seven patients who had a clinically significant downgrade (Table 6)

Follow-up of these patients via their national electronic health records (computerized patient record system and electronic medical record exchange) was done until December 2012 (1–2 years) to determine if they had subsequent radiological work-up done as a result of their ECFs. It was found that 4/27 = 14.8% of patients graded E3 and 8/18 = 44.4% of patients graded E4 had further relevant radiological investigations.

Statistical analysis of the findings revealed no significant difference in the prevalence of clinically significant (E3 + E4) and clinically insignificant (E1 + E2) findings in the overall study cohort ($p = 0.171$), comparing the pre- and post-contrast studies. The weighted κ for the E grades was 0.721 (95% confidence interval, 0.632–0.811), indicating good agreement. Analysis of the subgroups also showed no significant difference in the prevalence of clinically significant E gradings in patients with symptoms referable to the gastrointestinal tract ($p = 0.363$) and in patients >50 years old ($p = 0.09$).

DISCUSSION

At present, intravenous administration of iodinated contrast (IVC) is not indicated for patients undergoing screening CTC,¹¹ particularly since enhancement of colonic polyps does not correlate with the size or histological differentiation.¹² Although IVC may increase detection of ECFs,^{8,13,14} its actual benefit in the setting of CTC has not been well demonstrated.

In the case-control study of symptomatic patients by Spreng et al,¹⁴ the percentage of ECFs leading to further work-up or having an impact on therapy was higher for the IVC-enhanced group (31%) than for unenhanced group (13%), although this was not statistically significant. Therefore, IVC administration can be considered a double-edged sword: although it may theoretically help to characterize incidental findings, increased detection of such abnormalities requires additional tests and interventions;¹⁴ however, the majority of ECFs proved to be clinically insignificant.² This is also reflected in the recently published second European Society of Gastrointestinal and Abdominal Radiology consensus statement on CTC, which recommends that the administration of IVC in symptomatic patients should not be routine but rather should depend on clinical indications and the requirement to fully evaluate the extracolonic organs.¹⁵

Administration of IVC requires placement of a venous cannula (thereby causing pain), increases the risk for contrast-induced nephropathy, with potential for contrast extravasation and other adverse effects related to IVC, such as nausea and vomiting. Furthermore, unnecessary use of IVC would increase costs of the examinations.

To the best of our knowledge, there has been no study to date that specifically investigates the role of IVC in the detection of

Table 4. Various conditions for which patients were graded E4 on CT colonography

Condition	Number of patients
Abdominal	
Abdominal aortic aneurysm	3
Renal mass	2*
Hydronephrosis	1
Lymphadenopathy	2
Hepatocellular carcinoma	1*
Liver cirrhosis	1
Liver metastases	1
Mesenteric lymph node metastases	1
Pulmonary	
Lung nodules	2
Massive pleural effusions (with splenomegaly)	1
Pulmonary fibrosis	1
Other	
Bone metastases	1
Pelvic fracture	1
Total	18

The pre-contrast (NECT) and post-contrast (CECT) extracolonic findings were identical, other than for a complex renal cyst in one patient deemed to represent a Bosniak Type 2F cyst on CECT (E4 to E3), as well an indeterminate liver mass subsequently shown to represent a hepatocellular carcinoma on CECT (E3 to E4), indicated by an asterisk (*).

ECFs in CTC in a single cohort of patients. The results of our study highlight several important findings. Firstly, in our institution's referral population of largely symptomatic patients, the administration of IVC in CTC does not increase detection of clinically significant ECFs. Specifically, we refer to lesions that are graded E4 by the C-RADS classification proposed by Zalis *et al*¹⁰ (Working Group on Virtual Colonoscopy). We consider this to be an important finding because of the potential adverse effects of the aforementioned IVC administration.

We found clinically significant findings in 45/179 (25.2%) of patients. This is similar to the results of the study by Tolan *et al*¹³ comprising elderly asymptomatic patients, which found that clinically important ECFs occur in 29% of patients. Differences in the incidence of ECFs from other studies may be partially attributed to differences in age and symptoms. In the study by Pickhardt *et al*,⁶ in which the mean age was 58 years (range, 40–90 years), the incidence of ECFs of moderate importance was 8.6%, whereas studies by Hara *et al*⁴ and by Hellstrom *et al*¹⁶ found 11% and 13%, respectively, of symptomatic cases with clinically important findings.

The concern about not administering IVC in CTC is that, potentially, there would be patients in whom the ECF is not detected or its significance is underestimated, since the addition of IVC increases detection of ECFs. This would certainly be true by a per lesion analysis.¹⁴ We found additional lesions in nearly half (49.1%) of patients. However, other than for four patients

(4/179 = 2.2%), the rest of the patients had no clinically significant increase in E grade from the presence of other concomitant findings. Of the four patients, one was upgraded from E1 to E3 for an indeterminate liver lesion, which was subsequently found to represent a cyst on MRI. Two patients were upgraded from E2 to E3 because of a breast implant intracapsular rupture and a complex liver cyst, respectively. One patient was upgraded from E3 to E4 for a complex liver mass on the NECT, which would certainly require further work-up if interpreted alone, but was diagnosed as suspicious for hepatocellular carcinoma on the CECT.

On the contrary, there were 8 (4.5%) patients in whom the E grades were downgraded on the CECT (7 from E3 to E2, and 1 from E4 to E3). These were largely attributed to ill-defined hypodensities in the liver, kidneys and ovaries that were shown to represent cysts or liver haemangiomas upon contrast administration (Figure 3). Hence, it appears from our study that not administering IVC for CTC tends to overestimate rather than underestimate the incidence and grade of ECFs. To further illustrate this, it was calculated that 12.9% of patients graded E3 on the NECT were downgraded to E2 on the CECT. The expected reduction in the number of further radiological investigations (and thus cost savings) is likely to be limited, given that only 4/27 = 14.8% of our patients with E3 grade had related further radiological work-up. The majority of lesions that were graded E3 on CECT did not have follow-up imaging, as they were deemed to be insignificant by the referring clinician.

Figure 3. (a) Axial pre-contrast image shows a slightly enlarged right ovary containing subtle hypodensity. Without intravenous contrast, this would be indeterminate and would require further evaluation (E3). (b) Axial post-contrast image at the same level demonstrates the presence of a rim-enhancing cyst in the right ovary with typical morphology of a corpus luteum cyst. This is not of clinical significance (E2).

This reflects the current clinical practice that the decision to follow up on radiological findings must be guided by the overall clinical picture.

Overall, it is noted that, after the administration of IVC, there was a significant decrease in the number of patients graded E1 (−54.2%), whereas the number of patients graded E2 increased (+24.2%). This is an expected outcome, as IVC allows for detection of additional lesions; that there was no significant

Table 6. Clinically significant downgrades (E3/E4 on the pre-contrast scan to E2 on the post-contrast scan)

Grade	Number of patients	Condition
E3 to E2	7	3 Hyperdense renal cysts
		2 Liver haemangiomas
		1 Right ovarian cyst
		1 Thickened gallbladder
E4 to E2	0	

change in patients graded E4 and, in fact, a decrease in the number of patients graded E3 (−12.9%) further supports our hypothesis.

Subgroup analyses: In patients who are asymptomatic or those with symptoms referable to outside the gastrointestinal tract ($n = 58$), there was no significant change in E grading except for one patient who was downgraded from E4 to E3 for a Bosniak 2F renal cyst. All the patients with clinically significant upgrades in E grade had symptoms referable to the gastrointestinal tract ($n = 121$).

The main limitation of our study lies in its retrospective design. The majority of patients in our study were symptomatic; this makes our study less applicable to the screening cohort. However, this allowed us to compare those who had symptoms directly referable to the gastrointestinal tract with those who had general symptoms not directly referable to the gastrointestinal tract. Another limitation was the use of a consensus reading in interpreting the studies, which does not simulate performance under realistic conditions and does not account for interobserver variability.¹⁷ However, we believe that the degree of interobserver variability in our study was limited, as both readers were experienced abdominal radiologists and most of the findings were not particularly subjective in nature (e.g. hepatic and renal cysts).

Direct comparison between NECT and CECT scans is confounded by the radiation dose administered, since at lower doses in the NECT scan there will be increased image noise and beam hardening artefacts from barium contrast (faecal tagging) in the colon. This may theoretically account for some small hypodensities in the liver and kidneys being missed on the NECT scan; however, none of them were clinically important.

Table 5. Clinically significant upgrades, comparing the pre-contrast scan with the post-contrast scan (clinically significant being defined as E3 and E4)

Grade	Number of patients	Condition	Clinical outcome
E1 to E3	1	Indeterminate liver lesion	MRI liver showed liver cyst
E2 to E3	2	Breast implant intracapsular rupture	No further work-up was done
		Septated liver cyst	No further work-up was done

For the analysis of ECFs, we chose to compare the E grade of the lesions on a per patient basis, rather than on a per lesion basis. This may reduce the degree of discrepancy between the NECT scan and the CECT scan, since multiple ECFs are present in most patients. However, a per lesion analysis may diminish the study outcome, given that the management of patients would be based on the most significant, *i.e.* the highest E grade, lesion in each patient.

Among the lesions that were designated grade E2 on CECT, subcentimetre hypodensities were deemed benign, although we did not have follow-up imaging to demonstrate stability over time as a marker of benignity. This is in itself a limitation of current CT technology, which allows detection of small hypodensities that cannot be further characterized. Perhaps additional imaging with MRI in these patients may confirm the

diagnosis; however, as several prior studies have shown, the majority of these lesions, even in oncological patients, turn out to be benign.¹⁸ This has also been confirmed by the recent American College of Radiology's white paper on management of incidental lesions on CT in 2010.¹⁹ For categorization of the ovarian lesions, we referred to the consensus guidelines on management of ovarian cysts.²⁰

In conclusion, judicious handling of ECFs is needed to balance the cost and anxiety of additional work-up against the potential for early detection of important disease. The actual cost-benefit ratio of routine IVC administration in CTC is not known and should be a subject of future studies. Nevertheless, our study has shown that administration of IVC in CTC does not increase the detection of clinically significant findings in a cohort of symptomatic patients.

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