

# Digestive Endoscopy Is Not a Major Risk Factor for Transmitting Hepatitis C Virus

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**Background:** The potential role of digestive endoscopy as a mode for transmission of hepatitis C virus (HCV) is controversial.

**Objective:** To evaluate the role of digestive endoscopy in transmitting HCV by comparing the incidence of HCV infection in a cohort of patients undergoing endoscopy and in a cohort of blood donors.

**Design:** Prospective cohort study.

**Setting:** 3 endoscopic units and 2 blood banks in northwestern Italy.

**Patients:** The potentially exposed cohort consisted of 9188 outpatients consecutively recruited from 3 endoscopic units. Of 9008 patients negative for antibody to HCV (anti-HCV), 8260 (92%) were retested for anti-HCV 6 months after endoscopy. The unexposed cohort consisted of 51 230 healthy, anti-HCV-negative persons who donated blood at 2 blood banks in the same area and during the same time period; 38 280 of them (75%) were tested again for anti-HCV 6 to 48 months after the first blood donation (95 317 person-years of observation).

**Measurements:** Differences in the anti-HCV seroconversion rate between the exposed cohort (patients undergoing endoscopy) and

the unexposed cohort (blood donors). Seroconversion was evaluated by a third-generation enzyme immunoassay for anti-HCV; persons positive for anti-HCV were tested for HCV RNA by polymerase chain reaction.

**Results:** All 8260 persons undergoing endoscopy remained negative for anti-HCV 6 months after the procedure (risk per 1000 persons, 0 [95% CI, 0 to 0.465]); in particular, none of the 912 patients who underwent endoscopy with the same instrument previously used on HCV carriers showed anti-HCV seroconversion (risk per 1000 persons, 0 [CI, 0 to 4.195]). Four blood donors became positive for anti-HCV and HCV RNA (mean follow-up, 2.49 years; 0.042 case per 1000 person-years [CI, 0.011 to 0.107 case per 1000 person-years]); each had undergone minor surgery before the second test.

**Limitations:** In the endoscopy cohort, 8.3% of patients were lost to follow-up.

**Conclusions:** These findings support the hypothesis that properly performed digestive endoscopy is not a major risk factor for the transmission of HCV.

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Health care–related procedures have been implicated in the transmission of a consistent proportion of contemporary hepatitis C virus (HCV) infections. The role of major surgical operations, such as cardiovascular, gynecologic, and orthopedic procedures, is well established. However, the role of less invasive procedures, such as digestive endoscopy, remains a matter of debate.

A claim from a retrospective French study (1) that digestive endoscopic procedures are a major cause of HCV transmission among blood donors has not been substantiated by other authors (2, 3); acquisition of HCV through endoscopy has in fact been rarely reported in recent years (4, 5). Nevertheless, endoscopy as a vehicle for HCV transmission has been suspected since 1996, when blood banks in France and Italy suspended donors who reported a history of recent digestive endoscopy from donating blood for 6 months and up to 1 year, respectively. It is therefore important to establish whether digestive endoscopy represents a real risk and, if so, to define its magnitude.

We conducted a prospective study among outpatients referred to 3 endoscopic units in northwestern Italy from 1999 to 2002. The patients entering the study were tested for antibody to HCV (anti-HCV) at baseline and 6 months after endoscopy. The incidence of HCV infection

in this cohort was compared with that in blood donors recruited in the same area and during the same time period; these donors had not undergone any digestive endoscopic procedure.

## METHODS

### Endoscopy Cohort

Between January 1999 and December 2002, all of the outpatients referred for upper digestive endoscopy to 3 endoscopic units in northwestern Italy (1 secondary referral center and 2 tertiary referral centers) were asked to partic-

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**Context**

Controversy persists regarding the risk for transmission of hepatitis C virus (HCV) as a result of digestive-tract endoscopy.

**Contribution**

This prospective study of HCV-negative patients who underwent gastroscopy with the same endoscopes as HCV-positive patients showed no transmission of infection on follow-up 6 months later. Biopsy with reusable or disposable forceps did not increase the risk for HCV infection. Blood donors who were HCV negative without endoscopic exposure showed a few conversions to infected status an average of 2.5 years later.

**Implications**

The risk for HCV transmission by endoscopy is extremely low when standard instrument-cleaning techniques are used.

—The Editors

ipate in this study. Eligibility criteria were age older than 18 years and indication for gastroscopy. We restricted the procedure to gastroscopy in order to obtain a high rate of invasive procedures (for example, gastric biopsy).

We excluded patients if they were hospitalized, had previously undergone endoscopic procedures, were known anti-HCV carriers, or had to undergo additional endoscopic procedures other than gastroscopy. However, to identify the potentially infective population, we retrospectively looked for known HCV carriers who underwent gastroscopy in the 3 centers between January 1999 and December 2002.

Of 11 348 patients fulfilling the inclusion criteria, 9188 (81.0%) agreed to participate and gave written consent. They completed a questionnaire about risk factors for HCV infection during the past 6 months, and a serum sample was obtained from each immediately before endoscopy. Mild sedation with midazolam and hyoscine butylbromide was administered to each patient by using disposable syringes and vials. Gastroscopies were done by using various types of endoscopes, including fiberscopes and video endoscopes (Olympus GIF-Q20, GIF-Q30, GIF-IT30, GIF-IT140, Olympus Europe, Hamburg, Germany). Biopsies were performed with disposable biopsy forceps (Radial Jaw 3, Boston Scientific Microvasive, Natick, Massachusetts) in one center and reusable biopsy forceps (FB-24U-1, Olympus Europe) in another center; the third center used reusable forceps (EN-62143, Pescetto, Genova, Italy) in 1999 and disposable forceps (Max Capacity, Boston Scientific Microvasive) after 1999. Each patient was invited to attend a follow-up visit 6 months after endoscopy in order to obtain a serum sample for determining anti-HCV; at this visit, the patient was asked

to complete the HCV questionnaire again. To reduce the risk for false-negative results, potentially immunodeficient patients (those undergoing hemodialysis or receiving immunosuppressive treatment) were also tested for HCV RNA by polymerase chain reaction (PCR). All patients who did not attend the follow-up visit were recontacted by telephone.

Among patients in the endoscopy cohort, we identified an at-risk subset of patients: Overall, 912 endoscopic procedures (732 gastroscopies performed on known HCV carriers and 180 gastroscopies performed on newly discovered HCV carriers) were considered potentially infective. When we considered that each endoscope was used 3 times during the endoscopic session and assumed that the anti-HCV-positive patient was the first, second, or third at random, the number of exposed patients per HCV-infected-patient-day was 0, 1, or 2, with equal probability (the mean of those numbers is 1).

**Blood Donors Cohort**

Using a computerized database, we retrospectively identified all 51 645 consecutive blood donors at 2 transfusion centers in Torino and Pinerolo between January 1999 and December 2002 who were negative for HCV. Of these, 415 (0.8%) reported previous digestive endoscopy; the blood bank database did not record invasive procedures performed during endoscopy (such as biopsy and polypectomy). These 415 donors were asked to repeat the serologic and virologic HCV tests: 329 (79.3%) agreed, and 86 declined.

Of the 51 230 blood donors who did not undergo endoscopic procedures during the observation period, 38 280 (74.7%) were tested again after a mean of 2.49 years (range, 6 months to 4 years); the remaining 12 950 blood donors could not be contacted by telephone for retesting or declined to be retested.

Retested blood donors found to be newly positive for anti-HCV completed a structured questionnaire aimed at investigating risk factors for HCV infection, including endoscopic procedures, travel history, sexual activity, and potential parenteral exposures to blood or blood products (previous blood, platelet, or plasma transfusions; administration of coagulation factor concentrates; intravenous drug use; tattooing; acupuncture therapy; ear piercing; and major or minor surgery).

**Cleaning and Disinfection Method**

The instruments used for the known HCV carriers were not handled differently from those used for the HCV-negative patients; they were not removed from the general instrument pool, were disinfected in the same way as the others, and were then used promptly to perform endoscopy on the HCV-negative patients. Moreover, endoscopic procedures in known HCV carriers were not postponed at the end of the session but were performed according to the list of scheduled appointments.

All units participating in this study adhered to the

**Table 1. Baseline Characteristics of the Endoscopy Cohort**

Characteristic	All Patients	Patients Lost to Follow-up	Patients Retested
Patients, <i>n</i>	9008	748	8260
Mean age, <i>y</i>	47, SD 7	45, SD 8	46, SD 5
Men, <i>n</i> (%)	4431 (49.1)	396 (52.9)	4035 (48.8)
Biopsy performed, <i>n</i> (%)	6348 (70.4)	216 (34.6)	6132 (74.2)
Risk factors, <i>n</i> (%)			
None reported	6709 (74.4)	587 (78.4)	6122 (74.1)
Dental care	1568 (17.4)	112 (14.9)	1456 (17.6)
Surgery	613 (6.8)	41 (5.4)	572 (6.9)
Drug addiction	68 (0.7)	5 (0.6)	63 (0.7)
Blood transfusion	26 (0.2)	2 (0.2)	24 (0.2)
Unsafe sex	24 (0.2)	1 (0.1)	23 (0.2)

international guidelines for cleaning and disinfection practices in digestive endoscopy (6–10) and reprocessing endoscopic accessories (11); written protocols were available in each center. The staff involved in disinfection procedures consisted of trained nurses who were unaware of the ongoing study. At the end of the endoscopic procedure, the staff manually cleaned the instrument, including brushing the channels; each internal channel was flushed with detergent, rinsed with water, and blown through with air.

The endoscopic units used 3 different automated washer-disinfectors (DSD-91E, Medivators, Minneapolis, Minnesota; Circlean MC-12, Shoei, Tokyo, Japan; and ETD2, Olympus Europe), but the reprocessing cycle was similar: 1) The units were immersed in 2% glutaraldehyde for 20 minutes, and internal channels were flushed with the same solution; 2) the units were rinsed internally and externally with drinking-quality water to remove all traces of disinfectant; and 3) the units were dried externally and each channel was flushed with air. Before the first endoscopy of each day, all endoscopes were disinfected in a washer-disinfector.

After use, reusable biopsy forceps were immersed in enzymatic detergent solutions; next, they were cleaned first manually and then by a medical-grade ultrasonic cleaner. After rinsing and drying, the forceps were sterilized by autoclave at 134 °C for at least 5 minutes. Finally, the sterilized devices were stored in sterile packaging in a closed

cupboard where they were protected from dust, humidity, and temperature fluctuations.

### Laboratory Methods

We tested for anti-HCV by using a third-generation enzyme immunoassay (Ortho HCV EIA-3, Ortho Diagnostic Systems, Raritan, New Jersey). Anti-HCV immunoreactivity was confirmed with a third-generation immunoblot assay (RIBA-3, Chiron Corp., Emeryville, California, and Ortho Diagnostic Systems). We measured HCV RNA by using PCR (Cobas Amplicor 2.0, Roche Diagnostic Systems, Branchburg, New Jersey); the sensitivity of this assay was 1000 copies/mL.

### Statistical Analysis

We estimated person-years of observation and incidence rates of anti-HCV seroconversion for both cohorts. We used the difference between the incidence rates to compare the 2 cohorts.

For the endoscopy cohort, we also measured the risk for anti-HCV seroconversion 6 months after the procedure, using the number of persons as denominators. Further analyses were limited to subgroups of the endoscopy cohort: 1) 6132 patients who underwent biopsy (biopsy cohort) and 2) 912 patients who underwent endoscopy later in the same day as and with the same instruments used in HCV-positive patients (at-risk cohort). Because we could not identify with certainty each patient in the at-risk cohort, we estimated that number with a rough but conservative approach. If we assume that each endoscope was used approximately 3 times during an ordinary endoscopic session and that at least 1 HCV carrier would be seen at the center each day, 1 anti-HCV–negative patient could be considered potentially exposed every day. In fact, HCV carriers may have been the first, second, or last to undergo endoscopy with the same instrument.

We used 95% CIs to report the precision of the estimated incidence rates and risks (Confidence Interval Analysis software, second edition) (12).

**Table 2. Reported Risk Factors among Patients Retested 6 Months after Endoscopy**

Risk Factor	Value
Patients, <i>n</i>	8260
Biopsy performed, <i>n</i> (%)	6132 (74.2)
Risk factors, <i>n</i> (%)	
None reported	7410 (89.7)
Dental care	682 (8.2)
Surgery	156 (1.8)
Drug addiction	12 (0.1)
Blood transfusion	0
Unsafe sex	0

**Table 3. Characteristics of the Blood Donor Cohort according to Exposure to Digestive Endoscopy and Availability of Tests at the End of Follow-up**

Characteristic	Digestive Endoscopy			
	Yes		No	
	Retested	Lost to Follow-up	Retested	Lost to Follow-up
Patients, <i>n</i> (%)	329 (79.3)	86 (20.7)	38 280 (74.7)	12 950 (25.3)
Mean age, <i>y</i>	42, SD 8	43, SD 9	44, SD 10	42, SD 11
Men, <i>n</i> (%)	198 (60.1)	51 (59.3)	22 765 (59.5)	8122 (62.7)
Endoscopic procedure, <i>n</i> (%)				
Gastroscopy	263 (79.9)	69 (80.2)	–	–
Total colonoscopy	32 (9.7)	7 (8.1)	–	–
Partial colonoscopy	34 (10.4)	10 (11.7)	–	–

## RESULTS

According to the study protocol, we immediately excluded known HCV carriers; thus, we did not record their overall number. However, we retrospectively looked for inpatients who underwent endoscopic sclerosis or band ligation for esophageal varices from 1999 to 2002. Of 876 endoscopic procedures, 732 (83.5%) were performed on HCV-positive patients.

Of 9188 patients who were unaware of their virologic status and agreed to enter the study, we excluded 180 (1.96%) who were found to be positive for anti-HCV at baseline; 112 (62.2%) of these patients had biopsy. For 32 (28.5%) of these 112 patients, biopsy was done by using reusable forceps that were subsequently sterilized. The sterilization process required 3 days (shipping of forceps to the sterilization unit, sterilization, and storage). However, the same pool of reusable forceps was also used for the other patients (that is, those not included in the study); thus, we could not determine how many HCV-negative patients included in the study underwent biopsy with the same forceps previously used on anti-HCV-positive patients.

Table 1 shows the demographic characteristics of the remaining 9008 patients, along with the baseline features of the 748 patients (8.3%) lost to follow-up and those who were retested. Age, sex, and prevalence of exposure to risk factors did not differ among these 3 groups. During the 9008 endoscopic procedures, biopsies of the upper digestive tract were performed in 6348 (70.4%) patients. Overall, 2122 of 6348 (33.4%) biopsies were done by using

reusable biopsy forceps and 4226 (66.6%) were done by using disposable forceps.

Six months after endoscopy, 8260 patients (91.6%) again completed the preendoscopy questionnaire and were retested for anti-HCV. Table 2 reports their demographic characteristics and risk factors. Of these patients, 6132 (74.2%) had undergone biopsy during endoscopy; reusable forceps were used for 1998 (24.1%) patients.

Table 3 reports the characteristics of the 51 645 blood donors, including data on the minority who underwent endoscopy and the proportion who agreed to be retested after endoscopy. Table 4 compares the incidence rates of anti-HCV seroconversion and HCV RNA positivity in the 2 cohorts.

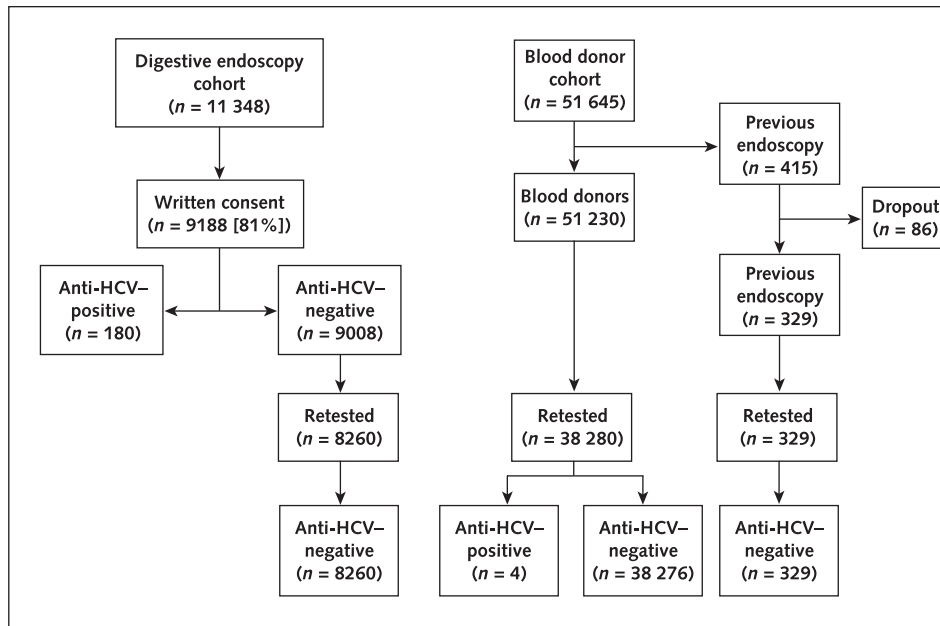
None of the 8260 patients in the endoscopy cohort developed anti-HCV; HCV RNA was not measured because immunodeficient status was not suspected in any recruited patient. The estimated upper limit of the 95% CI of the incidence rate (per 1000 person-years) is 0.893.

Among blood donors, 4 patients seroconverted to anti-HCV and had positive HCV RNA results, with an overall incidence of 0.042 case per 1000 person-years (CI, 0.011 to 0.107 case per 1000 person-years). The 4 seroconvertors reported a history of minor surgery (3 ophthalmologic surgeries, 1 dental surgery) 2 to 4 months before the second anti-HCV determination. The Figure shows the flow of patients in the endoscopy and blood donor cohorts. None of the 329 blood donors who underwent endoscopy seroconverted to anti-HCV. The difference in incidence rates

**Table 4. Incidence Rates (per 1000 Person-Years) of Hepatitis C Virus Infection in the Endoscopy and Blood Donor Cohorts**

Cohort	Patients, <i>n</i>	Mean Length of Follow-up, <i>y</i>	Person-Years of Observation	Incident Cases of Hepatitis C Virus Infection, <i>n</i>	Incidence Rate per 1000 Patient-Years (95% CI)
Digestive endoscopy	8260	0.5	4130	0	0.000 (0–0.893)
Patients having biopsy	6132	0.5	3066	0	0.000 (0–1.203)
Blood donors	38 280	2.49	95 317.2	4	0.042 (0.011–0.107)
Patients having endoscopy	329	2.78	914.6	0	0.000 (0–4.033)

Figure. Flow of the endoscopy cohort and blood donor cohort.



Anti-HCV = antibody to hepatitis C virus.

between the blood donor cohort and the endoscopy cohort was 0.042 per 1000 person-years (CI, 0.000 to 0.0831 per 1000 person-years).

Finally, we evaluated the risk for infection (per 1000 patients) during the 6 months after endoscopy in 2 at-risk subgroups: those who underwent gastric biopsies and those who had endoscopy that used the same instrument previously used on an HCV carrier (Table 5).

None of 6132 patients who underwent biopsy and were then retested for anti-HCV showed seroconversion (risk per 1000 persons, 0 [CI, 0 to 0.626]). The result was the same among the 912 patients who shared the potentially infective endoscope previously used on an HCV carrier (risk per 1000 patients, 0 [CI, 0 to 4.195]). However, even if the point estimates of the risks are zero, the uncertainty about this probability increased as the number of exposed patients was restricted to those considered at risk.

DISCUSSION

Nosocomial transmission of microorganisms during digestive endoscopy is well documented (13, 14) and is frequently associated with inadequately reprocessed endoscopes (2). Postendoscopy bacterial infections are easily recognized because of the short incubation period and the overt clinical symptoms. These infections may be fatal but usually are curable and do not induce chronic diseases. On the other hand, acute viral infections, such as with hepatitis B virus, HCV, or HIV, are usually asymptomatic and have a long incubation period. Thus, documenting patient-to-patient transmission of viral infection may be difficult. To date, HIV transmission through endoscopes has not been

reported, and hepatitis B virus does not seem to play a relevant role in endoscopy-induced hepatitis (15).

The overall risk for HCV transmission through digestive endoscopy is controversial. Two formal French studies (1, 16) showed a significantly higher prevalence of HCV infection among patients who underwent endoscopy, but these studies must be compared with 2 contrasting studies. The first, also from France (3), found no difference in the prevalence of HCV infection between 130 patients who underwent endoscopy and 172 patients who did not; the second (2) determined an incidence of infective transmission of approximately 1 in 1.8 million gastrointestinal endoscopic procedures. Indeed, few cases of HCV infection have been reported in the practice of endoscopy (4, 5). Virus exposure has been attributed to inadequate cleaning and disinfection of the endoscopes or to failure to autoclave reusable accessories after each use (17).

Subsequent studies (18, 19) on the effectiveness of the

Table 5. Estimates of Risks for Hepatitis C Virus Infection in Subgroups of the Endoscopy Cohort

Patient Group	Patients Exposed, n	New Cases of Hepatitis C Virus Infection, n	Risk per 1000 Patients (95% CI)
Total cohort	8260	0	0.000 (0–0.465)
Patients having biopsy	6132	0	0.000 (0–0.626)
At-risk patients*	912	0	0.000 (0–4.195)

\* Estimated number of patients who underwent endoscopy after hepatitis C virus-positive patients (on the same day) and with the same instrument.

usual disinfection procedures in eliminating HCV particles indicate that all anecdotal cases of endoscopic HCV transmission could be attributed to breaches in recommended regimens (20). However, because of the usual asymptomatic course of the primary infection, the possibility of underreporting or failure to recognize endoscopic transmission of HCV cannot be excluded.

Careful analysis of the single reports of HCV transmitted through endoscopes (4, 5) reveals that inadequate endoscope cleaning may be only one explanation of HCV transmission. Bronowicki and coworkers (5) reported that the scope and related accessories were not reprocessed according to the recommendations of the American Society for Gastrointestinal Endoscopy (6) and the British Society of Gastroenterology (7). However, the authors did not exclude the possibility that HCV was transmitted through the inadequate use of anesthesia (multidose vials); this risk has recently been confirmed by a report showing patient-to-patient HCV transmission through contaminated intravenous anesthetic ampoules (21).

An Italian survey (15) on the incidence of acute HCV hepatitis between 1994 and 1999 showed that beside obstetric–gynecologic interventions, abdominal surgery, and ophthalmologic surgery, endoscopic procedures also correlated with the risk for acquiring HCV. Although the authors did not determine whether infected patients underwent other potentially infective procedures or were given anesthesia, they concluded that sterilization procedures for biopsy and endoscopy needed to be improved. A national survey on digestive endoscopy disinfection procedures in Italy published in 1997 (22) reported that only 69.7% of the endoscopic units brushed the scopes and that only 25.4% performed some form of sterilization for biopsy forceps. Adherence to updated published guidelines (23, 24) seems to have grown recently, but there is still room for improvement (25, 26).

We evaluated whether digestive endoscopy is itself a source of HCV transmission and whether correct adherence to international guidelines can prevent the risk for HCV transmission. We found that no recruited patients seroconverted to anti-HCV during 6 months of postendoscopy follow-up. Moreover, the subgroup of patients who presumably underwent endoscopy with the same instrument used in HCV carriers also did not seroconvert to anti-HCV. This finding is particularly interesting considering that the number of at-risk endoscopic procedures was relatively large ( $n = 912$  [11%]). This outcome suggests that if endoscopic instruments and accessories are properly cleaned, disinfected, and sterilized, the risk for transmitting HCV is negligible. This finding also indicates that transmission of HCV after an endoscopic procedure is not an unavoidable accident but rather an event precipitated by failure to follow recommended guidelines.

Our study does have a potential bias. The proportion of patients in the endoscopy cohort who were lost to follow-up (8.3%) was consistent; nonadherence might have

been caused in part by an independent knowledge of the recent acquisition of HCV infection. However, age, sex, and risk factors did not differ between the adherent group and persons lost to follow-up.

The exclusion of endoscopic procedures other than gastroscopy cannot be considered a selection bias because disinfection and sterilization methods are the same for all types of endoscopy and because biopsy of the upper digestive tract is potentially as infective as colon polypectomy or papillotomy of the sphincter of Oddi. Moreover, our data confirm the general safety of reusable biopsy forceps (27, 28) because none of the 1998 patients who underwent gastric biopsies with reusable devices experienced seroconversion to anti-HCV.

A further point for discussion is the control group of blood donors. These patients were a selected group at low risk, and the incidence rate of anti-HCV seroconversion may not reflect the true incidence in the Italian population: 1.4 cases per 10 000 person-years (CI, 0.2 to 5.2 cases per 10 000 person-years) according to a recent report by Kondili and coworkers (29), a value about 3 times greater than that in our blood donor cohort (0.42 case per 10 000 person-years). The low prevalence of HCV infection in our patients (1.96%) might explain the discrepancy between our data and those of Kondili and colleagues (29).

In conclusion, reprocessing of equipment and control of infections during digestive endoscopy have changed substantially in the past decade, and epidemiologic studies are needed to evaluate recent practices or outcomes since widespread adoption of the guidelines released in 1995. To the best of our knowledge, ours is the first prospective study to comprehensively evaluate the effectiveness of currently available reprocessing regimens. Our data suggest that digestive endoscopy does not play a major role in transmitting HCV infection when current international guidelines of cleaning and disinfection are followed.

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