Oral Direct Acting Antivirals treatment failed to cure a patient with chronic hepatitis C due to shifts of viral genotype

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The "report card" to grade *H. Pylori* treatment regimens: is it achievable in real-world in areas with high clarithromycin resistance?

To the Editor,

A few months ago, in the Toronto Consensus for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults [1], there was, for the first time in the literature, a brief comment on Dr. Graham's proposal [2, 3] for a minimum acceptable *H. pylori* eradication rate of 90%. Fallone et al. considered that goal as an "arbitrary threshold", "not easily achieved, especially in real-world settings" [1]. Undoubtedly, the clinician's first goal should be an efficacious *H. pylori* eradication, while aiming to minimize cost, patient inconvenience and risks or adverse events from the regimens used. Even so, it seems unlikely that a clinical gastroenterologist will be able to use regimens that are considered to be "good" (intention-to-treat cure rate: 90–95%) according to Dr. Graham's "report card", especially in areas with high clarithromycin resistance such as in Southern Europe [2].

In their recent systematic review and network meta-analysis, Yeo et al. provided important insights into the relative efficacy and adverse events of the most common regimens in various durations [4]. It is worthwhile highlighting the pooled weighted eradication rates in countries with high clarithromycin resistance of the first line regimens that the recent guidelines have proposed [1, 5] and score the regimes according to Dr. Graham's therapy "report card" proposal (Table I). It is obvious that the majority of the proposed first line treatments accomplish an average eradication rate of less than 90% in areas with high clarithromycin resistance. Bismuth containing quadruple regimens (where bismuth is available) seem to be more promising, being scored as acceptable to good and good. On the other hand, concomitant therapies appear to have less promising eradication rates, between 80.8% and 88.2%, being scored as almost unacceptable to acceptable. As far as hybrid therapy is concerned, the score for the eradication rates ranges between poor and good.

According to the aforementioned, the proposal that the outcomes of therapy should be scored against an established target, the "report card" [2] seems impracticable. Even the general statement concerning clinical trials that should be "results based", with the goal of identifying regimens with > 90-95% success, seems unrealistic in areas with high clarithromycin resistance. Such high percentages cannot be achieved in the daily clinical practice either in a hospital outpatient clinic or in a gastroenterology private sector especially in countries with high antibiotic resistances. Undoubtedly, clinicians should "only use what works locally" and deviate from clinical practice guidelines if their recommendations are not consistent with local results [3]. But also the "arbitrary" threshold goal of ≥90% success in everyday clinician anti-*H. pylori* regimens seems "utopian".

Ideally, the treatment for an infectious disease should be chosen based on culture and susceptibility testing using specific biological material obtained from each patient. Nevertheless, this is not feasible in *H. pylori* infected patients as it necessitates invasive procedures, which currently are indicated only for a subset of patients (for example, dyspeptic patients aged > 45 years or younger patients with "alarm" symptoms). For that reason, the empirical first-line treatment should be based on what works best in each geographical area and must take into account the prevalence of antimicrobial resistance in that region. Therefore, it seems reasonable that clinicians in real-world settings and especially in areas with high clarithromycin resistance, such as in Southern Europe, should only use regimens that have been documented to work best locally, regardless of the scoring that these regimens would have received according to the "report card" grading of *H. pylori* treatments.

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Table I. Correspondence of the "report card" data for scoring the outcome of anti- *H. pylori* therapy [2] with weighted eradication rate of the proposed first line treatment choices used regimens in countries with high clarithromycin resistance [4] (based on the supplementary appendix of Yeo YH et al, systematic review and network meta-analysis).

			Report Card (ITT) [2]		
Country	Regimen	Weighted Eradication Rate	Grade	Cure Rate	Score
China	BQT≤10 days	89.7%	C-B	85-89% to 90-94%	Acceptable to Good
China	CT≥10 days	80.8%	F-D	≤ 80% to 81-84%	Unacceptable to Poor
Greece	CT≥10 days	87.1%	C	85-89%	Acceptable
Iran	HY≥10 days	89.5%	C-B	85-89% to 90-94%	Acceptable to Good
Italy	BQT≤10 days	92.6%	B	90-94%	Good
Italy	BQT-14 days	91.6%	B	90-94%	Good
Italy	CT≥10 days	86.4%	C	85-89%	Acceptable
Italy	HY≥10 days	81.5%	D	81-84%	Poor
Spain	CT≥10 days	88.2%	C	85-89%	Acceptable
Spain	HY≥10 days	90.8%	B	90-94%	Good
Singapore	CT≥10 days	81.7%	D	81-84%	Poor
Turkey	CT≥10 days	81.3%	D	81-84%	Poor

BQT: bismuth-containing quadruple therapy, CT: concomitant therapy, HY: hybrid therapy, ITT: intention-to-treat,

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The "two-devices-in-one-channel technique" for biliary through-the-scope stent removal

To the Editor,

Biliary plastic stent insertion with the aim to re-establish biliary drainage in a setting of acute bacterial cholangitis or bile duct strictures is commonplace in endoscopic retrograde cholangiography (ERC) services. Plastic stents are available in various designs, diameters and materials, with 10 French biliary plastic stents representing the standard stent type in our center [1]. We have recently introduced an easy-to-implement novel through-the-scope (TTS) maneuver for single-step extraction of the indwelling stent, involving tangential forceps grasping with subsequent TTS removal through the scope´s working channel. Beyond obviating the need for repeated scope insertion, this novel endoscopic approach may speed up the procedure with benefits in terms of time under sedation and reduction of complication risks (Fig. 1) [2].

Here, we present a variant refinement of the procedure called the "two-devices-in-one-channel technique" for TTS

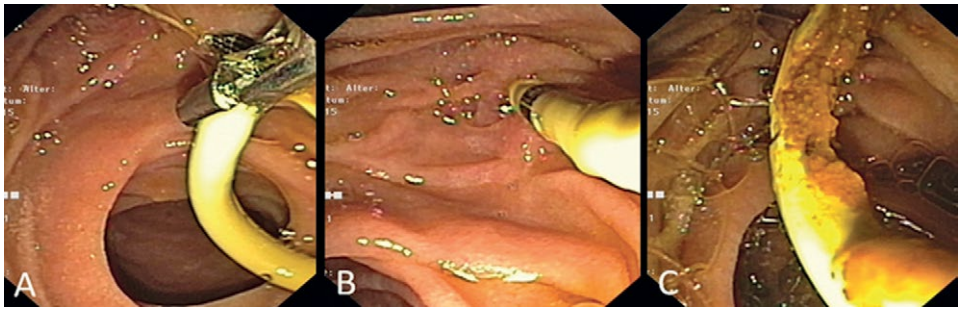

Fig. 1. Through-the-scope (TTS) extraction of a biliary double pigtail. A) Endoscopic view of the distal end of a 10 F biliary double pigtail stent (GastroSoft, Optimed, Ettlingen, Germany) tangentially grasped with a forceps. B) Careful withdrawal of the stent into the working channel and through-the-scope with the elevator down. C) On further extraction large amounts of sludge adherent to the middle portion of the stent become visible (Olympus TJF-160VR, Olympus, Hamburg, Germany: working channel 4.2 mm).

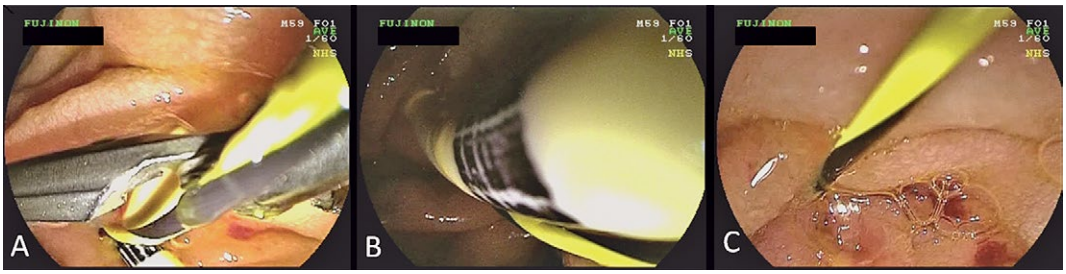

Fig. 2. "Two-devices-in-one-channel" approach of TTS stent removal. A) View of the 10 F biliary double pigtail and the guide wire, preloaded after successful biliary cannulation alongside the stent with a straight cannula (0.035" Jagwire Guidewire ST, Boston Scientific, Ratingen, Germany). The distal stent end is well exposed and grasped by a forceps. B) Firm alignment of the stent into the working channel and start of the withdrawal procedure. C) The guidewire remains in place for subsequent re-cannulation after backloading a cannula or papillotome. (Fujinon ED530XT8, Fujifilm, Düsseldorf, Germany: working channel 4.2 mm)

stent removal, which is similar to "over-the-wire" techniques employing snares or stent retrievers, which, however, are not feasible for biliary pigtail stents, because wire cannulation is virtually impossible for this stent type [3, 4]. Therefore, we combined our standard TTS stent removal with a comparable "two-devices-in-one-channel" approach in a subset of 15 patients with previous difficult biliary access so as to leave the stent in situ at first as a sign post marking the biliary axis (which additionally may become straightened) (Fig. 2). On the whole, beyond the benefits mentioned above, we consider the presented approach suitable for patients with anticipated difficulties of deep biliary cannulation after stent extraction, e.g. in tight or tortuous common bile duct strictures, when primary guide wire and canula advancement have proved difficult beforehand.

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Oral direct acting antivirals treatment failed to cure a patient with chronic hepatitis C due to shifts of viral genotype

To the Editor,

Chronic infection with hepatitis C virus (HCV) is one of the most important causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma [1]. Six major HCV genotypes have been identified. Genotype 1 is found worldwide. Its subtype 1a is predominant in the USA, and subtype 1b predominant in East Asia, including Japan, China, Korea, and Taiwan [2]. In Taiwan, a combined oral direct acting antivirals (DAAs) regimens, including sofosbuvir (SOF) + ledipasvir (LDV), paritaprevir/ritonavir/ombitasvir + dasabuvir, or daclatasvir (DCV) + asunaprevir (ASV) are approved for treating patients with HCV-1b infection. Here, we report a patient with chronic HCV hepatitis in whom treatment with DCV+ASV failed due to a shift in HCV subtype from 1b to mixed 1a+1b for the infection.

A 46-year-old man with a history of treatment-naïve chronic HCV hepatitis came to our clinic. Abdominal ultrasound showed normal hepatic echogenicity without the evidence of cirrhosis or hepatosplenomegaly. Laboratory work-up showed alanine aminotransferase (ALT) level of 53 U/L (normal values, NV 8–38 U/L), aspartate aminotransferase (AST) of 42 U/L (NV 4–44 U/L), total bilirubin of 0.4 mg/dL (NV 0.2–1.2 mg/dL). HCV RNA level (Roche, Cobas TaqMan48, USA) was 3.07 x 10^6 IU/mL, and HCV genotyping (Roche, Cobas Amplicor Analyser, USA) identified 1b genotype. Further evaluation disclosed the negative finding of baseline nonstructural protein 5A (NS5A) resistance-associated substitutions (RASs) at positions L31 and Y93.

A 6-month therapy with the combined medication of DCV+ASV was scheduled. Table I shows the laboratory data taken at the first month: ALT 25 U/L, and HCV RNA undetectable. We continued the treatment with DCV+ASV. However, laboratory data taken at the fifth month showed an elevated ALT level of 119 U/L, and the reappearance of HCV RNA up to a level of 3.02 x10^4 IU/mL. Repeating surveillance was negative for NS5A RAVs, but HCV genotyping reported a mixed 1a and 1b genotype for the infection.

Table I. Changes of liver function tests and HCV RNA levels during the therapy with daclatasvir+asunaprevir.

	HCV RNA (IU/mL)	Total Bilirubin (mg/dL)	ALT (U/L)	HCV genotype	NS5A RAS*
Baseline	$3.07x10^6$	0.4	53	1b	Negative
1 month	Undetectable	0.5	25		
2 month	Undetectable	0.3	22		
3 month		0.6	41		
4 month	$3.02x10^4$	0.8	119	1a+1b	Negative

ALT, alanine aminotransferase; NS5A, nonstructural protein 5A; RAS, resistance-associated substitutions; * NS5A RAS: test at positions L31 and Y93.

The therapeutic regimen was then replaced by a combined medication of paritaprevir/ritonavir/ombitasvir+dasabuvir and ribavirin (RBV). By the end of the 3-month therapeutic course, positive end-of-treatment (EOT) and sustained viral response at 12 weeks after treatment (SVR12) were achieved, and ALT levels remained normal.

In Taiwan, the proportion of HCV-1b is 45.5% ~71.4% [3, 4], and DCV+ASV are approved for treating patients with HCV-1b infection. Daclatasvir is a NS5A replication complex inhibitor with potent pan-genotypic antiviral activity, and ASV is a potent, selective NS3 protease inhibitor with antiviral activity against HCV genotype 1, 4, and 5. Dual combined therapy with DCV and ASV has provided high SVR rates in patients with HCV genotype 1b infection [5]. Among patients with NS5A RASs at baseline, only 51.2% achieved SVR12 and 41.9% achieved SVR24 [6]. Therefore, pre-existing NS5A RAS are associated with virological failure during DCV+ASV therapy. In our case, neither baseline nor within-therapeutic NS5A RASs was absent. Instead, the HCV subtype of our patient had shifted from single 1a to mixed 1a and 1b for the infection.

Because HCV replicates in the cytosol and does not integrate into target cells, there is no stable genomic reservoir for the virus. Therefore, a decline in numbers and the disappearance of the „less-fit" genotype over time occurs after competition in replication between distinct HCV genotypes in a given patient [7]. In agreement with this hypothesis, our patient might have had HCV co-infections with „more-fit" subtype 1b and „less fit" subtype Ia, but only the presence of a single HCV genotype 1b infection was detected initially. Treatment failure with DCV+ASV was due to a decline in the numbers of subtype 1b viremia followed by an overload of subtype Ia virus. Application of pan-genotypic DAAs, such as SOF-based regimens [8], could lower the risk of „superselection" process as described above, and avoid therapeutic failure as in our case.

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