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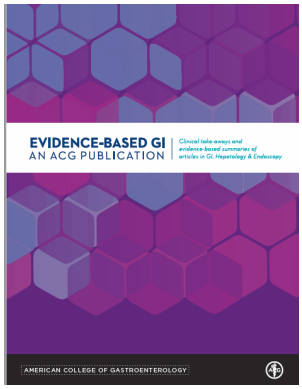

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ENDOSCOPY

Disposable Elevator Caps for Duodenoscopes Decrease Contamination Without Hindering Technical ERCP Performance: The ICECAP Trial

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Shria Kumar, MD, MSCE
Associate Editor

This article reviews Forbes N, Elmunzer BJ, Allain T, et al. Effect of Disposable Elevator Cap Duodenoscopes on Persistent Microbial Contamination and Technical Performance of Endoscopic Retrograde Cholangiopancreatography: The ICECAP Randomized Clinical Trial. JAMA Intern Med 2023;183(3):191-200. doi: 10.1001/jamainternmed.2022.6394.

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STRUCTURED ABSTRACT

Question: Do duodenoscopes with disposable elevator caps decrease persistent microbial contamination compared to standard design scopes without impacting technical performance in endoscopic retrograde cholangiopancreatography (ERCP)?

Design: Parallel-arm, multi-center randomized clinical trial (RCT). Immediately preceding ERCP, patients were randomly assigned in a 1:1 ratio to undergo ERCP using a disposable elevator cap duodenoscope (ED34-i10T2, Pentax Medical) or a standard duodenoscope (ED34-i10T, Pentax Medical)

Setting: Two tertiary-care ERCP centers in Canada, between December 1, 2019 and February 28, 2022, including a pause due to the COVID pandemic from March 2020 to September 2020.

Patients: Five hundred eighteen patients aged 18+ years who were undergoing ERCP for any indication were included. Exclusion criteria included inability/unwillingness to provide informed consent, pregnancy, breastfeeding, or potential inability to complete a 30-day follow-up.

Intervention: The use of duodenoscopes with disposable elevator caps was compared with duodenoscopes with a standard design.

Outcomes: Co-primary outcomes were 1) persistent microbial contamination of the duodenoscope elevator or channel (superiority outcome), and 2) technical success of ERCP according to *a priori* criteria (noninferiority outcome with an a priori noninferiority margin of 7%). Persistent microbial contamination was defined as either growth of 10 or more colony-forming units (CFUs) of any organism or any growth of gram-negative bacteria, within 72 hours of plating. Technical success of ERCP was determined independently by 2 persons blinded to group assignment based on *a priori* definitions and focused on successful completion of procedure according to indication (e.g., removal of stones in cases done for choledocholithasis, stent placement across stricture for a biliary stricture, or cholangioscopy completion in cases where visualization was planned).

Secondary outcomes included mortality, patient tolerability, and adverse events within 30 days of ERCP (cholangitis, pancreatitis, bleeding, perforation, and cardiopulmonary events).

The duodenoscopes in both study arms were required to have been in clinical use between 12 months and 24 months. Prior to sample collection to assess for the primary outcome, the duodenoscopes underwent 2 cycles of high-level disinfection followed by steam sterilization. Following this, they underwent point-of-care adenosine triphosphate (ATP) scanning, with any failed scan resulting in the scope being sent for another disinfection cycle. ATP scanning looks for bioluminescence from microbial residue. Once they have passed ATP scanning, they were "deemed cleared for clinical use," and microbiological sampling was performed within 60 minutes. Two samples were acquired from each duodenoscope: 1 from the elevator area (the elevator itself for standard duodenoscopes, and the cap attachment point for disposable elevator cap duodenoscopes) and 1 from the instrument channel.

Statistical Analysis: Intention-to-treat analysis without adjustment using chi-square tests.

Funding: Research support was provided by the ASGE and the Canadian Institutes of Health Research. Pentax Medical provided unrestricted temporary use of

duodenoscopes. None of the parties were involved in study conception, design, or execution, or in the interpretation and/or reporting of results.

Results: There were 518 patients enrolled and split evenly between disposable elevator cap group (n=259) and standard duodenoscope group (n=259). Patient demographics included mean age of 60-61 years; indication for ERCP: suspected/confirmed biliary stone (38%-44%), suspected/confirmed biliary stricture (9%-12%), repeat ERCP including stent removal or exchange (20%-22%); and, American Society for Gastrointestinal Endoscopy (ASGE) Grade Procedural Complexity: Grade I/II (76%).

Based on *a priori* sample size calculations, 208 patients in the disposable elevator cap group and 214 patients in the standard duodenoscope group had their duodenoscopes sampled after high-level disinfection (microbiology outcome). All patients were included for the technical success outcome.

Persistent microbial contamination was detected in 11.2% of duodenoscopes in the standard duodenoscope arm and 3.8% of duodenoscopes in the disposable elevator cap duodenoscope arm (P = .004), corresponding to a relative risk (RR) of 0.34 (95% confidence interval [CI], 0.16-0.75) and number needed to treat of 13.6 (95% CI, 8.1-42.7) to avoid 1 persistent microbial contamination event. Persistent microbial contamination occurred most frequently in the instrument channel sample (**Table 1**).

Technical success with disposable elevator cap duodenoscopes was noninferior to that with standard duodenoscopes (94.6% vs 90.7%, P=0.13). There were no differences in mortality, patient tolerability, and adverse events.

	Disposable elevator cap duodenoscope	Standard duodenoscope
Microbiology Outcomes	N=208	N=214
Persistent microbial contamination, n (%)	8 (3.8)	24 (11.2)
Area of persistent microbial contamination n (%)		
In elevator region	2 (1.0)	2 (0.9)
Within instrument chan-	5 (2.4)	21 (9.8)
Both	1 (0.5)	1 (0.5)
Technical Success Outcomes	N=259	N=259
Technical success	245 (94.6)	235 (90.7)

Table 1: Outcomes

COMMENTARY

Why Is This Important?

In 2013, the Centers for Disease Control and Prevention (CDC) alerted the Federal Drug Administration (FDA) to a potential association between multi-drug resistant bacteria and duodenoscopes. Upon further investigation, it became clear that these cases of infection were occurring despite confirmation that the users were following proper manufacturer cleaning and disinfection or sterilization instructions. The underlying theory suggests that if a person who is colonized undergoes ERCP, the duodenoscope can be colonized. If the colonization persists (even after cleaning), this can lead to transfer to the next person who undergoes ERCP with the duodenoscope, and possibly clinical infection.

Duodenoscopes are complex instruments. They include a working channel, through which instruments are passed, an elevator mechanism that allows for manipulation of devices through the papilla, and an O-ring that seals off the elevator channel from contamination. Contamination is possible either due to insufficient cleaning and reprocessing (due to the complex design), the development of a biofilm, and/or breaches of the O-ring seal.[1]

To address this issue, disposable elevator cap duodenoscopes and completely disposable duodenoscopes have both been introduced. Disposable duodenoscopes offer an attractive solution in theory, but they are expensive (particularly considering their single-used design), are technically inferior, and create medical waste.[2] Disposable elevator cap duodenoscopes can theoretically address the concerns of infections while overcoming the limitations of disposable duodenoscopes.

Duodenoscope-related infections are rare, occurring in 0.01% of persons.[3] While this may seem small, this estimate is from a systematic literature search of duodenoscope-related infections in the Netherlands, and was an important update in prior data that suggested the risk of duodenoscope-related infections was almost negligible. Furthermore, given that US endoscopists performed over 175,000 ERCPs in 2019, it is an important consideration that has been relatively under-investigated.[4]

Therefore, we commend the investigators for performing a very well-designed study to investigate tools to further minimize persistent microbial contamination of duodenoscopes after appropriate cleaning and disinfection.

Key Study Findings

In this RCT of 518 patients undergoing ERCP, duodenoscopes with disposable caps reduced persistent microbial contamination (RR, 0.34), with no differences in performance (technical success, 94.6% vs 90.7%) and safety outcomes. The most frequent area of persistent microbial contamination was within the instrument channel (as compared to the elevator area).

Caution

Duodenoscope-related infections are difficult to study. As the authors appropriately acknowledge, persistent microbial contamination is a surrogate outcome, which has limited correlation to clinically relevant duodenoscope-related infections that are much less common. This is not a criticism of the authors or study design, but simply reflects that it would be impractical to enroll the hundreds of thousands of patients needed to demonstrate a difference in duodenoscope-related infections.

My Practice

This is an evolving area that is growing in importance. Completely disposable duodenoscopes are not a practical solution currently because of high cost and limitations in technical performance. We are currently using disposable caps at one of our hospitals, and will begin using disposable caps at our hospital in the next few months.

For Future Research

Further validation of disposable caps should be performed across different settings (geographically and with different endoscope manufacturers). We need better surveillance protocols to identify, quarantine, and disinfect contaminated duodenoscopes since the accuracy of ATP scanning to look for bioluminescence from microbial residue misses contamination. Novel duodenoscope designs that make cleaning easier without sacrificing technical aspects are also needed.

Conflicts of Interest

Dr. Kumar reports no conflicts of interest.

The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary:

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EVIDENCE-BASED GI
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ENDOSCOPY

Over-the-Scope Clips Decrease Non-Variceal Upper GI Bleeding vs Standard Endoscopic Treatment… In the Right Patient

Jennifer M. Kolb, MD, MS

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This summary reviews Lau JYW, Li R, Tan C et al. Comparison of Over-the-Scope Clips to Standard Endoscopic Treatment as the Initial Treatment in Patients With Bleeding From a Nonvariceal Upper Gastrointestinal Cause: A Randomized Controlled Trial. *Ann Intern Med* 2023 Apr;176(4):455-462. doi: 10.7326/M22-1783

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STRUCTURED ABSTRACT

Question: Are over-the-scope clips (OTSC) more effective than standard endoscopic hemostatic treatments (hemoclips and/or contact thermocoagulation with or without pre-injection of diluted epinephrine) for nonvariceal upper gastrointestinal bleeding (NVUGIB) in patients with non-bleeding visible vessels (Forrest IIa) or actively bleeding ulcers (Forrest Ia/Ib)?

Design: Multicenter, unblinded, randomized controlled trial (RCT)

Setting: Seven university teaching hospitals in Hong Kong, China, and Australia. Approximately 58% of patients enrolled at Prince of Wales Hospital in Hong Kong.

Patients: Adult patients presenting with nonvariceal upper gastrointestinal bleeding were screened and recruited. Patients found to have active bleeding (pulsatile

or Forrest Ia bleeding, oozing from a visible vessel or Forrest Ib bleeding), or a non-bleeding visible vessel (Forrest IIa) on endoscopy were randomized. If clot over bleeding lesion was observed, then irrigation and elevation of area was performed. If a vessel was then seen, the patient was randomized. Patients could be excluded if they were not believed to be OTSC candidates due to the position of NVUGIB lesion (e.g., pyloric channel).

Interventions/Exposure: Patients were randomly assigned at time of endoscopy in a 1:1 ratio to standard hemostatic treatment (hemoclips and/or contact thermocoagulation with heater probe or bipolar device +/- pre-injection of diluted epinephrine) or OTSC 11T (cap size 11mm; teeth with small spikes) (**Figure 1**) followed by 72 hours of intravenous proton pump inhibitor (PPI) therapy followed by oral PPI. All study investigators/endoscopists received at least 2 weeks of training at Prince of Wales Hospital on OTSC use, including bench deployment and case observation. Randomization was stratified into blocks of 10 by lesion and size (1-ulcer size <10mm, ulcer size 10mm-20mm, 3-ulcer size >20mm, 4- non ulcer lesion) at Prince of Wales Hospital. At the other sites randomization was not stratified. Salvage therapy with any tool was allowed if initial therapeutic attempt failed.

Outcome: The primary outcome was the 30-day probability of further bleeding, which was a composite endpoint of failure to control bleeding (primary hemostasis) and recurrent bleeding within 30 days. Recurrent bleeding was defined as fresh hematemesis, hematochezia, or melena associated with hypotension/tachycardia and/or drop of 20g/l of hemoglobin within 24 hours and endoscopic confirmation of fresh blood in the GI tract on urgent repeat endoscopy. Additional outcomes included failure of primary hemostasis, recurrent bleeding after initial hemostasis, need for further intervention (endoscopic, angiographic, surgical), need for blood transfusion or hospitalization, and 30-day mortality.

Data Analysis: Intention-to-treat analysis used to calculate time-to-event analysis and Kaplan-Meier curves.

Funding: University Grant Committee to the Government of the Hong Kong Special Administrative Region. They had no role in the design, conduct, or study analysis.

Results: Between January 2018 to December 2020, 706 patietnts were screened, 527 were consented, 191 were randomized and 190 were included for analysis (standard group n=97, oTSC n=93). In the overall cohort, mean age was 62-62 year, male 77%-80%, and endoscopic finding of peptic ulcer was 90%-92%. In the

standard group, the most common hemostasis techniques were combined epinephrine injection plus hemoclips or thermocoagulation (n=51), hemoclips alone (n=26), or thermocoagulation alone (n=12). The cumulative 30-day probability of further bleeding was higher in the standard vs OTSC group: 14.6% vs 3.2%; risk difference: 11.4%, 95% confidence interval (CI): 3.3-20.0, *P*=0.006 (**Figure 2**). Failure at primary hemostasis was higher in the standard versus OTSC group (6.2% vs 1.1%; risk difference: 5.1, 95% CI: 0.7-11.8), while recurrent bleeding at 30 days was numerically higher in the standard vs OTSC group (8.8% vs. 2.2%, risk difference 6.6, 95% CI: -0.3 to 14.4). In the OTSC group, 1 death was related to ulcer perforation and pneumoperitoneum found at the time of readmission for femur fracture. There was 1 instance where an OTSC for an antral ulcer caused a

Figure 1: Type T over-the-scope-clip.

COMMENTARY

Why Is This Important?

NVUGIB is a common reason for hospital admission and one of the most frequent consults to the GI service. The endoscopic approach to treating peptic ulcer disease with active bleeding or a visible vessel has remained largely unchanged for many years and includes the use of through the scope hemoclips or thermal therapy, with or without injection of diluted epinephrine, followed by 72 hours of intravenous PPI therapy.[1-2] Nevertheless, primary hemostasis is not always achieved for actively bleeding ulcers and there is about 10%-20% risk of recurrent bleeding for high-risk lesions even when primary hemostasis is achieved with current endoscopic interventions.

OTSCs are a more recent addition to our armamentarium for the management of GI bleeding.[3-4] These are large nitinol clips that are mounted on a clear plastic cap that is attached to the endoscope (**Figure 1**). The cap facilitates suction to bring in tissue, followed by deployment and closure of the large jaws or "bear claw" to compress the tissue, similar to the jaws closing on a hunting trap. These OTSCs are used for closure of perforations in the colon and upper gastrointestinal tract.[5] RCTs assessing their efficacy for nonvariceal upper GI bleeding have

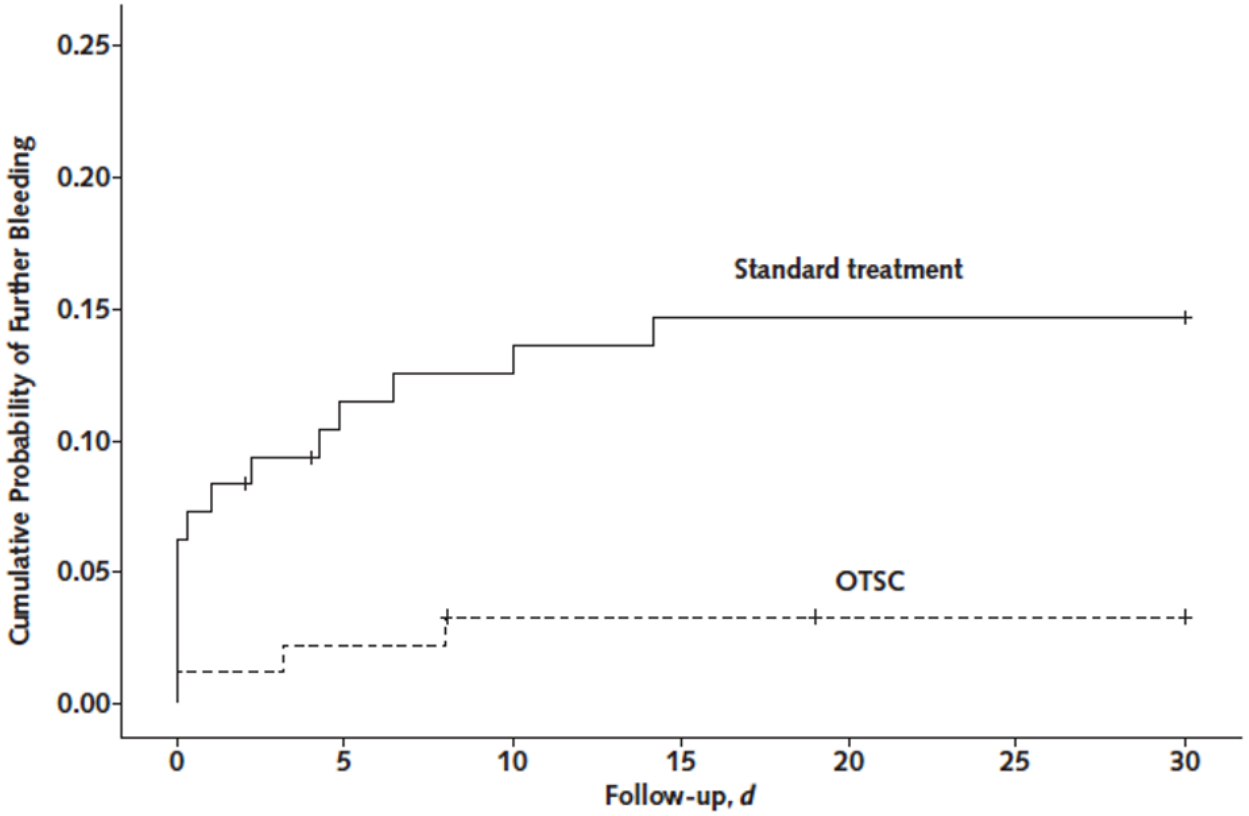

Figure 2: 30-day probability of further bleeding.

generally demonstrated superiority of OTSCs to standard endoscopic intervention but had various methodologic limitations. Thus, current guidelines only recommend use of OTSCs for persistent or recurrent NVUGIB and their positioning in the algorithm for primary hemostasis needed to be clarified. This well-designed RCT on OTSC as first line therapy may change future guideline recommendations.

Key Study Findings

OTSC had better outcomes than standard hemostatic therapies across all categories.

The cumulative 30-day probability of further bleeding (combined endpoint of failure to achieve primary hemostasis or endoscopically confirmed recurrent bleeding) was higher in the standard vs OTSC group: 14.6% vs 3.2%; risk difference: 11.4%, 95% CI: 3.3-20.0, P=0.006.

Caution

As the study investigators acknowledge in the publication, inherent methodologic limitations of endoscopic research may bias results towards superiority of OTSC. The study excluded 10 patients with lesions "with endoscopic appearance or positions considered not favorable for OTSC placement," such as duodenal ulcers where OTSC closure could lead to pyloric channel obstruction. There were also 3 patients randomized to the OTSC arm that were technically limited and OTSC could not be applied. Given prior data showing a benefit of OTSC for refractory bleed-

ing, this trial design allowed for rescue OTSC if classic hemostatic approaches were not working, and this could have impacted endoscopists subjective assessment of successfully achieving primary hemostasis. Finally, OTSC use requires training, although it's a relatively simple technique for skilled endoscopists to learn.

My Practice

I learned how to place OTSC during my fellowship training and routinely teach my GI fellows to use them. I often grab for these first when I see active bleeding or a high-risk lesion in the upper GI tract, such as ulcers with a visible vessel that are larger than 2 cm or located on the lesser curve of the stomach or if the ulcer is in gastroduodenal artery territory, such as the posterior duodenal bulb. I consider several other factors when deciding what hemostatic approach to use and keep in mind some limitations with OTSC. First, the clips work best when the vessel is clearly visualized straight ahead. It can be tricky to use these in certain parts of the duodenum if there is angulation or difficulty tipping the scope up. Once the clip is mounted on the scope, the cap can make visualization a bit more challenging, especially if there is active bleeding, so it is important to understand where the lesion is compared to surrounding structures. Injecting epinephrine prior to OTSC placement is an option to facilitate visualization by temporarily stopping bleeding. The tissue anchor is theoretically useful to grab and pull up a fibrotic ulcer base, though I have never needed this in clinical practice. If the patient has recently been on anticoagulation or needs to restart medication, I tend to prefer definitive treatment with OTSC and avoid thermal therapy. I also like using OTSC for dieulafoy lesions in the stomach since these submucosal arteries can be deeply penetrating and OTSC offers deeper, more secure hemostasis.

For Future Research

Future studies should evaluate predictors of rebleeding in acute NVUGIB treated with OTSCs and standard therapy to define algorithms for future use. These should incorporate elements of cost effectiveness.

Conflict of Interest

Dr. Kolb reports no potential conflict of interest.

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EVIDENCE-BASED GI
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Prophylactic Antibiotics Do Not Improve Mortality in Severe Alcoholic Hepatitis Treated with Corticosteroids

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Editor-in-Chief

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LIVER

This summary reviews Louvet A, Labreuche J, Dao T, et al. Effect of Prophylactic Antibiotics on Mortality in Severe Alcohol-Related Hepatitis. JAMA 2023; 329 (18): 1558-66. doi: 10.1001/jama.2023.4902

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STRUCTURED ABSTRACT

Question: Does amoxicillin-clavulanate decrease 60-day all-cause mortality among patients with severe alcoholic hepatitis treated with oral prednisolone?

Design: Multi-center, double-blind, placebo-controlled randomized controlled trial (RCT).

Setting: Twenty-five centers in France and Belgium between June 2015 and May 2019.

Patients: Included patients were: (a) age 18-75 years old; (b) consumption of $\geq$ 40 grams/day of alcohol (about 3 standard drinks/day) for women or $\geq$ 50 grams/day of alcohol (about 4 standard drinks/day) for men; (c) clinical diagnosis of alcohol-related hepatitis with new onset jaundice; and, (d) biopsy-proven alcoholic hepatitis with Maddrey score $\geq$ 32 and Model for End-stage Liver Disease (MELD) score $\geq$ 21. Multiple exclusion criteria

included type 1 hepatorenal syndrome. Patients being treated for diagnosed infection with antibiotics could be included after a 7-day wash-out period after completing antibiotics.

Interventions/Exposure: Amoxicillin 1g plus clavulanate 125mg orally 3 times a day vs identical placebo tablets for 30 days. All patients received 40mg per day of oral prednisolone for 30 days. Patients were evaluated in person weekly for the first 4 weeks, then at day 45, day 60, day 90, and day 180.

Outcome: The primary endpoint was 60-day all-cause mortality from date of randomization. Multiple secondary endpoints included all-cause mortality at 90-day and 180-day follow-up, incidence of infection or hepatorenal syndrome at 60-day follow-up.

Data Analysis: Intention-to-treat analysis with log-rank test using data from last available follow-up.

Funding: French Public Health Ministry

Results: Among 292 randomized patients, mean age was 52.8 (SD 9.2 years); 27% female; 18%-22% had previously been treated with antibiotics and were enrolled after a 7-day washout period. Thirteen percent had prior overt hepatic encephalopathy episodes. For the primary endpoint, there was no significant difference in all-cause 60-day mortality between the amoxicillin-clavulanate group vs placebo group: 17.3% vs 21.3%, *P*= 0.33; hazard ratio: 0.77 (95% confidence interval [CI]: 0.45-1.31). Cumulative incidence of infection was lower in the amoxicillin-clavulanate group at 60 days: 29.7% vs 41.5%; subhazard ratio: 0.62 (95% CI: 0.41-0.91, *P*= 0.02). (**Figure 1**). There were no significant differences in other secondary outcomes.

COMMENTARY

Why Is This Important?

Alcoholic hepatitis is associated with an increased risk of bacterial infection compared to patients with decompensated cirrhosis due to alcohol who do not have severe hepatitis.[1] This may be due to the relative immunosuppression associated with the high-grade systemic inflammation found in patients with alcoholic hepatitis. Furthermore, alcoholic hepatitis patients who don't get corticosteroids are less likely to get bacterial infections compared to patients who do get corticosteroids, which can worsen immunosuppression.[1] Considering that 25%-30% of alcoholic

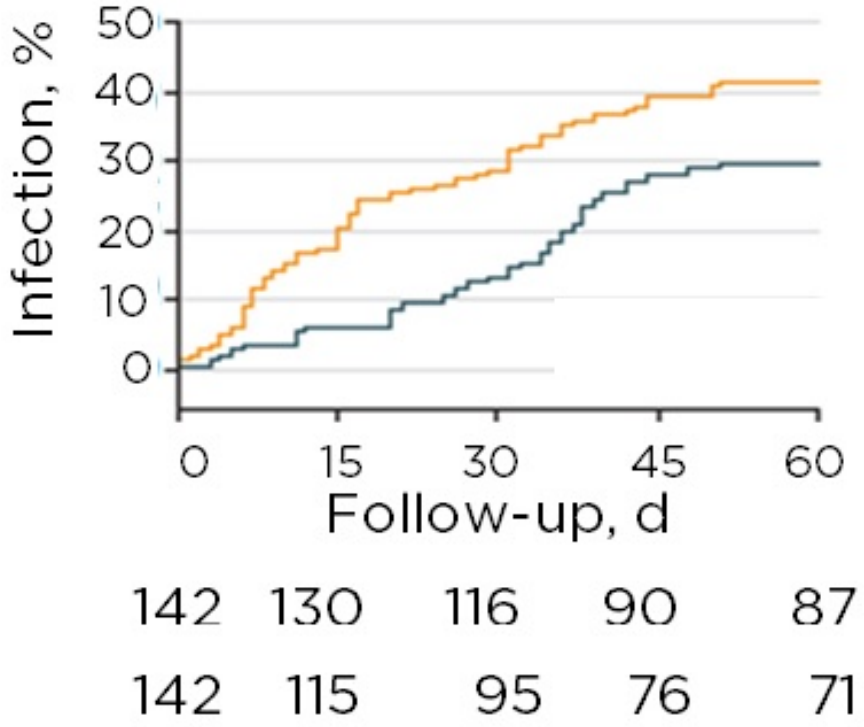

Figure 1. Cumulative incidence of infection at 60 days

hepatitis patients receiving corticosteroids are diagnosed with infections and that infections are associated with adverse outcomes like liver failure and hepatorenal syndrome, the use of prophylactic antibiotics has been proposed.

This RCT, the AntibioCor trial, confirmed the diagnosis of alcoholic hepatitis with biopsy and completed 180-day follow-up while assessing the most important outcome, all-cause mortality, along with the secondary outcome of incidence of infection. The investigators should be commended for their excellent study design and diligence to address new treatment beyond supportive care.

Key Study Findings

There was no significant difference in all-cause 60-day mortality between the amoxicillin-clavulanate group vs placebo group: 17.3% vs 21.3%, *P*=0.33; HR: 0.77 (95% CI: 0.45-1.31).

Cumulative incidence of infection was lower in the amoxicillin-clavulanate group at 60 days: 29.7% vs 41.5%; subhazard ratio: 0.62 (95% CI: 0.41-0.91, *P*= 0.02).

Caution

Approximately 20% of study patients previously treated with antibiotics were enrolled after a 7-day washout period with no antibiotics. The study protocol did not make any recommendations about whether or not to discontinue corticosteroids at day 7 if the Lille score $\geq$ 0.45. Since the sample size was calculated based on an absolute reduction in 60-day mortality of

14%, it's possible that the study was undersized to identify smaller, but still clinically important, reductions in mortality with prophylactic antibiotics.

My Practice

Although I'm a general gastroenterologist, I treat these patients on our inpatient service. Per advice from my hepatology colleagues and consistent with guidelines,[2-4] I usually prescribe corticosteroids if the Maddrey discriminant function (MDF) is $\geq$ 32 and MELD score >20, although I realize that corticosteroids have only proven benefit up to 28 days. If the Lille score is $\geq$0.45 at day 7, then I usually discontinue corticosteroids since they are associated with multiple side effects, including an increased risk of infection. I do not routinely use pentoxifylline per guidelines.[2-4]

Given the results of the AntibioCor trial, I will continue this approach and will not use prophylactic antibiotics in these patients. Based on the post hoc analysis of the ATTIRE trial[5] and guideline recommendations,[2-4] I also do not use prophylactic antibiotics for patients admitted with decompensated cirrhosis to reduce hospital-acquired infections. However, I do monitor these patients carefully for infection since they are at increased risk of infection and initiate antibiotics when appropriate. I also de-escalate antibiotic coverage based on culture and sensitivity if possible.

For Future Research

Although some anti-inflammatory medications are being studied for treatment of alcoholic hepatitis, there are no new treatments on the near horizon.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest.

The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary: @mathurinphilip1 (Philippe Mathurin).

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