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State of the Science Review

A systematic review of adenosine triphosphate as a surrogate for bacterial contamination of duodenoscopes used for endoscopic retrograde cholangiopancreatography

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Background: Bacterial culture is the accepted standard to measure the adequacy of high-level disinfection (HLD) of duodenoscopes. Adenosine triphosphate (ATP) bioluminescence assays have been suggested as an alternative method of evaluating the quality of reprocessing. We systematically reviewed published research describing the correlation between ATP and bacterial cultures.

Methods: The primary outcome was the correlation or concordance between concomitantly sampled ATP and bacterial contamination obtained from the instrument channel and/or elevator mechanism of the duodenoscope. A secondary outcome included the reduction in ATP measurements between paired samples before and after stages of duodenoscope reprocessing.

Results: Ten studies were included in the analysis. Four studies reported the relationship between concomitantly sampled ATP and cultures. Three studies reported receiver operating characteristic curves (1 study additionally reported a Wilcoxon rank sum test), and 1 study reported Spearman correlation coefficients and paired dichotomous measurements of ATP and bacterial contamination. All analyses suggested a poor relationship between the 2 measures. Studies measuring ATP before and after manual cleaning and before and after HLD reported a reduction in ATP after the reprocessing stage.

Conclusion: Current research does not support the direct substitution of ATP for bacterial culture surveillance of duodenoscopes. Serial ATP measurement may be a useful tool to evaluate the adequacy of manual cleaning and for training of endoscopic reprocessing staff.

BACKGROUND

Endoscopic retrograde cholangiopancreatography (ERCP) has a significant risk of contamination with enteric pathogens during a procedure.[1] The duodenoscope differs from other types of endoscopes in that its design is highly elaborate: the tip of the duodenoscope has an elevator plate that raises components passed through the instrument channel into the field of view to facilitate interventions. This complex design makes thorough cleaning and disinfection of these instruments very difficult. Published reports of outbreaks of invasive infections due to multidrug-resistant bacteria attributed to contaminated duodenoscopes have focused interest on the adequacy of duodenoscope reprocessing.[2-6]

The Centers for Disease Control and Prevention (CDC) has issued interim guidelines advocating for routine surveillance culture of duodenoscopes for early detection of contamination.[7] Although published experience suggests culture surveillance may be inadequate to reliably detect duodenoscope contamination, the current standard to assess for duodenoscope contamination is culture of the device, including the elevator mechanism and instrument channel. The method of using aerobic bacterial cultures is resource intensive and requires time for both processing of the sample and sequestration of the duodenoscope pending the findings. The 2015 CDC guidelines state that non-culture methods, including adenosine triphosphate (ATP), may be useful to detect residual organic material after cleaning. However, "more work is needed to interpret their results since non-culture methods lack consistent correlation to bacterial concentrations."[7]

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The ATP molecule is found in all living organisms and may be used as an indirect indicator of microbial contamination. ATP is measured using 1 of several proprietary bioluminescence assays that use a luciferine/luciferase reaction with the detection of ATP (measured in relative light units [RLUs]).[8] These simple-to-use assays provide point-of-testing results and have been implemented in food safety and to evaluate environmental cleaning in the healthcare setting.[9-12]

In this study, we systematically reviewed published evidence characterizing the relationship between measurement of ATP and bacterial contamination of ERCP duodenoscopes. Specifically, we sought to identify studies that concomitantly measured ATP and bacterial contamination, to estimate (a) the correlation or concordance between the 2 surveillance methods sampled from duodenoscopes and (b) the change in ATP levels before and after the manual and automated duodenoscope reprocessing stages.

METHODS

Search strategy

This literature review was conducted in accordance with Preferred Reporting Items of Systematic Reviews and Meta-Analyses guidelines.[13] The review was limited to ERCP duodenoscopes, since they have been a focus of recent published outbreaks, investigations, and specific guidance for surveillance. Moreover, experts have hypothesized that the complexity of their design—specifically, the elevator mechanism—may predispose these devices to contamination.[7,14] To minimize heterogeneity, linear echoendoscopes were not included in the analysis. The review was limited to English-language articles. An experienced medical librarian (J.W.) conducted the literature search, with input from the research team. We searched the following databases from inception to May 2017: PubMed/MEDLINE (National Center for Biotechnology 1966-2017), EMBASE (Elsevier 1974-2017), Web of Science (Thomson 1900-2017), and CINAHL ~1984-2017. Keywords were combined with the relevant index terms from each database, including permutations of the terms "endoscope," "duodenoscope," and "adenosine triphosphate." The complete detailed search strategy is outlined in Table A1 of the supplement. EndNote software (version X7; Thomson Reuters, Toronto, ON) was used for reference management.

Study selection and outcomes

Titles, abstracts, and articles were screened by a study investigator (L.B.O.). Studies were included in the analysis if they reported measurement of ATP and bacterial contamination from ERCP duodenoscopes, sampled from any area of the device, without regard to how the investigators quantified the measurements or the microbiologic methods used to characterize bacterial contamination. Data were included only from studies in which duodenoscope sampling followed routine clinical use and reprocessing (as opposed to simulated contamination or reprocessing). The analysis focused on ERCP duodenoscopes.

The primary outcome was the correlation of ATP (quantified as RLU) and bacterial contamination (quantified as colony-forming units [CFUs]) as continuous measures and the concordance of ATP and CFU as dichotomized measures, among concomitantly obtained paired measurements of ATP and bacterial contamination, from the instrument channel[1] and/or elevator mechanism (including samples from the sealed elevator channel[15]). Specific cutoffs for dichotomization of ATP and CFU measurements were analyzed as defined in the publication. The secondary outcome was the difference in ATP measurements between paired samples (from any area of the device) before and after manual reprocessing and before and after high-level disinfection (HLD) with an automated endoscope reprocessor.

Data extraction and synthesis

Data were abstracted and recorded into a custom-designed data extraction sheet and included the following fields: first author; year of publication; study setting; study objective; duodenoscope manufacturer; ATP bioluminescence assay manufacturer and model; sampling time relative to reprocessing stage; duodenoscope sampling location and technique; summarized concomitant ATP and microbiologic sampling results; ATP and CFU cutoff criteria to define clean for dichotomized measures; proportion of sampled duodenoscopes meeting ATP and CFU cutoff criteria; method of assessing correlation and/or concordance relationship; effect estimate (and confidence intervals and *P* values) of correlation and/or concordance; summary measurements of ATP RLU before and after reprocessing stage; and summary measurements of CFU before and after the reprocessing stage. Due to the anticipated heterogeneity of study methods and analysis on this topic, a meta-analysis of the data was not planned.

RESULTS

A total of 191 non-duplicate studies published as manuscripts, abstracts, or conference proceedings were considered for analysis. A detailed assessment was performed on 17 studies, of which 10 met the criteria for inclusion in this review (Fig 1). These 10 studies were published between 2005 and 2017 and included 9 articles and 1 abstract. Additional publication details, including the intended objective of each study and pertinent findings, are described in Table A2 of the supplement.

The study setting, devices, and sampling strategy of the 10 studies in this analysis are presented in Table 1. In 5 of 10 (50%) studies, the duodenoscope used was manufactured by Olympus (Center Valley, PA); for the remaining studies the duodenoscope manufacturer could not be identified. The ATP manufacturer was 3M Inc. (St. Paul, MN) in 7 (70%) studies, HyServe (Uffing, Germany) in 1 study, Charm Science (Lawrence, MA) in 1 study, and not reported in 1 study. The sampling time relative to the duodenoscope reprocessing stage differed among the studies, with 6 (60%) studies reporting sampling prior to manual cleaning, 6 (60%) studies reporting sampling after manual cleaning, and all studies reporting sampling after HLD (reported as either after HLD [7] or after storage [3]). All studies sampled the instrument channel either by flushing the channel to obtain the sample (8 studies, 80%) or by using the flush-brush-flush method (2 studies, 20%) The elevator mechanism was swabbed in 3 (30%) of the studies, flushed in 1 (10%) study, and not sampled in 6 (60%) studies.

Table 2 describes the primary outcome, including reported correlation or concordance between ATP and microbiologic sampling of duodenoscopes after all cleaning and disinfection procedures. Two (20%) studies did not provide data regarding bacterial contamination that would allow an assessment of the relationship between the 2 methods. Four (40%) studies provided the distribution of ATP and CFU but no direct assessment of the relationship between paired data. Of the remaining 4 (40%) studies, 2 reported only receiver operating characteristic (ROC) curves, 1 reported ROC curves as well as a "nonparametric Wilcoxon test," and 1 reported paired dichotomous measurements of ATP and bacterial contamination as well as a Spearman correlation coefficient.

[1]The terms instrument channel, suction-biopsy channel, and working channel are used synonymously within cited publications. For simplicity, this endoscope channel is referred to as "instrument channel" in this publication.

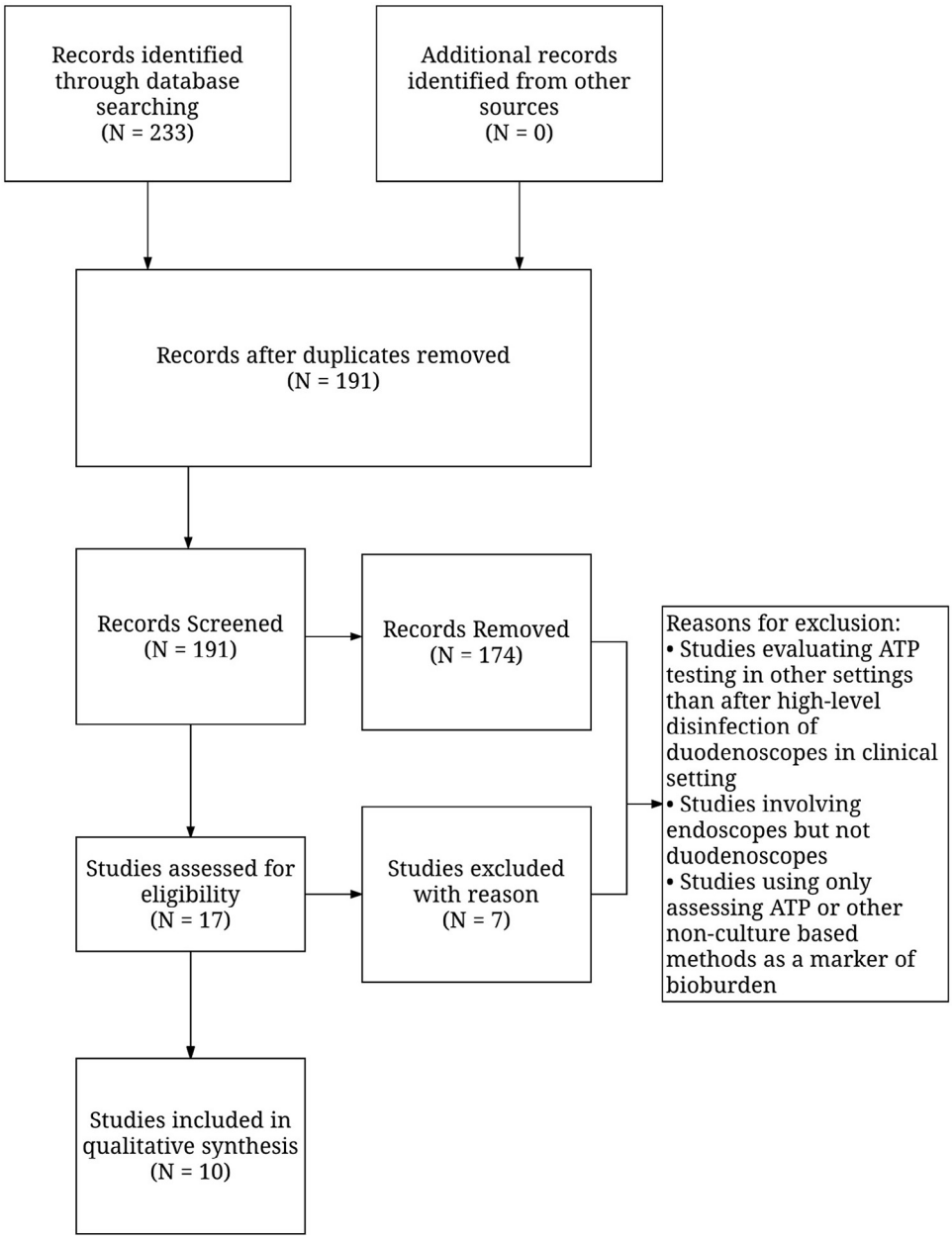

Fig 1. Flow diagram of publications identified in this review.

Detailed findings of correlation or concordance

Batailler et al.[17] compared the continuous distribution of ATP by dichotomized CFU and reported median with interquartile range (IQR) ATP measurements among samples with ≤25 CFU/100 mL and >25 CFU/100 mL, as well as a ROC curve with area under the curve (AUC) for multiple types of endoscopes. Of 15 duodenoscope samples, 10 (67%) demonstrated culture ≤25 CFU/100 mL for both the first flush sample and the whole sample, and 5 demonstrated culture >25 CFU/100 mL. ATP findings for duodenoscopes that were reported only as median ATP without IQR by sample and culture result: for first flush sample, ≤25 CFU/100 mL, 36.5; for first flush sample, >25 CFU/100 mL, 38.7; for whole sample, ≤25 CFU/100 mL, 37.0; and for whole sample, >25 CFU/100 mL, 37.0. The results of Wilcoxon test and ROC curve/AUC for correlation among the duodenoscope samples were not presented; after adjustment for the batch of diluent solution, the AUC among all gastrointestinal endoscopes was 0.49 (95% confidence interval [CI], 0.30-0.69) for the first jet sample and 0.43 (95% CI 0.26-0.59) for the whole sample. Concordance between ATP and CFU was not estimated. Overall, the authors concluded that "ATPmetry cannot be used as an alternative or complementary approach to microbiologic tests for monitoring the reprocessing of endoscopes in France."

Hansen et al.[20] evaluated concordance between ATP quantification and bacterial contamination using 10 different ATP cutoffs. Of the 8 duodenoscopes sampled, only 1 (13%) was culture positive, and the ATP measurement was >100 for that sample. For the 7 samples with a negative culture, ATP measurements were >30 for 2 samples, 31-40 for 2 samples, 71-80 for 1 sample, 81-90 for 1 sample, and >100 for 1 sample. The authors generated a ROC curve for all endoscope types but did not report a ROC curve specifically for duodenoscopes or gastrointestinal endoscopes. Of all

Table 1
Study setting, adenosine triphosphate sampling assay, and sampling strategy employed in studies reporting concomitant adenosine triphosphate and bacterial contamination of duodenoscopes

Author, year (reference)	Duodenoscope manufacturer	Make and model of ATP bioluminescence assay	Duodenoscope sampling location and technique						
			Prior to manual cleaning	After manual cleaning	After HLD/storage	IC, flush	IC, flush-brush-flush	Swab of EM	EM, flush
Alfa MJ, 2013[15]	Olympus	3M Water test*	✓	✓	✓	✓			✓
Alfa MJ, 2014[16]	Olympus	3M Water test*	✓	✓	✓	✓			
Batailler P, 2015[17]	-	3M Water test*			✓	✓			
Fernando G, 2014[18]	-	3M Water test*	✓	✓	✓	✓			
Gillespie E, 2016[19]	-	3M Water and Surface test†	✓		✓	✓			
Hansen D, 2004[20]	-	Lumitester PD 10‡			✓	✓		✓§	
Kweon O, 2013[21]	-	-	✓	✓	✓				
Olafsdottir LB, 2017[22]	Olympus	PocketPLUS¶			✓		✓	✓	
Sethi S, 2017[23]	Olympus	3M Water test*	✓	✓	✓	✓			✓
Visrodia K, 2017[24]	Olympus	3M Water and Surface test†		✓	✓	✓		✓	

ATP, adenosine triphosphate; *EM*, elevator mechanism; *HLD*, high-level-disinfection; *IC*, instrument channel. "-" indicates assessment not performed or data not reported.
*The Clean-Trace ATP Water device (3M).
†The Clean-Trace ATP Water device and The Clean-Trace Surface ATP device (3M).
‡Luminester PD10 (HyServe).
§Swab of distal end, not stated if the elevator mechanism specifically was sampled.
¶PocketPLUS (Charm Science).

Table 2
Assessment of correlation and concordance between adenosine triphosphate and bacterial contamination of duodenoscopes among studies reporting concomitant measurements

Author, year (reference)	Sample size	Method of assessing correlation and/or concordance	Cutoff criteria to define non-contaminated		Proportion of samples meeting criteria for non-contamination	
			ATP (RLU)	Culture (CFU)	ATP	Culture
Alfa MJ, 2013[15]	40	*	< 200	< 4 $\log_{10}$/ cm^2	IC: 100% EM: 75%	IC: 100% EM: 100%
Alfa MJ, 2014[16]	35	*	< 200	< 4 $\log_{10}$/ cm^2	100%	-
Batailler P, 2015[17]	15	"Wilcoxon test", ROC curve† Estimate of concordance not calculated	-	≤25 CFU/100 mL	-	93%
Fernando G, 2014[18]	11	-	≤ 50, 100, 300, 500	-	≤ 50 RLU: 73% ≤ 100 RLU: 91% ≤ 300 RLU: 100% ≤ 500 RLU: 100%	-
Gillespie E, 2016[19]	40	*	≤100	-	100%	-
Hansen D, 2004[20]	8	ROC curve† Estimate of concordance not calculated	< 30, 40, 50, 60, 70, 80, 90, 100	0	30 RLU: 25% 100 RLU: 75%	87%
Kweon O, 2013[21]	-	-	-	-	-	-
Olafsdottir LB, 2017[22]	390	Spearman correlation coefficient 2x2 contingency table	0	0	IC: 87% EM: 6%	IC: 88% EM: 91%
Sethi S, 2017[23]	10	*	< 200	0	100%	100%
Visrodia K, 2017[24]	37	ROC curve Estimate of concordance not calculated	< 200	0	IC: 84% EM: 35%	IC: 49% EM: 78%

ATP, adenosine triphosphate; *CFU*, colony forming unit; *HLD*, high-level disinfection; *IC*, instrument channel; *RLU*, relative light units *ROC*, receiver operating characteristic.
"-" indicates assessment not performed or data not reported.
*Sample means or medians provided but no paired data.
†The ROC curve was calculated with the combined results from all endoscopes included in the study (not duodenoscope-specific results).

endoscopes, including gastrointestinal endoscopes and bronchoscopes, the AUC was 0.63 (95% CI not provided). Concordance between ATP and CFU was not estimated. The sensitivity of ATP to detect a positive culture among all endoscopes ranged from 0.46 (100 RLU cutoff, 95% CI 0.28-0.66) to 0.75 (30 RLU cutoff, 95% CI 0.55-0.89). The specificity ranged from 0.43 (30 RLU cutoff, 95% CI 0.32-0.54) to 0.81 (100 RLU cutoff, 95% CI 0.71-0.89). The authors concluded that "ATP bioluminescence does not replace routine microbiologic methods but it should be applied additionally to check endoscope reprocessing. In contrast to microbiologic methods results of ATP bioluminescence are available at once and can indicate the need for checking the reprocessing practice immediately."

Olafsdottir et al.[22] analyzed 390 duodenoscope samples from both the instrument channel and elevator mechanism. Cultures were negative in 344 (88%) instrument channels and in 354 (91%) elevator mechanisms. ATP measurements were 0 RLU in 338 (87%) instrument channels and in 23 (6%) elevator mechanisms. The Spearman correlation coefficient between ATP (RLU) and CFU was 0.047 (95% CI not provided, $P = .35$) for the instrument channel and 0.039 (95% CI not provided, $P = .44$) for the elevator mechanism. ATP and CFU assessments of contamination were discordant in 82 of 390 (21%) instrument channel measurements and in 331 of 390 (85%) elevator mechanism measurements (statistical test of significance not provided). The authors concluded that "ATP measurements correlate poorly with a microbiologic standard assessing duodenoscope contamination, particularly for the EM (elevator mechanism) sampling. ATP may reflect biological material other than nonviable aerobic bacteria and may not serve as an adequate marker of bacterial contamination."

Visrodia et al.[24] investigated 20 duodenoscope samples, including 18 that underwent a second reprocessing cycle and 6 that underwent a third reprocessing cycle due to high levels of ATP after reprocessing (for a total of 44 cycles, including 132 ATP and 74 culture tests). In their analysis of 74 concomitant samples for ATP and culture, 18 (49%) instrument channel samples and 29 (78%) elevator mechanism samples were culture negative, and 31 (84%)

instrument channels and 13 (35%) elevator mechanisms demonstrated ATP <200 RLU. The authors generated ROC curves separately for each sampling site: for the instrument channel, the AUC was 0.52 (95% CI not provided); for the elevator mechanism, the AUC was 0.56 (95% CI not provided). Concordance between ATP and CFU was not estimated. The sensitivity/specificity (%) for channel samples (n = 36) for different ATP threshold (RLU) 25, 50, 100, 150, 200, 250, and 300 was 47/50%, 26/70%, 21/72%, 11/72%, 22/78%, 5/83%, and 5/100%, respectively; for elevator samples (n = 36) the sensitivity/specificity (%) for different ATP thresholds (RLU) 100, 200, 300, 400, 500, and 1000 was 75/24%, 75/38%, 38/48%, 25/59%, 25/66%, and 0/72%, respectively. They found that the overall sensitivity and specificity of ATP testing compared to terminal cultures was 30% and 53%, respectively. The authors concluded that "ATP sampling appears to correlate poorly with terminal cultures and cannot be recommended as a surrogate for terminal cultures. The performance and interpretation of cultures remains complicated by the potential of environmental contaminants."

Change in ATP and CFU levels between stages of reprocessing

All of the studies that evaluated ATP RLU and CFU levels between different stages of the reprocessing process demonstrated a reduction in the distribution of measurements before and after each reprocessing stage. Table 3 describes the studies that reported sample mean/median ATP RLU and CFU measurements before and after manual cleaning and before and after HLD with an automated endoscope reprocessor. Of the 4 studies that reported ATP RLU values from both the instrument channel and elevator mechanism, the sample distribution from the elevator mechanism was consistently higher than the instrument channel, including when sampled after manual cleaning[15,16,23,24] and when sampled after disinfection[15,16,23-25] (Table 3).

Assessment of bias

It was difficult to assess bias for the included studies because they were not studies with subjects categorized into comparison groups. Additionally, the aims of the studies (Table A2) were heterogeneous and not necessarily congruent with the primary aim of this systematic review. We evaluated the gray literature when searching for studies for this systematic review to try to prevent publication bias and included both abstracts and full-length articles. The studies were conducted in high-volume ERCP centers, which could introduce a design bias, since high-volume institutions might have more proficient reprocessing staff with higher quality of cleaning, with additional Hawthorne effect during the study period. This could be an effect modifier, since the sensitivity of ATP RLU results is lower with low microbiologic burden.[12,26] It is unclear if the age and condition of the duodenoscopes affected the relationship between ATP RLU and culture results; however, the studies in this analysis that reported age or condition did not provide sufficient information to analyze these concerns. Three studies reported how the duodenoscopes were enrolled into the study, all of them as a

Table 3
Changes in adenosine triphosphate and bacterial contamination before and after manual cleaning and before and after high-level disinfection of duodenoscopes

			ATP Log_{10}(RLU) distribution			Log_{10}(CFU) distribution		
Author, year (reference)	Location	Measure	Pre MC	Post MC	Post AER	Pre MC	Post MC	Post AER
Alfa MJ, 2013[15]	Instrument channel	Mean (SD)	4.0 (4.5)	1.7 (1.7)	1.5 (1.1)	3.1(3.1)	0.1 (0.2)	0 (0)
	Elevator mechanism	Mean (SD)	3.4 (3.5)	2.2 (2.3)	2.1 (2.2)	3.2 (3.0)	0.3 (0.3)	0 (0)
Alfa MJ, 2014[16]	Instrument channel (Biopsy port to distal end)	Mean (SD)	3.9 (4.1)	1.8 (1.5)	1.6 (1.3)	2.7 (1.0)	0.4 (0.5)	0.001 (0.003)
	Instrument channel (Umbilical end to distal end)	Mean (SD)	2.7 (2.9)	1.6 (1.3)	1.6 (1.4)	1.3 (1.0)	0.4 (0.5)	0.002 (0.003)
Batailler P, 2015[17]	Instrument channel (First jet, ≤25 CFU/100 mL)	Median	-	-	1.6	-	-	-
	Instrument channel (First jet, >25 CFU/100 mL)	Median	-	-	1.6	-	-	-
	Instrument channel (Whole sample, ≤25 CFU/100 mL)	Median	-	-	1.6	-	-	-
	Instrument channel (Whole sample, >25 CFU/100 mL)	Median	-	-	1.6	-	-	-
Fernando G, 2014[18]	Instrument channel	Median (IQR)	4.5 (4.4-4.7)	2.7 (2.6-2.8)	1.7 (1.6-1.8)	-	-	-
Gillespie E, 2016[19]	Instrument channel (Study site 1)	Median (IQR)	-	-	1.2 (0.3-1.4)	No growth or <0.3 CFU skin flora		
	Instrument channel (Study site 2)	Median (IQR)	-	-	1.0 (0.6-1.3)	No growth or <0.3 CFU skin flora		
Hansen D, 2004[20]	-	-	-	-	-	-	-	-
Kweon O, 2013[21]	-	-	-	-	-	-	-	-
Olafsdottir LB, 2017[22]	Instrument channel	Median (IQR)	-	-	1.0 (1.0–1.0)	-	1.0 (1.0–1.0)	-
	Elevator mechanism	Median (IQR)	-	-	4.1 (3.6-4.6)	-	1.0 (1.0–1.0)	-
Sethi S, 2017[23]	Instrument channel	Median (IQR)	2.6 (2.5-2.9)*	1.9 (1.5-2.2)*	1.1 (0.9-1.4)*	No growth		
	Elevator mechanism	Median (IQR)	2.8 (2.4-3.0)*	2.5 (1.9-2.6)*	1.2 (1.0-1.5)*	No growth		
Visrodia K, 2017[24]	Instrument channel	Median (IQR)	-	1.6 (1.0-2.5)	-	-	-	-
	Elevator mechanism	Median (IQR)	-	2.7 (2.1-4.4)	-	-	-	-

NOTE: All numbers in the table are transformed with a Log_{10} scale.
AER, automated endoscope reprocessor; *ATP*, adenosine triphosphate; *CFU*, colony forming unit; *MC*, manual cleaning; *RLU*, relative light unit; *SD*, standard deviation. "-" indicates assessment not performed or data not reported.
*Number taken from the Phase C of the study, which was the only phase that had concurrent microbiologic cultures.

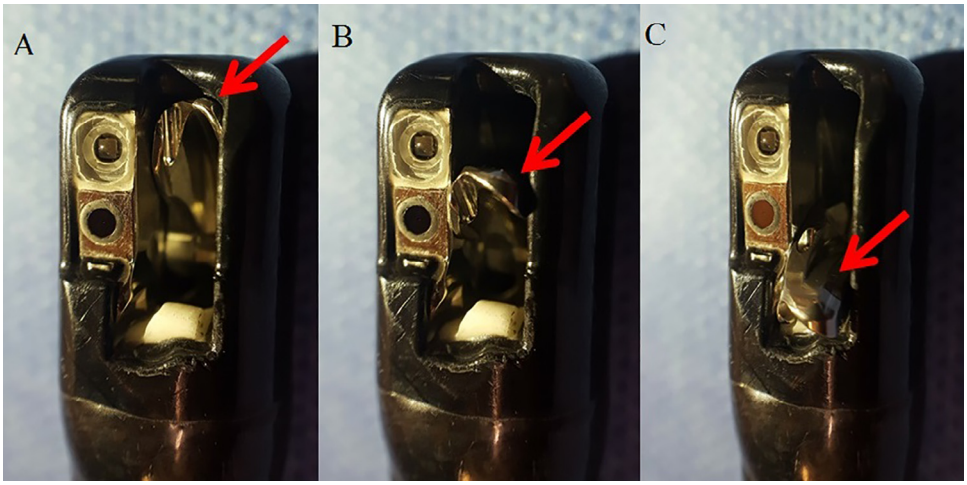

Fig 2. Picture of the elevator mechanism of a duodenoscope (TJF-Q180V, Olympus, Center Valley, PA).
NOTE: The figure illustrates the orientation of the elevator mechanism, air nozzle, side-viewing camera, and light source. The hinged elevator lever (red arrow) enables instrumentation perpendicular to the plane of the duodenoscope. A) The elevator lever in a lowered position. B) The elevator lever in a middle position. C) The elevator lever in a raised position. Photographs by the authors (L.B.O., G.M.S.).

convenient sample (daytime samples, not during after-hours), and this might have introduced a sampling bias, since when there was an emergent case or on very high-volume days, scopes might not have been sampled.[15,17,22] Six (60%) of the studies reported that the ATP assays/kits were provided by the manufacturer company: 3M, 3M Australia, or CharmScience.[15,16,18,19,22,23] This represents a measurement or misclassification bias, since not all of the ATP assays have the same RLU cutoff, and authors additionally used different microbiologic contamination cutoffs. Only the Clean-Trace (3M) has been validated for an ATP RLU cutoff <200, which the included studies using this assay used.[26] Another source of measurement bias was that the yield of microbiologic culture from a biofilm might also be variable,[6] and the microbiologic culture methods, which have not been standardized and validated, measure only aerobic bacteria.[7] It is difficult to assess external validity of these studies since different combinations of ATP assays, microbiologic testing methods, and automatic reprocessors were used, and this might affect the results of ATP RLU and microbiologic contamination. In 2 of the studies, the authors reported a potential conflict of interest as a consultant, inventor of a proprietary ATP-related testing assay, and/or invited speaker sponsored by a company involved with duodenoscopes or ATP testing assays (Olympus and 3M).[15,23]

DISCUSSION

We systematically reviewed published evidence of the relationship between the measurement of ATP and bacterial contamination of duodenoscopes, with the aim of estimating (a) the correlation and/or concordance between the 2 methods to determine adequacy of HLD and (b) the distribution and reduction in ATP levels before and after the manual and automated reprocessing stages. Of the 10 studies that measured ATP and bacterial contamination of duodenoscopes, there were heterogeneous aims and analytic techniques, which therefore limited direct estimation of the relationship between ATP and CFU. Four studies concomitantly measured ATP and CFU, and all 4 studies found weak evidence to suggest a relationship between ATP and bacterial contamination. We agree with the authors' conclusions generally that ATP is not an appropriate surrogate for bacterial contamination of duodenoscopes.[17,20,22,24]

Duodenoscopes are unlike other forward-viewing endoscopes used for routine upper gastrointestinal endoscopies or colonoscopies. They have a side-viewing camera and an elevator mechanism (Fig 2). The elevator mechanism is a mobile lever that is hinged at one end and enables the instruments that are passed through the instrument channel to move into the field of view, thus facilitating interventions performed during ERCP procedures. The elevator mechanism is sealed by an O-ring that should prevent contamination of the interior of the duodenoscope, including the enclosed elevator mechanism wire and channel. This complex design, along with the narrow lumen of the duodenoscopes, makes them difficult to clean.[6,7,27] Additionally, they cannot be steam sterilized due to their material composition. The recommendation is to use HLD, with the goal of eliminating all microbial life except bacterial spores.[7] Recent outbreaks have demonstrated that the methods used to clean and disinfect these widely used and expensive instruments are not foolproof, and this created a demand for "a point-of-care test" to determine if a duodenoscope has been successfully disinfected.[3-6] The ATP bioluminescence test has been proposed in this setting to expedite the surveillance process.[15,16,26]

According to this systematic review, ATP testing does not correlate well with microbiologic cultures during and after the reprocessing of duodenoscopes. The lack of correlation between the 2 methods might be explained by ATP being a gross measure of organic material. Studies have shown that the relationship between bacterial contamination measured as CFU and ATP levels is not linear[12]; to detect 1 RLU, a sample may need to contain 10^3 CFU of gram-positive bacteria or 10^2 CFU of gram-negative bacteria.[26] This can lead to negative ATP results when bacterial cultures show contamination from the duodenoscope after HLD. It is, however, unclear why ATP RLU results can be high when bacterial cultures are negative. A possible explanation is that the ATP testing is capturing organic residue other than viable bacteria, including biofilm, from which organisms may be difficult to culture using routine methods. Biofilm is a mucilaginous protective coating (extracellular polymeric substance), secreted by bacterial colonies, that adheres to surfaces frequently in contact with water. This coating increases bacterial resistance to biocides and decreases the efficacy of both cleaning and disinfecting agents.[28,29] Biofilm has been demonstrated to form in association with the elevator mechanism, including from presumptive O-ring malfunction, leading to inadequate sealing of the elevator wire channel and persistent bacterial contamination despite adequate reprocessing.[6] Multiple reports have described

biofilms found within the channels of used endoscopes, even after thorough cleaning and decontamination.[30,31] Consistent with the hypothesis that biofilm, which may be most strongly associated with the structure of the elevator mechanism, accounts for the nonrelationship between ATP and cultures, studies sampling both the elevator mechanism and instrument channel in this review demonstrated higher ATP levels sampled from the elevator mechanism than from the instrument channel (Table 3). Furthermore, this difference may be underestimated since the size of the swab in the ATP bioluminescence test kits may not adequately contact elevator mechanism surfaces and therefore may underestimate ATP levels in the elevator mechanism.

The 4 studies that evaluated levels of ATP contamination at different stages of the reprocessing process universally demonstrated a reduction in the sample mean or median before and after the evaluated stage of reprocessing (Table 3).[15,16,18,23] Additionally, 2 studies in this analysis demonstrated that ATP targets can be reached with repeated manual cleaning prior to automated reprocessing.[23,24] These data were evaluated as summary data for the population; data on the frequency with which individual samples demonstrated an appropriate decrease in contamination with ATP are very limited.[22] Therefore, ATP testing may play a role as a quality indicator of manual cleaning and training of endoscopy reprocessing technicians. Even though the detection of microbiologic contamination may not necessarily reflect the presence of viable pathogens, it could determine the need for additional manual cleaning stages prior to HLD in an attempt to decrease possible biofilm formation. This possible use of ATP to assess for duodenoscope contamination warrants further investigation.

By using terms specific to duodenoscopes and general to all endoscopes, as well as lower endoscopy endoscopes to identify publications that may describe various types of gastrointestinal endoscopes, our search strategy attempted to identify all studies that performed ATP and culture of ERCP duodenoscopes. However, data from studies using alternative or less descriptive terms, or data from publications that did not differentiate multiple endoscope types, may not be included in this analysis. An important limitation of this analysis is that the studies were heterogeneous in design with regard to methods and sampling strategy, making a meta-analysis of the data not possible. In particular, the relationship between ATP and bacterial contamination may vary based on the microbiologic methods used to quantify bacterial contamination (eg, incubation period after sampling and enrichment techniques). The number of published studies and heterogeneity of methods precludes subgroup analysis by microbiologic techniques. Future studies with maximally sensitive methods to identify bacterial contamination may identify a stronger—or weaker—relationship between bacterial contamination and ATP. We performed this analysis with the CFU cutoffs for contamination established by the source authors; a specific CFU cutoff that correlates with transmission of pathogens to patients has not been established. Analogously, we did not assess the concordance between investigators' method of ATP sampling in comparison to the manufacturers' instructions for use for each device. None of the publications reported correcting ATP results for sampling area, and heterogeneity of the proprietary system and sampling method may affect the relationship between ATP and bacterial contamination.

In conclusion, ATP testing does not correlate well with microbiologic cultures after HLD of duodenoscopes. ATP testing cannot be recommended as a surrogate for terminal cultures, since it is not an adequate marker of bacterial contamination. ATP testing might have a role as a quality assurance test after the manual cleaning stage and for training endoscope reprocessing staff. Standardized guidelines for the sampling and reporting of ATP and bacterial contamination measures may improve the study and surveillance of duodenoscope reprocessing.

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APPENDICES

Table A1
Search strategy for online databases

PubMed	(("Adenosine Triphosphate"[Mesh] OR atp[tiab] OR adenosine triphos*[tiab] OR adenosintri*[tiab] OR adenosinetri[tiab] OR rapid testing[tiab] OR rapid indicator*[tiab]) AND ("Endoscopes"[Mesh] OR endoscop*[tiab] OR duodenoscop*[tiab] OR colonoscop*[tiab] OR proctoscop*[tiab]))
Embase	(("adenosine triphosphate"/exp OR atp:ab,ti OR (adenosine NEXT/1 triphos*):ab,ti OR adenosintri*:ab,ti OR adenosinetri:ab,ti OR (rapid NEXT/1 (testing OR indicator*)):ab,ti) AND ("endoscope"/exp OR endoscop*:ab,ti OR duodenoscop*:ab,ti OR colonoscop*:ab,ti OR proctoscop*:ab,ti))
Web of Science	TS=("atp" OR "adenosine triphos*" OR "adenosintri*" OR "adenosinetri" OR "rapid testing" OR "rapid indicator*") AND TS=("endoscop*" OR "duodenoscop*" OR "colonoscop*" OR "proctoscop*")
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	((MH "Adenosine Triphosphate") OR TI ("atp" OR "adenosine triphos*" OR "adenosintri*" OR "adenosinetri" OR "rapid testing" OR "rapid indicator*") OR AB ("atp" OR "adenosine triphos*" OR "adenosintri*" OR "adenosinetri" OR "rapid testing" OR "rapid indicator*") AND (MH "Endoscopes+") OR TI ("endoscop*" OR "duodenoscop*" OR "colonoscop*" OR "proctoscop*") OR AB ("endoscop*" OR "duodenoscop*" OR "colonoscop*" OR "protoscop*"))

Table A2
Overview of the objectives and primary results of the included studies

Author, year (reference)	Study objective	Primary results
Alfa MJ, 2013[15]	". . .to verify that the ATP benchmark of <200 RLUs established for manual cleaning using stimulated-use testing is achievable in a busy endoscopy clinic that is following the manufacturer's manual cleaning process"	Various channels (instrument, air-water, auxiliary water, and elevator guide-wire) were sampled from 20 colonoscopes and 20 duodenoscopes. In 115/120 (96%) samples ATP measurement was < 200 RLU. The 5 channels that exceeded 200 RLU were elevator guide-wire channels. All 120 samples met standards for levels of protein contamination.
Alfa MJ, 2014[16]	". . .(1) to determine whether most of the organic and bioburden residuals from patient-used GI endoscopes was found in the biopsy port to distal portion or the umbilical to biopsy port portion of the suction-biopsy (SB) channel, to help determine optimal sample collection strategies, and (2) to compare the levels of ATP, protein and bioburden residuals to evaluate whether the previously established benchmarks for adequate channel cleaning remain valid"	From 20 samples among gastroscopes, duodenoscopes, and colonoscopes, the instrument channel did not exceed benchmark contamination levels for bacteria (<2 $\log_{10}$ CFU/cm^2) or protein (<2 μg/cm^2) for any samples. In 4 of 20 (20%) gastroscope samples for each the biopsy-distal and umbilical-biopsy segments of the endoscope ATP measurements exceeded the benchmark (<200 RLU). All 20 gastroscope and duodenoscope samples demonstrated ATP < 200 RLU.
Batailler P, 2015[17]	". . .to evaluate the diagnostic value of ATPmetry to monitor the effectiveness of reprocessing of endoscopes in real hospital practice compared with microbiologic assays using microbiologic contamination thresholds defined in the French recommendations"	Among 62 bronchial and 103 gastrointestinal endoscope samples, 11 (7%) demonstrated >25 CFU and 12 (7%) demonstrated an "indictor" Gram negative pathogen (7 of which had growth >25 CFU). There was no significant difference in the ATP measurement sampled from the first "jet" (1 mL) of the channel samples compared to a complete full sample, and while ATP levels were higher among the 11 endoscopes with >25 CFU, this relationship was not sustained after adjusting for the batch of cleansing solution used. Batch-adjusted ROC curves of the demonstrated AUC 0.57 (0.39-0.75) for the first jet and 0.54 (0.40-0.68) for the whole sample.
Fernando G, 2014[18]	". . .to evaluate the overall efficacy of standard gastrointestinal (upper and lower) endoscope reprocessing in endoscopy units and to evaluate ATP as a means of assisting in the management of the decontamination process, compared with standard microbiological testing"	*In vitro* testing of a standardized inoculum of various pathogens demonstrated a good correlation between log-transformed organism concentration and ATP value sampled from the broth solution (adjusted $R^2 \geq .88$). Among 120 endoscope samples (59 colonoscopes, 50 gastroscopes, 11 duodenoscopes), the mean $\log_{10}$(ATP) levels correlated with the stage of sampling: pre-patient (prior to use), 1.53 (1.47-1.58), post-patient, 4.54 (4.38-4.69), post-cleaning, 2.66 (2.55-2.77) and post-disinfection, 1.70 (1.60-1.79). The corresponding cultures were positive (not defined by authors) in 0/120 samples pre-patient, 4/120 (3%) post-patient, and 0/120 post-cleaning and post-disinfection. Among 21 (17%) samples with ATP >100 RLU following disinfection, corresponding cultures were negative and protein levels were undetected.
Gillespie E, 2016[19]	". . .to develop a reliable and user friendly method for monitoring the cleaning of duodenoscopes prior to ERCP"	Twenty duodenoscopes were sampled following procedures and disinfection at each of two study sites. There was no growth of pathogenic bacteria (or <10 CFU skin flora) from any of the 40 samples. The ATP median (range) at the two sites were 14 (1-27) and 10 (3-17) RLU.
Hansen D, 2004[20]	". . .to compare the ATP bioluminescence for hygiene checking of reprocessing with routine microbiological cultures"	Among 108 endoscopes (40 gastroscopes, 18 colonoscopes, 8 duodenoscopes and 42 bronchoscopes), 28 (26%) demonstrated any bacterial growth. Using RLU threshold in deciles from 30 to 100 RLU, the sensitivity of ATP to detect bacterial growth ranged from 46-75% and the specificity ranged from 43-81%. An ROC curve demonstrated an ROC of 0.63 (no confidence interval or *P*-value given).
Kweon O, 2013[21]	". . .to evaluate efficacy of ATP tracer as the method in the management of the endoscope reprocessing"	Seventy-two endoscopes—including gastroscopes, colonoscopies, and duodenoscopes—were sampled for ATP and culture at the post-procedure, pre-cleaning, and post-disinfection stages. The post-procedural ATP values decreased after pre-cleaning in all three surfaces sampled ($P < .05$ provided without effect estimate; the statistical test used was not provided). There was "no statistical difference" in average ATP values among samples that were culture-positive (ATP 39 ± 42) versus culture-negative (31 ± 63).
Olafsdottir LB, 2017[22]	". . .to quantify the correlation between ATP measurements and bacterial cultures from duodenoscopes for evaluation of contamination following HLD"	Among 390 duodenoscope samples, 46 (12%) demonstrated any bacterial growth from the instrument channel and 36 (9%) demonstrated any growth from the elevator mechanism. ATP was >0 RLU for 52 (13%) of instrument channels and 367 (94%) of elevator mechanisms sampled. The Spearman correlation coefficient for the relationship between ATP and CFU was 0.047 ($P = .35$) for the instrument channel and 0.039 (*P*-.44) for the elevator mechanism. ATP and CFU assessments of contamination were discordant in 82/390 instrument channel measurements (21%) and 331/390 of EM measurements (85%).
Sethi S, 2017[23]	". . .to assess the utility of ATP bioluminescence as a method for surveillance of flexible endoscopes during and after the HLD process, with specific attention to duodenoscopes.. . .(1) to verify whether the ATP bioluminescence benchmark of 200 RLUs after manual cleaning was routinely achievable in rinsates from the working channels of all endoscopes used in a busy endoscopy suite of a U.S. tertiary care hospital and (2) to specifically evaluate rinsate ATP bioluminescence values from the elevator channels of duodenoscopes and linear echoendoscopes"	Researchers sampled 48 endoscopes (including gastroscopes, colonoscopies, radial and linear echoendoscopes, and dudodenoscopes) from the instrument channel (and elevator channel of duodenoscopes). Mean ATP values showed a significant decrease for each endoscope type between pre-cleaning and post-cleaning stages, and between the post-cleaning and post-disinfection stages. All 48 endoscope instrument channels sampled demonstrated ATP <200 RLU after disinfection. Only 1 of 10 (10%) duodenoscope elevator channel samples achieved ATP <200 RLU; when ATP testing was performed after 2 sequential cycles of precleaning/manual cleaning and a cycle of disinfection, and when ATP testing was performed after 2 sequential cycles of precleaning/manual cleaning and 2 sequential cycles of disinfection, ATP levels met benchmark levels and cultures were negative.
Visrodia K, 2017[24]	". . .to assess clinically used duodenoscopes and whether this benchmark [ATP <200RLUs] for manual cleaning correlated with microbiological cultures obtained after HLD"	Duodenoscopes were sampled 20 times, including 18 undergoing reprocessing cycle twice and 6 undergoing reprocessing cycle three times due to persistently elevated ATP (≥200 RLU). After the initial reprocessing cycle, 12/20 (60%) had positive cultures. An ATP cutoff of <200 RLU had a sensitivity of 30% and specificity of 53% to detect bacterial contamination on the instrument channel or elevator mechanism.

ATP, adenosine triphosphate; *CFU*, colony forming unit; *ERCP*, endoscopic retrograde cholangiopancreatography procedure; *HLD*, high-level disinfection; *IQR*, interquartile range.