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New Perspectives on Development of Curative Strategies for Chronic Hepatitis B

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A functional cure of chronic hepatitis B defined as sustained hepatitis B surface antigen loss after finite course of therapy is rarely achieved with current therapy but is the goal of novel treatments. Understanding the virological and immunological mechanisms of hepatitis B virus persistence has enabled the identification of novel treatment targets, drug discovery, and the evaluation of novel agents in clinical trials. Lessons were learned from early phase 1 and phase 2 trials regarding the antiviral activity and safety profile of these agents. There is a strong rationale to combine agents to reduce viral replication, reduce viral antigen load, invigorate immune responses, and induce specific adaptive immune responses. Nucleos(t)ide analogs will likely remain an essential backbone of future combinations to control viral replication and prevent resistance to antiviral drugs. In this review, we discuss perspectives on approaches to achieving functional cure, with a review of virological and immunological strategies, highlighting challenges and unresolved questions with the various attempts to achieve cure, as well as exploring alternative

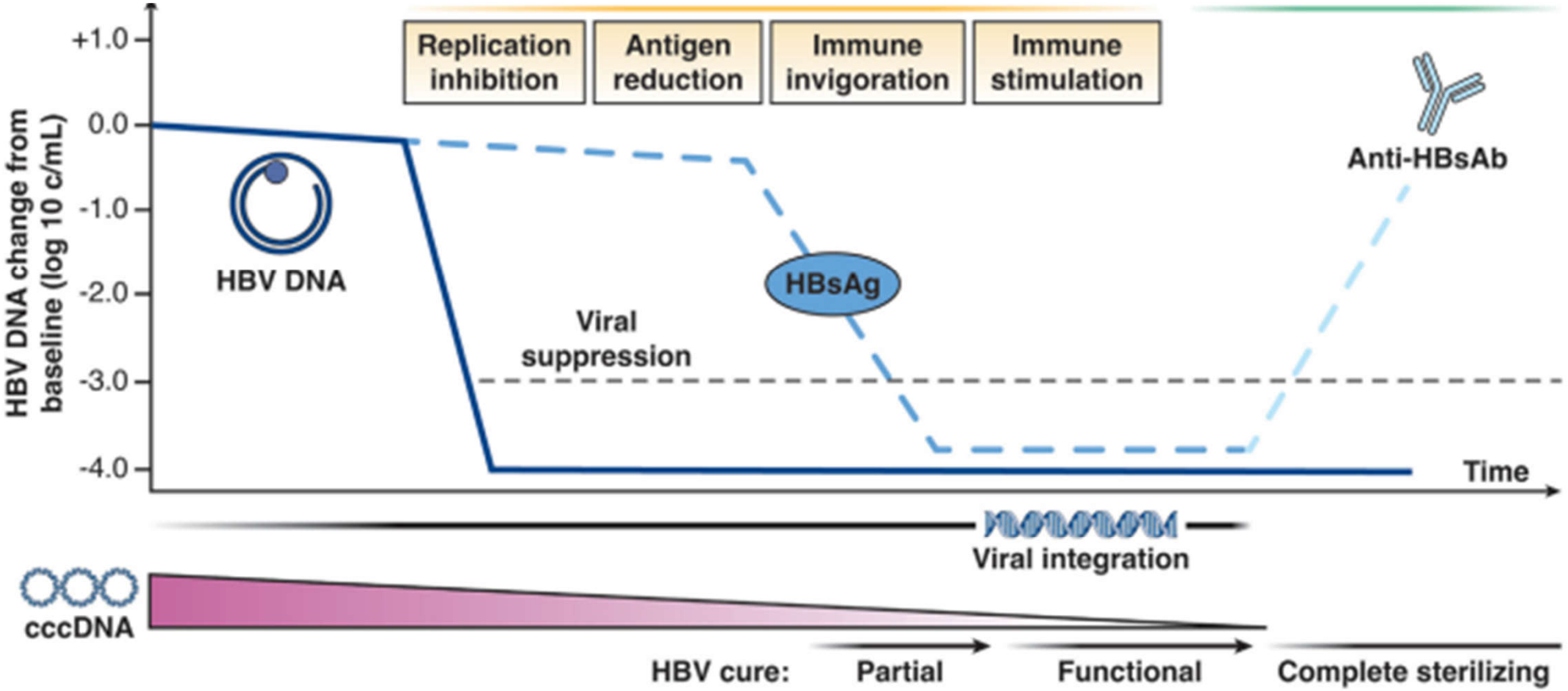

Figure 1. The different classes of direct acting antivirals and immune modulators. Potential for combination therapy based on complementary mode of action on the HBV life cycle and host immune responses. HBsAb, hepatitis B surface antibody.

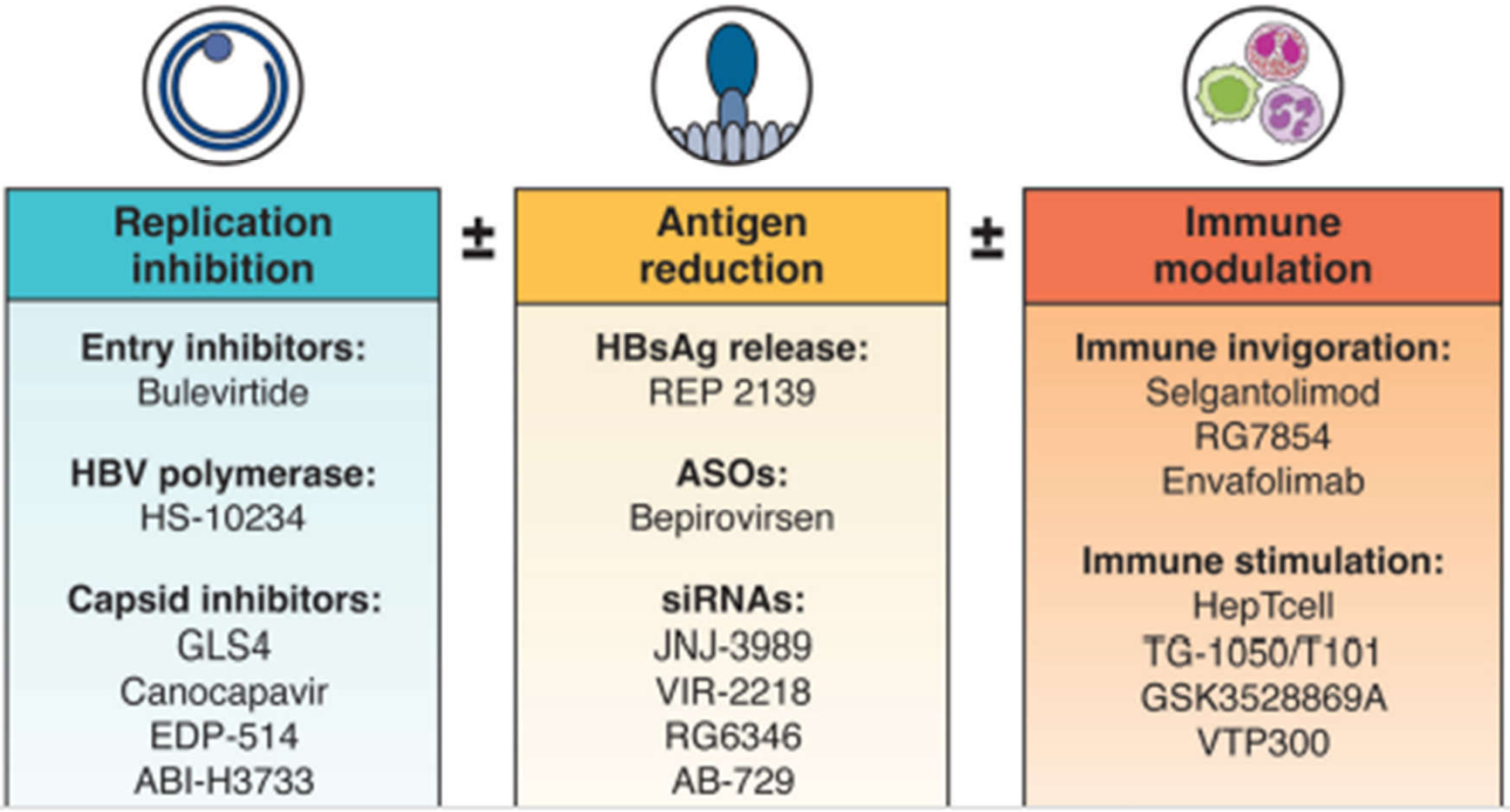

Figure 2. Potential trial strategies to achieve partial or functional cure based on viral replication inhibition, decrease in viral antigen burden, invigora-

toward the ultimate goal of functional cure.

Concluding Perspectives

Multiple new antivirals and immunomodulatory therapies aimed at HBV cure are in clinical trials, and many more are in development. While the previous goal of 30% sustained HBsAg loss after 1–2 years treatment has not yet been achieved, several new therapies have achieved functional cure in a lower percentage of patients in phase 2 clinical trials, and results of phase 3 trials are eagerly awaited. To improve efficiency, platform trials in which multiple drugs can be tested using the same infrastructure and the same controls and in which patients are directed to treatment arms that are the best fit based on clinical, virological, and immunological characteristics should be employed. Stringent safety monitoring and detailed plans for managing adverse events must be in place, particularly given the excellent safety profile of NA. Sensitive and reliable assays to assess the cccDNA reservoir, the source of circulating HBsAg, and immune response to HBV should be developed in parallel with the new therapies.[80]

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EDITORIAL

Improving prediction of hepatocellular carcinoma in chronic hepatitis B by machine learning: Productive relationship of medicine with computer science

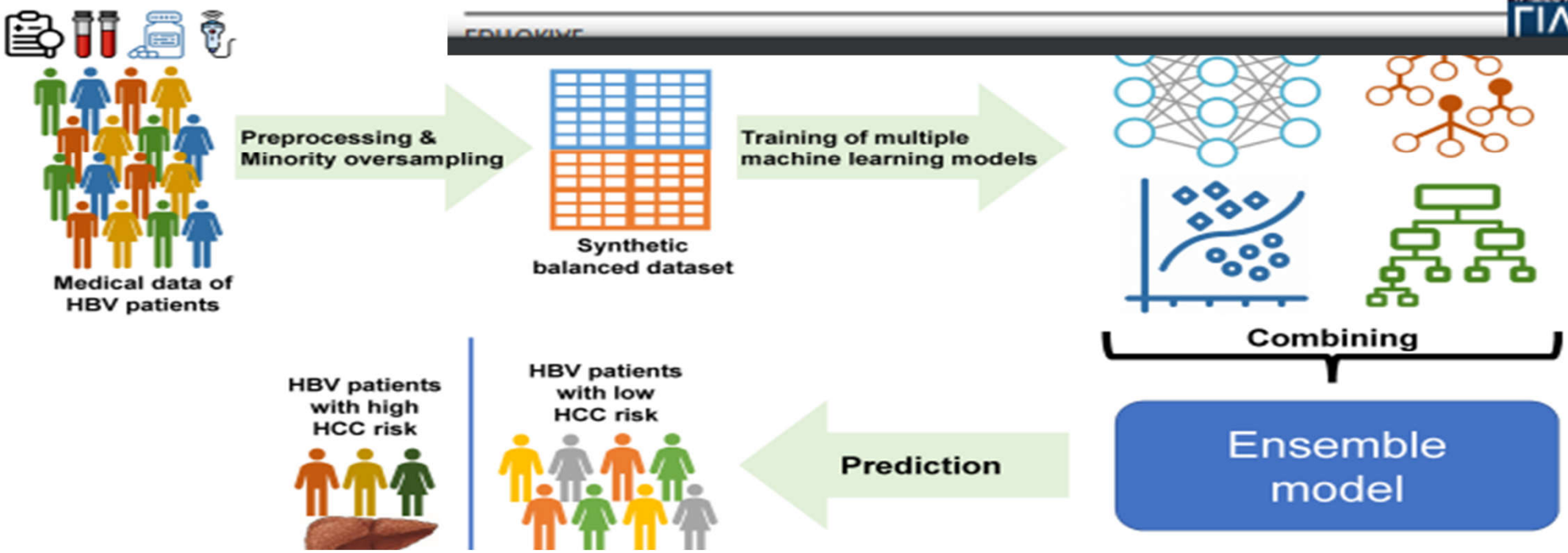
using common clinical and laboratory parameters (Figure 1). In the future, it is expected that more and more HCC risk scores based on machine-learning and deep-learning algorithms, which may provide even higher accuracy but require a larger data set, will be developed. These may better guide us in selecting high-risk patients for HCC surveillance while safely exempting patients with minimal risk from HCC surveillance in the next few years. Nevertheless, several barriers exist before we can largely utilize artificial intelligence models in routine clinical practice. Firstly, to demonstrate the generalizability of models, further external validations using independent cohorts are necessary. However, some of the machine-learning models developed were not accompanied by source code or user-friendly online calculators. This inevitably hinders external validations. Also, it would be difficult to compare different machine-learning models on performance. Secondly, many machine-learning algorithms are available and they can have different performances depending on the data. In the existing literature, researchers tend to preselect one or some machine-learning algorithms for investigation rather than examining a larger set of available machine-learning algorithms without preselection. This approach may have confined the performance of the final model

apply the model decision to their patients. The explainability of machine-learning models commonly relies on different metrics of feature importance, which can tell us which parameters contribute the most to the decision by the models. Interestingly, creatinine appeared to be the most heavily weighted parameter in the novel machine-learning model.[20] While creatinine is not a traditional risk factor for HCC, Lee, Kim and colleagues explained that patients with cirrhosis tend to have worse kidney function due to portal hypertension. Meanwhile, patients with chronic kidney disease also have a high risk of developing HCC as they share common risk factors related to vasoactivity, environmental toxins, viral hepatitis and metabolic diseases. These two reasons probably contributed to the high feature importance of creatinine in their model.

Despite all these challenges, nowadays we are more convinced by the power of artificial intelligence as they have become indispensable in our daily lives. We anticipate that with a better understanding of the underlying logic and mechanism of the models, artificial intelligence will have a positive impact on HCC risk prediction and patient management.

Chronic hepatitis B virus (HBV) infection is a global public health problem affecting over 296 million people, with a global prevalence of 3.8%.[1] Current clinical guidelines recommend potent HBV antiviral treatment in CHB patients who are at risk of disease progression to cirrhosis, hepatocellular carcinoma (HCC) and hepatic decompensation.[2-4] Nucleos(t)ide analogues (NA) including entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide are the first-line oral antiviral therapies that effectively suppress HBV replication and decrease the risk of developing HCC in CHB patients.[5,6] Nevertheless, the risk of HCC is not completely abolished in CHB patients receiving NA therapy.[5,7] Therefore, the Hepatology field has been devoted to better predicting the risk of HCC in NA-treated CHB patients using various risk scoring systems,[8-13] aiming to inform strategies on HCC surveillance.[14,15] In recent years, machine-learning and deep-learning models have been popularized in different domains for enhancing the prediction power over traditional statistical regression models. This needed a paradigm shift in our understanding to deal with the prediction of disease complica-

will not develop HCC has a high yet unmeaningful accuracy of 92.8% as only 7.2% of patients developed HCC in 5 years. SMOTE avoids this undesirable situation by overrepresenting the patients with HCC in the machine-learning algorithm. Machine-learning algorithms have the advantage of considering all potential interactions among clinical parameters and do not use predefined hypotheses. After SMOTE, three popular machine-learning algorithms namely random forest, eXtreme Gradient Boosting (XGBoost) and logistic regression were applied to predict HCC using common clinical and laboratory information including age, gender, height, weight, platelets, albumin, total bilirubin, cirrhosis, diabetes, hypertension, hepatitis B e antigen positivity, HBV DNA, aspartate aminotransferase, alanine aminotransferase, alpha-fetoprotein, international normalized ratio, sodium, creatinine and the type of antiviral therapy. All hyperparameters of the machine-learning algorithms were optimized via random grid search involving stratified 5-fold cross-validation using the selection metric of the area under the receiver operating characteristic curve (AUC). The final machine-learning model was a soft voting ensemble model that combined the


Medical data of HBV patients
Preprocessing & Minority oversampling
Synthetic balanced dataset
Training of multiple machine learning models
Combining
Ensemble model
Prediction
HBV patients with low HCC risk
HBV patients with high HCC risk

Cancer Detection and Diagnosis Research

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the presence of cancer in the body and assessing the extent of disease—whether it is the initial diagnosis of a cancer or the detection of a recurrence. For some cancers, this definition can be expanded to include identifying precancerous lesions that are likely to become cancer, providing an opportunity for early intervention and preventing cancer altogether.

Unfortunately, effective screening tests for early detection do not exist for many cancers. On the other hand, studies have strongly suggested that, in addition to benefits, screening has downsides. There is the risk of overdiagnosis and overtreatment—detecting and treating people for cancers that would not threaten life or cause symptoms. Overdiagnosis means that patients are exposed unnecessarily to the potential physical harms of unneeded and often invasive diagnostic tests and treatment, as well as to the psychological stresses associated with a cancer diagnosis.

Early detection is a proven strategy for saving lives from cancer. Some patients whose cancers are detected and treated early may have better long-term survival than patients whose cancers are not found until symptoms appear.

Once the presence of cancer is verified, diagnostic tools that identify specific molecular

2) Identify and validate new biomarkers that can be used for the early detection and diagnosis of cancer and its precursors

The use of tumor biomarkers (specific proteins or other molecules in tumor specimens) and imaging biomarkers (radioactive substances taken up by tumors and visualized through PET scans) is widespread in oncology. NCI's objectives in developing additional biomarkers include:

- Identifying novel biomarkers, such as changes in cellular metabolites measured in exhaled breath
- Identifying and validating new types of blood-based biomarkers, such as cell-free DNA fragmentation patterns
- Identify new types of tissue-based biomarkers based on differences in the electrical or mechanical properties of cells or tissues

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Original Article

The Diagnostic Significance of the BI-RADS Classification Combined With Automated Breast Volume Scanner and Shear Wave Elastography for Breast Lesions

Tiantian Ren MD, Xiaoran Li BD, Yu Xiang BD, Yuanyuan Zhang BD, Mingfei Jiang MD, Chaoxue Zhang MD, PhD

The incidence of the retraction phenomenon on ABVS images of the malignant group was significantly higher ($P < .001$) than that of the benign group. The specificity, sensitivity, and positive and negative predictive values of the BI-RADS classification were 88.72, 79.38, 83.70, and 85.50%, respectively. BI-RADS plus SWE-Max exhibited enhanced specificity, sensitivity, and positive and negative predictive values of 88.72, 92.78, 85.70, and 94.40%, respectively. Similarly, when BI-RADS + ABVS was utilized, the sensitivity and negative predictive value increased to 95.88 and 96.40%, respectively. BI-RADS + ABVS + SWE possessed the highest overall sensitivity (96.91%), specificity (94.74%), and positive (93.10%) and negative (97.70%) predictive values from all four indices.

Conclusion

ABVS and SWE can reduce the subjectivity of BI-RADS. As a result, BI-RADS + ABVS + SWE resulted in the best diagnostic accuracy.

Complications of diagnostic upper Gastrointestinal endoscopy: common and rare – recognition, assessment and management

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ABSTRACT

A clear understanding of the potential complications or adverse events (AEs) of diagnostic endoscopy is an essential component of being an endoscopist. Creating a culture of safety and prevention of AEs should be part of routine endoscopy practice. Appropriate patient selection for procedures, informed consent, periprocedure risk assessments and a team approach, all contribute to reducing AEs. Early recognition, prompt management and transparent communication with patients are essential for the holistic and optimal management of AEs. In this review, we discuss the complications of diagnostic upper gastrointestinal endoscopy, including their recognition, treatment and prevention.

KEY POINTS

⇒ Prevention of complications can be optimally achieved through appropriate patient selection and fostering a safe team working environment.

⇒ Cardiopulmonary-related events account for over 60% of unplanned events during endoscopy and can be minimised by safe sedation and preprocedure risk assessment.

⇒ Early recognition and prompt management is essential to minimise downstream harm once a complication has occurred.

⇒ Management of a complication is often multidisciplinary requiring early involvement of surgical and radiological teams.

⇒ Reporting of complications through departmental meetings and audits is essential and includes a timely apology and duty of candour letter.

⇒ Mechanisms for debriefing, learning and professional support should be available to clinicians involved in a procedure-related complication.

SUMMARY

AEs are an inherent but uncommon part of performing endoscopy. It is essential that endoscopists have a clear understanding of what the potential AEs are for the procedures they perform, what steps are needed to reduce the risk of their occurrence, how to recognise them and how to manage them appropriately. This review provides an

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