Modeling Lengthy Work-ups in Gastrointestinal Bleeding

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Multiple procedures and medical devices are being used in a complex interplay to diagnose and treat gastrointestinal bleeding. The aim of the study was to develop a mathematical model that helps in estimating the average number of procedures to be expected in the general management of gastrointestinal bleeding. The modeling process serves as an example of how mathematical analysis in general can be used to answer unresolved clinical questions, lead to a better understanding of the underlying influences in a disease process, and provide a starting point for future clinical trials. The analysis uses a Markov chain to model the transition probabilities among consecutive interventions used to find and treat a bleeding site. The results show that starting a work-up of gastrointestinal bleeding with an esophagogastroduodenoscopy will lead on average to 2.69 procedures per patient. Of these expected procedures, 1.46 will be esophagogastroduodenoscopies, 0.69 colonoscopies, 0.25 video capsule endoscopies, 0.14 double-balloon enteroscopies, and 0.14 procedures from interventional radiology. Management chains initiated with a colonoscopy result in similar outcomes. Among 10,000 simulated individual patients, the number of procedures varies between 1 and 16 consecutive procedures, with 95% of all patients undergoing 6 procedures or less. The outcomes of the model suggest that the published success rates of endoscopic and radiographic procedures are overly optimistic. The results also point to the need to generate clinical data through future studies that more reliably account for treatment failures and the interchange among various complementary diagnostic modalities.

Keywords: Gastrointestinal Bleeding; Markov Chain; Medical Decision Analysis; Modeling.

Mathematical models have been used in gastroenterology to predict disease behavior or the outcomes of competing medical policies. Modeling is especially helpful in instances when insufficient clinical data exist and when it is difficult to generate the data through randomized trials or epidemiologic studies, because such studies are too expensive, time-consuming, or difficult to conduct. There may also be ethical reservations, insufficient number of patients, or otherwise limited resources that preclude an empirical approach. Screening and surveillance of precancerous lesions in the gastrointestinal tract represent typical examples where models of Markov chains have been widely used to test and compare different management strategies.[1–4] In a different venue, mathematical modeling of disease is also helpful in conceptualizing disease behavior and understanding how multiple interacting forces influence the outcomes of medical intervention. The results of these latter mathematical analyses can then prepare the ground for future epidemiologic studies, clinical trials, or experimental research.[5,6] Although such theoretical approaches to pursue research questions are frequently used in physics, economics, and biology, they are still relatively uncommon in medicine or gastroenterology.

A large proportion of all endoscopic procedures are performed to find and treat suspected gastrointestinal bleeding sites. This typical pursuit in gastroenterology is used as an incentive to develop a model that would explain the variation in length among different work-ups. Imagine a 65-year-old patient with maroon-colored stool and a recent drop in his hematocrit. A gastroenterologist is being consulted to help diagnose and treat the gastrointestinal bleeding. What is the expected resource utilization in managing the patient's illness? Generally, one hopes that the bleeding site will be found and treated with 1 or 2 endoscopic procedures. A brighter color associated with hematochezia is suggestive of a more distal bleeding site. Accordingly, a gastroenterologist will decide to start the endoscopic work-up with a colonoscopy, followed by an esophagogastroduodenoscopy (EGD) in case of inconclusive evidence. Vice versa, a darker-stained stool would direct the gastroenterologist to begin the work-up with an EGD first to be possibly followed by colonoscopy.[7,8]

Although such strategy achieves success in the majority of patients, for various reasons it is not uncommon for a patient to occasionally undergo many more than just 1 or 2 procedures. Because the EGD and colonoscopy may both fail to reveal the bleeding site, other means, such as video capsule endoscopy, double-balloon enteroscopy, or procedures by interventional radiology, become necessary to deal with the problem. Poor visualization because of residual blood clots and incomplete bowel preparation may necessitate repeat procedures. Similarly, unsuccessful hemostasis would lead to a repeat

Abbreviations used in this paper: **CT, computed tomography; EGD, esophagogastroduodenoscopy.**

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endoscopy. The initial endoscopy may reveal a lesion of questionable benignity, and a repeat procedure is scheduled to ascertain its relevance with regard to the bleeding. Capsule endoscopy may reveal a bleeding site that becomes subsequently treated by using push enteroscopy or double-balloon enteroscopy. During upper endoscopy a clip is placed adjacent to the bleeding site to orient interventional radiology where to embolize the feeding vessel. The variety of such scenarios abounds. In instances when localization and treatment are difficult, a patient may end up with multiple EGDs, colonoscopies, capsule endoscopies, followed by double-balloon enteroscopy or angiography.

In general, physicians committed toward a particular procedure tend to be overly optimistic in estimating its success rate. This phenomenon also applies to gastroenterologists, who as experts in gastrointestinal endoscopy underestimate the number of interventions it will take to successfully diagnose and treat a bleeding site. Occasionally one encounters patients who undergo 10 or more consecutive procedures to localize and treat an elusive bleeding source inside the gastrointestinal tract. How is this possible? The present analysis serves to understand the mechanisms underlying such occurrences and provide an estimate of the average procedure number to be expected in the general management of gastrointestinal bleeding. It also serves as example of how mathematical modeling of the medical management process can be used to tackle unresolved clinical questions and prepare the ground for future clinical studies.

Markov Chain Model

The problem of lengthy work-up in gastrointestinal bleeding is phrased in terms of a Markov chain model. For the present analysis, consider a patient with occult or overt gastrointestinal bleeding of unknown etiology. In the baseline model of the present analysis, 5 possible medical procedures are considered in the work-up of gastrointestinal bleeding from an unknown source, that is, EGD, colonoscopy, video capsule endoscopy, double-balloon enteroscopy, and interventional radiology. Each individual procedure could lead to success in finding and treating the bleeding site or just be the final intervention in a sequence of several previous procedures. Otherwise, each procedure would also be followed by another procedure, including a repeat procedure of the same kind. Figure 1 depicts a graphical representation of the Markov chain model with 5 different procedures used in the management of gastrointestinal bleeding. The transition probabilities among the individual procedures are depicted by the corresponding matrix in the upper part of Table 1. The probabilities were estimated on the basis of published systemic reviews or meta-analyses that reported success rates associated with EGD, colonoscopy, video capsule endoscopy, double-balloon enteroscopy, computed tomography (CT) angiography, and nuclear scan.[9–17] Each row represents a different procedure. For example, in 30% of instances, EGD leads to success or completion of the work-up. In 10% of instances, the EGD is followed by another EGD, in 40% by colonoscopy, in 10% by capsule endoscopy, in 5% by double-balloon enteroscopy, and in 5% by a procedure of interventional radiology. The transition probabilities associated with an initial colonoscopy, video capsule endoscopy, double-balloon endoscopy, or interventional radiology are listed in the third through sixth rows, respectively. The transitions of each row add up to 100%. The first row (and first column) of the matrix contain only one element, that is 100%, indicating the absorbing state of success or work-up termination. Once a patient has transitioned into this state, no further procedures are being scheduled. The analysis is applied to a cohort of patients with unknown gastrointestinal bleeding site without further characterization.

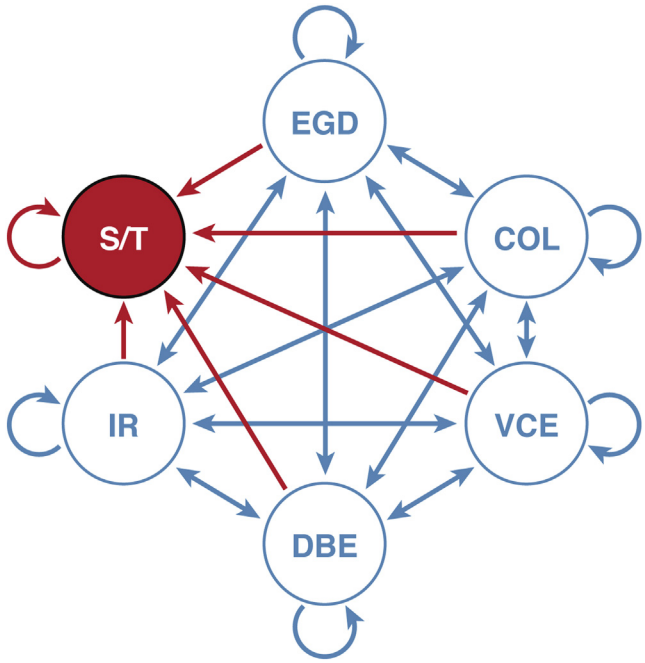

Figure 1. Markov chain model of 5 different procedures in work-up of gastrointestinal bleeding. COL, colonoscopy; DBE, double-balloon enteroscopy; IR, interventional radiology; S/T, success/termination; VCE, video capsule endoscopy.

Calculating the Model

The overall appearance of the transition matrix corresponds with a finite Markov chain of 6 states, one being an absorbing state. The shaded area represents the sub-matrix T of the 5 transient states (as opposed to the single absorbing state). According to the laws of probability theory, the expected number of procedures can be calculated from the matrix $E = (I - T)^{-1}$.[18,19] (In this formula, I represents the identity matrix, with 1 chosen