

# Competing Influences in the Management of Gastrointestinal Bleeding

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**OBJECTIVES:** Management of gastrointestinal (GI) bleeding centers on the issues of location, type of mucosal lesion, effects of anticoagulation, diagnosis, and therapy. Each one of these five individual factors is affected by multiple interactions with the other coexisting factors. The aim of the present study is to analyze which set of factors ultimately exerts the largest and most lasting influence on the disease process.

**METHODS:** The interactions among the five contributing factors are analyzed using a transposed Markov chain model.

**RESULTS:** The analysis reveals that, in declining order, location, anticoagulation, and type of lesion exert the largest influence on the disease process. Under steady state conditions, their magnitudes of influence are 50, 33, and 17%, respectively. The other two factors, diagnosis and therapy, result as a consequence of the aforementioned three primary factors, but do not exert any major influence themselves. The outcome of the analysis remains robust to multiple wide-ranging variations in the assumptions underlying the model.

**CONCLUSIONS:** The model of a transposed Markov chain translates an initially bewildering array of interacting influences into a coherent and transparent model of gastrointestinal bleeding.

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**Subject Category:** Stomach

## INTRODUCTION

A large fraction of gastrointestinal endoscopy is devoted to gastrointestinal (GI) bleeding.<sup>1,2</sup> The management of GI bleeding strives to address few key questions: where is the bleeding located: lower or upper GI tract or small intestine? What type of lesion is responsible for the bleeding? Do exogenous risk factors, such as treatment with non-steroidal anti-inflammatory drugs or anticoagulation medications, contribute to the bleeding? And how can the bleeding site be found, diagnosed, and treated? Management of the GI bleeding, thus, centers on the issues of location, lesion type, anticoagulation, diagnosis, and therapy. Each of these five individual factors is affected by interactions with the other four factors. For instance, the location within the GI tract influences the type of potential lesion, the effects of anticoagulation, as well as the means of diagnosis and therapy. Similarly, the lesion type influences the effects of anticoagulation, as well as the means of diagnosis and therapy. With many different interactions possible among the various factors, the question arises which set of factors ultimately exerts the largest and most lasting influence on the disease process. The aim of the present study is to utilize Markov chain analysis to address this question.

## METHODS

Figure 1 contains a model of the five key factors that underlie the management of gastrointestinal bleeding. Each arrow indicates the influence of one factor (at which the arrow originates) on a second factor (at which the arrow points). The curved arrows indicate instances of influences, where the

magnitude of a given factor is affected by intrinsic conditions unrelated to outside involvement. For instance, the location of a bleeding site within the gastrointestinal tract may be primarily influenced by the underlying pathophysiology and some local factors leading to mucosal breakdown or injury, but with little contribution from the outside except, possibly, for the effects of anticoagulation.

The model shown in Figure 1 is analyzed similarly to a regular Markov chain. In a regular Markov model chain, the percentage values associated with all outgoing arrows of any given Markov state add up to 100%. In contradistinction with a regular Markov chain, in the present model, the percentage values of all incoming arrows of any given Markov state add up to 100%. Rather than being concerned with the sum of resources or patient flow leaving individual states (as in a regular Markov chain), the present model is concerned with the flow of resources or sum of influences that contribute to an individual state.

The features of any Markov chain can be also presented by a square matrix where the row and column labels represent the individual Markov states. The upper matrix in Table 1 provides a numerical representation of Figure 1. Each percentage value corresponds with an arrow starting at a row label and pointing at a column label. The entirety of factors contributing to a single factor is arranged within a column headed by the factor's name. The intrinsic influences are all contained in the diagonal of the matrix, highlighted by using a bold font. For each factor, the individual contributions add up to 100%. For instance, the first factor "location" is influenced 75% by itself and 25% by anticoagulation. "Lesion type" is influenced by location and anticoagulation 25% each, and

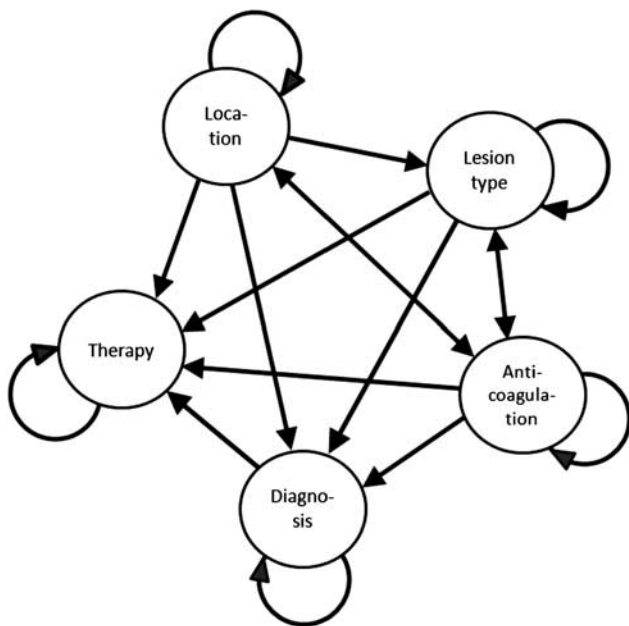
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then 50% by itself, again indicating that lesion type is determined mostly by intrinsic factors independently of outside influences. Similarly, the effect of anticoagulation on bleeding is partly dependent on the location and type of lesion, but mostly by intrinsic factors, such as the type of medication or extent of anticoagulation. Diagnosis is assumed to be equally affected by all factors, except for therapy. Lastly, therapy is assumed to be influenced mostly by intrinsic factors and then equally by all outside influences. In a set of multiple sensitivity analyses, the rates shown in the upper matrix of Table 1 have been varied over a broad range.

Whereas in the matrix of a regular Markov chain the row elements add up to 100%, in the matrix discussed above and shown in Table 1, the column elements add to 100%. This



**Figure 1** Markov chain model of five interacting factors in the management of gastrointestinal bleeding.

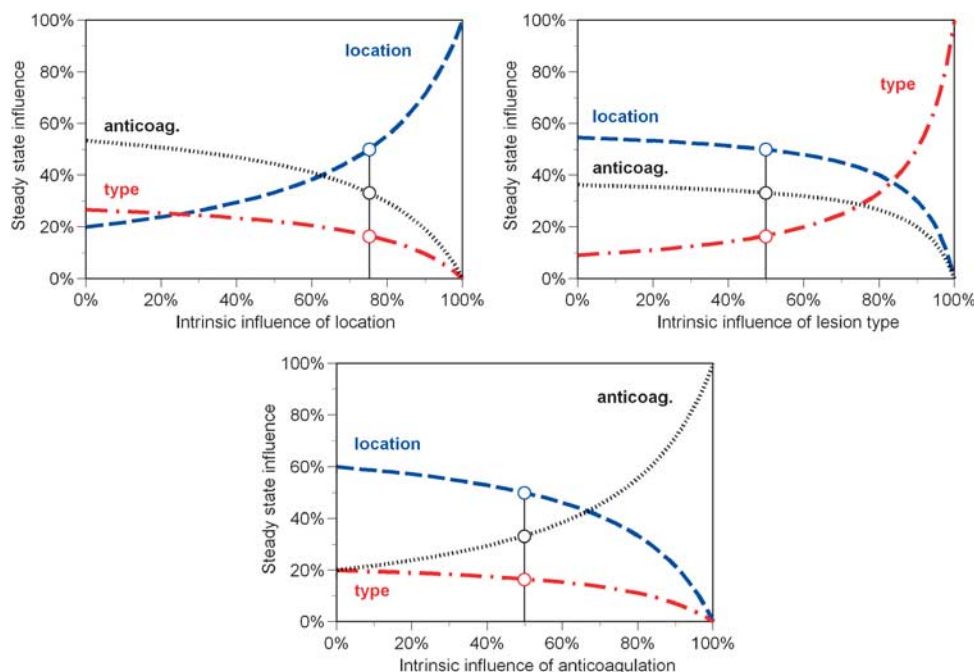
difference reflects the fact that in a regular Markov matrix the emphasis is placed on the outputs of each factor (adding up to 100%), whereas in the present analysis, the emphasis is placed on the inputs of each factor (again adding up to 100%). Mathematically, this type of matrix in the upper part of Table 1 corresponds with a transposed Markov matrix.<sup>3,4</sup> Otherwise, the mathematical analysis is the same for a transposed as for a regular Markov matrix.<sup>5-7</sup> The steady state of a transposed Markov matrix can be calculated by multiplying the matrix many times (> 32) with itself.

**RESULTS**

The bottom part of Table 1 contains the steady state of the initial influence matrix from above. In declining order, location, anticoagulation, and lesion type exert the strongest influence on the disease process. Under steady-state conditions, the magnitudes of influence associated with location, anti-coagulation, and lesion type are 50, 33, and 17%, respectively. This outcome remains largely unaffected by multiple changes to the influence matrix. For instance, changing the magnitude of any of the various influences on diagnosis or therapy does not alter this result. Figure 2 contains the results of a sensitivity analysis, in which the influences contributing to location, lesion type, and anticoagulation are varied over a broad range. In each separate analysis, the diagonal element indicating intrinsic influence is varied between 0 and 100% while adjusting the remaining extrinsic influences proportionately. For instance, if the intrinsic influence of lesion type is reduced from 50 to 30%, the extrinsic contributions of location and anticoagulation are both raised from 25 to 35%. In every analysis, shifting the baseline conditions to the left (towards low intrinsic influence) exerts relatively little effect on the magnitude of influence until extreme (and unlikely) conditions are reached. Similarly, shifting the baseline conditions to the right (towards high intrinsic influence) decreases the magnitude of influence by the other two factors, but leaves the order of relevance among the three influences largely unaffected unless rather extreme values are chosen.

**Table 1** Markov matrix of interacting influences in the management of gastrointestinal bleeding

	Location	Lesion type	Anti-coagulation	Diagnosis	Therapy	Sum	Proportional sum
<i>Matrix of interacting influences</i>							
Location (%)	75	25	25	25	15	165	33
Lesion type (%)	0	50	25	25	15	115	23
Anticoagulation (%)	25	25	50	25	15	140	28
Diagnosis (%)	0	0	0	25	15	40	8
Therapy (%)	0	0	0	0	40	40	8
Sum (%)	100	100	100	100	100	500	100
<i>Steady-state matrix</i>							
Location (%)	50	50	50	50	50	250	50
Lesion type (%)	17	17	17	17	17	83	17
Anticoagulation (%)	33	33	33	33	33	167	33
Diagnosis (%)	0	0	0	0	0	0	0
Therapy (%)	0	0	0	0	0	0	0
Sum (%)	100	100	100	100	100	500	100



**Figure 2** Sensitivity analysis of varying the intrinsic influences of location, lesion type, and anticoagulation and their effect on the steady state matrix. The vertical lines with the three dots represent baseline conditions of the influence matrix.

## DISCUSSION

The present analysis describes the interaction of multiple different contributing factors in the management of gastrointestinal bleeding. Using a transposed Markov chain model, the aim of the study has been to analyze, which of the many factors have a primary, and which ones have only a secondary role in the disease process and its management. The analysis reveals that, in declining order, location, anticoagulation, and type of lesion exert the strongest lasting influences. With regards to its impact, location supersedes the influence by all other factors, as it accounts for 50% of the overall problem. One-third of the management problem relates to the effects of anticoagulation. Of the three major factors, the type of lesion is associated with the smallest influence of only 17%. All other factors do not influence the disease process, but only result as a consequence of the other more influential primary factors.

In a regular Markov chain, the outputs of each state add up to 100%, and the analysis is focused on a future steady state to estimate the final allocation of resources or patients among the various states. In the transposed Markov chain of the present analysis, the inputs of each state add up to 100%, and the analysis is focused on calculating a steady state to estimate, which states contribute most to the overall flow of resources or influences. In loose terms, whereas a regular Markov chain aims to answer the question of “how will it end in the long run?” the transposed Markov matrix aims to answer the question of “how did it start and what are its root causes?” The analytical approach of using a transposed Markov chain provides a means to capture an initially bewildering array of influences among different interacting factors and distill those influences that matter most, and ultimately drive a disease process.

The aim of the present model is to depict the general features of managing gastrointestinal bleeding. The model is

not meant to provide a prescription on how to best treat individual patients, but provide a description of the universal interactions that shape the underlying disease process and its management. Individual patients are characterized by different age, comorbidities, particular bleeding types, and other specific risk factors, which may affect the magnitude of influences chosen in the matrix in Table 1. The influence of diagnosis on therapy, for instance, may be limited by severe coagulopathy of end-stage liver disease. Similarly, anticoagulation may affect therapy more profoundly in patients with placement of a recent stent or artificial heart valve than in patients on a low-dose aspirin for primary cardiovascular prophylaxis. As shown by the sensitivity analysis, however, the major characteristics of the model remain valid over a broad range of assumptions built into the model.

At first sight, it may seem strange that in the interplay of multiple factors, location, anticoagulation, and lesion type have the biggest role, whereas diagnosis and therapy exert little, if any, influence. This outcome, however, has been proven to remain robust under multiple wide-ranging changes in the assumptions underlying the present model. Several essential features of the Markov matrix may help to explain this seemingly strange result. As shown by Figure 1 and its corresponding influence matrix in Table 1, diagnosis and therapy are mostly influenced by other factors in the model, but exert very little, if any, influence themselves on any of the other factors. By contradistinction, location exerts a strong intrinsic influence, as well as multiple extrinsic influences on all other factors. Anticoagulation is similarly characterized by a relatively strong intrinsic influence and multiple extrinsic influences on all other factors of the model. Lastly, lesion type also interacts with all but one of the other factors. In the final steady-state model, therefore, these latter influences are shown to be the primary driving forces. This result of the

analysis must not be misinterpreted to mean that diagnosis and therapy are generally irrelevant in the clinical outcome of gastrointestinal bleeding. Obviously, both are key aspects in trying to achieve the ultimate management goals of hemostasis and cure, but in the overall disease process, both diagnosis and therapy follow as a consequence of other prior and more basic influences rather than represent driving forces of the disease process in their own right.

The results of the present analysis are confirmed by general clinical practice, which is focused on localizing the lesion, eliminating risk factors, such as therapy with non-steroidal anti-inflammatory drugs or anticoagulation, and delineating the nature or type of lesion that causes the bleeding. From these given pre-conditions, the diagnostic and therapeutic means follow, which are utilized subsequently in disease management to find and stop the bleeding. The present analysis provides a means to conceptualize such interactions among a multitude of contributing factors and express these interactions in mathematical terms. The transposed Markov chain, thus, translates an initially bewildering array of interacting influences into a coherent and, ultimately, relatively simple and transparent mathematical model. The model reveals that management of gastrointestinal bleeding is predominantly influenced by the location of the bleeding site within the gastrointestinal tract and the side effects of anticoagulation therapy, and—to a lesser extent—by the type of bleeding lesion.

#### CONFLICT OF INTEREST

**Guarantor of the article:** Amnon Sonnenberg, MD, MSc.

**Specific author contributions:** Amnon Sonnenberg: conception and design, mathematical analysis, and writing of manuscript.

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**Potential competing interests:** None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Management of gastrointestinal bleeding centers on the issues of location, type of mucosal lesion, effects of anticoagulation, diagnosis, and therapy.

### WHAT IS NEW HERE

- ✓ Using a transposed Markov chain model, the decision analysis reveals that, in declining order, location, anticoagulation, and type of lesion exert the largest influence on the disease process of gastrointestinal bleeding.
- ✓ The transposed Markov chain provides a novel decision tool to distill from a bewildering array of influences the ones that matter most in a complex disease process.

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