SCINTIGRAPHIC EVALUATION OF ACUTE LOWER GASTROINTESTINAL HAEMORRHAGE: CURRENT STATUS AND FUTURE DIRECTIONS.

1,2,3Geoffrey M Currie, M MedRadSc, M AppMngt, MBA, PhD
1,2,3Hosen Kiat, MBBS
1,2,3Janelle M Wheat, BAppSc, M MedRadSc, DHlthSc

1School of Dentistry and Health Sciences, Charles Sturt University, Wagga Wagga, Australia.
2Centre of Research in Complex Systems (CRiCS), Charles Sturt University, Australia.
3Australian School of Advanced Medicine, Macquarie University, Sydney, Australia.

There are no conflicts of interest for any of the authors.
Each author contributed significantly to the draft development, critical revision and refinement of the manuscript.
No funding sources were used in the development of this manuscript.

Correspondence:
Geoff Currie
School of Dentistry and Health Sciences
Locked Bag 588
Charles Sturt University
Wagga Wagga 2678
Australia
Telephone: 61 2 69332822
Facsimile: 61 2 69332866
Email: gcurrie@csu.edu.au
ABSTRACT
This review examines the role and limitations of scintigraphic evaluation in acute lower gastrointestinal haemorrhage. A detailed discussion of methods for improving diagnostic outcomes is provided. Techniques and recommendations are offered for optimisation of red blood cell scintigraphy for earlier detection and more accurate localisation of acute lower gastrointestinal haemorrhage.
INTRODUCTION

Gastrointestinal haemorrhage presents in a range from benign, self limiting bleeding through to catastrophic, life threatening blood loss (1). Bleeding can originate at any point along the gastrointestinal tract (GIT) and 20% to 25% of patients admitted with gastrointestinal haemorrhage have a lower GIT origin (2). The risk of acute lower gastrointestinal haemorrhage (LGIH) increases with age (3). Ongoing population aging (absolute and relative increase in age) in developed countries is likely to be paralleled with a higher incidence of LGIH in the future.

Due to the intermittent nature of acute LGIH the detection and localisation of bleeding sites is often difficult which may lead to a delay in treatment of this potentially life threatening condition (4). Successful management of patients with acute LGIH is reliant on the early diagnosis and accurate localisation of the bleed site (2). While 85% of LGIH patients stop bleeding spontaneously and, indeed, cessation of active bleeding may have occurred prior to the patient presenting for clinical evaluation, it is prognostically important to identify the remaining 15% of patients who are at a higher risk and in whom there are likely to be benefits of timely intervention management (2). Therapeutic strategies for acute LGIH are based on both the bleed location (or suspected location) and the rate of bleeding. There are three main interventional approaches; colonoscopy, angiography and surgery.

A variety of diagnostic modalities are now clinically available to assist clinicians in detecting and the localization of the source of LGIH. In the clinical realm there are currently three main options for detection and localisation of LGIH sites; colonoscopy, angiography and technetium-99m (99mTc) red blood cell (RBC) scintigraphy. Among the earliest diagnostic tools is 99mTc RBC scintigraphy (5). Despite the well documented strengths of 99mTc RBC scintigraphy in acute LGIH, only 10-15% of patients presenting with LGIH are investigated with Nuclear Medicine scintigraphy (3). This apparent under-utilization may reflect selective avoidance by clinicians due to either a relative lack of familiarity with or confidence in the application of 99mTc RBC scintigraphy in the assessment of acute LGIH.

Clinicians frequently need to choose between competing diagnostic modalities in the course of their clinical practice. By providing an up-to-date appraisal of the role,
strengths and limitations of scintigraphy consistent with the current and future capabilities of nuclear medicine science, this review aims to provide clinicians with a blueprint for the appropriate use of nuclear medicine scintigraphy in the management of LGIH. The blueprint provides a tool to improve clinician familiarity with the role and capability of scintigraphy, to provide clinicians with the confidence to request specific procedural requirements, and to instil clinicians with confidence in the scintigraphic findings to guide patient management.

SCINTIGRAPHIC EVALUATION OF ACUTE LGIH
The first documented use of scintigraphy in the evaluation of gastrointestinal haemorrhage was in 1977 using \(^{99m}\text{Tc}\) sulphur colloid \((5)\). The use of \(^{99m}\text{Tc}\) RBC scintigraphy followed in 1979 \((5)\). While each radiopharmaceutical has recognised advantages, \(^{99m}\text{Tc}\) tagged RBC is generally the agent of choice for acute LGIH in current nuclear medicine practice \((2,5)\). The procedural requirements are summarised in table 1.

Test efficacy:
The efficacy of \(^{99m}\text{Tc}\) RBC scintigraphy has been extensively evaluated \((2,4,6-8)\). Scintigraphy does, however, rely on the assumption that the patient is actively bleeding during the imaging procedure. Consequently, the standard measures of efficacy may be inappropriately applied to \(^{99m}\text{Tc}\) RBC imaging in the acute bleeder if a false negative is simply defined as a negative \(^{99m}\text{Tc}\) RBC scan in a patient who presented with symptoms of LGIH. Sensitivity for detecting active bleedings has been reported in the range 78.6% to 97% \((2,7-10)\). Conversely, specificity provides a useful indicator of the value of \(^{99m}\text{Tc}\) RBC imaging in the acute bleeder. Specificity has been reported in the range 70.4% to 100% \((2,7-10)\) with the lower ranges reflecting potential sources of false positive findings resulting from the high background radionuclide activity. Importantly, using surgical evidence as the gold standard, \(^{99m}\text{Tc}\) RBC imaging has been shown to accurately localise the bleed site in 88% to 97% of patients \((11,12,13)\). It has also been reported that a positive scintigram is associated with a five fold increase in likelihood that the patient would require surgery \((13)\). Surgical pathology was also used by Guitierrez et al. \((14)\) to demonstrate an 88% accuracy of localisation in acute LGIH with \(^{99m}\text{Tc}\) RBC scintigraphy. Based on their
study findings, the investigators \((13,14)\) concluded that nuclear medicine RBC scintigraphy should be the primary investigation in acute LGIH.

**THE STRENGTHS OF \(^{99m}\)Tc RBC SCINTIGRAPHY**

**Superiority over angiography and colonoscopy:**
\(^{99m}\)Tc RBC scintigraphy has been shown to be an effective diagnostic and prognostic tool in the evaluation of LGIH, and in many circumstances provides superiority over angiography and colonoscopy in localising bleed sites. In animal and experimental models, \(^{99m}\)Tc RBC scintigraphy has been shown to detect LGIH at bleeding rates as low as 0.04 to 0.1 ml.min\(^{-1}\) \((4,15-17)\) which is appreciably superior to the 1.0 ml.min\(^{-1}\) minimum bleeding rate of angiography \((4,16)\). \(^{99m}\)Tc RBC scintigraphy has also been shown to have greater sensitivity than angiography for detection of slow bleeding rates or chronic bleeding \((15)\). \(^{99m}\)Tc RBC scintigraphy allows examination of the entire lower GIT simultaneously and continuously \((2,17)\) over a period of time, affording the luxury of a 60 to 90 minute effective window of opportunity to detect active bleeding because the labelled RBCs remain in circulation for a protracted period. \(^{99m}\)Tc RBC imaging allows repeat imaging out to 24 hours which is useful for localising intermittent bleeding \((5,15)\). Angiography, in contrast, is limited, particularly in intermittent bleeding, by a narrow window of opportunity for detection corresponding to several minutes (3-4 minutes) following the contrast administration \((16,17)\).

**Prognostic Impact:**
Importantly, the use of \(^{99m}\)Tc RBC scintigraphy has been shown to provide relevant information that is of prognostic significance in the identification of those patients at high risk of recurrent bleeding and in whom more aggressive management is warranted \((2,17)\). Furthermore, the relatively simple nature of \(^{99m}\)Tc RBC scintigraphy minimises the potential delays between presentation and diagnosis, which may be experienced with colonoscopy or angiography due to the more complex nature of the latter two procedures. The time to diagnosis has been reported to be an important determinant of outcome in high risk LGIH \((15)\).
Safety profile:

$^{99m}$Tc RBC scintigraphy is cheap, low risk, non invasive, accurate, readily available and easily performed in acute illness with no associated morbidity (2,6,15). It should also be noted that the radiation burden to the patient is significantly lower using scintigraphy than angiography (5,18). A precise comparison of radiation doses, however, is difficult because separation of the diagnostic and therapeutic components of an angiogram is not practical, the actual angiographic dose vary between operators and the dose determinants differ substantially between individual circumstances.

Colonoscopy is often unsuccessful during active bleeding since, with the exception of slow bleeding rates, the blood can obscure the colonic lumen (15,17). Retrograde movement of blood in the colonic lumen can also mimic a more proximal bleeding origin. Colonoscopy during active bleeding is associated with higher risk, is more difficult and, thus, requires a more skilled operator (19). The colonic preparation required for colonoscopy can result in fluid overload or excess purging may cause dehydration and electrolyte imbalance (15,20). Peter and Dougherty (19) indicated that colonic preparation means a delay of four to six hours after admission prior to commencement of colonoscopy. The overall complication rate for colonoscopy is 1.3% and includes serious events such as perforation, haemorrhage, respiratory depression from over sedation in patients with lung disease, bacteraemia, vasovagal reactions, dehydration, volvulus, myocardial ischemic episodes, splenic laceration and explosion of combustible gases (15,21).

The disadvantages of angiography in acute LGIH are the availability of skilled staff on short notice, the risk associated with contrast administration and complications associated with the invasive nature of the procedure (15,22). The procedure is commonly regarded as expensive, hazardous and arduous (23). The overall complication rate of angiography is 2.0% (15,19,24) although there are significant variations between authors. Cohn et al. (25) reported an 11% complication rate for angiography in acute LGIH while Baldoff et al. (26) only reported a 2.1% complication rate. Other than coronary and intracerebral events other major reported complications of angiography include haematoma, femoral artery thrombosis, contrast reactions, renal failure and transient ischaemic attacks (20).
Cost comparisons:
The relative costs of scintigraphy versus angiography in the acute LGIH patient is approximately 1:3 in favour of cheaper scintigraphy (27). Importantly substantial greater cost saving comes in the ability of scintigraphy, when performed optimally, to reduce unnecessary angiograms, reduce empiric or ‘blind’ laparotomy and bowel resection, decrease mortality and morbidity and reduce the total health expenditure on patient management (27).

LIMITATIONS OF SCINTIGRAPHY

False positive studies:
A negative $^{99m}$Tc RBC scan may be seen as a failure despite the patient not actually bleeding during the procedure. Thus, a true negative might be viewed as a false negative; undermining perceived reliability and subsequent inclination to rely on scintigraphy. The variability in the specificity of $^{99m}$Tc RBC scintigraphy in acute LGIH reflects potential sources of false positive findings. Certainly, one of the more important challenges in strengthening the clinical utility of $^{99m}$Tc RBC scintigraphy in acute LGIH is minimising the impact of sources of false positive findings. False positive findings generally fit one of two categories; vascular structures or free $^{99m}$Tc pertechnetate (unlabelled $^{99m}$Tc or unattached to the RBCs).

Reliance on temporal coupling with the time of bleeding:
Traditionally, $^{99m}$Tc RBC scintigraphy was performed in an emergent fashion. While the current clinical practice of stabilising the patient prior to pursuing diagnostic evaluation is meritorious, the inherent delay often sees patients presenting well after cessation of bleeding and contributes to the number of negative scans. Indeed, anecdotal evidence suggests that many patients present for ‘elective’ $^{99m}$Tc RBC scintigraphy following discharge from hospital. Some clinical centres do not have the capacity to allocate 60 minutes for continuous dynamic imaging while others can not accommodate ‘on request’ imaging. This leads to suboptimal protocols and non emergent imaging times, both of which contribute to increased numbers of negative studies. Furthermore, after hours services are not as routinely offered as they once were.
Influence of bleeding rate on the accuracy of bleeding site localization:
A limitation of $^{99m}$Tc RBC scintigraphy is the movement of blood in both retrograde and antegrade directions, limiting the accuracy of localisation (2,5,22,28). A small volume of focal accumulation of blood might be readily detected while a larger volume of blood with rapid migration in the bowel lumen may not delineate the bleeding site (28). Regardless of bleeding rate, the minimum extravasated blood volume for detection by scintigraphy of acute LGIH is reported as 3.0 to 5.0 ml (16,22). Consequently, bleeding rates well in excess of the theoretical minimum detectable rates (0.1 ml.min$^{-1}$) may escape detection due to migration of blood away from the bleeding site before focal accumulation of the critical volume of blood (3-5 ml) required for detection. Furthermore, if the bleed started at a point after the commencement of image acquisition (eg. 45 minutes into a 60 minute acquisition), insufficient time might remain to allow focal accumulation of the minimum detection blood volume, even in the absence of intra-luminal migration of the blood.

REFINING SCINTIGRAPHY FOR ACUTE LGIH
With the exception of computer acquisition and new invitro RBC kits, acute LGIH scintigraphy has remained largely unchanged since it was first developed in 1977. The absence of technical and procedural advances consistent with more general advances in nuclear medicine and, indeed, competing imaging modalities, undermines clinical utility.

Improving the techniques employed for scintigraphic evaluation of acute LGIH is important to both improved patient management and enhanced resource management which could combine to make patient management more efficient and contribute to decreasing health care costs. There is a need for both technical developments and rigorous adherence to recommended protocol. A number of techniques aimed at improving scintigraphic evaluation of the acute bleeder will be discussed below.

Continuous Dynamic Sampling
Early imaging protocols used discrete (static) images at intervals as wide as five to 15 minutes (2). This sampling frequency may result in false negative studies or inaccurate localisation due to rapid movement of extravasated blood away from the bleed site in either antegrade or retrograde directions (2,15). Computer technology has
facilitated continuous imaging of the abdomen which has provided more accurate localisation of bleeding sites compared to static acquisitions (2,15). O’Neill et al. (15) believe that the success of $^{99m}$Tc RBC scintigraphy in acute LGIH hinges on strict adherence to continuous dynamic imaging techniques with a minimum sampling interval of one frame per minute. The dynamic data can be displayed in a continuous real time loop (cinematic display) to more accurately define the nature, origin and behaviour of an accumulation of activity; improving both sensitivity and specificity (15). Accurate localisation of the bleeding site relies on detection of the site of earliest accumulation of blood rather than simply the most proximal and the cinematic display of rapid dynamic data allows identification of retrograde and antegrade movement away from the actual bleed origin that may not be obvious with standard image assessment.

**Delayed Imaging**

In negative studies after 60 to 90 minutes of continuous dynamic imaging, delayed imaging at 6 to 24 hours post initial administration of $^{99m}$Tc RBCs might be considered. Delayed images are generally limited to categorising the severity of bleeding or confirmation that bleeding has occurred (both of which can be determined by physical examination) unless active bleeding occurs during the delayed imaging procedure (6,29). Thus, delayed imaging should be undertaken as a continuous dynamic series rather than static images. A second ‘top up’ radiopharmaceutical administration ($^{99m}$Tc RBC) might also be considered, particularly if an *invivo* blood label was not used for the initial study.

**Intervention**

Glucagon can be used in conjunction with $^{99m}$Tc RBC scintigraphy to improve detection and localisation of the bleeding site (29,30). It is a polypeptide produced by the pancreas and released to raise blood glucose levels (31). Glucagon has a similar action to the beta adrenoreceptor mediated actions of adrenaline and, thus, decreases contraction in the gut (decreases peristalsis) which causes stasis of colon transit (31). Glucagon may also cause an increase in blood pressure, increased cardiac contraction and vasodilation which combine to encourage bleeding. Interestingly, glucagon has the potential to potentiate the effects of oral anticoagulants, increasing the tendency to bleed. The standard dose of 0.25-2.0 mg is administered intravenously (30). Glucagon
has rapid onset with inhibition of motility with one minute of IV administration and a peak inhibition at just 2-4 minutes post IV (30). The duration, however, is brief at just 9-17 minutes (30). Consequently, the administration of glucagon should be considered either immediately preceding the administration of $^{99m}$Tc RBCs, at a point where bleeding is evident without an identified point of origin or immediately prior to the commencement of delayed imaging (eg. 24 hours). A minimum of 30 minutes of continuous dynamic sampling should follow glucagon administration.

**Hybrid Systems**

Scintigraphy provides sensitive physiological mapping yet suffers from a comparatively poor spatial resolution (anatomical definition) when compared to other diagnostic imaging modalities (eg. CT and MRI). The use of radionuclide enema (32) and tap water enema (33) represent less than successful approaches to provide an outline of the colonic anatomy and to improve bleed localisation. A promising approach that warrants further investigation might be to use image fusion software to co-register the scintigraphic data set with the high anatomic detail provided by computed tomography (CT).

SPECT/CT hybrid scanner technology affords the luxury of both $^{99m}$Tc RBC scintigraphy and the anatomical detail of CT (including potential detection of either the bleed or causative pathology). Indeed, a recent report demonstrated that SPECT/CT had an impact on scintigraphic results in 37% of acute LGIH studies (34). The article draws attentions to several key issues in the optimisation of SPECT/CT hybrid imaging for the detection and localisation of the bleeding site in acute LGIH:

1. There are two types of SPECT/CT systems. The first employs a rotating CT system that provides low resolution CT images primarily for the purpose of attenuation correction and localisation. These systems do not provide diagnostic quality CT images and, thus, have limited use in accurate localisation of acute LGIH and in defining causal pathology. This was the system utilised by Schillaci et al. (34). The preferred multi-slice spiral CT systems provide both attenuation correction yielding high resolution diagnostic quality images.

2. High resolution multi-slice CT systems incorporating 32 slices or more might allow simultaneous CT contrast angiography to be performed which,
combined with the $^{99m}$Tc RBC scintigraphy, could potentially provide an incremental improvement in localisation accuracy.

3. The SPECT/CT acquisition is undertaken at some time point after dynamic planar imaging has identified a bleeding source. The SPECT acquisition requires 10 to 15 minutes of data collection at various projections around the body. Thus, a bleed may move within the bowel lumen during this time or may not be present in each of the projection data sets which will produce reconstruction errors that undermine the accuracy of localisation. This might be addressed by employing glucagon to reduce intra-luminal transit of blood. Alternatively, multiple rapid dynamic SPECT acquisitions might permit generation of a single summed data set representing a period of intra-luminal blood stability.

4. Since the SPECT/CT study is performed after planar identification of a bleed, the bleed site identified on SPECT/CT may actually represent a pooling of blood at some point antegrade or retrograde to the actual bleeding site.

SPECT/CT presents an exciting opportunity to refine a procedure for incremental improvement in both diagnosis and localisation of acute LGIH. Perhaps the greatest potential of SPECT/CT technology has been overlooked in our collective haste to adopt cutting edge technology. A simpler and more effective approach might be to simply co-register (fuse) the planar dynamic $^{99m}$Tc RBC studies with the coronal projection CT ‘scout’ scan for improved localisation. The high resolution CT scan can then be more closely examined for causal pathology along the transverse plane corresponding to the first appearance of intra-luminal $^{99m}$Tc RBCs; independently of the SPECT data. This approach would provide very accurate localisation without the possible localisation errors associated with blood migration during SPECT.

Subtraction Scintigraphy

The use of subtraction scintigraphy in $^{99m}$Tc RBC evaluation of LGIH has been reported to improve contrast by a number of authors (6,29). Subtraction scintigraphy has also been employed to overcome interpretation difficulties associated with the higher background activity in $^{99m}$Tc RBC evaluation of LGIH (35). Subtraction scintigraphy allows removal from the image those structures that are either
superimposed on a bleed site (potential false negative) or concentrate $^{99m}$Tc RBC (potential false positive). A number of methods can be employed for subtraction scintigraphy and selecting the best method is crucial to incremental improvement in detection and localisation. Methods employing a single reference image (either the first image or a summation of images) are confounded by changes (physical or physiological) occurring during the course of imaging.

Sequential subtraction methods (subtraction of each image from the next image in the sequence; figure 1) provides an imaging containing only that which has changed in the interval between images (36-38). The technique was first described by Kouris, Abdel-Dayem and Awdch (35) and later refined (36-38) using five minute images to more accurately delineate fresh bleeding. A more recent investigation employed more desirable sampling at one minute intervals and showed significant reductions in the false positive rate (figure 2), improved localisation of the actual bleed site (figure 3), earlier detection and greater interpreter confidence (39,40).

**RECOMMENDATIONS**

$^{99m}$Tc RBCs scintigraphy continues to offer potential benefits in the evaluation of acute LGIH (figure 4). For that potential to be fully realised, procedural guidelines require rigorous adherence and advanced tools need to be refined. The following procedural recommendations are consistent with a central role of $^{99m}$Tc RBCs scintigraphy for acute LGIH (table 2):

- *invitro* RBC labelling commenced as soon as possible (as opposed to as soon as practical),
- a rapid dynamic phase (three second sampling) for the first minute after dose administration,
- one minute continuous dynamic sampling for a minimum of 60 minutes (up to 90 minutes) or until convincingly positive,
- perform sequential subtraction imaging on all data sets,
- interpretation should include examination of both one and summed five minute images, subtraction images and cinematic displays,
- delayed imaging, if used, should employ dynamic sampling and a second ‘top up’ RBC label,
• SPECT/CT data should be interpreted with caution due to potential migration of blood away from the actual bleed site during or prior to the SPECT acquisition, and
• consider planar fusion of the crucial dynamic images (capturing initial bleed) with CT scout image if using SPECT/CT.

Further clinical evaluation of the role of SPECT/CT, particularly using high resolution CT, should be undertaken to define the role of SPECT/CT in acute LGIH. An evaluation is also required to explore the role of glucagon in improving SPECT localisation by reducing intra-luminal migration of blood during the SPECT acquisition period. The emerging capability of SPECT/CT systems warrants investigation of a potential role for integrated scintigraphy and CT contrast angiography; combining the benefits of scintigraphy and angiography in a single examination.

CONCLUSION

$^{99m}$Tc RBC scintigraphy is a practical and safe diagnostic and prognostic tool in the evaluation of acute LGIH. It has an evidence based clinical role in both detection and precise localisation of bleeding sites that ultimately improve patient outcomes and reduce health care costs. Delays in performing the procedure, high background radiotracer activity and rapid movement of extravasated blood away from the bleed site present limitations which can be overcome by optimisation of study protocol, incorporation of novel imaging technology and techniques such as subtraction scintigraphy and CT co-registration.
REFERENCES


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Table 1: A summary of the standard procedural requirements for $^{99m}$Tc RBC evaluation of acute LGIH.

Table 2: Summary of strategies for optimisation of RBC scintigraphy in LGIH. The table also provides a guide to alternatives, their risks and methods to mitigate the risk for circumstances where the optimal parameters are not satisfied.
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**Figure 1:** Schematic representation of the Currie, Towers and Wheat (reprinted with permission: 39, p. 164) method where each new 1 minute frame is produced by subtraction of its preceding frame from the subsequent frame.

**Figure 2:** An apparent accumulation of blood in the ascending colon on the standard $^{99m}$Tc RBC study is shown to remain constant over time. The subtraction images indicate neither increasing intensity nor movement within the bowel, eliminating an active bleed as the source and preventing a false positive finding. Currie, Towers and Wheat (reprinted with permission: 40, p. 110).

**Figure 3:** Standard $^{99m}$Tc RBC images shows activity superimposed on the blood vessels that might be reported as a normal variant or tortuosity. Subtraction imaging clearly identifies both the presence of and precise origin of a bleed, preventing a false negative. Currie, Towers and Wheat (reprinted with permission: 40, p. 110).

**Figure 4:** Summary of the decision tree for LGIH focused on the role of RBC scintigraphy.