Idiopathic membranoproliferative glomerulonephritis: does it exist?

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Abstract
When membranoproliferative glomerulonephritis (MPGN) was first delineated as a discrete clinicopathological entity more than a half-century ago, most cases were regarded as idiopathic (or primary) in nature. Advances in analysis of pathogenetic mechanisms and etiologies underlying the lesion of MPGN have radically altered the prevalence of the truly idiopathic form of MPGN. In addition, MPGN as a category among renal biopsies showing glomerulonephritis has diminished over time. In the modern era, MPGN is mainly classified morphologically on the basis of immunoglobulin (Ig; monoclonal or polyclonal) and complement (C3 only or combined with Ig) deposition and secondarily on the basis of its appearance on ultrastructural examination. Idiopathic MPGN is a diagnosis of exclusion, at least in many adults and a portion of children, and a systematic approach to evaluation will often uncover a secondary cause, such as an infection, autoimmune disease, monoclonal gammopathy, neoplasia, complement dysregulation or a chronic thrombotic microangiopathy. Idiopathic MPGN remains an ‘endangered species’ after its separation from these known causes.

Keywords: complement abnormalities; dense deposit disease; glomerular diseases; glomerulonephritis; C3 glomerulonephritis; membranoproliferative

Introduction
Membranoproliferative glomerulonephritis (MPGN also called mesangiocapillary glomerulonephritis) is a ‘lesion’ not a ‘disease’. As such, the discovery of the ‘lesion’ of MPGN in a renal biopsy is the start of an exploratory process leading to a diagnosis, not an end in itself. The lesion was first demarcated from other forms of glomerulonephritis in 1961–62 by Royer et al. [1, 2]. However, the lesion had undoubtedly been in existence for centuries as two of the original cases described by Richard Bright in his epoch-making studies of 1827 had MPGN by later microscopic analysis [3]. The discovery that many cases of MPGN, particularly in children, display persistent hypo-complementemia (low C3 levels) by West et al. [4] in 1965 was a harbinger of the identification of the heterogeneity of mechanisms underlying the ‘lesion’ of MPGN. Initial reports describing MPGN were predominantly in children without known underlying disease. In an early survey by Cameron et al. [5] in 1970, 50 cases of MPGN were described; 83% had an initial or subsequent decline in serum C3 levels and 76% were under age 20 at diagnosis. The term ‘idiopathic’ MPGN slowly gained currency to delineate a group of subjects with the ‘lesion’ of MPGN in whom no evidence of an underlying disease (such as lupus erythematosus or infection) could be detected. Thus, from the beginning, ‘idiopathic’ (or primary) MPGN was a diagnosis of exclusion.

Over time, as sophistication in analysis of biopsy material and serological methodology improved, many cases heretofore called ‘idiopathic’ MPGN were recategorized as secondary to a defined cause (such as hepatitis C infection or neoplastic diseases) and the frequency of ‘idiopathic’ MPGN diminished accordingly. In addition, a secular decline in the overall incidence and prevalence of MPGN was noted, at least in many developed countries [6] (see also below). This was, at least in part, attributed to better hygiene and control of infectious diseases that had historically contributed to the burden of secondary MPGN [7]. These evolutionary events have called into question whether an entity of ‘idiopathic’ (or primary) MPGN really exists in our contemporary world, and if it does, how can it best be identified. This essay is designed to address these issues. The evolving classifications of the lesion of MPGN are integral to this analysis and will first be discussed.

The pathology and classification of MPGN: a transformation from an ultra-structural categorization into a mechanistic classification

MPGN is a pattern of glomerular injury resulting from predominantly subendothelial and mesangial deposition of immune complexes and/or complement factors and their products. It is histologically defined on light
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What is wrong with the current MPGN classification?

The major shortcoming of the current classification is that it implies that MPGN types I, II and III are idiopathic (or primary). Furthermore, MPGN types I and III are often considered immune-complex-mediated glomerulonephritis because of the presence of ‘immune-type’ electron-dense deposits on EM [8]. However, as noted earlier, many cases classified as MPGN types I and III show only C3 deposits with no Ig deposits on IF. This suggests that in cases of MPGN in which only C3 is present on IF, the deposits observed on EM consist of complement and complement products (and not Ig deposits). It has been known for a long time that the alternative pathway (AP) of complement is abnormal in many patients with MPGN types I and III, as manifested by a markedly depressed serum level of C3 (even more so than patients with DDD), while serum levels of components of the classical complement pathway (C4 and C1q) are normal or decreased mildly [8]. This suggests that many cases of MPGN types I and III are related to abnormalities of the AP of complement. As currently classified, MPGN types I and III are likely to include cases of both Ig deposition (and thus are likely immune complex-mediated) and complement deposition (that are likely complement-mediated because of dysregulation of the AP of complement). Thus, the current classification fails by not distinguishing between the two major pathophysiologic factors leading to the development of a MPGN, i.e. abnormalities resulting in Ig-deposition and abnormalities resulting in complement—deposition’. The correct understanding of the differences between these two entities is of paramount importance because the underlying etiology is different and thus both management and prognosis are also different.

A proposal for a new classification of MPGN based on underlying mechanisms

We have proposed that a classification of MPGN based on the IF findings rather than the EM findings will lead to better understanding of the etiology of MPGN [14, 15] (see Figure 2). According to this proposal, MPGN can be classified as immune complex-mediated and complement-mediated. Immune complex-mediated MPGN shows Ig and/or complement factors on IF studies. Complement-mediated MPGN shows complement factors and lack of significant Ig on IF studies. Immune complex-mediated MPGN includes MPGN resulting from chronic infections,
autoimmune diseases and dysproteinemias. On the other hand, complement-mediated MPGN results from dysregulation of the AP of complement. It should be noted that extensive complement (C3 and C4) deposition is also present in immune complex-mediated MPGN. However, the complement deposition in these cases results from activation of the classical and terminal pathway of complement by the immune complexes.

Complement-mediated MPGN can be further classified into C3 glomerulonephritis and DDD, both of which result from AP dysregulation. Thus, in C3 glomerulonephritis, the complement deposits are present predominantly in the subendothelial and mesangial location with some intramembranous and subepithelial deposits. C3 glomerulonephritis with subendothelial deposits is most likely to be labeled MPGN type I, whereas those with intramembranous and subepithelial deposits are likely to be labeled MPGN type III. On the other hand, the complement deposits in DDD are mostly intramembranous and mesangial. It is important to point out that in some cases a transition between C3 glomerulonephritis and DDD is noted on EM, with some loops showing subendothelial deposits of C3 glomerulonephritis and other loops showing classic intramembranous deposits of DDD. Thus, C3 glomerulonephritis and DDD likely represent a morphologic spectrum due to AP abnormalities. In fact, data from laser microdissection and mass spectrometry analysis of glomeruli obtained from a number of patients with C3 glomerulonephritis are consistent with unrestricted activation of the AP, and the proteomic profile in these cases is similar to that found in patients with DDD [16, 17].

**Non-idiopathic MPGN—the identifiable causes**

The incidence and prevalence of MPGN (as a pattern of injury) has been well described in the epidemiological literature [18–20]. The incidence of MPGN (as a lesion in renal biopsies) ranges from 1.4 to 9.3 cases per million population (pmp) per year [18] and with few exceptions, the incidence has decreased over time (from about seven cases pmp per year in the 1970s to about two cases pmp per year in the 1990–2000 [21–23]. MPGN accounts for 2–10% of all cases of glomerulonephritis confirmed on renal biopsy and ranks as the sixth leading cause of end-stage renal disease among the glomerulonephritides and the fifth leading cause of ESRD among the primary glomerular diseases. The disorder commonly presents in childhood but can be seen at all ages. In the comprehensive epidemiological study of Brigani et al. [18] in Australia in 2001, the lesion of MPGN was observed in ~2–3 pmp per year in children (ages 5–14 years) and in ~1–10 pmp per year in adults (ages 14–75+ years). In this study, the peak incidence of MPGN was seen in subjects 55–74 years of age. In the study of Cameron et al. [5] in 1970 (cited earlier), 36% of patients with MPGN were over age 19 at diagnosis. None of these studies carefully delineated the possible underlying causes of the MPGN. There is very little contemporary information on the relative frequency of idiopathic and non-idiopathic MPGN in pediatric and adult subjects using modern approaches to identification of secondary forms of MPGN (e.g. infections, autoimmune, neoplastic, complement dysregulation and chronic thrombotic microangiopathy); however, it is our impression that truly ‘idiopathic’ MPGN is now more commonly seen in the pediatric age populations than in older adults.

Table 1 gives a listing of the known causes of the lesion of MPGN (non-idiopathic MPGN).

**Immune complex-mediated MPGN**

Immune complex-mediated MPGN results from the deposition of immune complexes in the glomeruli due to persistent antigenemia with antigen–antibody immune complex formation as a result of chronic infections, autoimmune diseases or a monoclonal gammopathy.

The immune complexes activate complement via the classical pathway, with deposition of complement factors of the classical pathway and terminal complement pathway that preferentially localize to the mesangium and subendothelial space. These cases of MPGN are typically Ig positive and complement positive on IF microscopy on kidney biopsy.

**Infections.** Chronic hepatitis C viral infection is the main cause of immune complex-mediated MPGN, where it is very commonly associated with mixed (IgG/IgM) cryoglobulinemia [10, 24]. In addition to hepatitis C, hepatitis B and chronic bacterial (e.g. endocarditis, shunt infections.

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**Fig. 2.** Evaluation of MPGN: on the basis of IF findings, MPGN can be broadly divided into immune complex-mediated or complement-mediated. Immune complex-mediated MPGN should lead to evaluation of infections, autoimmune diseases and monoclonal gammapathies. Complement-mediated MPGN is further subdivided into DDD or C3GN, depending on the EM findings, and should lead to evaluation of the alternative pathway of complement.
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Table 1. Causes of a membranoproliferative pattern of injury

<table>
<thead>
<tr>
<th>Immune complex-mediated:</th>
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<tr>
<td>Infections</td>
</tr>
<tr>
<td>- Viral: hepatitis C, hepatitis B (rarely)</td>
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<tr>
<td>- Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis</td>
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<td>- Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis</td>
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<td>Autoimmune diseases</td>
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<td>- Systemic lupus erythematosus</td>
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<td>- Sjögren’s syndrome</td>
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<td>- Rheumatoid arthritis</td>
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<td>Monoclonal gammapathies</td>
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<tr>
<td>Complement-mediated (C3 glomerulonephritis and dense deposit disease):</td>
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<tr>
<td>- Mutations in complement-regulating proteins: CFH, CFI, CFHR5</td>
</tr>
<tr>
<td>- Antibodies to complement-regulating proteins: C3 nephritic factor, CFH, CFI, CFB</td>
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<tr>
<td>Mutation in complement factors: C3</td>
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| Non-immunoglobulin/complement mediated: |
| - Healing phase of HUS/TTP** |
| - Anti-phospholipid (anti-cardiolipin) antibodies syndrome |
| - POEMS syndrome** |
| - Radiation nephritis |
| - Nephropathy associated with bone marrow transplantation |
| - Drug-associated thrombotic angiopathies |
| - Sickle cell anemia and polycythemia, dysfibrinogenemia and other pro-thrombotic states |
| - Transplant glomerulopathy |
| ‘Idiopathic’ forms of MPGN |
| - None of the aforementioned conditions is present |

*HUS is a complement-mediated thrombotic microangiopathy; however, there is no complement deposition on IF.
**HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura; POEMS: polynuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes

Table 1. Causes of a membranoproliferative pattern of injury

nephritis and abscesses), fungal and parasitic infections are also important causes of MPGN [25–28].

Autoimmune diseases. In addition to chronic infections, autoimmune diseases such as systemic lupus erythematosus and lupus nephritis, Sjögren’s syndrome, rheumatoid arthritis and mixed connective tissue disorders are also associated with persistent circulating immune complexes that can lead to the development of a lesion of MPGN [29, 30].

Monoclonal gammapathies. Another recently recognized and important cause of MPGN, especially in older adults, is the presence of a monoclonal gammapathy, with or without cryoglobulins [31–33]. Sethi et al. [31] showed that 41% of MPGN patients without an autoimmune process or chronic infection had serum and/or urine electrophoresis studies positive for a monoclonal gammapathy. The majority of these patients had a monoclonal gammapathy labeled ‘undetermined significance’ (MGUS). We do not wish to imply that a monoclonal gammapathy encountered in the setting of MPGN should be called ‘undetermined significance’ or MGUS, but rather these patients should be diagnosed with a ‘monoclonal gammapathy-associated MPGN’ [31].

Complement-mediated MPGN: DDD (type II MPGN) and C3 glomerulonephritis

The complement system can be activated via the classical, lectin or alternative (AP) pathway all of which converge to form C3 convertase, the central point of the complement cascade. The association of C3b and C3 convertase leads to the formation of C5 convertase, leading to the terminal complement complex pathway activation represented by the formation of the membrane attack complex (C6–9 or MAC) on cell surfaces with resulting cellular lysis [34, 35].

Multiple complement-regulatory and -inhibitory proteins [(e.g. factor H, factor I, complement recept 1, CD59, membrane cofactor protein (MCP/CD46)] regulate cascade activation in order to prevent self-mediated damage [34, 36]. Factor H accelerates the breakdown of C3 convertase and is a cofactor for factor I-mediated cleavage and inactivation of C3b [35, 36], thus controlling AP in the fluid phase. On the other hand, surface regulators control C3 convertase via inactivation of C3b deposited on cell surfaces and basement membranes [35]. Mutations in factor H and I, or the presence of antibodies against C3 convertase enzyme (C3Bb), also known as C3 nephritic factor (C3Nef), may render a protein resistant to cleavage, inactivation or degradation, resulting in persistent complement activation [16, 31, 37–40]. A number of ‘genetic polymorphisms’ have also been associated with an increased risk of development of MPGN. The best-known risk allele is the Tyr402His variants of factor H, leading to reduced factor H-mediated regulation of C3 convertase on cell surfaces [16, 39, 41].

Whatever the mechanism, dysregulation of the AP results in activated complement products, including C3b and terminal complement factors (C6–9), that are delivered indiscriminately to all cell surfaces [17, 35]. In the glomeruli, deposition of complement products and debris in the mesangium and subendothelial region triggers inflammation with subsequent development of MPGN. Since Igs are not directly involved, MPGN is typically Ig-negative complement-positive on IF studies [16, 42].

A classical example of a MPGN resulting from an inherited or acquired dysregulation of the AP of the complement cascade is DDD [17, 34, 43, 44]. More recently, cases closely resembling DDD on LM and IF evaluation have been described: the so-called ‘glomerulonephritis with isolated C3 deposits’ or ‘C3 glomerulonephritis’ [37, 38, 45]. As discussed earlier, IF examination shows extensive C3 deposition along the capillary walls and mesangium along with the absence of Igs deposition. However, EM examination in C3 glomerulonephritis does
Not show the typical electron dense intramembranous deposits characteristic of patients with DDD. Instead, the deposits appear similar to the immune deposits noted in immune-complex-mediated MPGN, but lack Ig. It is now clear that these cases are also caused by dysregulation of the AP complement cascade and the term ‘C3 glomerulopathy’ is often used to include C3GN and DDD [14]. Both C3GN and DDD are distinguished from immune-complex-mediated glomerulonephritis by the lack of Ig staining on IF [14].

Since in many patients, an MPGN due to complement abnormalities does not develop until late in life, it suggests that genetic risk factors are not enough to trigger the disease but that additional ‘hit(s)’ is/are required. It is possible under normal circumstances that mild AP dysregulation may not result in MPGN due to redundancy in the AP regulatory system. However, an additional ‘hit’ (e.g. infection) can activate the complement system and overwhelm the regulatory mechanism resulting in high levels of complement factors that are then deposited in glomeruli [35]. This may explain why recurrent episodes of macroscopic hematuria associated with infection episodes are seen in some patients with MPGN. Similarly, an additional ‘hit’ such as production of monoclonal proteins that act as autoantibodies to a complement-regulating protein can result in dysfunction of the AP and development of MPGN [14, 15].

Non-Ig/complement-mediated MPGN

A pattern of injury consistent with MPGN is also noted in healing/chronic phases of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (HUS), atypical HUS (aHUS) associated with complement abnormalities, anti-phospholipid antibody syndrome, drug-induced thrombotic microangiopathy, nephropathy associated with bone marrow transplantation, radiation nephritis, malignant hypertension and connective tissue disorders [46, 47]. (Table 1) In these cases, Igs and complement are typically absent on IF, and electron-dense deposits are not present on EM although in HUS the disease is mediated by uncontrolled complement activation. Finally, the transplant glomerulopathy is used to denote the MPGN pattern of injury in the renal allograft. This form of glomerular injury is most often associated with development of antibodies to HLA class II molecules that are present on glomerular endothelial cells, resulting in antibody-mediated injury to the endothelial cells. However, IF shows no Ig deposition. In the acute phase, neutrophils and mononuclear cells are noted in the glomerular capillaries (glomerulitis), which is followed by the reparative/chronic phase showing mesangial expansion and capillary wall remodeling with development of double contours.

An algorithm for the separation of non-idiopathic and idiopathic MPGN

In view of the evidence discussed earlier, we propose that cases in which renal biopsy shows an MPGN pattern of injury the evaluation should be directed toward two major pathophysiologic factors: ‘immune complex-mediated’ and ‘complement-mediated’ disease. If immunoglobulins (IgG or IgM, most typically) are present on IF, the evaluation should include testing for infections (such as blood cultures or serology), autoimmune diseases (serology) and monoclonal gammopathies (immunofixation; free light chain assays), including a search for mixed IgG/IgM cryoglobulins. Determination of the ‘clonality’ of the Ig deposits is essential—utilization of κ and λ light chain-specific and heavy chain isotype and subclass-specific reagents in IF microscopy is usually sufficient. In patients with immune complex-mediated MPGN, activation of the classical pathway will be reflected by the presence of a normal or low C3, low C4 and low CH50 in the serum and often by C1q deposits co-localizing with Ig by IF microscopy. Hepatitis C-related MPGN can be suspected when the serum levels of C4 are more greatly reduced than the serum levels of C3, and confirmed by appropriate serological studies.

On the other hand, if IF microscopy shows predominantly C3 deposition and is negative or shows no significant deposition of Ig, then the MPGN should be further evaluated as a ‘complement-mediated’ MPGN, which can be further subdivided into DDD or C3-GN on the basis of the results of the EM examination. In this situation, patients may present with low C3, normal C4 and low CH50. A diagnosis of complement-mediated MPGN warrants an in-depth study of the AP, regardless of whether the renal biopsy shows DDD or C3-GN. In few cases of complement-mediated MPGN, an infection, autoimmune disease or a monoclonal gammapathy may result in the development of antibodies or monoclonal proteins that are directed against epitopes on complement-regulating proteins, thus leading to dysfunction of the AP of complement [48]. However, in such cases, the MPGN will be due to AP dysfunction not due to Ig deposition, and the renal biopsy will show C3 without any significant Ig deposition [49]. On the other hand, a rare case of immune complex-mediated MPGN may also have dysfunction of the AP of complement.

A simplified version of MPGN based on the current understanding is shown in Figure 1. We recommend that the term MPGN type I or III be abandoned, since it implies an idiopathic (or primary) form of MPGN, while it is likely that an underlying etiology can be found in the majority of cases of MPGN. It is possible that even after extensive evaluation of the two groups, one will still be unable to determine the underlying etiology in a small number cases of immune complex-mediated MPGN or complement-mediated MPGN. It is better to refer to type II MPGN as DDD. We firmly believe that new tests/techniques will continue to reveal novel causes for a lesion that until recently was considered to be idiopathic in a significant number of patients. Evaluation of MPGN according to the underlying pathophysiologic process will also allow us to better characterize (and hopefully treat) patients with a MPGN on the basis of etiology, instead of grouping these cases together into MPGN types I–III. Lastly, with regards to kidney transplantation, patients with ESRD secondary to an immune complex-mediated MPGN, such as infection or autoimmune diseases, have a low risk for recurrent disease following transplantation. In contrast, patients with
MPGN secondary to a monoclonal gammopathy or underlying complement cascade abnormalities are much more likely to show recurrence of MPGN post-transplant, unless the monoclonal gammopathy is adequately treated prior to transplantation or the origin of the complement dysfunction is corrected [50]. In the complement-mediated MPGN, it is possible that those associated with genetic mutations in complement-regulating proteins are more likely to recur than those associated with antibodies to the complement-regulating proteins [51].

Perspectives and conclusions

It seems very clear to us that the recognizable clinical and pathologic spectrum of MPGN has evolved considerably since its first description more than a half-century ago. Then MPGN was largely a pediatric disorder and was believed to be mostly idiopathic (or primary) in character. Now it is seen throughout a broad span of ages and, viewed through the prism of pathogenesis, is far more often secondary to a defined underlying disease than idiopathic (or primary) in nature. In fact, in many areas of the world, MPGN tends to be a disorder seen more commonly in older adults and mostly of a secondary origin. Overall, the incidence and prevalence of MPGN appears to be diminishing, at least in developed nations, perhaps because of better hygiene and control of infectious disease. As a diagnosis of exclusion, truly idiopathic MPGN is substantially decreasing in frequency because of a better appreciation of the heterogeneity of its etiology and pathogenesis and by application of improved technology to uncover the diverse pathophysiological mechanisms lying beneath the phenotypical MPGN pattern of injury. Has idiopathic MPGN been relegated to the dust-bin of history? Not yet, but it is definitely an ‘endangered species’.

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References

Sodium polysterene sulfonate (Kayexalate®) is a cross-linked polymer to which reactive sulfonic groups are attached and preloaded with sodium (Na⁺). When placed in a solution, its reactive sulfonate groups exchange their bound Na⁺ for potassium (K⁺) in the lumen of the gastrointestinal (GI) tract, causing loss of K⁺ in stool. Because it tends to cause constipation, SPS is usually given with sorbitol as a cathartic. In September 2009, the US Food and Drug Administration recommended against the ‘concomitant use of sorbitol’ with Kayexalate® powder because of concerns about the risk of colonic necrosis and other serious GI side effects (bleeding, ischemic colitis and perforation). This warning, however, did not apply to premixed SPS in 33% sorbitol. A debate followed on the concomitant use of sorbitol

Asking the question again: are cation exchange resins effective for the treatment of hyperkalemia?

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Sodium polysterene sulfonate (Kayexalate®) is a cross-linked polymer to which reactive sulfonic groups are attached and preloaded with sodium (Na⁺). When placed in a solution, its reactive sulfonate groups exchange their bound Na⁺ for potassium (K⁺) in the lumen of the gastrointestinal (GI) tract, causing loss of K⁺ in stool. Because it tends to cause constipation, SPS is usually given with sorbitol as a cathartic. In September 2009, the US Food and Drug Administration recommended against the ‘concomitant use of sorbitol’ with Kayexalate® powder because of concerns about the risk of colonic necrosis and other serious GI side effects (bleeding, ischemic colitis and perforation). This warning, however, did not apply to premixed SPS in 33% sorbitol. A debate followed on the issue of use of cation-exchange resins in the treatment of...