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Ice castle carving in Lake Louise, Alberta.

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Health Promotion Heroes

The Canadian Journal of General Internal Medicine—your Journal—exists to promote scholarship in general internal medicine and to raise awareness of issues important in our practices. I am delighted to announce a new initiative in the Journal aimed at disseminating the work of the CSIM’s Health Promotion Committee. This group is capably (and enthusiastically!) led by Dr. Bert Govig and aims to support health promotion activities by CSIM members and beyond. Each issue will showcase the activity of a Health Promotion (HP) Hero. The first to be recognized in our upcoming CJGIM issue is Dr. Thomas Brothers, who also holds the distinction of being the 2018 recipient of the CSIM’s Hui Lee Health Promotion Scholarship.

Regaining a focus on health promotion is important because many of us were drawn to medicine to prevent disease and suffering. Our training, however, and the structure of the health care system focuses our attention on measurable biologic defects, leading most of us to remain busy diagnosing and treating patients with acute and chronic problems. Despite the realities of our daily practice, we need to find time (however little it may be) to seek an island of health promotion while navigating the sea of diagnosis, treatment and short-term crisis management.

Health promotion can have many faces. Twenty years ago, I co-developed evidence-based guidelines for the prevention and treatment of obesity. At that time, we found little evidence to guide clinicians towards effective community-based prevention programs or towards prevention or treatment strategies for individuals. This was frustrating as our intuition was that population-based interventions like compulsory physical education from grades 1–12, made sense. As we know, lack of evidence is not the same as lack of effect, and in this case was possibly due to a lack of research funding. Health Promotion now is a priority for governments and health care systems everywhere, and emerging research is starting to address an increasing range of interventions addressing social determinants of health. We are excited about raising the profile of Health Promotion with this new feature of the Journal and look forward to being inspired and educated by our HP Heroes.

James Douketis, MD

Editor-in-Chief
Heros de la promotion de la sante

La Revue canadienne de médecine interne générale - votre revue - existe pour promouvoir l'érudition en médecine interne générale et pour sensibiliser les gens aux questions importantes dans nos pratiques. J'ai le plaisir d'annoncer dans la Revue une nouvelle initiative visant à diffuser les travaux du Comité de promotion de la santé du CSMI. Ce groupe est dirigé avec compétence (et enthousiasme !) par le Dr Bert Govig et vise à appuyer les activités de promotion de la santé des membres du CSMI et d'ailleurs. Chaque numéro présentera l'activité d'un héros de la promotion de la santé (HP). Le premier à être reconnu dans notre prochain numéro du CJGIM est le Dr Thomas Brothers, qui a également reçu la bourse d'études Hui Lee en promotion de la santé.

Il est important de se concentrer à nouveau sur la promotion de la santé parce que beaucoup d'entre nous ont été attirés par la médecine pour prévenir la maladie et la souffrance. Cependant, notre formation et la structure du système de soins de santé concentrent notre attention sur les défauts biologiques mesurables, ce qui nous amène, pour la plupart d'entre nous, à demeurer occupés à diagnostiquer et à traiter les patients atteints de problèmes aigus et chroniques. Malgré les réalités de notre pratique quotidienne, nous devons trouver le temps (même s'il y en a peu) de chercher un flot de promotion de la santé tout en naviguant dans la mer du diagnostic, du traitement et de la gestion de crise à court terme.

La promotion de la santé peut avoir plusieurs visages. Il y a vingt ans, j'ai participé à l'élaboration de lignes directrices fondées sur des données probantes pour la prévention et le traitement de l'obésité. À l'époque, nous avons trouvé peu de données probantes pour guider les cliniciens vers des programmes de prévention communautaires efficaces ou vers des stratégies de prévention ou de traitement pour les individus. C'était frustrant, car notre intuition était que les interventions axées sur la population, comme l'éducation physique obligatoire de la 1re à la 12e année, avaient un sens. Comme nous le savons, le manque de preuves n'est pas la même chose que le manque d'effet, et dans ce cas-ci, c'est peut-être dû à un manque de financement de la recherche. La promotion de la santé est maintenant une priorité pour les gouvernements et les systèmes de soins de santé partout dans le monde, et les nouvelles recherches commencent à aborder une gamme croissante d'interventions portant sur les déterminants sociaux de la santé. Nous sommes enthousiastes à l'idée de rehausser le profil de la promotion de la santé grâce à cette nouvelle rubrique du Journal et nous avons hâte d'être inspirés et éduqués par nos héros HP.

James Douketis, MD

Éditeur en chef
BMJ Rapid Recommendations: Creating Tools to Support a Revolution in Clinical Practice Guideline Adoption

Gordon H Guyatt, MD, MSc, FRCP, OC, Thomas Agoritsas, MD, PhD, Lyubov Lytvyn, BSc, MS, Reed Siemieniuk, MD, PhD(c), FRCP, ABIM, Per Vandvik, MD, PhD

Abstract
BMJ rapid recommendations hold the potential to revolutionize clinical practice guidelines, achieving both timeliness, trustworthiness, and usefulness to clinicians and patients to allow well informed decisions in clinical practice.

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In this article we describe the limitations of currently existing clinical practice guidelines; how the BMJ Rapid Recommendations were developed to address these limitations; the process underlying BMJ Rapid Recommendations; and make a case that BMJ Rapid Recommendations represent a model for the future of clinical practice guidelines.

Three Kinds of Problematic Guidelines
Clinicians increasingly rely on clinical practice guidelines produced either by prestigious medical organizations, or by very widely used electronic textbooks such as Dynamed or UpToDate. There are, however, three kinds of problematic guidelines that may tempt, and mislead, clinicians: (1) guidelines that seriously violate standards of trustworthiness; (2) those that were once current but are now out of date; (3) guidelines that are current and meet many standards of trustworthiness, but nevertheless fail in some other important criteria.

The first, and worst, are produced by prestigious organizations, but seriously violate current, widely accepted standards of trustworthy guidelines. Indeed, many are best characterized as following the GOBSAT model: good old boys sitting around a table. Over the years, investigations have documented the limitations in such guidelines.1-3

In March, 2011, in response to the problem, the Institute of Medicine promulgated standards for trustworthy guidelines.4 The standards include effective management of conflict of interest; appropriate panel selection; conduct or identification of systematic reviews addressing all important questions related to the guidelines; rating quality of evidence and strength of recommendations; and undergoing peer review. In 2013 the Guideline International Network published similar standards, based on wide agreement between their 100 organizational members.5

A study reported in 2012 documented the necessity for the Institute of Medicine suggestions.6 The authors selected at
random, 130 guidelines from the National Guideline Clearinghouse (which, by the way, is no longer be available as of July 16, 2018 because the US government has discontinued its funding). Of 18 Institute of Medicine standards, 50% of guidelines met 8 or fewer. Fewer than half provided information regarding conflicts of interest, and of the guidelines that did provide the information, committee chairs had important conflicts in 71.4% and co-chairs in 90.5%. Committees developing guidelines rarely included an information scientist or patients and caregivers with experience of the condition. Guidelines published from 2006 through 2011 varied little with regard to average number of standards satisfied.

Fortunately, although documentation is unavailable, it is our impression that since 2012 an increasing number of guidelines produced by prestigious organizations do meet trustworthiness standards based on use of the GRADE framework: identify clear questions; use systematic reviews of the best available evidence; enlist panels that included experts, front-line clinicians, methodologists, and patients, all of whom are free of problematic address conflict of interest; rate the quality of evidence and strength of their recommendations; provide evidence summaries in a clinician-friendly manner; and make their underlying values and preferences explicit.

Over 100 organizations worldwide have adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, likely increasing the availability of trustworthy recommendations. The GRADE working group has developed a methodologically sophisticated, transparent approach to rating the quality of a body of evidence to inform a guideline. In this approach a body of randomized trials start as high-quality evidence (on a scale of high, moderate, low, or very low) but may be rated down because of risk of bias, imprecision, inconsistency, indirectness, or publication bias. Observational studies start as low quality evidence, but may be rated up, usually because of large or very large effects. Figure 1 summarizes the GRADE approach to rating quality of evidence.

GRADE has identified issues that guideline panels should consider in moving from evidence to recommendations, and deciding on the strength of the recommendations. The primary criteria are the magnitude of the benefits, harms and burdens of the interventions and the comparators; the quality of evidence associated with the evidence of benefits, harms and burdens; and the underlying values and preferences of the population to whom the recommendation applies. Additional criteria include cost, equity, feasibility, and acceptability.

GRADE specifies two categories of strength of recommendations, strong and weak. Strong recommendations represent “just do it” situations in which benefits clearly outweigh harms and burdens – or the reverse. Weak recommendations represent “think about it” situations in which the right course of action will differ depending on patients’ circumstances, and their values and preferences, and should involve shared decision-making.

In some cases, patients may also appreciate such discussions even when recommendations are strong.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Confidence in estimates</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized trials</td>
<td>High</td>
<td>Risk of bias: -1 Serious - 2 Very serious</td>
<td>Large Effect: +1 Large +1 Very large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inconsistency: -1 Serious - 2 Very serious</td>
<td>Dose response: +1 Evidence of a gradient</td>
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<tr>
<td></td>
<td></td>
<td>Indirectness: -1 Serious - 2 Very serious</td>
<td>All plausible confounding: +1 Would reduce a demonstrated effect or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imprecision: -1 Serious - 2 Very serious</td>
<td>+1 would suggest a spurious effect when results show no effect</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Publication bias: -1 Likely - 2 Very likely</td>
<td></td>
</tr>
<tr>
<td>Observational studies</td>
<td>Low</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Very Low</td>
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Figure 1. GRADE’s approach to rating quality of evidence
Over 100 organizations worldwide have adopted the GRADE approach, markedly increasing the availability of trustworthy recommendations. These include international organizations such as the World Health Organization and the Cochrane Collaboration; major American professional groups including the American College of Physicians and the American Thoracic Society; and health technology assessment organizations such as the Swedish Agency for Health Technology Assessment. Canadian organizations that have adopted GRADE include the Canadian Cardiovascular Society, the Canadian Agency for Drugs and Technology in Health (CADTH), and the Ontario Health Technology Advisory Committee.

The second type of problematic guidelines are produced by medical organizations, are well done and thus trustworthy, but end up being rapidly outdated due to the publication of important new evidence long before their next iteration. This unfortunate circumstance results because professional organizations typically take years to produce trustworthy guidelines\(^1\) in part, perhaps, because of the bureaucratic structures they have in place.

The third type of problematic guideline, perhaps best characterized by the recommendations appearing in UpToDate, are current. Despite considerable methodologic sophistication (UpToDate includes over 10,000 that adhere to GRADE criteria\(^2\) and are presented as GRADEd recommendations\(^3\) they do not meet all important criteria for trustworthiness. In particular, they rely on previously published evidence summaries that may be limited or unavailable; they seldom present structured evidence summaries; they do not adhere to rigorous conflict of interest policies; and their process for deciding on the direction and strength of recommendations is not transparent.

Is it possible to produce guidelines that overcome the limitations of all three types of existing guidelines: that is, they meet trustworthiness standards and take into account the latest evidence?

A Fourth Type of Guideline that Addresses Problems of the First Three

A group of physicians and methodologists who ultimately became the Rapid Recommendations team, believed it was. We set out to create, in response to the publication of practice-changing evidence, new trustworthy guidelines over a very short period – 90 days was our initial target. Following a set of innovations to improve the authoring, publication and updating of trustworthy guidelines, we created the Rapid Recommendations project. We thought that the research and innovation program with which we are involved and which we call “MAGIC” (Making GRADE the Irresistible Choice, www.magicproject.org),\(^4\) a non-profit research and innovation could provide the base from which to launch the project. In particular, the MAGIC electronic platform for systematic reviews and guidelines (MAGICapp), would be well suited to the dissemination of the guidelines produced. The MAGIC executive, potentially with other key players, would form a Rapid Recommendations steering committee (the current steering committee includes four of the authors of this article, TA, GG, RS and PV).

The MAGIC group developed a number of innovations to improve the authoring, publication and updating of trustworthy guidelines in the context of practice-changing evidence.\(^5\) These included establishing a network of people to collaborate on the creating systematic reviews and guidelines, thus circumventing barriers of organizations currently undertaking guideline development. In pilot work, a group directed from McMaster University produced a series of systematic reviews, each in a matter of a few weeks. Knowing that this key step was possible, the steering group led two pilot recommendations that included gathering an appropriate panel, reviewing systematic review evidence, and producing recommendations.

Convinced from this pilot work that the endeavour was feasible, the Rapid Recommendations team now faced the challenges of ensuring the product was credible to medical audiences, and developing a dissemination strategy that would ensure medical practitioners would notice the new recommendations. To deal with this challenge, the Rapid Recommendations team succeeded in establishing a partnership between MAGIC and the BMJ.

The terms of the arrangement are as follows. The MAGIC group scans the literature, picking practice-changing new studies, updating the relevant systematic reviews, and producing guidelines that meet trustworthiness standards – all within a target of 90 days from the publication of the new evidence. All reviews and guidelines are consistent with GRADE guidance.

The BMJ is responsible for vetting the potential Rapid Recommendations topics and the guideline panel members’ conflicts of interest, and conducting the peer review of the systematic reviews and the guidelines that emerged from the process. The outline of the endeavour and its process,\(^6\) and the first of the Rapid Recommendations,\(^6\) including the associated systematic reviews,\(^7\) were published in the BMJ in September 2016. Since then, ten such Rapid Recommendations have appeared (Table 1).

Producing Rapid Recommendations requires the development and implementation of a rigorous process that would meet all the trustworthy recommendation standards and still allow guideline production in an extremely tight time frame. The first step in the development of a Rapid Recommendation is to identify potentially practice-changing new evidence. To do this, MAGIC has partnered with the McMaster Health Information Research Unit (HIRU), which produces a stream of pre-appraised evidence, widely disseminated, such as in the American College of Physicians Journal.
Table 1. Published and ongoing Rapid Recommendations

<table>
<thead>
<tr>
<th>RapidRec</th>
<th>Guidance</th>
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| **Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline.**<sup>18</sup> | We suggest TMP-SMX or clindamycin plus incision and drainage rather than incision and drainage alone (weak recommendation).  
We recommend trimethoprim and sulfamethoxazole or clindamycin over cephalosporins (strong recommendation).  
We suggest trimethoprim and sulfamethoxazole over clindamycin (weak recommendation). |
| **Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline.**<sup>19</sup> | We suggest a zidovudine and lamivudine-based antiretroviral regimen over one that includes tenofovir and emtricitabine (weak recommendation).  
We recommend a zidovudine and lamivudine-based antiretroviral regimen over tenofovir and emtricitabine with ritonavir-boosted lopinavir (strong recommendation). |
| **Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline.**<sup>20</sup> | We recommend against arthroscopic knee surgery in patients with degenerative knee disease (strong recommendation). |
| **Atraumatic (pencil-point) versus conventional needles for lumbar puncture: a clinical practice guideline.**<sup>21</sup> | We recommend the use of atraumatic over conventional needles (strong recommendation). |
| **Corticosteroids for sore throat: a clinical practice guideline.**<sup>22</sup> | We suggest short course steroids (weak recommendation). |
| **Corticosteroid therapy for sepsis: a clinical practice guideline.**<sup>23</sup> | We suggest corticosteroid therapy rather than no corticosteroid therapy (weak recommendation). |
| **Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline.**<sup>24</sup> | We recommend against the use of LIPUS (strong recommendation). |
| **Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline.**<sup>25</sup> | For patients to whom all options are acceptable, we suggest PFO closure followed by antiplatelet therapy over anticoagulation therapy (weak recommendation).  
For patients to whom antiplatelets contraindicated, unacceptable, or unavailable, we recommend PFO closure followed by antiplatelet therapy over anticoagulation therapy alone (strong recommendation).  
For patients to whom PFO closure is contraindicated, unacceptable, or unavailable, we suggest anticoagulation over antiplatelet therapy (weak recommendation). |
| **Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk.**<sup>26</sup> | For patients aged <65 years, we recommend SAVR over transfemoral TAVI (strong recommendation).  
For patients aged 65-74 years, we suggest SAVR over transfemoral TAVI (weak recommendation).  
For patients aged 75-84 years, we suggest transfemoral TAVI over SAVR (weak recommendation).  
For patients aged 85+, we recommend transfemoral TAVI over SAVR (strong recommendation).  
For people with severe aortic stenosis who are unsuitable for transfemoral TAVI, we recommend SAVR over transapical TAVI (strong recommendation). |
| **Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline.** | In press |
| **Oxygen therapy for acutely ill medical patients: a clinical practice guideline.** | In development |
| **Colorectal cancer screening: a clinical practice guideline.** | In development |
| **Arthroscopy for patients with shoulder impingement syndrome: a clinical practice guideline.** | In development |
| **Clopidogrel and aspirin versus aspirin alone in patients with mild stroke or high risk transient ischemic attack: a clinical practice guideline.** | In development |
As part of HIRU’s screening for new articles, they provide the Rapid Recommendations team, every day, with the latest articles that have the highest relevance and quality rating.

One member of the Rapid Recommendation steering group reviews the articles from HIRU. If a particular article looks promising (i.e., possibly practice changing) the team member identifies any recent systematic reviews addressing the topic, and reviews existing guidelines. If, at this point, the reviewer still considers the article has potential (in particular, they have a strong sense that one or more recommendations would change on the basis of the new evidence) the article is referred to the Rapid Recommendations steering group.

The steering group considers a number of issues in deciding whether to pursue the article further. These include the current Rapid Recommendations team workload (if overwhelmed, less likely to move forward); the complexity of the issue (more complex, less likely, though the team has repeatedly violated this criterion); the availability of a recent systematic review (if available more likely); and the probability that the Rapid Recommendation would indeed differ from existing recommendations (higher probability, more likely). After considering all the issues, the steering group either decides against moving forward, or presents the issue to our BMJ colleagues who then accept or decline the suggestion.

An acceptance at the BMJ level triggers the production of an updated systematic review. The exceptions are situations in which the article is itself a high-quality review – providing all needed information as defined by the guideline panel - that triggers the process in first place. There have been two such situations thus far: systematic reviews that demonstrated that atraumatic needles decrease post lumbar puncture headaches compared to conventional needles, and that high levels of inspired supplemental oxygen can increase mortality.

The reviews, when undertaken by the Rapid Recommendations team meet, as one might anticipate, criteria for rigor. These include explicit eligibility criteria; a comprehensive search; assessment of risk of bias; duplicate assessment of both eligibility and risk of bias; a quantitative summary; and rating of quality of evidence using GRADE criteria. Typically, an international team of methodologically trained individuals undertakes the review.

While the review is taking place, the Rapid Recommendations team recruits panelists, attending to issues of international representation and gender balance. Panels include content experts, front-line clinicians, patients and/or carers, and methodologists. (LL) is responsible for all aspects of patient/carer partnership, including their recruitment and training. One notable feature of the process is zero tolerance for financial conflict of interest, and attention to and management of non-financial conflict.

The latter, non-financial conflict, occurs most frequently when authors become attached to a particular piece of work they have produced, and the inferences one might make from that work – a frequent phenomenon in academic medicine. Other examples include previous statements of strong opinions regarding an issue, and professional conflict (e.g., radiologists sitting on guideline panels, in comparison to family physicians, tend to favour breast cancer mammograms as a screening strategy).

Patient partners are typically those who have experienced the condition under consideration (individuals within the patient population of the Rapid Recommendation), whereas carer partners are informal caregivers of such patients. We recruit patients from multiple sources including organizations such as Citizens United for Evidence-Based Healthcare or the Society for Participatory Medicine, from the Cochrane Consumers/Task Exchange databases, and organizations relevant to the guideline topic (e.g., in a guideline addressing prevention of vertical transmission of HIV, the International Community of Women Living with HIV), Twitter, and referrals from guideline panel members.

To ensure optimal involvement, patient/carer partners receive training in the technical aspects of the condition of interest, the methodology of evidence summaries, and the interpretation of magnitudes of effect. At the panel meeting, the chairs ensure that for many issues, and for all issues that pertain to values and preferences, the patient/carer partners have the first input into the discussion.

Despite the very strict conflict of interest rules, finding content area experts, typically academic clinicians, has generally proved relatively easy. There have been two exceptions: for one recommendation related to orthopedics, almost all candidates had received funds from device manufacturers that precluded their participation. The same was true for a recommendation regarding the vertical transmission of HIV. Nevertheless, even in those instances, we succeeded in obtaining the necessary expertise.

The Rapid Recommendation steering group seeks a diverse group of both experts (surgeons, medical specialists, academics from the allied professions) and front-line clinicians. Recruiting front-line clinicians often involves both primary care and specialist physicians, but also allied health professionals including nurses, nurse practitioners, physio- and occupational therapists. For both specialist and front-line clinician roles, Rapid Recommendations seek both geographical (typically four or more continents are represented) and gender diversity.

The least difficult recruitment for the panel is clinician methodologists. Both the chair and methods co-chair typically fall in this category, and thus far several of the Steering Group have been involved, ensuring that all of the leadership becomes acquainted with the not insubstantial challenges that repeatedly have arisen.
The primary leadership for each Rapid Recommendations rests with the chair and the methods co-chair. The latter is a particularly onerous role because it involves ensuring that the systematic review is conducted in a timely and optimally rigorous manner; the panel is recruited ensuring all relevant parties; all runs according to a very tight time line; and the recommendation, along with supporting documentation including an interactive decision aids, appear online in the MAGICapp for widespread dissemination.

The final Rapid Recommendations product includes innovative presentation formats (for example, see Figure 2). To facilitate shared decision-making, the team produces electronic decision aids in MAGICapp designed for the patient-clinician encounter that are available for every BMJ Rapid Recommendation.

One limitation of the Rapid Recommendations is that the funding constraints, time frame, and geographical diversity of the panel preclude any face-to-face panel meetings. Even for the electronic meetings required, with typically in the order of 20 panel members, scheduling meetings represent a challenge. Scheduling exigencies not infrequently require more than one parallel panel meeting. Other challenges have included ensuring open access to the recommendations, limitations in evidence available regarding user testing and dissemination of recommendations, co-ordinating with the journal editorial process, and achieving publication timelines.

The first of these Rapid Recommendations appeared in September 2016 and addressed transcatheter versus surgical aortic valve replacement (TAVI for the older, SAVR for the younger). The review required not only a systematic review of the relevant randomized trials, but also a review of the prognosis of SAVR. Table 1 presents all the BMJ Rapid Recommendations to date, both those published and those in process. Clinicians can access all published RapidRecs guidelines and affiliated systematic reviews through the following link: https://www.bmj.com/rapid-recommendations.

BMJ Rapid Recommendations hold the potential to revolutionize clinical practice guidelines, achieving both timeliness,
trustworthiness and usefulness to clinicians and patients to allow well informed decisions in clinical practice.

References
Gender Equity in Academic Medicine: Why Should We Care?
Sonia S. Anand MD, PhD, FRCPc, Anita I. Anand, BA, LLB, LLM

Abstract
Gender disparity exists generally in academia and specifically in research and education among academic medical specialists. Reasons for this disparity include overt and unconscious biases that result in women being offered fewer opportunities to lead, receiving less compensation, being excluded from networking channels in which academic positions are discussed, and facing bias in research, including in the peer review grant process. The recent spotlight on these disparities in other sectors leads us to probe the causes and consequences of gender disparity in academic medicine and to advocate for structural changes to ensure gender equity in academia.

Resume
La disparité entre les sexes existe généralement dans le monde universitaire, et plus particulièrement dans la recherche et la formation des spécialistes médicaux en médecine. Parmi les raisons de cette disparité, citons les préjugés évidents et inconscients qui ont pour résultat moins de possibilités de diriger offertes aux femmes; elles reçoivent une plus faible rémunération, sont exclues des réseaux de discussion dans lesquels les postes universitaires sont discutés et font face à des biais dans la recherche, y compris dans le processus de subvention par les pairs. La récente mise en lumière de ces disparités dans d'autres secteurs nous amène à rechercher les causes et les conséquences de la disparité entre les sexes en médecine universitaire et à plaider en faveur des changements structurels pour assurer l'équité entre les sexes dans les universités.

Keywords: gender, academic, medicine, bias

Gender equality in the areas of health, education, business leadership, law, and political leadership remains a work in progress. According to the World Economic Forum Report on Gender, at current rates of change, it will take 217 years for women to reach gender parity (defined as the female-to-male equality for a given indicator), with the greatest increases required in the areas of economic and political leadership. Canada is ranked 16th in gender parity among countries of the world, with Iceland being the best country and Yemen being the worst. In Canada, gender parity has been achieved to some extent in certain areas of health and education but not in business and political leadership positions.

Specifically, gender parity among medical school graduates in Canada was attained in the mid-eighties, and now more women than men graduate from medical schools in Canada. The 2015-16 Canadian Post-MD Education Registry (CAPER) Census reveals that of the almost 14,000 physicians in Canadian postgraduate medical training, 53.4% are female and 46.6% are male. Entry into specialties such as internal medicine appears about equal, with 54% women entering postgraduate training.
programs in medical specialities. The percentage of women entering academic medical specialist practices at the lecturer or assistant professor level is also approximately 50%.4

However, among academic medical specialists in Canada and the United States, in the decade after taking up a faculty position, women are less likely to achieve full professor status, and more likely to leave academic medicine. This phenomenon can be referred to as a “leaky pipeline” since women do not follow the hierarchical path or “pipeline” towards senior positions.4 They leave or experience stagnation by rank in internal medicine and its related specialities over time, with only 25% of full professors being women, and only 15% of leadership positions such as dean are held by women.4

Statistics such as these encourage us to examine more deeply the factors that underlie the leaky pipeline. Although it is commonly believed that women choose to leave academic medicine, emerging evidence suggests that women face both overt and unconscious biases, and may in effect be pushed out of an academic career in medicine. Overt biases that drive women from the pursuit of an academic career can include workplace bullying and sexual harassment. In the United States, it is estimated that amongst the career development (K) award holders, 30% of women have personally experienced sexual harassment,3 and it is likely similar in Canada.6 Overt biases such as these can have long-lasting effects on the career paths of women in medicine, especially if they become disillusioned by systemic biases and thus do not seek career advancement. They may also suffer from low self-esteem5 and/or imposter syndrome.7

In the past year, the #MeToo movement has increased society’s awareness of workplace biases, which stifle career advancement in all domains of society including in business, entertainment, academia, and hospital systems.8 At the same time, students graduating from medical school have a greater awareness that such behaviours are unacceptable, and they seek to inform their leaders about it.9 Heads of both hospitals and universities are thus reviewing their policies and procedures so that complaints of sexual harassment and workplace bullying can be effectively addressed.10

The second type of bias that women face is known as “unconscious” or “implicit” bias. That is, women may not be encouraged to apply for promotion or leadership positions. They may not seem like a “natural fit” given that they are often not privy to the same informal networking opportunities as their male colleagues. Implicit biases can also creep into play when selection committees are comprised of only or mostly men, with little female or LGBTQ representation. Subtle biases can result in lower assessment ratings or subjective decisions by the committees about women’s academic record and their ability to take on work given their home responsibilities.

Finally, research shows us that, even when women have equal or greater qualifications than male colleagues, they can suffer from the “imposter syndrome,” feeling underqualified or incapable to apply for or have the confidence to take on leadership positions.7 A recent computer simulation model of the business sector created at Rice University demonstrates that subtle differences in performance ratings (which may reflect gender bias) over time lead to leadership positions being held by 65% men and only 35% of women at the most senior level, even if they entered the organization at equal rates.11

Research bias in peer grant review also exists, with women scientists being less likely than male scientists to be funded and published.12 In keeping with these biases, there may be greater concerns about the ability of successful women scientists to lead multiple funded projects, resulting in lower application scores and lower funding success. A recent analysis of all grant applications submitted to the Canadian Institutes of Health Research (CIHR) between 2012 and 2014 by Tamblyn et al. showed that women’s applications were more likely to be scored lower than men’s to a degree that could impact grant funding success rates after accounting for many potential modifying factors (i.e., past funding success, scientific productivity, reviewer characteristics, etc.).13 Given women’s lower success rates in CIHR funding, a vicious cycle can result, with women making fewer applications, receiving rejections, and therefore having fewer research successes. Grant reviewer training – including unconscious bias training – would be useful to alter this trend.

But the bias is not simply implicit. A recent Canadian Medical Association analysis demonstrates that women earn less than men in medical professions. As billings are fee-for-service, this differential may indeed represent choices by women to work in different domains which are less lucrative, or to reduce working time in order to devote attention to child-rearing and household management. However, there may well be underlying issues at play, including men receiving greater access to more lucrative billing opportunities, such as in diagnostic testing or choice clinical billing domains.

Within academic centres, there are multiple sources of salary from public institutions (i.e., hospital or university stipends and research funds), and these sources are used to support academics in their educational and research programs. Apart from billings, additional salary sources can be negotiated with the hospital or university leadership. Because women attain fewer leadership positions, they are less likely to be in a position to negotiate for increases to base salaries and stipends.
How can we mitigate and overcome unconscious biases? In the past, the onus has been placed on women to change themselves to suit the work environment by taking leadership courses, joining women’s networking groups, and seeking out more mentorship. However, research from the business sector suggests the most effective way to mitigate unconscious bias is through structural change. Such changes could include: committing to unconscious bias training for all faculty members; ensuring equal representation of men and women on leadership selection committees; encouraging more women towards applying for leadership positions; and, setting gender or diversity targets for leadership positions.

Those at the highest levels of leadership (i.e., deans or chairs) should lead the effort to make structural changes rather than leaving it to women, or groups of women, in subordinate positions to advocate for these changes. Programs such as the Athena Scientific Women’s Academic Network (SWAN), established in 2005 in the United Kingdom, are designed to encourage and recognize the commitment of academic institutions to advance the careers of women in science, technology, engineering, and mathematics (STEM) in higher education and research. (Table 1) Such frameworks have a significant role to play in eliminating the biases that negatively affect women in academia, but much of the work must begin from within the institutions themselves.

A recent study conducted at University of Toronto’s department of medicine demonstrated that stereotypes about women were reinforced in the department as a result of women’s exclusion from certain specialities and informal networking (for instance, when meetings were held at times of day which conflicted with child care responsibilities). The same study found that unprofessional behaviour (including sexist remarks) were perceived to impact gender diversity in workplace culture in academic medicine. Participants proposed several interventions to counteract the gender gap, including changes in recruitment, hiring and promotion practices, improvements to work environments, mentorship, and ongoing monitoring and examination of the gender gap.

To mitigate and overcome unconscious biases in leadership roles, research chairs other important positions.

Table 1. Specific Action for Academic Medical Programs

1. Recognize unconscious bias and provide unconscious bias training for faculty and staff.
2. Adopt similar training programs across universities as has been put forward by Athena SWAN in the United Kingdom.
3. Recognize gender pay inequity in academic medicine and make base salaries and stipends transparent by rank and academic stream.
4. Ensure gender equity in committee composition and distribution of leadership roles, research chairs other important positions.

Summary

Women in academic medicine face overt and unconscious biases which in turn contribute to a leaky pipeline and differential success in academic research and educational advancement. We advocate for structural changes in Canadian medical schools and medical departments in order to promote a merit-based, unbiased path to equality for women in academic medicine. Such change will occur only by recognizing the persistence of gender bias and working to ensure that the leadership of these institutions reflects the demographic constituencies that they serve. We believe that similar analyses are warranted in other disciplines and sectors.

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Not Every Low Back Pain is a Radiculopathy

Pankaj Bansal MD, CCFP, Laura Grennan, Karthik Mahadevappa, MBBS, MSc, DM, Emilia Semenov MD, Shanker Nesathurai MD, MPH, FRCP(C)

A 66-year-old man with a history of chronic low back pain and three previous spine surgical procedures presented with new onset, acute, excruciating low back pain with dysesthesias radiating to the left leg, left leg weakness, and difficulty walking. There were no red flag signs. There was no focal weakness. The left ankle reflex was diminished. Sensation was decreased on the lateral foot, ankle, and lower leg. An acute left S1 radiculopathy was suspected. Magnetic resonance imaging did not reveal any changes from previous.

Three weeks later, a diffuse vesicular rash appeared on his left leg (Figure 1A, 1B, and 1C) without any changes clinically and it was complicated by lumbosacral postherpetic neuralgia (PHN).

Herpes zoster can manifest as low back pain and dysesthesias, despite initially suggesting a radiculitis. The most common neurologic complication is postherpetic neuralgia (abnormal sensations and severe, intractable pain or allodynia occurring one month after rash onset). ¹

All persons over 50 years of age and most persons under, should receive an oral antiviral within 72 hours of rash onset.²

Adjunctive corticosteroids do not have any effect on quality of life or development of PHN. ¹

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Figure 1. Images of diffuse vesicular rash

A 66-year-old man with a history of chronic low back pain and three previous spine surgical procedures presented with new onset, acute, excruciating low back pain with dysesthesias radiating to the left leg, left leg weakness, and difficulty walking. There were no red flag signs. There was no focal weakness. The left ankle reflex was diminished. Sensation was decreased on the lateral foot, ankle, and lower leg. An acute left S1 radiculopathy was suspected. Magnetic resonance imaging did not reveal any changes from previous.

Three weeks later, a diffuse vesicular rash appeared on his left leg (Figure 1A, 1B, and 1C) without any changes clinically and it was complicated by lumbosacral postherpetic neuralgia (PHN).

Over a period of 2.5 months, the patient was treated with oral acyclovir, tricyclic antidepressants, oxycodone, gabapentin, physical therapy, and TENS (transcutaneous electrical nerve stimulation). His pain improved and he eventually returned to full function.

Herpes zoster can manifest as low back pain and dysesthesias, despite initially suggesting a radiculitis. The most common neurologic complication is postherpetic neuralgia (abnormal sensations and severe, intractable pain or allodynia occurring one month after rash onset).¹

All persons over 50 years of age and most persons under, should receive an oral antiviral within 72 hours of rash onset.²

Adjunctive corticosteroids do not have any effect on quality of life or development of PHN.¹
Abstract
We will review the case of a 71-year-old woman with an atypical presentation of stage IV breast cancer. She presented with symptomatic normocytic anemia (Hb 85 to 100 g/L) for the past two years, with a normal extended laboratory evaluation. Due to deterioration of her anemia, a bone marrow biopsy was done and concluded to myelodysplastic syndrome. Treatment with epoetin alfa and a trial of lenalidomide didn’t improve her hemoglobin and she was still transfusion dependent. A second bone marrow biopsy revealed breast carcinoma infiltration, which was initially missed on the first biopsy. The patient was started on letrozole and palbociclib with good clinical response. Here, we present the clinical evolution, diagnosis and management of bone marrow micrometastasis due to breast cancer.

Résumé
Nous présentons l'étude de cas d’un cancer du sein de stade IV, chez une femme de 71 ans, ayant eu une présentation atypique. Elle s’est présentée avec une anémie normocytaire (Hb 85 à 100 g/L) symptomatique depuis deux ans, non explicable par un bilan biochimique approfondi. Suite à la dégradation de son anémie, une biopsie de moelle osseuse a été effectuée concluant à un syndrome myélodysplasique. Un traitement à l’époetin alfa ainsi qu’un essai de lenalidomide ne permirent pas l’amélioration de son hémoglobine et elle est demeurée dépendante aux transfusions. Une seconde biopsie de moelle osseuse démontra une infiltration par un carcinome mammaire qui n’avait pas été constatée lors de la première biopsie. Un traitement avec du letrozole et du palbociclib a alors été débuté avec une réponse clinique satisfaisante. Nous passons en revue la présentation clinique, la démarche diagnostique ainsi que la prise en charge des micro métastases de la moelle osseuse dans le cancer du sein.

Keywords: metastatic breast cancer, bone marrow micrometastasis, cytopenia.
Breast cancer is the most common cancer affecting women in Canada, with an estimated 25,700 new cases each year. It is the second most prevalent cause of cancer death in women, particularly because of distant metastases. Indeed, approximately 15% of women with operable breast cancer relapses within 15 years. In pooled multicenter analysis, bone marrow micrometastasis (BMM) was detected in 30% of patients with breast cancer stage I, II, and III. The presence of micrometastasis was an independent prognostic factor of poor outcome.

While BMM is considered relatively frequent, the development of cytopenia and bone marrow failure is rare. Here we present a patient with progressive symptomatic anemia over three years, who was initially diagnosed with myelodysplastic syndrome but was later found to be a manifestation of breast cancer metastasis to the bone marrow.

**Case Presentation**

A 71-year old female patient was referred to our service for evaluation of a heterogeneous aspect of the thoracic spine on a chest computed tomography (CT). Her past medical history is significant for hypertension, hyperlipidemia, subarachnoid hemorrhage with a type I Chiari malformation, and a bioprosthetic aortic valve. The initial skeletal survey and bone scan were negative for metastasis. Blood tests revealed normocytic anemia, with a hemoglobin 85 to 100 g/L and a mean corpuscular value of 95 fL for the past two years. The white cells and platelets were within the range of normal. The extended laboratory evaluation for anemia was normal. Bone marrow evaluation was done in the following months, because of progressively worsening symptomatic anemia. Bone marrow aspiration was not diagnostic due to a dry tap, while the biopsy showed an hypercellular bone marrow with erythroid dysplasia, megakaryocytes and myelofibrosis grade 1 and 2, compatible with myelodysplastic syndrome. Patient was referred to a hematologist and started on epoetin alfa. Her hemoglobin improved with higher doses of epoetin, but red cell transfusions were still needed every four to six weeks to maintain a hemoglobin above 80 g/L. A trial of lenalidomide was stopped after one month, because there was no improvement of the anemia and the patient presented a skin rash. The patient later developed an iron overload due to the transfusions.

Since the anemia didn't respond as expected with typical treatment of myelodysplastic syndrome, a second bone marrow biopsy was done eight months after the first one and revealed breast carcinoma infiltration with positive estrogen receptor, negative HER2 and progesterone receptor. In light of the findings, the first biopsy was reviewed and showed positive epithelial cells to cytokeratin AE1/A3, GATA 3 and slightly positive to CD 138, consistent with a mammary carcinoma infiltration of 10–15% of the specimen surface. Those cells were probably mistaken on the first biopsy for granulocytic precursors cells. Based on these results, a review of the patient's gynecological history was taken. There was no past or familial history of breast or ovarian cancer. Her mammography's of the last two years were negative, the last one done a month prior. The physical exam was within normal and didn't reveal breast lump or lymphadenopathy. Tumour marker panel indicated increased serum level of Ca15-3, Ca19-9 and CEA. LDH were normal. The patient underwent a skeletal scintigraphy, which was remarkable for many bilateral costal lesions. An abdominal and pelvic CT scan confirmed the presence of diffuse lytic lesions and right axillary lymphadenopathy, which has been stable for the past two years. Diffuse metastasis of the spine was revealed on magnetic resonance imaging (MRI). No primary breast lesion was found on echography or MRI. After discussion, with the oncology team, we decided against doing a positron emission tomography (PET) scan since it wouldn't change the management of the cancer.

Patient was started on letrozole and palbociclib, an highly selective inhibitor of CDK 4/6. Cytopenia improved significantly in the next 6 months, with hemoglobin level of 112 g/L and normalization of white blood cells and platelets level. A single dose of palliative radiotherapy was delivered on the left knee to alleviate the pain from metastasis infiltration.

**Discussion**

Patients presenting with chronic unexplained cytopenia can be a clinical challenge and warrant an extensive evaluation. The
differential diagnosis is large and include nutritional deficiency, chronic inflammatory reactions, autoimmune diseases (e.g., autoimmune hemolytic anemia), chronic renal or hepatic diseases, infectious disorders, inherited conditions and bone marrow failure. Several causes of bone marrow failure need to be considered, such as myelodysplastic syndrome, aplastic anemia, infiltration of the bone marrow by hematologic or non-hematologic neoplasm, myelofibrosis or toxic damage. In our case, the second bone marrow biopsy was diagnostic for breast cancer bone marrow infiltration.

While breast cancer is commonly diagnosed in the early stages of the disease without evidence of distant metastases, recurrence at distant sites may arise years after the initial diagnosis and treatment. We now know that breast cancer has an early spread of tumour cells. The dissemination of tumour cells can take two pathways, either lymphatic dissemination or hematogenous dissemination. The detection of BMM is evidence of dissemination through the blood circulation.

As reported earlier, a third of patients have BMM detected at the time of breast cancer diagnosis. The majority of those patients have normal blood counts and no specific symptoms. A previous study (Kopp et al.) reported an incidence of only 0.17% clinically apparent BMM. The actual incidence may be underestimated, as stated by the investigators, because the diagnosis may have been missed and their database was incomplete.

When BMM is clinically evident, the most common finding is anemia, present in 40–60% of patients, while 12–25% of patients have leukopenia and thrombocytopenia. Other laboratory abnormalities include hypoproteinemia and elevated serum lactate dehydrogenase. Symptoms reported are asthenia, anorexia and bone pain secondary to osteolytic lesions. In a past series of 22 cases, a close association between bone metastasis and bone marrow involvement was confirmed, with all patients having bone metastasis. Other studies found that 2–8% of patients with BMM had no evidence of skeletal involvement.

Demir et al. reported that the median time to diagnosis of BMM was of 3 years after the initial diagnosis of breast cancer. The interval was shorter in hormonal receptor negative tumours (17.9 months) which is consistent with past studies. Risk factors for BMM include large tumour size, poor differentiation, lymph node metastasis, and negative hormone receptors. There are some reports of bone marrow involvement as the initial presentation of breast cancer. To our knowledge, there is no other reported case of evidence of BMM months before the diagnosis of breast cancer without breast lesion on physical exam and a normal mammography.

Non-invasive test for diagnosis of BMM include whole-body PET, with a sensitivity of 87% with a positive predictive value of 94%. Since most patients undergo PET scan for the staging of the disease, PET seems the modality of choice for the diagnosis of BMM. Whole-body PET with 18F-FDG exploits the high glycolytic rate of malignant tissue compared with that of non-malignant cells, which can reveal previously unknown metastatic disease to the bone marrow. Peripheral blood smear can show signs of marrow infiltration with the presence of leukoerythroblastosis, if other causes, such as myelodysplastic syndrome and myeloproliferative syndromes are ruled out. Leukoerythroblastosis is defined as the presence of nucleated erythrocytes and immature myeloid cells in the peripheral blood. Bone marrow evaluation is often needed to confirm the diagnosis. Past series suggested that bone marrow biopsy is more useful than aspiration for the diagnosis of BMM, with less than 15% of false-negative results.

There is limited literature regarding the safest and most effective treatment of patients with BMM. The presence of cytopenia, due to breast cancer infiltration of the marrow, poses a difficult problem in the treatment of affected patients. Past reports demonstrated the need for intensive hematological support in more than 50% of patients treated with full-dose chemotherapy and a risk of infection around 20%. More recently, small studies have presented benefit, including improvement of cytopenia, with the use of low-dose chemotherapy with capcitabine, endocrine therapy, anthracycline or trastuzumab. More studies are needed before a standard regimen can be established.

The prognosis of breast cancer patients with BMM, while variable, is usually poor. The median survival time after the diagnosis of apparent BMM varied from more than 6 to 19 months, in past studies. The extent of bone marrow infiltration may have prognostic value. In a multivariate analysis of prognostic factors in patients with breast cancer, a pre-treatment hemoglobin less than 110 g/L and platelets below 100 × 10^9/L was associated with a poor prognostic. BMM may be an indicator of early recurrence. Cote et al. reported an association between the presence of micrometastasis in operable breast cancer stage I and II, and early recurrence. The 2 years’ recurrence rates were 3% and 33% in 49 patients without and with micrometastases respectively.

**Conclusion**

In conclusion, unexplained cytopenia is a strong indicator of the necessity of bone marrow examination. Bone marrow is a frequent site of metastasis of breast cancer and other solid tumours. Patients with BMM usually don’t have bone marrow failure, but they can present with anemia, thrombocytopenia or pancytopenia. Further studies are needed to develop more effective therapies.
References
Abstract

*Klebsiella pneumoniae* liver abscess syndrome (KLAS) is an emerging infection caused by hypermucoviscous strains (K1, rmpA, mgA) with a particular virulence at risk of metastatic dissemination. We describe a case of metastatic KLAS in a Canadian immunocompetent patient of Vietnamese origin who presented with fever and abnormal liver function tests. Imaging studies revealed unique liver and pulmonary abscesses. Blood and liver abscess cultures showed colonies of *K. pneumoniae* with hypermucoviscous phenotype, a K1 serotype and the presence of a rmpA gene confirming biomolecular features of the invasive syndrome. Mostly reported in patients of Asian origin, KLAS has been reported in Canada since 2007. Prompt identification and treatment prevents severe complications such as endophthalmitis, meningitis, lung abscess and spondylodiscitis.

Résumé


**Keyword:** liver abscess metastatic syndrome, hypermucoviscous *klebsiella pneumoniae*
In March 2015, a 34-year-old patient presented at the emergency department of CHU de Québec (CHUL) and was admitted to the internal medicine clinical teaching unit. He reported one week of fever and chills, profuse sweating, temporal headache, loss of appetite, and myalgia. The patient emigrated from Vietnam to Canada 11 years earlier and had not returned there since then. His only recent trip had been to Boston in 2011. He completed a treatment for latent tuberculosis in 2005. He worked as an informatician, had no allergies, and did not take medication. The patient reported no infectious contact, illicit drug abuse, or other at-risk exposures for malaria, viral hepatitis, Q fever, leptospirosis, or brucellosis. The patient did not complain of rash, weight loss, or any abdominal, pulmonary, urinary, or neurological symptoms.

The patient was diaphoretic without rash or jaundice. Physical findings included a blood pressure of 90/58 mmHg, a temperature of 38.9°C, a heart rate of 100 beats per minute, non-painful cervical lymphadenopathy (less than 2 cm), and hepatomegaly (2 cm below costal margin). The remainder of the physical examination was normal without meningeal signs, abdominal mass, tenderness, or ascites. Vital signs stabilized rapidly with treatment and intravenous fluids.

Laboratory studies showed hyponatremia at 131 mmol/L (135–145 mmol/L), white blood cell count at 9.9 × 10⁹, thrombocytopenia at 50 × 10⁹ g/L (150–400 × 10⁹ g/L), abnormal liver and pancreas functions tests: aspartate aminotransferase 0.68 µkat/L (<0.67 µkat/L), gamma-glutamyl transferase 3.57 µkat/L (<0.83 µkat/L), total bilirubin 31 µmol/L (0–21 µmol/L), direct bilirubin 16 µmol/L (<4 µmol/L) amylase 2.99 µkat/L (<1.67 µkat/L), lipase 4.21 µkat/L (< 0.92 µkat/L). Tests for amebiasis, echinococcosis, human immunodeficiency virus, and hepatitis B–C were negative and tests for Epstein-Barr virus and cytomegalovirus showed an ancient exposition.

Abdominal ultrasound, contrast-enhanced computerized tomography (CT) scan, and magnetic resonance imaging (MRI) showed a unique hepatic abscess with a diameter of 3.3 cm in the eighth segment of the liver (Figure 1). A chest CT revealed an asymptomatic pulmonary abscess in the right lower lobe (Figure 2).

Blood cultures and cultures from percutaneous drainage of the hepatic abscess grew Klebsiella pneumoniae with hypermucoviscous phenotype, defined by a positive ‘string test’ (viscous string > 5 mm when bacterial colonies on an agar plate are stretched by an inoculation loop) as shown in Figure 3. The Canadian Science Centre for Human and Animal Health (Winnipeg, Canada) confirmed a K1 serotype and the presence of a rmpA gene confirming biomolecular features of the invasive syndrome.

The pulmonary metastatic lesion was the hallmark for the diagnostic of Klebsiella pneumoniae liver abscess metastatic syndrome (KLAS). Based on in vitro susceptibilities, piperacillin-tazobactam, empirically given, was replaced by ceftriaxone for six weeks of IV ambulatory treatment. The liver abscess, of less than 5 cm, was entirely drained with a single percutaneous needle aspiration, without surgery. Drainage was not indicated for the uncomplicated pulmonary abscess. A cerebral MRI did not show endophthalmitis, abscess or meningeal anomalies.
Lumbar puncture was not initially performed because of the thrombocytopenia. Followed until July 2015 by CT scans, hepatic and pulmonary lesions disappeared, and liver tests normalized after antibiotic treatment. The patient has not relapsed.

**Discussion**

*Klebsiella pneumoniae* is a well-known gram-negative bacillus with a thick polysaccharide. Standard clinical diseases are related to *K. pneumoniae* and *K. oxytoca* such as pneumonia, urinary tract infections, abdominal cavity surgery-related infections and several nosocomial syndromes often associated with a history of alcohol abuse or diabetes mellitus.

KLAS is a distinctive infection related to specific subcapsular serotypes and a marked virulence that produces liver abscesses and several distant metastatic infections. Described mostly in the Asian population since the 1980s, cases have been diagnosed in North and South America, Europe, Canada, and Australia.

A liver abscess caused by this particular microbiological strain with extra-hepatic infections should be recognized as KLAS. The clinical signs of KLAS are fever, chills, headache, and abdominal pain. Nausea and vomiting occur in about 25% of patients. Half of the patients have jaundice and hepatomegaly. Blood test findings are leucocytosis, increased C-reactive protein, abnormal liver function tests, and thrombocytopenia.

Metastatic spread, unusual for most enteric gram-negative bacilli, is a hallmark of the hypermucoviscous Klebsiella pneumonia strain infecting immunocompetent hosts. From 8 to 30% of metastatic disease in KLAS, a case series of 23 patients with metastatic lesions reported mostly endophthalmitis, uveitis, pulmonary abscess, and purulent meningitis.

Hypervirulent *Klebsiella pneumoniae* (hvKP) is directly linked to the hypermucoviscous phenotype, related to the k1, k2 serotypes and the regulator of mucoid phenotype A (rmpA) gene. This feature gives this type of pathogen the ability to produce lethal extra liver infections in non-immunocompromised patients. Numerous virulence factors have been elucidated and implicate the presence of mucoviscosity genes like magA, rmpA, aerobactin but the exact mechanism by which this spreading take place is unknown. Shon et al. observed that hvKP was resistant to complement- and neutrophil-mediated bactericidal activity in a rat subcutaneous abscess model and produces more biofilm than others strains. This capacity increases intestinal colonization. In this case, the patient developed KLAS even if he had been colonized in an endemic area several years ago. Colonization usually happens when there is a disruption of the natural barriers (ascension into the bladder, aspiration into the respiratory tract, gastrointestinal colonizers) but KLAS has been reported in people, like this patient, without evidence of altered mucosal barriers.

Even though the majority of patients with hvKP infection are healthy, there is a significant mortality rate between 3 and 42% in part following necrotizing fasciitis and severe community-acquired pneumonia. Moreover, survivors can suffer appalling consequences such as blindness and neurologic sequelae. Even if most hvKP infections are treatable with common antibiotics, long-term follow-up is necessary because of the high risk of relapsing. Several cases of resistant strains with extended spectrum B-lactamases and carbapenemases have already been reported. All these characteristics could make hvKP one of the next "superbugs."

**Conclusion**

To our knowledge, this is the first report of a complete metastatic syndrome by HvKp in Canada, following the first published case of pyogenic liver abscess caused by hvKP in Manitoba in 2007. Compelling questions about hvKP remain unanswered. Its natural course is barely understood. Diagnostic features such as a positive 'string test' and capsular serotypes like K1 or K2 are not always distinctive of hvKP. Its capacity for metastatic spread, an unusual trait for an enteric gram-negative, is a worrying characteristic of this strain of Klebsiella that is no longer confined to Asia.

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A Challenging Case of Non-resolving Pneumonia: Keeping Antisynthetase Syndrome in the Differential Diagnosis

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Abstract
A 62-year-old Caucasian female ex-smoker presented to the emergency department with progressive shortness of breath with associated pleuritic chest pain, new arthralgias, and muscle weakness for two months. She had already been treated with two courses of antibiotics for suspected community acquired pneumonia with no improvement in her respiratory symptoms. This is a case that illustrates the eventual diagnosis of antisynthetase syndrome, a subtype of the idiopathic inflammatory myopathies. The current standard of diagnostic criteria and treatment for this autoimmune condition will also be discussed.

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A 62-year-old Caucasian female ex-smoker presented to the emergency department with progressive shortness of breath with associated pleuritic chest pain, new arthralgias, and muscle weakness for two months. She had already been treated with two courses of antibiotics for suspected community acquired pneumonia with no improvement in her respiratory symptoms (Figure 1). She denied any recent travel, remarkable environmental or occupational exposures. She had no history of fever, weight loss or other constitutional symptoms. Her past medical history included hypertension, irritable bowel syndrome, and previous diverticulitis. She took no medications. Her brother had severe rheumatoid arthritis.

Upon initial assessment, she was hypoxic (oxygen saturation 85% on room air and on exertion). Physical examination revealed bibasilar inspiratory crackles, rosacea, tender wrists and metacarpophalangeals (MCPs) bilaterally and symmetrical proximal muscle weakness in both upper and lower extremities.

Her laboratory investigations showed elevated creatinine kinase levels of 3373 U/L (peak 4795 U/L; Normal range <149U/L), and an erythrocyte sedimentation rate of 40 mm/hr (Normal 0–20 mm/hr). She had a mildly elevated troponin level of 0.18 ug/L (Normal <0.07ug/L) with an electrocardiogram (ECG) showing evidence of left ventricular hypertrophy but no ischemia and a normal bedside echocardiogram.

Computed tomography (CT) of the chest showed a peripheral and basilar pattern of bilateral pulmonary opacities favouring organizing pneumonia (Figure 2). Subsequent pulmonary...
function testing was symptom-limited but nonetheless, there was a proportional reduction in forced expiratory volume (FEV1) and forced vital capacity (FVC) (51% and 56% predicted respectively) and moderate lung restriction with reduced functional residual capacity and residual volume (RV) (66 and 50% respectively). Malignancy screen (including mammogram and transvaginal ultrasound) was negative.

Possible autoimmune involvement was suspected given her positive family history. She was positive for antinuclear antibodies (ANA). Anti-SSA (Ro) and Anti-Jo-1 titres were both greater than 8.0 AI Units (normal < 0.9 AI Units). Rheumatoid factor, Anti-Cyclic Citrullinated Peptide, C3, C4 and the remainder of the extractable nuclear antibody screen was negative.

Electromyography showed a diffuse myopathic process consistent with an inflammatory myopathy with evidence of muscle fibre inflammation and necrosis. Magnetic resonance imaging of her lower extremities confirmed the presence of diffuse subcutaneous edema consistent with polymyositis.

The positive serology and the electromyography suggested an immune-mediated myopathy at the top of the differential diagnosis. Specifically, the positive Anti-Jo-1, anti-SSA, ANA, respiratory manifestations and myositis, highly favoured the diagnosis of antisynthetase syndrome (AS). Thus, the patient was initiated on high-dose prednisone (60 mg daily) and mycophenolate mofetil 1.5 g twice a day. She demonstrated symptomatic improvement on the therapy. A left-thigh muscle biopsy was performed one-month post-initiation of treatment and revealed findings consistent with an immune-mediated myopathy and type II fiber atrophy. Finally, a two-month follow-up with a respirologist demonstrated the patient had improved pulmonary function tests (increased vital capacity, improved walk test, and diffusion capacity) from baseline with immunosuppressive therapy.

**Pathological Discussion**

The idiopathic inflammatory myopathies (IIMs) are a group of related autoimmune syndromes diagnosed based on a combination of clinical features of skeletal muscle inflammation, characteristic findings on muscle biopsy, and specific autoantibodies. The IIMs include dermatomyositis (DM) and polymyositis (PM), along with other overlapping connective tissue diseases. AS is another systemic autoimmune condition included in this group. AS consists of a constellation of the following symptoms: myositis, arthropathy, fever, Raynaud’s phenomenon, mechanic’s hands, and interstitial lung disease (ILD), along with the presence of serum autoantibodies against aminoacyl-tRNA synthetases, most commonly the anti-Jo-1 antibody. Other relevant AS antibodies include anti-PL-7 and anti-PL-12. In a patient who presents with both myositis and ILD, an anti-Jo-1 antibody is a very sensitive and specific test for AS.

The clinical presentation of AS is variable, and the precise phenotype is dependent upon the specific autoantibodies present. In addition, many findings of AS overlap with the findings of other connective tissue disorders and it can take months-to-years for all manifestations of AS to be revealed, leading to delays in diagnosis. Studies have found some correlations between specific autoantibodies and the clinical manifestations presented by AS patients. For instance, Anti Pl-7 is correlated with more severe ILD and myositis is almost always present in those with Anti-Ro/SSA.

Myositis is present in 78–91% of patients with anti-Jo-1 positive AS, but is usually not the first presenting symptom and may only present after many years of disease. The myositis may present as an isolated elevation of creatine kinase, or can present with clinical symptoms of proximal muscle weakness and pain. The muscles of the esophagus, hypopharynx, and the respiratory muscles can also be involved, leading to a risk of aspiration and shortness of breath. Electromyogram (EMG) studies, MRI of the muscle, and muscle biopsies can all aid in the diagnosis of AS and in monitoring disease progression; however, they are not necessary to make a diagnosis. The findings on muscle biopsy in AS are similar to those seen in other IIMs; however, with some unique features including fragmentation of perimysium connective tissue, perimysium inflammation, and perifascicular atrophy. Arthralgia is present in approximately 75% of patients with AS, and tends to be asymmetric, non-deforming, non-erosive arthritis, which can present similarly to rheumatoid arthritis. It is the primary presenting symptom in approximately 27% of patients with AS.

Interstitial lung disease has been shown to be present in 69–90% of anti-Jo-1 positive patients and is commonly an initial
presenting symptom, prior to the onset of a myopathy.\textsuperscript{3,7,8} The ILD associated with AS can be severe and is the major cause of morbidity and mortality in patients with AS. It typically presents as exertional dyspnea, often with a non-productive cough.\textsuperscript{8} High-resolution CT scans can be used in the diagnosis of ILD and most commonly show a diffuse, patchy, ground glass opacities and basal consolidations whereas honeycombing and bronchiectasis are seen infrequently.\textsuperscript{9,10} A lung biopsy is also useful in the diagnosis and characterization of ILD in AS, with common findings including non-specific interstitial pneumonitis, usual interstitial pneumonitis, cryptogenic organizing pneumonitis or bronchiolitis obliterans organizing pneumonia (COP/BOOP), and diffuse alveolar damage. Spirometry often shows decreased FVC and reduced diffusion capacity, and upright and supine spirometry may reveal evidence of respiratory muscle weakness. When comparing AS to non-AS IIMs, those with AS are more likely to show ILD as the initial presenting symptom, are more likely to be corticosteroid responsive and are more likely to have recurrences of the ILD.\textsuperscript{9} Studies have shown that anti-Jo-1 positive disease tends to have worse pulmonary outcomes, compared to other AS antibodies including anti-PL-12, and the combination of anti-Jo-1 and anti-Ro (anti-SSA) antibodies tends to be associated with more severe respiratory illness.\textsuperscript{11} Other cardiopulmonary manifestations of AS include pulmonary hypertension, cardiomyopathy, myocarditis, pericardial effusions, and pleural effusions.\textsuperscript{12}

Strict diagnostic guidelines for AS is a challenge with such variable clinical presentation for patient cases. Certain features of AS, including Raynaud’s, fever, and mechanic’s hands, are only seen in a minority of patients and are non-specific findings. The other clinical findings, including myositis, arthralgias, and ILD have been shown more consistently in patients with AS. Soloman et al provided stricter diagnostic criteria in 2011 with a diagnosis of AS being the presence of tRNA synthetase auto-antibodies and at least one major manifestations (myositis, dermatomyositis, ILD) and at least two minor manifestations (mechanic’s hands, Raynaud’s, arthritis, unexplained fever).\textsuperscript{13}

Because AS is associated with high morbidity, prompt diagnosis and treatment is important, especially as it is generally responsive to immunomodulatory therapy. There are no controlled trials of the treatment of AS, however, the recommended first-line treatment of AS involves corticosteroids at a dose of 1 mg/kg/day, tapered after 6–8 weeks. Treatment can also involve steroid-sparing immunomodulatory agents, such as cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, and IVIG. One case report of refractory AS after a trial with a number of immunosuppressive treatments showed remission with 4 months of treatment with mycophenolate mofetil (MMF) at a dose of 2 g/day, which was well-tolerated.\textsuperscript{14} Although case reports and case series have shown success in treating AS with these agents, it has also been shown that AS has a tendency to relapse and can be severe and unresponsive to treatment.\textsuperscript{9} Thus relapse is another important factor to monitor for in AS patients who are tapered or discontinued off immunotherapy. Predictors of poor prognosis include older age of onset, malignancy, and negative immunologic tests.\textsuperscript{15} Management of AS should also include a malignancy screen as there exists an association between various malignancies and AS. It is unclear whether these malignancies may play a causal role in the development of AS through a paraneoplastic process. Appropriate clinical precautions applicable to patients on long-term immunosuppressants such as vaccination, Pneumocystis jiroveci Carinii pneumonia prophylaxis and management of adverse effects (e.g., osteoporosis prevention with glucocorticoids) also applies for AS patients.\textsuperscript{16}

Conclusions

1. Antisynthetase Syndrome
AS is a clinically heterogeneous small subset of DM-PM which can present with isolated respiratory symptoms such as cough and shortness of breath with associated, delayed or absent muscle symptoms. It should be considered in the differential of non-resolving pneumonia.

2. Initial Symptoms and Clinical Presentation
   - Initial symptoms: dyspnea, cough, fever, muscle weakness
   - DM-PM-like muscle weakness, myalgias, arthralgias or skin changes can follow months later
   - Major manifestations: myositis, dermatomyositis, ILD
   - Minor manifestations: mechanic’s hands, Raynaud’s, arthritis, unexplained fever

3. Important Diagnostic Tests with Reported Prognostic Value
   - Diagnostic tests can aid in early diagnosis and therefore early treatment
   - Markers of muscle inflammation (CK) and autoantibodies against aminoacyl-tRNA synthetases (especially anti-Jo-1, Anti-PL12/7)
   - Presence of Anti-SSA/SSB antibodies
   - Respiratory investigations including high-resolution CT scan (pattern and extent of disease); bronchoscopy with bronchoalveolar lavage and lung biopsy are often not required for diagnosis but can be considered in unclear cases to confirm the diagnosis.
   - Pulmonary function testing for diffusion capacity, and maximum inspiratory/expiratory pressure (MIPS/MEPS) to assess respiratory muscle involvement
4. **Also, Consider Within Diagnostic Workup**
   - Echocardiogram to screen for pulmonary hypertension
   - Rule out malignancy: ultrasound, imaging

5. **Treatment**
   - No formal guidelines currently for a standard of treatment, patients often initiated on high-dose glucocorticoids and immunosuppressants
   - Monitor for relapse in patients particularly after tapering glucocorticoids
   - Even with appropriate treatment, including high-dose glucocorticoids and immunosuppressants (e.g. MMF), respiratory symptoms may persist and are the major cause of morbidity and mortality (up to 40% increase in mortality). This may require long-term supportive care, including home oxygen and referral to an outpatient respirologist.

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None.

**Competing Interests**
None to declare.

**References**
Renal Limited Lupus-Like Nephritis – A Case Report and Review of Literature

Jumana Amir, Salwa Sheikh, Abdulrazack Amir

Abstract

Biopsy diagnosis of lupus nephritis with no extra-renal features of systemic lupus erythematosus, normal complement levels, negative or weekly positive anti-nuclear antibody and negative other serology is a rare entity known as “Renal Limited Lupus Like Nephritis” (RLLLN). So far, only 39 cases of RLLLN in adults have been reported in literature. The prognosis of these patients varied depending on their clinical presentation. Herein, we report a case of an elderly Arab female with RLLLN who presented with massive proteinuria and acute kidney injury with crescents, however had a good outcome contrary to reported cases with similar presentations. We also reviewed all reported cases thus far.

Resume

Le diagnostic par biopsie de la néphropathie lupique dépourvue de caractéristiques extra-rénales du lupus érythémateux disséminé, de niveaux de complément normal, d’anticorps anti-nucléaire négatifs ou hebdomadaires positifs et d’une autre sérologie est une entité rare appelée « Néphrite Rénale Limitée semblable au Lupus » (RLLLN). Jusqu’à présent, seuls 39 cas de RLLLN chez les adultes ont été rapportés dans la littérature. Le pronostic de ces patients variait en fonction de leur présentation clinique. Ici, nous rapportons le cas d’une femme arabe âgée souffrant de RLLLN qui présentait une protéinurie massive et une lésion rénale aiguë accompagnée de croissants, mais dont le résultat était satisfaisant contrairement aux cas rapportés avec des présentations similaires. Nous avons également examiné tous les cas signalés jusqu’à présent.

Keywords: Renal-Limited Lupus-Like Nephritis, Lupus Nephritis, Full-House pattern

Lupus nephritis is a common feature of systemic lupus erythematosus (SLE) usually occurring in young females and diagnosed by renal biopsy. Only 10 cases have been reported in adults where patients with lupus nephritis have negative serology and no extra-renal SLE manifestations. This rare entity is known as Renal Limited-Lupus-Like Nephritis (RLLLN). Reported outcomes varied from good to poor. We herein report a case of an elderly female with Renal-Limited Lupus-Like Nephritis who presented with massive proteinuria, gross hematuria and acute kidney injury with crescents. However, she had a good outcome unlike previous cases with similar presentation.

Case Report

A 63-year-old Arab female with no previous history of renal or autoimmune disease presented in November 2014 to an outside facility with 1-day history of gross hematuria and decreased urine output. On arrival, she was found to have proteinuria. 2 days after presentation, she became anuric with signs of volume overload, severe hyponatremia, and had worsening renal function requiring urgent hemodialysis. She was referred to our facility 1 week after initial presentation for further care and management. The patient had no history of joint pain/swelling, rash, oral ulcers,
recent infections, fever, or other constitutional symptoms. No history of medication use.

On examination, she had stable vital signs, no rash, or evidence of active synovitis. She had minimal bilateral pitting edema and remainder of the examination was unremarkable.

Laboratory investigations showed creatinine 6.1 mg/dL, serum sodium 128 mEq/L, Hemoglobin 11.4 g/dL, platelets 310,000, and leukocytes 12.8 k with no left shift. Urine analysis showed gross hematuria with dysmorphic RBCs. Serum albumin 2.9 g and total urinary protein excretion 23 g. No abnormal “M” spike or monoclonal protein on serum protein electrophoresis. She had a borderline ANA (titer 1:80); speckled pattern. Negative Anti double stranded DNA, Anti-Smith, and Anti-neutrophil cytoplasmic antibodies. Anti SS-A/Ro, Anti SS-B/La, Anti-Jo1, Glomerular base antibodies were negative. C4 level was normal and C3 was borderline suppressed 8 mg/dL (normal 9–180). HIV, hepatitis B and C were negative.

Computed tomography-guided percutaneous renal biopsy revealed endocapillary proliferative, crescentic and membranous glomerulonephritis consistent with class IV and V lupus nephritis. Most glomeruli showed marked global mesangial and endocapillary hypercellularity with abundant intracapillary infiltrating lymphocytes, monocytes, and neutrophils. The basement membranes were thickened and 43% of glomeruli showed active crescents (Figure 1). Immunofluorescence showed a “full-house” pattern with positive mesangial and capillary wall staining for IgG, IgA, IgM, C1q, kappa, and lambda. On electron microscopy, there was segmental duplication of basement membrane with cellular interposition, and abundant global mesangial, intramembranous, subendothelial, and segmental subepithelial electron dense granular deposits (Figure 2). Few endothelial tubuloreticular inclusions were present. These findings are consistent with RLNN.

The patient continued dialysis and was started on methylprednisolone and cyclophosphamide (CYC). As per the National Institutes of Health (NIH) protocol, the patient was given intravenous (IV) cyclophosphamide (500 mg/m²) during this hospital stay. She received a total of 6 doses of cyclophosphamide over 1 month (500 mg/m²) as induction, IV pulse cyclophosphamide as maintenance once every 3 months (quarterly) for 2 years, for a total of 14 cycles. The cyclophosphamide dose was adjusted based on the patient’s renal function and hemodialysis; as recommended by Aronoff in 2007. The patient completed her therapy and tolerated it well. She had no cyclophosphamide-related side effects during and after receiving treatment. The patient was also weaned off dialysis. Over 3 years after initial presentation, she continues to be in remission with normal creatinine level and only moderate proteinuria (30 mg/dL) (Figure 3). She follows up regularly with the nephrology service, has no change in serology status and no signs or symptoms of SLE.

Discussion
Lupus nephritis is a known major cause of morbidity in SLE. Up to 60% of adult lupus patients eventually develop renal
impairment. It usually happens early in the SLE disease course, and in 15–20% of patients, nephritis may be the first clinical presentation of SLE. The incidence of lupus nephritis varies depending on the population. It occurs more in those of Asian descent, followed by Africans, Hispanics, and finally Caucasians. SLE in general, has a clear female predominance, and renal disease in SLE specifically tends to be more common in the younger age group. The presence of lupus nephritis in SLE is an indicator of poor prognosis.

The most common clinical feature of lupus nephritis is proteinuria. In 1999, Cameron found that proteinuria occurred in 100% of patients with lupus nephritis. Other features include microscopic hematuria, granular or red cell casts, hypertension, and decreased renal function. Biopsy remains the best modality of diagnosis. In 2003, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) developed a lupus nephritis classification system based on biopsy findings. Positive staining for IgG, IgM, IgA, C3, and C1q, known as the "full-house pattern," on immunofluorescence is strongly suggestive of lupus nephritis. It is seen in one-quarter of patients with nephritis due to lupus and is very rarely seen in other causes of nephritis. Other strongly suggestive pathology findings include immune-complex deposits present diffusely in the mesangium, subendothelium, and subepithelium, extraglomerular immune-complex deposits in the tubular basement membranes, interstitium, and blood vessels, and the presence of endothelial cells tubuloreticular inclusions. These tubuloreticular inclusions are mostly associated with lupus nephritis and may be seen less commonly with other renal disease causes such as hepatitis B, hepatitis C, or HIV. Patients with lupus nephritis also have low complement levels and positive serology for ANA, Anti-DNase DNA and Anti-Smith antibodies seen in SLE.

There have been cases with biopsy diagnosis of lupus nephritis but have no extra-renal manifestations of SLE, have normal complement levels, negative or weakly positive ANA and negative reminder serology. This rare entity is known as RLLLN. The majority of cases reported are in children with some subsequently developing SLE features or positive serology. Very few cases have been reported in adults. Based on literature review using PubMed, Cochrane Library, and Google Scholar, using the terms “Renal-Limited Lupus-Like Nephritis,” “Renal Limited Lupus,” and “Full-House Nephritis,” we found only 39 reported cases of RLLLN in adults. We looked for cases of patients age 18 or above to target the adult age-group literature in our review. Edward Jones first reported this disease in 5 adults in 1982. Andrew Sharman then reported 5 similar cases in adults in 2004. In 2005, Ozdemir reported an additional case. In 2010, Y.K. Wen published a study which included 21 patients with Renal Limited Lupus. Ana Huerta later reported 4 similar cases in 2011, and in 2013, Chi Young reported an additional case. The cases varied in their presenting features and subsequently their outcome (Table 1).

We present the first case of RLLLN in an elderly female with excellent outcome despite her initial presentation of acute kidney injury, creatine of 6.1, and crescentic nephritis. We included her initial presentation, disease course, diagnostic findings, management plan, and finally her outcome and follow up. We emphasized some unique findings in our case by comparing them to all similar cases reported so far and information obtained from our review of literature.

A study done in 2016 including 924 SLE patients, found that renal disease is more common in the young, specifically in those under 55 years of age. The majority of reported cases (2/3) were in younger adults (< 55 yrs) and a majority presented with proteinuria or microscopic hematuria; the 2 most common findings in lupus nephritis. Our patient, presented at an older age (66 years), had proteinuria, in addition to gross hematuria and acute kidney injury which occur in 1–2% of patients. Our patient’s lack of extra-renal manifestations, negative serology, and renal biopsy findings are all consistent with RLLLN.

Treatment of patients with RLLLN is of utmost importance, and the regimen includes 2 phases; induction and maintenance. IV cyclophosphamide is the usual induction drug. Oral mycophenolate mofetil has also been used as another option for induction. Oral azathioprine, oral mycophenolate mofetil, or IV cyclophosphamide are used for maintenance. Different protocols have been established for the management of lupus nephritis. We followed the standard protocol published by the NIH in 1992. Despite the possible risk of cumulative cyclophosphamide effect, the NIH protocol was selected for this patient as it is the protocol preferred by the treating teams at our institute. This protocol includes the use of monthly intravenous cyclophosphamide (500–1000 mg/m²) for 6 months as induction therapy, followed by the use of intravenous pulse cyclophosphamide every 3 months (quarterly) for 2 years as maintenance. We also adjusted the cyclophosphamide dose based on renal function.
## Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults*

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Number of Cases</th>
<th>Patient’s Age (Years)</th>
<th>Initial Presentation</th>
<th>Initial Creatinine (mg/dL)</th>
<th>Crescents</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Chi Young</td>
<td>1</td>
<td>40</td>
<td>Proteinuria</td>
<td>Normal</td>
<td>None</td>
<td>1. CYC &amp; Methylprednisolone 2. MMF &amp; Prednisone</td>
<td>• Good; Normal renal function • Proteinuria &lt;43000 mg/24 hrs</td>
</tr>
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<td>2012</td>
<td>Ana Huerta</td>
<td>4</td>
<td>36</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal</td>
<td>Present (46%)</td>
<td>1. Prednisone 2. MMF 3. CYC with MMF &amp; Prednisone 4. Hemodialysis</td>
<td>• Poor; ESRD then Renal Tx</td>
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<td></td>
<td></td>
<td>19</td>
<td></td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Elevated (1.7)</td>
<td>Present (55%)</td>
<td>1. Prednisone 2. MMF 3. Methylprednisolone 4. MMF &amp; Prednisone</td>
<td>• Poor; ESRD then Renal Tx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td>Lower limb edema &amp; worsening HTN</td>
<td>Elevated (2)</td>
<td>Present (43%)</td>
<td>1. Prednisone 2. Temporary Hemodialysis</td>
<td>• Poor; CKD stage 3</td>
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<tr>
<td></td>
<td></td>
<td>46</td>
<td></td>
<td>Fever, Vomiting &amp; Nephrotic Syndrome</td>
<td>Elevated (3.5)</td>
<td>Present (75%)</td>
<td>1. Prednisone &amp; CYC 2. Switched to MMF (due to CYC side effects) 3. Hemodialysis</td>
<td>• Poor; ESRD on Hemodialysis</td>
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<td>2010</td>
<td>YK Wen</td>
<td>21</td>
<td>57</td>
<td>Acute renal failure</td>
<td>Present in 4 patients (i)</td>
<td>Methylprednisolone, CYC, &amp; Prednisone</td>
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<td>79</td>
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<td>Acute renal failure</td>
<td>Present</td>
<td>Methylprednisolone, CYC, &amp; Prednisone</td>
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<td></td>
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<td>28</td>
<td></td>
<td>Chronic renal failure</td>
<td>Present</td>
<td>ACEI</td>
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<td></td>
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<td></td>
<td>61</td>
<td></td>
<td>Nephrotic syndrome</td>
<td>Present</td>
<td>Prednisone</td>
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<td>35</td>
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<td>Rapid progressive renal failure</td>
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<td>Prednisone &amp; AZA</td>
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<td>Prednisone, CYC &amp; ARB</td>
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<td>Prednisone &amp; ARB</td>
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<td>Prednisone, CYC, ACEI</td>
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<td></td>
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<td>Prednisone, CYC, ACEI</td>
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<td>Present</td>
<td>Prednisone &amp; CYC</td>
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<td>Year</td>
<td>Author</td>
<td>Number of Cases</td>
<td>Patient's Age (Years)</td>
<td>Initial Presentation</td>
<td>Initial Creatinine (mg/dL)</td>
<td>Crescents</td>
<td>Management</td>
<td>Outcome</td>
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<td>2005</td>
<td>FN Ozdemir</td>
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<td>28</td>
<td>Proteinuria, HTN, Lower limb edema</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal (0.8)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal (1.1)</td>
<td>None</td>
<td>None</td>
<td>Poor; CKD Stage 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>Proteinuria</td>
<td>Normal (0.6)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>Proteinuria</td>
<td>Normal (0.6)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal (0.8)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td>1982</td>
<td>Edward Jones</td>
<td>5</td>
<td>19</td>
<td>Nephrotic Syndrome</td>
<td>Normal (0.7)</td>
<td>None</td>
<td>Prednisone &amp; AZA</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal (0.8)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>Nephrotic Syndrome &amp; Microscopic hematuria</td>
<td>Normal (0.8)</td>
<td>Present (&lt; 20%)</td>
<td>Prednisone &amp; AZA</td>
<td>Good; Normal renal function</td>
</tr>
</tbody>
</table>

Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults* (Continued)
Table 1. Literature Review on Reported Cases of Renal-Limited Lupus-Like Nephritis in Adults* (Continued)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Number of Cases</th>
<th>Patient’s Age (Years)</th>
<th>Initial Presentation</th>
<th>Initial Creatinine (mg/dL)</th>
<th>Crescents</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>Edward Jones</td>
<td>5</td>
<td>38</td>
<td>Proteinuria &amp; Microscopic hematuria</td>
<td>Normal (1.2)</td>
<td>None</td>
<td>AZA</td>
<td>Poor; Moderate decrease in renal function (Cr 1.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate proteinuria 2600 mg/24 hrs</td>
</tr>
<tr>
<td>1982</td>
<td></td>
<td>30</td>
<td></td>
<td>Microscopic hematuria</td>
<td>Normal (1.3)</td>
<td>None</td>
<td>None</td>
<td>Good; Normal renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate proteinuria 75 mg/dL</td>
</tr>
</tbody>
</table>

*Adult: age ≥ 18.

CYC = cyclophosphamide, MMF = mycophenolate mofetil, AZA = azathioprine, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, HTN = hypertension, ESRD = end stage renal disease, CKD = chronic kidney disease, Tx = transplant, Cr = Creatinine. I = data not reported in literature.

and hemodialysis status as Aronoff recommended in 2007. We found this protocol to be effective in managing our patient. Achieving disease remission is reported to be associated with evidentially better renal and patient survival. This remission may be complete; where proteinuria is less than 0.5 g/day, or partial; where there is a decrease in proteinuria to less than or equal to 50% from baseline.

Due to the limited data, no definite prediction of the prognosis of RLLLN has been made so far. The outcomes reported in literature were variable. In our review, 17 of the 39 cases had reported outcomes with regards to creatinine and proteinuria values. 52.9% had a good outcome with no renal impairment, and 47% had a poor outcome with permanent decrease of renal function. We noticed that all cases with good outcome had normal creatinine levels upon initial presentation but found no predicting association between those of poor outcome and their initial creatinine. Also, 62% of patients with poor outcome had glomerular crescents involving 43–75% of the glomeruli. Only one patient with a good prognosis had crescents but seen in less than 20% of glomeruli. Gupta and Sachdeva noted in 2012 that the presence of crescentic lupus nephritis indicated a poor prognosis with derangements of renal function, and the percentage of crescentic glomeruli was related to the severity of renal failure.

In contrast to literature, our patient went into remission with no residual effect on renal function despite her severe disease, elevated creatinine level on initial presentation and presence of crescents involving 43% of glomeruli. We thus, propose a possible good prognosis for this disease with early treatment, and emphasize the importance of early diagnosis and early initiation of aggressive treatment during management of similar cases.

References
CSIM Mission Statement

Mission Statement
The CSIM is a non-profit professional society that promotes the health and well being of Canadian patients, their communities, and their health care systems. We seek to foster leadership and excellence in the practice of General Internal Medicine (GIM) through research, education, and advocacy for health promotion and disease management.

Vision
We believe that General Internal Medicine in Canada plays a central role in the training of current and future clinicians, in clinical research, in patient care, in health promotion, and in health advocacy; and that it unites a body of knowledge, values, and principles of care that lay the foundation for excellence in the Canadian health care system.

Values
We embrace the ethical and professional standards that are common to all healing professions, as well as the specific values of generalism, teamwork, competency-based training, life-long learning, evidence-based medicine, holism, and humane, patient-centered care.

Mission
La Société canadienne de médecine interne (SCMI) est une association professionnelle sans but lucratif qui entend promouvoir la santé et le bien-être des patients, des collectivités et des systèmes de santé canadiens. Elle souhaite également promouvoir le leadership et l’excellence dans l’exercice de la médecine interne générale en favorisant la recherche, l’éducation, la promotion de la santé et la gestion des soins thérapeutiques.

Vision
La Société a l’intime conviction que la médecine interne générale occupe une place centrale dans la formation des cliniciens aujourd’hui et à l’avenir, dans la recherche clinique, dans la prestation des soins et des services de santé et dans la promotion de la santé, et que la discipline se fonde sur un savoir, des valeurs et des principes thérapeutiques essentiels à la poursuite de l’excellence dans le système de santé canadien.

Valeurs
La Société fait sienne les normes éthiques et professionnelles communes aux professions de la santé ainsi que les valeurs particulières du généralisme, du travail dénué, de la formation axée sur les compétences, de l’éducation permanente, de la médecine factuelle, de l’holisme et des soins et des services de santé humains, centrés sur le patient.

CSIM Continuing Professional Development Mission Statement

Our ultimate goal is to go beyond the simple transmission of information. Our goal is to make a lasting impact on the knowledge, skills and attitudes of clinicians and future clinicians; to narrow the theory to practice gap; to improve the health of all Canadians.

Mission de la SCMI sur le plan du développement professionnel continu

Notre but ultime débordé du cadre de la simple transmission d’information. Il consiste à produire un effet durable sur le savoir, les compétences et les attitudes du médecin, à combler l’écart qui sépare la théorie de la pratique, à améliorer la santé de tous les canadiens.