THE CARE HEMATOLOGY FACULTY

HEMA-TIMES

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
NEEDS ASSESSMENT RESULTS

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, and under-recognized complement-mediated disease. Because of its rarity, it is not well understood. In order to understand both current perception and knowledge of PNH with hematologists, a needs assessment was conducted. The research is being led by Dr. Christopher Patriquin (McMaster University, The Canadian PNH Network) and Dr. Loree Larratt (University of Alberta, The Canadian PNH Network).

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HEMA-TIMES

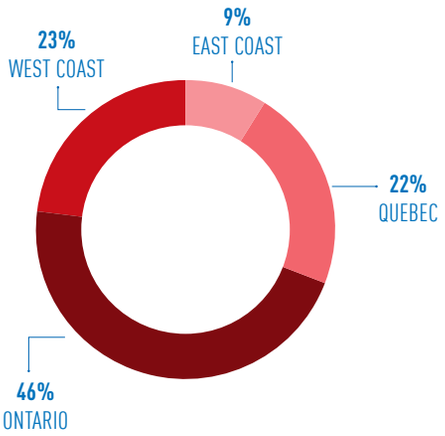
PNH NEEDS ASSESSMENT RESULTS

RESEARCH LED BY
DR. CHRISTOPHER PATRIQUIN &
DR. LOREE LARRATT
CARE HEMATOLOGY FACULTY

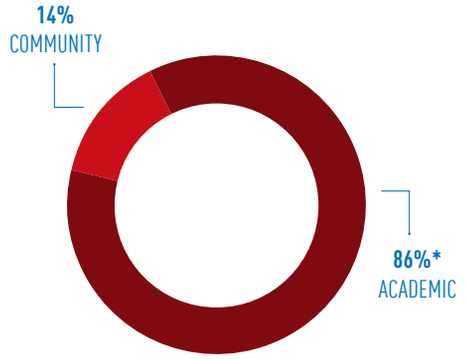
DISTRIBUTED TO
CANADIAN
HEMATOLOGISTS

This needs assessment was distributed by mail and electronically to upwards of 400 Canadian hematologists working in academic teaching centres and/or community practices. The response rate to this needs assessment is 19% (n=77). What follows is an overview of the key takeaways from the needs assessment, along with the response data.

RESPONDER INFORMATION
BY REGION



RESPONDER INFORMATION
BY INSTITUTION



*RESIDENTS MAKE UP 16% OF ACADEMIC RESPONDERS.

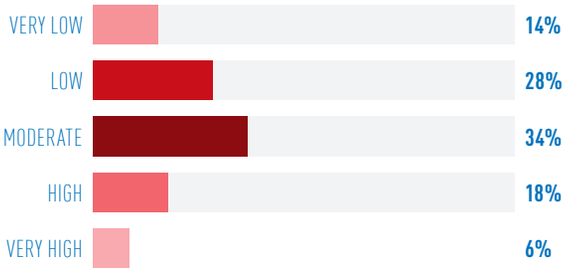
KEY TAKEAWAYS

- The complement system is not well understood (Question 1) and only 19% of the respondents identified it as the underlying condition that causes PNH (Question 3).
- 75% of responders do not treat PNH, (Question 2), however those that do are comfortable treating patients. (Question 4)
- PNH is tested for most frequently in the following disorders: aplastic anemia, hemoglobinuria, and coombs-negative hemolytic anemia (Question 5).
- Arterial or venous thrombosis, aplastic anemia, hemolytic anemia and myelodysplastic syndrome are clinical conditions most commonly associated with PNH. (Question 3)
- There is a wide range of variability in responses to how many patients are tested on an annual basis for certain disorders. (Question 5)
- Although hemoglobinuria (89%) is recognized as the most common lab result used to determine a PNH diagnosis (Question 6), not all of the responders test patients presenting with hemoglobinuria for PNH (Questions 4 and 5).
- Peripheral blood flow cytometry is always used to confirm a PNH diagnosis. (Question 7)
- While PNH is a complement-mediated hemolytic disease, 36% of the responders do not believe that presence of hemolytic symptoms warrant treatment (Question 8d).
- While responders acknowledge PNH is a life threatening disease, it may not be sufficiently diagnosed in routine practice (Question 8b)
- 29% of the respondents are not aware of a standard treatment (Question 10).

"THE COMPLEMENT SYSTEM IS NOT WELL UNDERSTOOD AND ONLY 19% OF THE RESPONDENTS IDENTIFIED IT AS THE UNDERLYING CONDITION THAT CAUSES PNH."

RESPONSE DATA

1. How well do you understand the complement system?

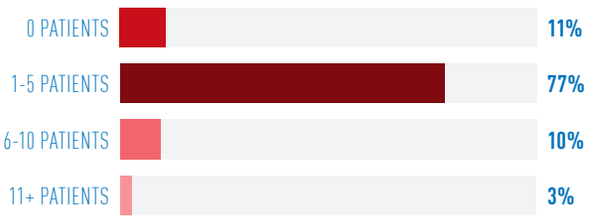


DISCUSSION: The complement system is not well understood. PNH is a complement-mediated disease that may arise de novo or in the context of pre-existing aplastic anemia. PNH occurs because of somatic mutation in the *PIGA* gene of hematopoietic stem cells, which leads to deficient expression of GPI-anchors and their bound proteins. PNH is caused by the absence of CD55 and CD59, two GPI-linked complement regulators which normally protect host cells from complement-mediated damage. Due to the multiple potential signs and symptoms of PNH, patients often wait months or years before final diagnosis. Because 35% of patients will die within 5-years of diagnosis if given only supportive care[i], early diagnosis is essential for improved patient management, early intervention, and prognosis.[ii]

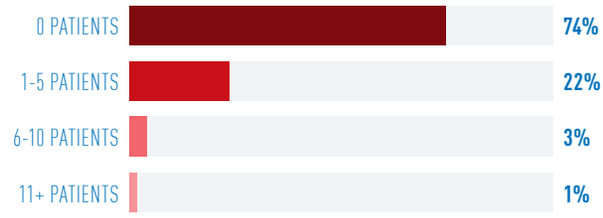
"BECAUSE 35% OF PATIENTS WILL DIE WITHIN 5-YEARS OF DIAGNOSIS IF GIVEN ONLY SUPPORTIVE CARE,
EARLY DIAGNOSIS IS ESSENTIAL FOR IMPROVED PATIENT MANAGEMENT, EARLY INTERVENTION, AND PROGNOSIS."

2. In a given year, how many PNH patients do you:

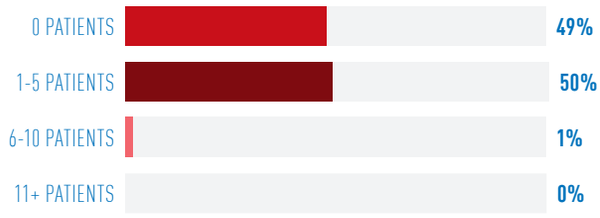
SUSPECT



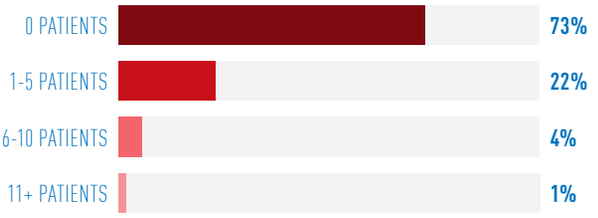
TREAT



DIAGNOSE



MANAGE



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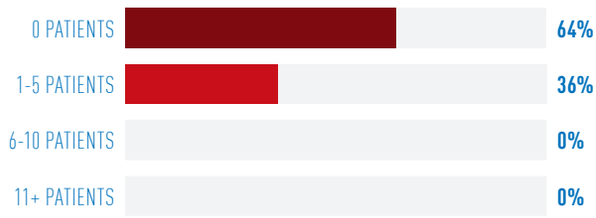


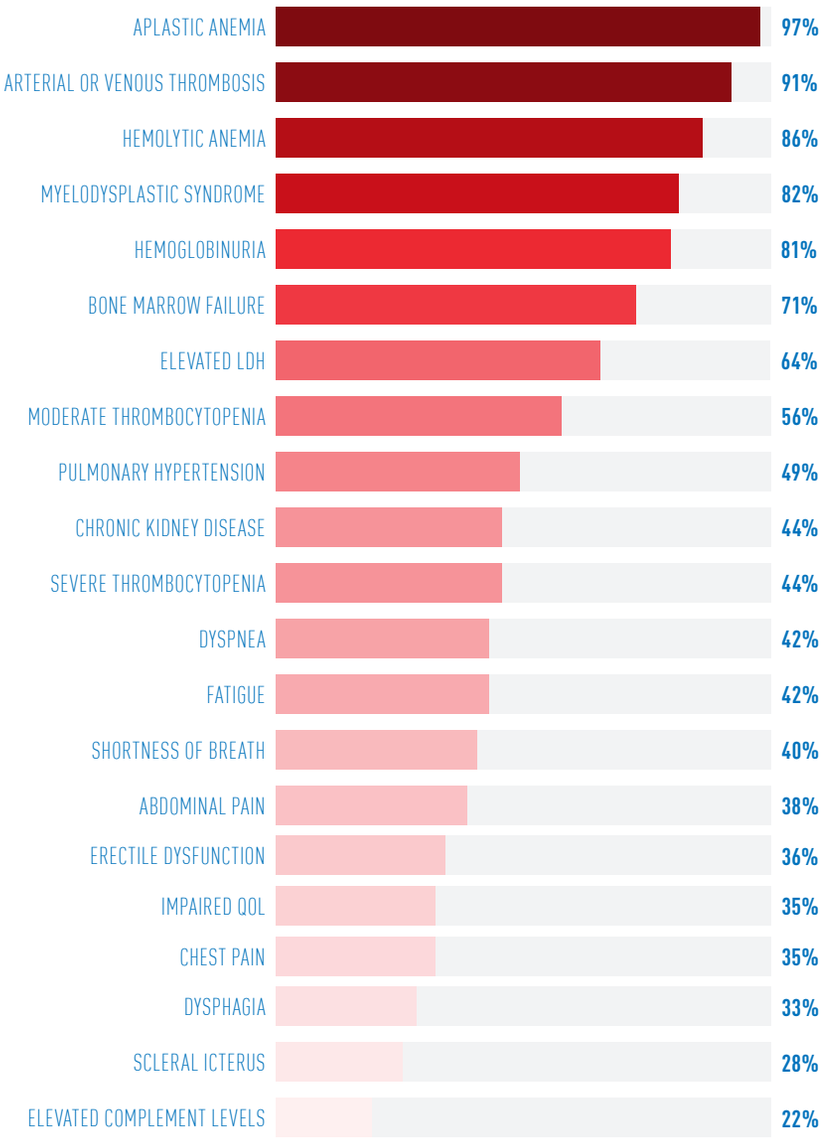
> **"DUE TO THE RARITY OF PNH**, IT IS IMPORTANT THAT **EXPERIENCED PHYSICIANS TREAT** (OR HAVE A ROLE IN TREATING) **PNH PATIENTS**, AS THOSE WILL LIKELY BE THE PHYSICIANS WHO STAY MOST UP TO DATE WITH THE CHANGING LITERATURE."

DISCUSSION: It is positive to see that almost all responders suspect PNH in at least 1-5 patients per year, which tells us that they are aware of the disease and its symptoms. However, there appears to be a relatively low level of diagnosis among responders (49% stated 0 patients/year).

Given the rarity of PNH (incidence of 1 per million annually), it is surprising that over a quarter of responders are treating and managing patients. Of those who treat, there is a small percentage of hematologists who treat (4%) and manage (5%) upwards of 6 patients. Due to the rarity of PNH, it is important that experienced physicians treat (or have a role in treating) PNH patients, as those will likely be the physicians who stay most up to date with the changing literature.

3. Which clinical conditions do you associate with PNH?

(Responders were able to select more than one response)



DISCUSSION: The clinical presentation of PNH varies for each person and there are a number of associated clinical conditions associated with the disorder. Most (in many cases all) classic PNH patients have hemolysis sufficient to raise their LDH. LDH has also been shown to be an independent predictor of thrombosis and mortality in registry studies.[iii,iv] Additionally, it is interesting that this survey's results illustrated that hemolytic anemia was more highly associated with PNH than LDH, as most hemolysis in PNH patients would be sufficient to increase the LDH.

PNH seems to be found mostly in low-risk MDS patients (in approximately 20% of cases, most often in the context of hypoplastic disease)[v,vi], Some of the other commonly associated conditions include: severe abdominal pain, severe headaches, back pain, excessive weakness, fatigue, and recurrent infections.[vii,viii]

"THE CLINICAL PRESENTATION OF PNH VARIES FOR EACH PERSON AND **THERE ARE A NUMBER OF ASSOCIATED CLINICAL CONDITIONS ASSOCIATED WITH THE DISORDER."**

4. Please indicate whether you currently test for PNH in patients with the following disorders: YES SOMETIMES NO

DISCUSSION: Results from this question are, for the most part, aligned with how Canadian PNH Network members practice, including the following:

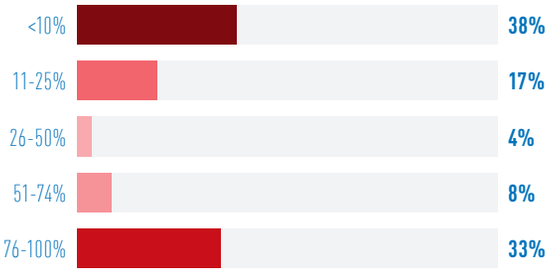
- All members test patients with aplastic anemia.
- There is still a lot of uncertainty over whom/when to test in MDS
  - Education on current research is needed.
- Testing should be done for patients with otherwise unexplained thrombotic events, especially in young people (<50 years), unusual sites (e.g. abdominal or cerebral vessels), recurrence despite anticoagulant therapy, and in anyone with evidence of an elevated LDH or reticulocyte count to suggest active hemolysis.
  - Simple, inexpensive testing of CBC + LDH to determine the hemolytic condition of the patient, and when warranted, HSFC from a peripheral blood sample can effectively rule PNH out.
- Most hematologists test for unexplained hemoglobinuria and Coombs-negative hemolysis patients. Unexplained cytopenias are also frequently tested for, however this may be a second-line test unless there are other markers to support a diagnosis of PNH (e.g. hemolysis, thrombosis, etc.). Number, type, and severity of cytopenias as predictors of PNH is an area needing further research.

These patient types need to be regularly tested if PNH is suspected, in order to be able to provide the best treatment for patients suffering with this devastating disease.

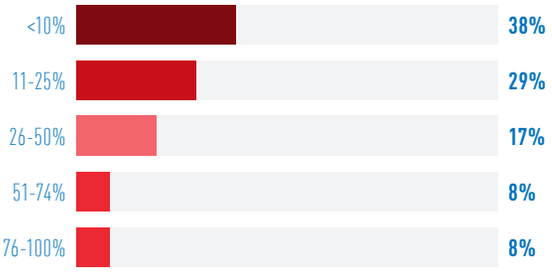
The Canadian PNH Network provides a number of resources on their website, including how to screen patients with PNH. Visit **www.pnhnetwork.ca** to learn more about screening.

5. In 2015 (or on a yearly basis), approximately how many patients in each of the following categories did you test?

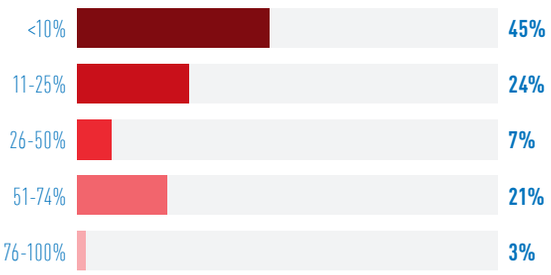
APLASTIC ANEMIA



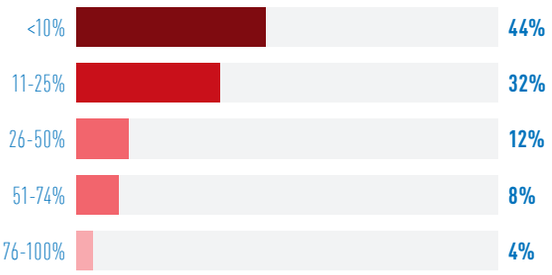
MYELODYSPLASTIC SYNDROMES



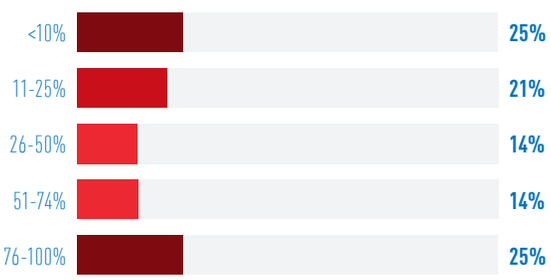
UNEXPLAINED VENOUS & ARTERIAL THROMBOSES



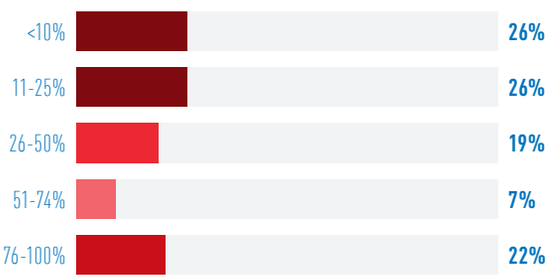
HEMOGLOBINURIA



COOMBS-NEGATIVE HEMOLYTIC ANEMIA



UNEXPLAINED CYTOPENIAS

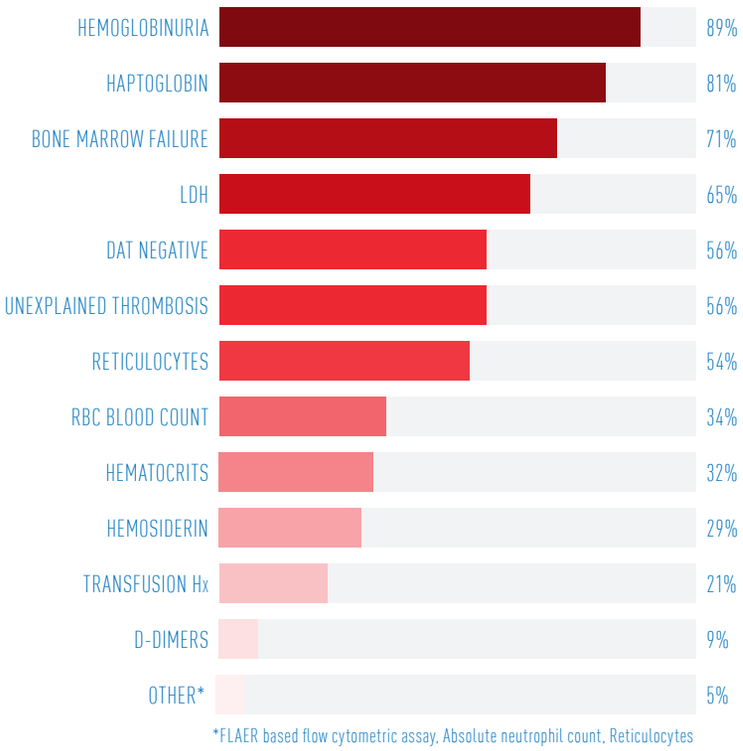


DISCUSSION: There is a wide range of variability in response to how many patients are tested on an annual basis for certain disorders. This is to be expected considering the diversity in patient conditions seen by hematologists and that some hematologists may not be regularly seeing all of these disorders within their practices. This is true, particularly as it relates to thrombosis. It would have been expected that more testing be done for certain patient types, such as those with: aplastic anemia, Coombs-negative hemolysis, unexplained thrombosis, and/or hemoglobinuria. It is important to ensure that patients are being proactively screened.

"IT IS IMPORTANT TO ENSURE THAT **PATIENTS** ARE BEING **PROACTIVELY SCREENED.**"

6. What lab results do you look to in the determination of a PNH diagnosis?

(Responders were able to select more than one response)



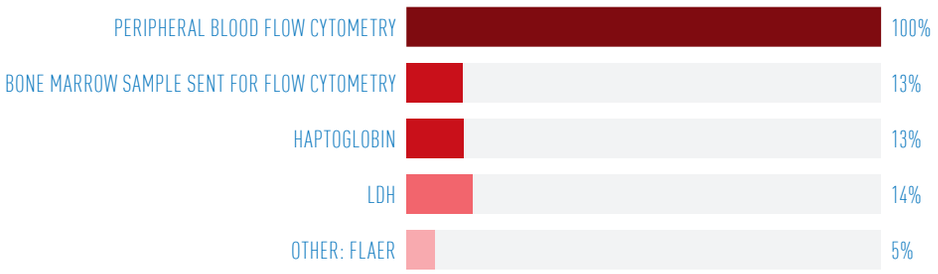
*FLAER based flow cytometric assay, Absolute neutrophil count, Reticulocytes

DISCUSSION: There were a few surprising results with this question. Firstly, it is interesting that LDH was not rated higher, as it can signify active hemolysis. LDH ≥ 1.5-fold above normal is an independent marker for thrombosis risk in PNH patients[iii] Additionally, 89% of responders indicated they look for hemoglobinuria to determine a PNH diagnosis, however only 60% of those enrolled in the global PNH registry have hemoglobinuria but otherwise may have active disease. Since not all patients present with hemoglobinuria, it should not be used as a confirmatory test, only a corroborative one. Lastly, it is interesting that 56% of hematologists do not consider DAT is a useful test for a PNH work-up to help differentiate it from other types of hemolysis.

"IT IS INTERESTING THAT **LDH WAS NOT RATED HIGHER,** AS IT CAN SIGNIFY ACTIVE HEMOLYSIS."

7. To confirm a PNH diagnosis, what test(s) would be requisitioned?

(Responders were able to select more than one response)

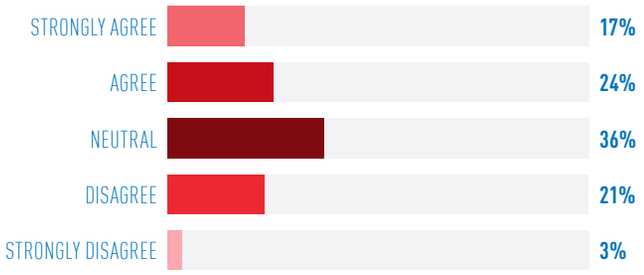


"**FLOW CYTOMETRY** IS THE **METHOD OF CHOICE** TO DIAGNOSE PNH."

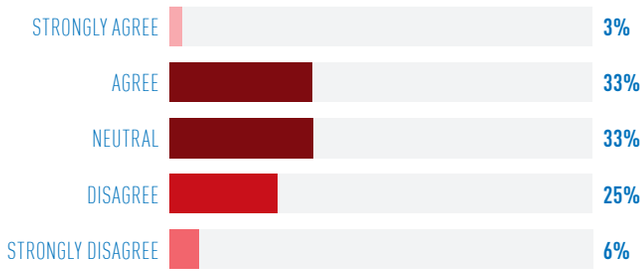
DISCUSSION: Flow cytometry is the method of choice to diagnose PNH. It is able to detect the absence of GPI-anchors and their associated molecules, and has led to improved patient management. Most laboratories have limited experience with PNH testing, and many different flow approaches are used.[ix] The International Clinical Cytometry Society have published guidelines for the appropriate testing protocols and parameters.

8. To what extent do you agree with the following:

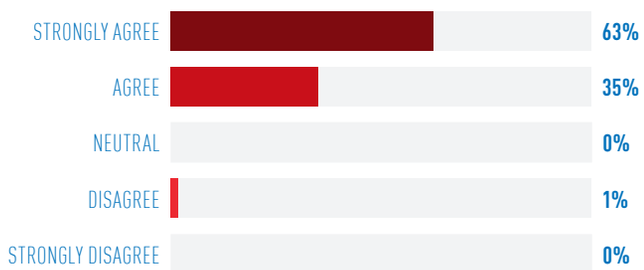
A. THERE IS SUFFICIENT TESTING FOR PNH.



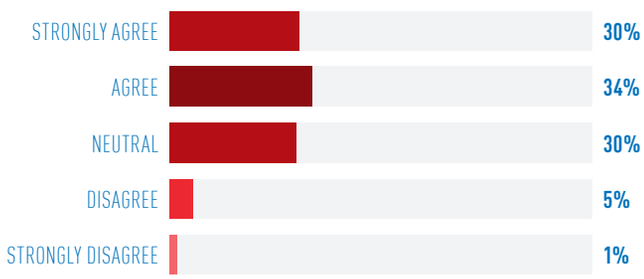
B. PNH IS BEING SUFFICIENTLY DIAGNOSED IN ROUTINE PRACTICE.



C. PNH IS A SERIOUS, LIFE-THREATENING DISEASE.



D. PATIENTS WITH PNH WITH EVIDENCE OF HEMOLYSIS (ELEVATED LDH) SHOULD BE TREATED IMMEDIATELY, REGARDLESS OF ORGAN STATE/COMPLICATIONS.

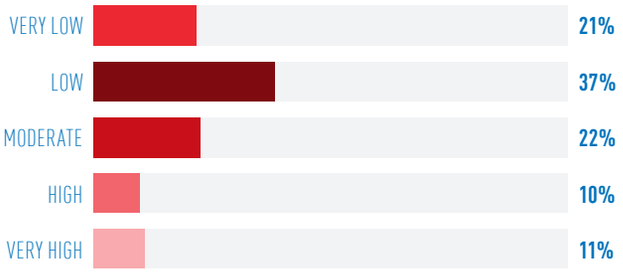


DISCUSSION: 40% of survey responders believe there is sufficient testing for PNH, and 36% feel the disease is being sufficiently diagnosed in routine practice. Given an estimated disease incidence of 1 per million annually (which may be an underestimate), we should theoretically be diagnosing approximately 35 new cases per year in Canada (given a national population of 35 million). We are most likely missing patients due to lack of consistent adherence to testing recommendations and perhaps limited recognition of the disease in general.

The most important point here is that the overwhelming majority of responding physicians recognize PNH to be a life-threatening disease. Treatment of patients for hemolysis alone is currently not an option based on eculizumab funding criteria (unless covered by private plans), but there are data to suggest that LDH elevation as a surrogate for hemolysis is an independent predictor of thrombosis and even mortality. Further studies are required to assess this concept.

"WE ARE MOST LIKELY MISSING PATIENTS DUE TO
LACK OF CONSISTENT ADHERENCE TO TESTING RECOMMENDATIONS
AND PERHAPS **LIMITED RECOGNITION OF THE DISEASE** IN GENERAL."

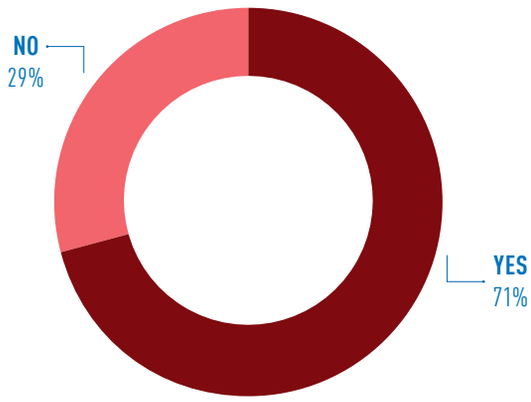
9. What is your comfort level in treating patients diagnosed with PNH?



DISCUSSION: It is interesting that just over 1 in 5 responders feel highly/very highly comfortable managing the disease. For those that are not comfortable, they should be aware/informed on symptoms to look for, know how to test, and when and where to refer. This provides very strong support that patients should be referred to a centre of expertise (either to assume or participate in care in a shared-care model).

The Canadian PNH Network offers a number of resources for practicing hematologists. Visit **www.pnhnetwork.ca** to learn more about monitoring and managing patients with PNH.

10. Do you believe there is a standard treatment for PNH?



"DATA SHOW THAT **COMPLEMENT BLOCKADE WITH ECULIZUMAB IS PROVIDING A LIFE-SAVING BENEFIT TO PNH PATIENTS.** THUS, EARLY AND ACCURATE DIAGNOSIS OF THIS DISEASE IS CLEARLY WARRANTED. "

DISCUSSION: When asked what the standard treatment is for PNH, all responders stated eculizumab (100%). Up until a few years ago, the only treatment that was available for PNH was supportive care and/or hematopoietic stem cell transplant. Eculizumab was introduced into the Canadian market in 2009. It inhibits chronic uncontrolled complement activation by blocking terminal complement and hemolysis. Eculizumab is an effective treatment for PNH that improves survival, quality of life, transfusion dependence, and many symptoms. Data show that complement blockade with eculizumab is providing a life-saving benefit to PNH patients. Thus, early and accurate diagnosis of this disease is clearly warranted.[x]

CONCLUDING REMARKS

"IT IS IMPORTANT FOR HEMATOLOGISTS TO BE CONTINUALLY EDUCATED ON THIS RARE DISEASE IN ORDER TO KNOW WHAT TO LOOK FOR, KNOW WHICH PATIENTS ARE AT RISK, AND HOW TO TREAT (OR REFER).

This was a very insightful activity. Due to the rarity of the disease, it is not surprising that there are still some knowledge gaps. There seems to be some misconceptions about the most common signs/symptoms of PNH, as well as which patients to test. While hematologists seem to understand how to test, they need to understand which patient types are at risk and be proactively screening them in order to treat this serious-life threatening disease. Referring a patient to a PNH expert centre or having the institution involved in treatment would also ensure that patients are getting the best care possible.

It is important for hematologists to be continually educated on this rare disease in order to know what to look for, know which patients are at risk, and how to treat (or refer).

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REFERENCES

[i] Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. N Engl J Med. 1995;333(19):1253-1258.
[ii] Richards SJ, Barnett D. Clin Lab Med.2007;27(3):577-590
[iii] Lee JW, Jang JH, Kim JS, et al. Int J Hematology. 2013; 97(6):748-757
[iv] Jang JH, et al. J Korean Med Sci. 2016; 31: 214-221
[v] Sugimori C, Mochizuki K, Qi Z, Sugimori N, Ishiyama K, Kondo Y, et al. BJH. 2009: 147:102-112.
[vi] Greenber P, et al. NCCN Clinical Practice Guidelines in Oncology: MDS. JNCCN 2016; v.1.2016.
[vii] John Hopkins Medicine 2015. Accessible at <http://www.hopkinsmedicine.org/kimmel_cancer_center/types_cancer/paroxysmal_nocturnal_hemoglobinuria_PNH.html>
[viii] Sahin F, Yilmaz AF, Ozkan OM, Gokmen NM, and Saydam G. Am J Blood Res. 2015; 5(1): 30–33.
[ix] Sutherland DR, Illingworth A, Keeney M, Richards SJ. Current Protocols in Cytometry. 2015. Accessible at: <http://onlinelibrary.wiley.com/doi/10.1002/0471142956.cy0637s72/abstract>
[x] Soliris® (eculizumab) Product Monograph, 2015.

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The vision of the CARE Faculty is to share opinions and update Canadian specialists with news and developments from key conferences framed in a Canadian perspective.

The mission of the CARE Faculty is to enhance medical education, with the explicit goal of improving patient outcomes.

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