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Review

Approach to pancytopenia: Diagnostic algorithm for clinical hematologists

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ABSTRACT

Pancytopenia is a relatively common phenomenon encountered in clinical practice. The evaluation of a patient with pancytopenia requires a comprehensive approach and identifying the underlying cause can be challenging given the wide range of etiologies including drugs, autoimmune conditions, malignancies, infections, hemophagocytosis, and inheritable conditions. Recent advances in molecular hematology which include genomic profiling and next-generation sequencing have helped gain major insights into various hematological conditions and can guide diagnosing specific diseases in a shorter time at lower costs. However the approach to manage patients with pancytopenia in the current era of genomics is not well defined in the literature and is widely variable in practice. Herein, we conducted a systematic review to help devise an algorithm and management approach for pancytopenia, which serves as a general consultative approach.

1. Introduction

Pancytopenia is defined as a decrease in all three blood cell lines and it could manifest with symptoms resulting from anemia, leukopenia or thrombocytopenia; patients may however be asymptomatic. Pancytopenia may also be diagnosed incidentally especially if mild or it can be present in some critically ill states such as in sepsis. It is a relatively common phenomenon in daily medical practice and one of the most common reasons for consultation from hematologists. A survey of primary care physicians showed that about 9 out of 10 times a hematologist is consulted when pancytopenia is found on lab studies [1]. It is not a disease in itself but rather a finding due to an underlying disease process affecting the bone marrow or the peripheral cell lines.

Although there are studies reviewing the underlying pathologies and the bone marrow findings in pancytopenia, only few are published on the approach to pancytopenia in clinical practice [2–4]. Internists, psychiatrists, obstetricians, pediatricians, and intensivists encounter the majority of cases and these are frequently referred to hematologists for further workup. The differential diagnoses in a patient presenting with pancytopenia are broad and extensive. These are only reviewed in textbooks and a literature gap is identified regarding the management of pancytopenia. In this review, we propose a common management approach to pancytopenia, which is essential for hematologists who perform consultative service in academic and community settings.

2. Methods

We conducted a comprehensive electronic literature search from January 1990 to July 2016. We followed the guidelines of PRISMA statement for systematic reviews for collecting the data. Only human studies published in English language were included. We searched the following electronic databases: PubMed, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review. MeSH Terms “Pancytopenia” was combined with “Diagnosis”, “Drug Therapy”, “Epidemiology”, “Physiopathology” and “Therapy” using Boolean Language (“OR”, “AND”). We included all studies including Controlled Trials, prospective and retrospective observational studies, case reports and systematic reviews. Case reports describing pancytopenia from unusual causes were excluded.

3. Results

Our systematic search identified many causes of pancytopenia as well as a wide variety of treatments given for conditions causing

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Table 1
Common causes of pancytopenia.

Impaired production	Peripheral destruction	Impaired production and peripheral destruction
Aplastic anemia – acquired and congenital	Autoimmune hemolytic pancytopenia	Paroxysmal nocturnal hemoglobinuria
Bone marrow infiltrating disorders	Splenic Sequestration	SLE
- Malignancy		Drugs
- Primary and autoimmune myelofibrosis		Leukemia
- Granulomatous disorders		Hemophagocytic Lymphohistiocytosis (HLH)
- Metabolic disorders		
Nutritional deficiencies		Transfusion-associated Graft-versus-host disease
- Vitamin B12		Infections
- Folic acid		
- Copper		
Myelodysplastic syndrome		

pancytopenia (Supplementary Table S1). We summarize our results below categorizing pancytopenia into three broad categories (Table 1):

- Impaired production which encompasses both bone marrow failure disorders and marrow infiltration disorders
- Peripheral destruction of different cell lines (includes splenic sequestration)
- Combination of above.

These three processes can be distinguished from one another by hematologic testing but the crucial first steps of evaluation must include a hemogram (called complete blood count [CBC] or complete picture [CP] in various countries), peripheral blood smear, reticulocyte count and comprehensive history and a meticulous physical examination. The reticulated platelet count or the immature platelet fraction, though not used commonly, can also help distinguish if the pancytopenia is due to impaired production or increased consumption.

3.1. Impaired production

3.1.1. Acquired aplastic anemia

Aplastic anemia is caused by failed hematopoiesis either due to an acquired or a congenital cause. Several observational studies from South East Asia looking for the causes of pancytopenia by bone marrow examination point to aplastic anemia and leukemia being the most common cause in children [5,6] and aplastic anemia and megaloblastic anemia among the general population [7]. Congenital causes of bone marrow failures are far less common compared to acquired causes.

3.1.1.1. Idiopathic. Although the cause of aplastic anemia (AA) is not clear, it is thought to be due to autoimmune destruction of pluripotent hematopoietic stem cells (HSC) by T lymphocytes [8–11]. Unregulated lymphocyte activation, impaired regulatory T cells and increased activity of IL-17 have also been proposed as causes for the autoimmune mechanism [12,13]. Evaluation starts with a reticulocyte count and a peripheral smear. The absolute reticulocytes are reduced and sometimes totally absent. The peripheral blood smear may show macrocytic red blood cells with other cell lines having a normal morphology. The diagnosis is established by bone marrow aspiration and biopsy, which show reduced cellularity with absence of fibrosis and malignant cells. In order to conclude the diagnosis of AA, besides drugs and infections, one must exclude the absence or co-existence of paroxysmal nocturnal hemoglobinuria (PNH), inherited bone marrow failure syndromes and myelodysplastic syndrome, as the management of the latter disorders may be different. In the current genomic era, besides obtaining cytogenetics, we prefer a directed panel for use of severe AA (SAA) using the next-generation sequencing (NGS), since patients with mutations in ASXL1 or DNMT3 typically have a poorer response to immunosuppressive therapy (IST) and a greater propensity for clonal evolution development thus prompting a referral to a hematopoietic stem cell transplant (HSCT) center. Generally, for SAA, the treatment for patients under the age of 50 is by HSCT (matched related or alternative donor) but for those over 50 without a fully matched donor, IST (with or without eltrombopag) may a reasonable option [14].

3.1.1.2. Drugs and radiation. Many drugs can cause aplastic anemia. Toxins like benzene, chemotherapeutic drugs, NSAIDs, antiepileptic drugs, steroids, and chloramphenicol are commonly known to cause AA. The mechanism of aplasia is either by direct toxic effect on the stem cells or from autoimmune mechanisms. Studies have shown that activity of P – Glycoprotein in the cells is decreased among patients with AA [15]. Reduced activity of P – Glycoprotein can cause accumulation of the drugs in the cytoplasm leading to toxic levels. In some occasions, as in the idiosyncratic reaction seen in chloramphenicol, effects of the drugs on the bone marrow can be irreversible, which led consequently to a marked decline in its use. Most conventional chemotherapeutic agents cause pancytopenia by direct bone marrow toxicity. Specifically, fluropyrimidines such as flurouracil and capecitabine can cause severe and sometimes fatal toxicities if administered in patients with deficiency of dihydropyrimidine dehydrogenase, an enzyme involved in the metabolism of uracil and thymine. Biological agents such as inhibitors of TNF and IL-6 can cause neutropenia but pancytopenia is rare.

Alcohol abuse can affect all the three cell lines. There are several ways how alcohol can cause these hematological toxicities. Alcohol can cause direct bone marrow toxicity as evidenced by hypoplastic bone marrow in some of these patients. Excess alcohol consumption can also increase the absorption of iron from the gastrointestinal tract leading to iron overload, which in turn can contribute to hepatitis and cirrhosis. Other possible mechanisms are interference with folate absorption and acetaldehyde forming adducts with cell membrane phospholipids [16,17].

Radiation therapy can also damage the HSC and result in pancytopenia [18]. Bone marrow hypoplasia develops at cumulative doses > 5 Gy. The cytopenia reaches a nadir 1 to 4 weeks after the treatment and can persist for months. Having a more ventral exposure and sparing the dorsal bone marrow (in spine, ribs and pelvis) during the radiation might protect a significant percent of bone marrow activity. This is an important aspect of radiation biology for hematologists, as some cancer patients (particularly gynecologic cancers) receive radiation to the pelvic bones and may develop profound and prolonged pancytopenia but it is generally reversible.

3.1.1.3. Infections. Infections, mostly viral, are another cause of cytopenias in both adults and children. A prospective study among children by Alexandropoulo et al. showed that an infectious agent was identified in about 63.8% of febrile non-cancer patients with cytopenias [19]. About 45% of these were due to viral infection and the cytopenia was transient in 83% of the cases. Parvovirus B19 can directly attack proerythroblasts whereas aplasia caused by other viruses is usually due to T cell mediated mechanisms [20], however, parvovirus more commonly causes anemia only and patients with chronic hemolytic anemias are usually the most vulnerable. The pancytopenia caused by the viruses is usually transient and reversible with resolution of the infection. In a hematology consultation for pancytopenia, if a viral infection is suspected, then the common agents which should be evaluated include infectious hepatitis (Hepatitis A, B, and C), cytomegalovirus (CMV), Epstein-Barr virus (EBV), Human HerpesVirus 6 (HHV-6), Parvovirus B19, and human immunodeficiency virus (HIV). Pancytopenia associated with hepatitis

is more severe than that associated with other infections and is less likely to resolve spontaneously [21]. Hepatitis associated AA (HAA) is a distinct variant of aplastic anemia, which occurs after an episode of acute hepatitis. The mechanism is thought to be due to T cell mediated cytokine release. Leishmaniasis and tuberculosis can rarely result in chronic bone marrow suppression via direct affect and should be tested for in the countries where these diseases are endemic.

3.1.2. Congenital aplastic anemia

A multitude of inheritable causes of AA have been discovered. A better terminology for this condition is inherited bone marrow failure syndromes (BMF) since "anemia" is not the only presentation, and in fact, the majority of the patients suffer from profound pancytopenia with neutropenia being the most important culprit to which these patients can succumb. Our search yielded that the most common causes of inherited BMF syndromes are Fanconi's Anemia (FA), Dyskeratosis congenita (DC), GATA2 associated syndromes (e.g. Emberger and MonoMAC syndromes), and Shwachman-Diamond syndrome (SDS). Congenital amegakaryocytic thrombocytopenia (CAMT) rarely leads to pancytopenia and most patients are either transplanted before this or they die of bleeding if they are not transplanted soon enough. The associated clinical findings help distinguish the different types (Table 2), although they are not present consistently due to extreme variability in phenotypic expression. These disorders are usually diagnosed in early childhood but about up to 25% of patients may have cryptic presentations and are not diagnosed until adulthood. However, statistically speaking, congenital aplasia is far less common than the acquired aplastic anemia, even in children. In a large study of myelodysplastic syndrome (MDS) patients undergoing allogeneic HSCT who were enrolled in the Center for International Blood and Marrow Transplant Research Repository (CIBMTR), targeted mutational analysis on samples obtained pre-HSCT was performed, and 4% of the young patients were found to have compound heterozygous mutations in the SDS–associated SBDS gene, thus underscoring the importance of appropriate genomic testing for young patients with pancytopenia even if they present with MDS [22].

Telomere length measurement for DC and chromosomal breakage (and diepoxybutane [DEB] or mitomycin C) testing for FA should be performed for suspected cases from peripheral blood (peripheral blood is preferred over bone marrow aspirate for these tests). The leukocyte telomere length measurement (ideally via Flow-FISH, but qPCR may suffice) is generally expensive and may not be readily available in all institutions, and efforts must be made to utilize this test only in strongly suspected cases for the sake of a cost-effective approach.

Once the diagnosis of inherited BMF syndromes is made, gene sequencing and Human leukocyte antigen (HLA) typing of the patient, and the HLA typing of the family members should be done as early as possible which is crucial for management and for HSCT [23,24].

Unlike idiopathic SAA, inheritable BMF syndromes should not be treated with IST and immediate referral to a HSCT center should be made which is the only known curative therapy. Since the therapy of idiopathic AA is different from BMF syndromes, it is crucial that hematologists make correct diagnosis – thus if the chromosomal breakage studies are negative i.e. the report indicates "no growth", then further testing via skin biopsy (for dermal fibroblasts) should be performed in strongly suspected cases of inheritable BMF syndromes.

3.1.3. Bone marrow infiltrative disorders

3.1.3.1. Primary myelofibrosis. Primary myelofibrosis (PMF) is one of the chronic myeloproliferative neoplasms (MPN) characterized by clonal proliferation of abnormal megakaryocytes. Patients usually present with pancytopenia, extreme fatigue and an enlarged spleen and liver due to extramedullary hematopoiesis. The peripheral smear shows leukoerythroblastic reaction (myelophthisic smear), with teardrop cells, left-shifted (immature) white blood cells (WBC) and nucleated RBCs. Circulating CD34+ cells can help in distinguishing this entity from other forms of myeloproliferative disorders [25]; however a BMB is required for definitive diagnosis in order to fulfill the current World Health Organization's criteria for MPN. Bone marrow aspiration usually is difficult yielding a dry tap, and bone marrow biopsy is necessary for demonstrating reticulin fibrosis [26]. Patients with high and intermediate risk PMF according to the DIPSS plus score (Dynamic International Prognostic Scoring System) should be referred urgently for HSCT [27], since this procedure remains the only potentially curative therapy for PMF up-to-date. In other risk groups of PMF, management is focused on supportive care.

3.1.3.2. Systemic diseases infiltrating bone marrow. Diseases that metastasize to the bone marrow may cause pancytopenia by interfering with the production of the blood cells. Leukemia, lymphoma, fibrosis, autoimmune and granulomatous diseases typically infiltrate the marrow and cause profound pancytopenia. In the pediatric population, metastatic neuroblastoma very commonly also invades the marrow and many children present with pancytopenia as the only symptom at first. Acute leukemias infiltrate the marrow more rapidly than chronic leukemias. Acute lymphoblastic leukemia (ALL) is one of the most common cancers of childhood, whereas acute myeloid leukemia (AML) is the most common acute leukemia affecting adults [28]. They are usually diagnosed with blasts on the peripheral smear, which is typically the common reason to consult a hematologist. Then a bone marrow biopsy (BMB) and aspirate, flow cytometry, immunophenotyping and cytogenetic studies are indicated for diagnosis and prognosis. The BMB should be performed early in suspected cases of acute leukemias given the aggressive biology of the disease. An exception to this rule of essential testing with BMB is elderly patients with severe comorbidities who are unable to undergo any kind of aggressive chemotherapy and the diagnosis is clear via peripheral blood testing. Occasionally in such patients, palliation can

Table 2
Inheritable bone marrow failure syndromes.

Congenital syndrome	Characteristic features	Gene affected	Laboratory finding
Fanconi's Anemia	Predisposition to MDS/AML squamous cell cancers VACTERL-H deformities, café-au-lait lesions, microcephaly, developmental delay	Multiple FA genes from FANCA to FANCQ	Increased chromosome fragility
Dyskeratosis congenita	Reticulated skin hyperpigmentation, nail dystrophy, mucosal leukoplakia	Multiple genes regulating telomerase complex and shelterin protein	Shortened telomeres in flow cytometry
Shwachman-Diamond syndrome	Pancreatic dysfunction, various skeletal deformities, recurrent infection, myelodysplasia and AML	Shwachman –Bodian – Diamond Syndrome (SBDS)	Abnormal pancreatic functions
GATA2 associated syndromes	Familial MDS/AML, increased susceptibility to non-tuberculosis mycobacteria and viral infections	GATA2 gene	Monocytopenia, B and NK cell lymphocytopenia
Amegakaryocytic thrombocytopenia	Absence of megakaryocytes on bone marrow	Myeloproliferative leukemia virus (MPL) oncogene	Elevated serum thrombopoietin MPL undetectable in flow cytometry

*VACTERL-H: V*ertebral anomalies, *A*nal atresia, *C*ardiac defects, *T*racheoesophageal fistula and/or *E*sophageal atresia, *R*enal & *R*adial anomalies and *L*imb defects – *H*ydrocephalus.

be started without a BMB since the current pathology techniques (particularly flow cytometry) can usually differentiate between ALL and AML. All other eligible patients (especially below the age of 70 years), should be referred to a HSCT center upon diagnosis and HLA typing should be obtained since allogeneic HSCT currently remains the only potentially curative option in high risk, refractory or relapsed patients. If the treating or consulting hematologist has any doubts about the candidacy for HSCT for a leukemia patient, it is best to make the referral so that the transplant physician can decide about the candidacy based on the baseline health and the disease characteristics.

Genetic testing through next-generation sequencing is also making significant impact in the diagnostic work-up of acute leukemias since mutations can provide prognostic as well as therapeutic information from precision medicine perspective e.g. such as who requires transplant and for targeted therapies. Plasma cell dyscrasias (both myeloma and amyloidosis), hairy cell leukemia (HCL), and other metastatic diseases (e.g. carcinomas) can also infiltrate the bone marrow. HCL typically presents with massive splenomegaly and pancytopenia, and consulting hematologist can look at the peripheral blood smear preferably with Romanowsky-stain to evaluate for this entity. A “dry tap” during BMB further points towards HCL, and in the current decade, hematologists should NOT order the “TRAP stain” since flow cytometry can provide adequate information for the diagnosis of HCL and is technically less challenging than the TRAP staining. Large granular Lymphocyte (LGL) leukemia is a clonal disorder affecting the large granular lymphocytes which can cause marrow infiltration leading to cytopenia. The diagnosis is based on immunophenotypic analysis of the peripheral smear but bone marrow biopsy/aspirate may be required in some cases. Solid tumors that frequently metastasize to the bone marrow in adults are prostate, breast and lung [29].

Other bone marrow infiltrative disorders include autoimmune myelofibrosis, which can be related to lupus [30], however many autoimmune causes can result in infiltration. It is generally rare but occasionally hematologists are consulted for inpatients suffering from autoimmune disease flares. Most of the autoimmune cytopenias are steroid responsive and initial treatment includes corticosteroid dosages in the range of 0.5–1 mg/kg/day. Granulomatous diseases like miliary TB and sarcoidosis and metabolic disorders like Gaucher disease can also cause pancytopenia by causing intense marrow infiltration [31]. Generally the clues towards a diagnosis of Gaucher disease in a pancytopenia patient are massive hepatosplenomegaly, bone disease (avascular necrosis [AVN], osteoporosis, bone pain, osteolytic fractures), neurologic symptoms (seizures, neuropathy and parkinsonism), and growth retardation. Some cases may be diagnosed in adulthood and thus a high degree of clinical suspicion is required by the astute hematologist. The hematopathologist or hematologist should carefully evaluate the BMB for the large macrophages laden with cereberosides. Mutational analysis and biochemical enzyme analysis follows next and then immediate referral to a HSCT center with metabolic diseases expertise should be made for consideration of HSCT and/or enzyme replacement therapy. Patients with Gaucher type 2 disease don't respond well to enzyme replacement therapy and are usually treated with HSCT.

3.1.4. Nutritional deficiencies

Folate and vitamin B12 deficiencies can cause megaloblastic anemia. Though anemia and thrombocytopenia are the common features, they could present with pancytopenia as well. In a cross sectional observational study in Pakistan, pancytopenia was found in 70% of patients with megaloblastic anemia [32]. B12 deficiency is most likely due to ineffective absorption whereas folate deficiency is due to inadequate dietary intake and alcoholism. Since the fortification of food with folic acid in the late 1990s, folate deficiency has been extremely rare in the United States (US) and is seen mostly in patients who are malnourished [33]. However, folate deficiency has not been eradicated in many regions of the world. B12 and folate deficiency should be suspected in any patient with unexplained pancytopenia, macrocytosis, hypersegmented neutrophils, and unexplained neurological signs and symptoms. Diagnosis is by measurement of serum B12 levels, folate levels and also levels of their metabolic intermediates, which accumulate in these deficiencies. Homocysteine accumulates in both folate and B12 deficiencies, while methylmalonic acid accumulates only in B12 deficiency. When the diagnosis is not clear, therapeutic trials with B12 are needed. Bone marrow examination is not needed to diagnose B12 and folate deficiency. In the current era of explosive growth of bariatric surgeries, hematologists should be well prepared to deal bariatric surgery induced cytopenias, since both sleeve gastrectomy and Roux-en-Y gastric bypass can cause vitamin B12 deficiency [34].

Copper deficiency commonly causes anemia and leukopenia. However, it can rarely also cause pancytopenia. The common causes of acquired copper deficiency are gastric surgery, malabsorption syndromes, excessive zinc intake and chelation therapy [35]. Bone marrow examination shows cytoplasmic vacuolization in the erythroid and myeloid precursors [36]. Serum copper and ceruloplasmin levels should help in the diagnosis.

3.1.5. Myelodysplastic syndrome

Myelodysplastic syndrome is a clonal stem cell disorder characterized by dysplastic bone marrow. It usually affects people over the age of 65 with a male predominance [37], however, therapy related myeloid neoplasms which constitute both AML and MDS can occur at any age after leukemogenic exposures (chemotherapy or radiation). The peripheral blood smear may show Pelger Huet – like anomaly in neutrophils (a bilobed nucleus in the neutrophil connected by a thin isthmus) and immature myeloid or erythroid cells. Hypogranulated neutrophils can also be present in the smear. Bone marrow aspirate is also essential for diagnosis. Diagnosis is made by the presence of the following features –decrease in one or more of the blood elements without another cause, morphologic evidence of dysplasia in the peripheral smear, bone marrow aspirate and biopsy and blast forms $< 20\%$ of the total cell count of the bone marrow aspirate. Immunophenotyping studies may show a decrease in the number of myeloid maturation antigens or presence of new antigens, which are not normally present. Flow cytometry and immunophenotyping also helps in differentiating MDS from other cytopenias in post cancer therapy patients [38].

Although diagnostic criteria have yet to incorporate the genetic underpinnings of MDS except for the 5q minus syndrome, MDS has witnessed significant advances in mutation analysis via NGS. At many institutions, this has become as common as a bone marrow biopsy, and is providing valuable prognostic information. Frequently, MDS-associated mutations are found, such as SF3B1, TET2, SRSF2, DNMT3A, and ASXL1. However, patients may not yet fulfill MDS criteria, so they have been given the new diagnosis of CHIP (clonal hematopoiesis of indeterminate potential) or CCUS (clonal cytopenias of undetermined significance), both precursors to MDS, itself a precursor to acute leukemia [39,40].

Treatment is supportive care, chemotherapy, and/or HSCT based on a prognosis score called the “Revised International Prognosis Scoring System” (IPSS-R). Patients who score < 2 points are treated either with supportive care or low intense chemotherapy or immunosuppressive therapy. For patients with higher risk (> 4 points) treatment should ideally include HSCT in eligible patients. For those with intermediate risk, the treatment should be based on patient preferences and other individual pre-existing conditions. Thus it is imperative that the diagnosis of MDS should prompt referral to a transplant center unless the patient is very old or suffers from many comorbid conditions.

MDS in childhood is a distinct entity with a different WHO classification. MDS is rare in childhood and has a poor prognosis without HSCT. Refractory cytopenia of childhood is the most common subtype of MDS in children and monosomy 7/del 7q is the most frequently seen clonal abnormality. The main treatment is focused on early HSCT as

there is risk for relapse and clonal evolution with immunosuppressive treatment [41], thus referral to a transplant center early in the course is advised.

Mutations in the GATA2 gene can cause familial MDS/AML. GATA2 belongs to a family of transcription factors that are critical regulators of gene expression in hematopoiesis [42]. Different kinds of mutations including missense mutation, nonsense mutation, large genomic rearrangements can cause GATA2 deficiency. In addition to Familial MDS and AML it is also associated with monocytopenia, B and NK cell lymphopenia, increased susceptibility to non-tuberculosis mycobacterial and viral infections. Early diagnosis with genetic testing is crucial for management, preventive care and screening of other family members [43].

3.2. Peripheral destruction

3.2.1. Autoimmune-mediated pancytopenia

SLE can present with pancytopenia when all the three cell lines are affected, however it is less common than isolated cytopenias. In addition to immune-mediated process, multiple other factors contribute to cytopenias in lupus patients. Pancytopenia in SLE could be due to medications, infections, splenomegaly, autoimmune myelofibrois and rarely HLH/MAS [44]. Most lupus patients with pancytopenia need a bone marrow biopsy to rule out other causes. Patients with autoimmune rheumatological disorders like rheumatoid arthritis, psoriasis, SLE are at increased risk for lymphoproliferative disorders and it is important to exclude underlying malignancies like lymphoma while evaluating these patients [45–47].

Autoimmune cytopenias are also seen in autoimmune lymphoproliferative syndrome (ALPS) and common variable immunodeficiency disease (CVID). Autoimmune hemolytic anemia and immune thrombocytopenia are more common than autoimmune neutropenia (AIN) in both ALPS and CVID. All cytopenias including AIN are more common in CVID in children compared with adults. Since these patients also have splenomegaly, it is important to differentiate if the cytopenias are related to autoimmune condition rather than hypersplenism.

Autoimmune cytopenias can also occur with chronic lymphocytic leukemia (CLL). It could present as autoimmune hemolytic anemia, thrombocytopenia or pure red cell aplasia (PRCA). The first line treatment for these autoimmune diseases is corticosteroids. In patients not responding to steroid treatment, chemo-immunotherapy and splenectomy are reasonable alternatives [48,49].

Blood cytopenias, which remain undiagnosed despite adequate evaluation, are classified as idiopathic cytopenia of undetermined significance (ICUS). They should not have any known clonal disorders. ICUS is not a specific disease per se and they usually resolve over time or are found to be due to a non-myeloid malignancy, nutritional disorder or immune-mediated disorder. A study by Liu et al. has shown at least some of these immune-mediated cytopenias might be due to antibodies targeting the EPO receptor [50].

3.2.2. Splenic sequestration

Hypersplenism is characterized by splenomegaly, a decrease in one or more blood elements with a subsequent increase in their bone marrow precursors and correction of the cytopenia by splenectomy [51]. Hypersplenism causes pancytopenia by splenic sequestration and in some cases by hemolysis [52]. Patients can present with pain or fullness in the left upper quadrant, abdominal distension or referred pain to the shoulder. The causes are numerous. Cirrhosis, congestive heart failure, malignancies like leukemia/lymphoma, hemoglobinopathies and infections are some of the common ones. The diagnostic approach should begin with imaging studies like CT of the chest and abdomen looking for malignancies and signs of portal hypertension. Splenectomy should be considered if appropriate, although splenectomy alone is not curative. Long-term complications of splenectomy include an increased risk for infections and thromboembolism and these should be considered while making a decision to perform a splenectomy.

3.3. Combination of impaired production and peripheral destruction

3.3.1. Paroxysmal nocturnal hemoglobinuria

PNH is a rare acquired stem cell disorder characterized by mutation in the PIGA gene resulting in defective cell membrane leading to hemolysis, pancytopenia and thrombosis. PIGA protein is necessary for the synthesis of GPI anchor, which helps a subset of cell proteins (CD55 and CD59) adhere to the plasma membrane. Lack of this GPI anchor ultimately leads to complement-mediated intravascular hemolysis. The mechanism of thrombosis is unclear. Patients usually present with symptoms of hemolytic anemia and thrombosis in atypical locations. The RBC breakdown causes release of hemoglobin pigments into the urine, which presents as dark red colored urine in the early morning. If initial blood tests show negative direct coombs test along with intravascular hemolysis, then PNH should be suspected. Confirmatory test is flow cytometry with FLAER (Fluorescent AERolysin – a reagent which binds to the GPI anchor which is defective in PNH) [53]. Treatment of classical PNH is with eculizumab or HSCT. Thromboembolism is a major cause of death and patients should be monitored for signs and symptoms of venous thrombosis and treated promptly [54].

3.3.2. Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening disorder, which can present with pancytopenia. It can be either familial or sporadic, caused by various triggers like infections, malignancies, rheumatologic and immunodeficiency syndromes [55]. It is characterized by tissue and cell destruction due to activation of macrophages (histiocytes) and lymphocytes from defective down regulation [56]. HLH presents with multiple organ failure and initial evaluation should include complete blood count with differential, coagulation studies, fibrinogen, serum ferritin (usually > 1000 mg/mL), liver function tests and triglycerides, soluble CD25. Biopsies often reveal red cell ingestion by histiocytes (hemophagocytosis). Familial HLH (FLH) is caused by mutation affecting either one of the FLH loci or a gene causing one of several congenital immunodeficiency syndromes. The mutations usually target one of the components of the perforin mediated cytotoxic pathway. Treating the underlying conditions may lead to improvement of HLH but patients who deteriorate need HLH specific treatment. Untreated patients usually have a very high mortality rate and timely diagnosis is often a challenge due to its atypical presentation [57]. It is a frequent but often overlooked complication of sick patients who are hospitalized especially in the intensive care units (commonly due to infections), therefore a consulting hematologist must be aware of the current criteria for diagnosis and management paradigm which may include prompt administration of corticosteroids and/or chemotherapy (etoposide).

4. Summary

Pancytopenia is a clinical entity representing a wide array of medical conditions. The first step in the management of pancytopenia involves identifying the underlying cause and providing supportive care till the pancytopenia is resolved. A complete history and physical examination usually helps in narrowing down the cause, which could then lead to further specific diagnostic studies. We have devised an algorithm (Fig. 1) to guide physicians in diagnosing pancytopenia. Identifying whether the pancytopenia is caused by a production disorder or a consumption disorder or a combination of both is a key step in both diagnosing the cause and for management of the patient.

5. Practice points

- Next-generation sequencing has made genome sequencing faster

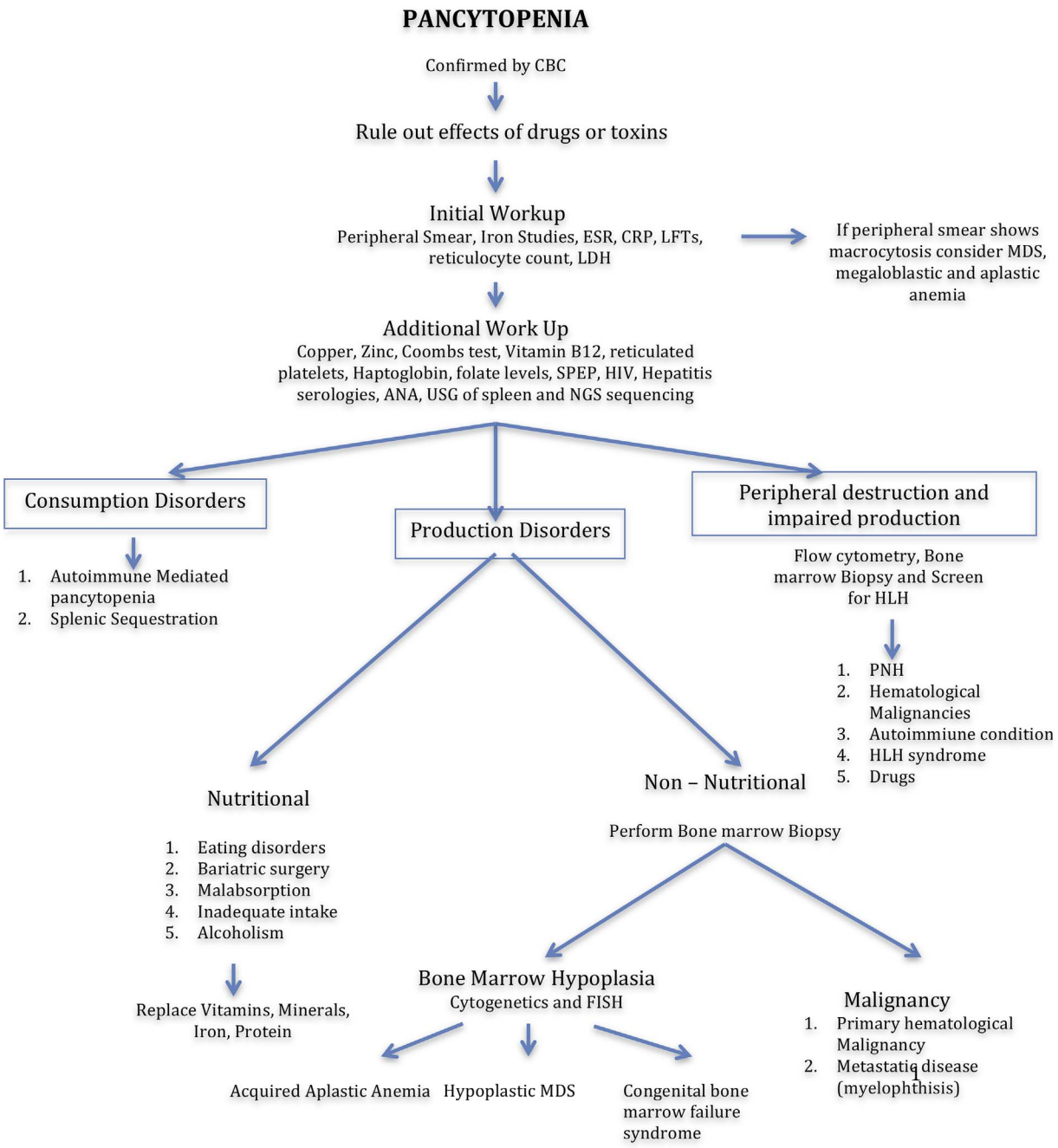

Fig. 1. General management approach and algorithm to help diagnose the cause of pancytopenia. A comprehensive initial workup helps to differentiate the underlying mechanism of pancytopenia and a more focused testing help identify the specific cause.

and more affordable, which helps to diagnose many congenital causes of aplastic anemia

- It is vital to identify disorders which require HSCT early in the course of management as these patient might need to be transferred to Transplant centers
- Although nutritional cause of pancytopenia has decreased due to folate fortification of food, alcohol abuse, malabsorption syndromes and bariatric surgeries can all lead to pancytopenia

6. Research agenda

Identifying whether the pancytopenia is caused by impaired production or increased destruction helps narrow down from a wide variety of disorders causing pancytopenia and an algorithm such as the one presented here helps in determining the specific cause.

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Conflict of interest

The authors report no conflict of interest.

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