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Commentaries

Stigma

We are all aware of the notion of stigma attached to seeing a psychiatrist. We all have tried to refer patients to psychiatrists, only to have the patient refuse. Yet recently the SSRI anti-depressants and the benzodiazepine anxiolytics have transformed the treatment of depression and anxiety in the US partly because these drugs are so easy to use, and partly because patients are willing to take medications for psychiatric reasons, so long as a non-psychiatrist prescribes the drugs.

Although I'm a neurologist, I am now, quite surprisingly to myself, dealing with that stigma directly. In February I moved to Butler Hospital. It is my fourth employer since I moved to R.I. in 1982, and hopefully my last. Since I am a movement disorders neurologist, one might reasonably ask why I would want to be at Butler, a psychiatric hospital, and why Butler would want me. These two questions have different answers. However, what is more interesting is why patients who wanted to see me when my offices were in Warwick and East Providence, do not want to see me at the Butler campus?

I am at Butler for two major reasons. The main one is to expand research endeavors into movement disorders, primarily **Parkinson's disease (PD),** but also Huntington's disease, drug-induced movement disorders and psychogenic movement disorders (more common than Huntington's disease).

Almost all movement disorders have concomitant behavioral disorders. My own personal research interests have focused on these behavioral problems, so that while I treat, hopefully, the "whole" patient, movement and non-motor problems, I would like to expand research into the most debilitating aspects of PD, namely dementia, fatigue, depression and sleep disorders. And Butler, of course, has research groups interested in some of these areas.

The second answer to this question reflects my age. Although it was only after I moved that one of my patients left me a note asking for the name of the neurologist she should see when "something happens" to me and I stop seeing patients. The question had occurred to me as well. I have worried about where my many PD patients would go when "something" happens to me. While there are many superb neurologists in our area, there were none with special expertise and interest in PD. Now, with Victoria Chang, MD, working with me, there is, and hopefully another specialist will join us to follow these patients.

The second question, why would Butler want me, is more interesting. Butler views itself, and would like itself to be viewed, as a hospital for "brain disorders," not just psychiatric disorders. It had a distinguished dementia center, and adding a movement disorders program advanced the notion that brain disorders don't respect classification fault lines that separate neurologic and psychiatric disorders. Like the maps drawn arbitrarily through Africa in 19th century imperialist days, "officially" sanctioned lines separating disciplines may not reflect the reality on the ground. Brain disease is an all encompassing concept. A good example of the arbitrariness of classification is Bonnet's syndrome, in which otherwise normal elderly people with severe visual impairment develop complex visual hallucinations. When onset is acute the patients go the emergency room, which then directs them to the psychiatric service, which then directs them to the neurologist.

Is Alzheimer's disease a neurological or psychiatric disorder? As Dr. Easton would say, "Yes." Obviously it is a brain disease. I'm a movement disorders neurologist but my research is in "neuropsychiatry," which, by the way, is different from "behavioral neurology," a field which addresses aphasia, abnormal emotional responses, and apraxia. But all of these are brain disorders. That aphasia is a neurological disorder while hallucinations are psychiatric is due purely to random historical events.

The stigma of Butler Hospital has affected my own practice. When I moved, my referrals slowed. Some patients who saw me in a private office were reluctant to transfer care. Occasionally family members would tell me, "He didn't want to see you at Butler. We had to convince him."

When I first opened my office at Butler, I asked the hospital not to advertise because I thought I would be overwhelmed and that I would alienate the doctors who referred patients because of lengthy waiting times. I wish. I've been here over 6 months and my schedule is still not full.

The orthopedists have offices on the Butler campus but I doubt they have this problem. Bones and brains aren't confused and I doubt that patients refuse to see an orthopedist because the building is on the Butler campus. "I saw Dr X at Butler for my hip," sounds different than, "I saw Dr. Friedman at Butler for my Parkinson's." Some do worry about seeing me on the Butler campus ("Will I have to stay there?" some occasionally ask my secretary, only semi-joking), and I believe this reflects the stigma of being treated at a psychiatric hospital. Butler and I are keen to correct this.

The neurological literature certainly reflects the changes in the discipline's thinking about behavior in the last 15 years. Increasing numbers of articles discuss dementia, mood and other behavioral problems in PD, ALS, stroke, epilepsy, MS and all the other "neurological" disorders that used to be considered as not having a behavioral component. Increasing numbers of conferences now focus on the behavioral aspects of neurological disorders. There are few brain changes that do not have either direct or indirect behavioral consequences and, while for historical reasons certain disorders fall into one discipline rather than another, the basic identification of a disorder as "brain or not brain," is really what counts.

Non-psychiatric physicians must help lead the way.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001-2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.

From Sequence to Consequence

A stranger walks down a country lane and sees a small farmhouse at the margins of a plowed field. He wonders: "Did that visibly fertile field attract the farmer who then built his dwelling next to the field?" Or, alternatively, "Did the farmer, inheriting the farmhouse from his parents, then clear the adjacent woodland to make a meadow capable of growing a crop?" A farmhouse and a plowed field: which came first? And did the farmhouse "cause" the plowing? Or did the fertile field "cause" the farmer to construct his farmhouse beside this obviously fecund field? Or, perhaps, was there no causal relationship between the two physical entities?

A tourist from the States visits Stonehenge in southern England and exclaims: "Wasn't it thoughtful of those early Druids to build their primitive monument next to an accessible highway and parking lot!" Or an equally credulous tourist in Virginia questions: "How come so many Civil War battles were fought in National Parks?" People take two or more disparate things and speculate about their interrelationships, wondering, sometimes, if one came about because of the other.

Before they perceive the rudiments of language, young children learn the fundamentals of causal relationships. One of the first principles that they learn is the temporal connection between causes and effects: if A truly causes B, then A must precede B. A baseball game is not rained out if it rains the next day. Eating forbidden cookies comes before a spanking – not after (except, perhaps, in dysfunctional families.)

Nature respects the rules of causality but displays a cosmic indifference to how the many and varied consequences are perceived. It acknowledges neither penalties nor prizes, just outcomes.

But how reliable is a temporal relationship in assigning causality when the outcome is a complexity such as a human disease? For example, most people with Alzheimer's disease have grey hair; furthermore, the grey hair almost always precedes the development of dementia. Can we conclude then that the grey hair "caused" the dementia? Or will we require more stringent evidence to indict greyness as the etiologic agent? How might innocent sequence be separated from evil consequence?

The time is 1942 and a healthy man works in a New England shipyard constructing ocean-going freighters to sustain the war effort. His job is to coat the many interior pipes with an insulating sludge containing asbestos. Many years later, after an interval during which he held many diverse jobs and smoked countless cigarettes, he developed difficulties in breathing, lost weight and was diagnosed as a victim of the lung cancer mesothelioma. In the year 2011 we now recognize that inhaled asbestos particles may eventually lead to this unusual form of malignant tumor. The time interval, the latent phase, was not minutes but decades, and so much transpired in the interim. A child touches a hot stove and a fraction of a second later feels the pain. If the interval between touching a hot surface and experiencing pain had been many days, the likelihood of the child, or the adult, learning something from the experience is probably lost. And with the many shipyard workers it required much painstaking epidemiologic inquiry and laboratory research to indict asbestos finally as the cause of mesothelioma.

It also required over a century of research to convince the conservative medical profession that microscopic organisms – called microbes – might cause human distress, even fatal illness. And further, that each strain of bacteria generally causes its own specific, often idiosyncratic infection. It didn't seem reasonable to most physicians that an invisible organism could fell a 200 pound adult. A German physician named Robert Koch (1843 - 1910) assembled a sequence of laboratory steps, now called Koch's postulates, to provide proof of causality.

First, the suspect microbe must be consistently associated with the specific disease. Second, the suspected microbe must be isolated from one or more organs and grown in pure culture. And third, a healthy susceptible host (an experimental animal such as a mouse) when inoculated with the putative microbe will then develop the disease. A fourth proviso was later added: the same microbe must be re-isolated from the experimental animal.

As clinical medicine learned more of the intricacies of infectious disease, some of these postulates have been modified; but Koch's postulates, recognizing that the world is awash with bacteria and other risks – some of which may be harmful to humans – still offer a rational means by which disease-producing germs might be distinguished from non-disease-producing germs: a laboratory method effectively separating the innocent microbiologic bystanders from the hostile invaders.

As water runs downhill so, too, does effect follow cause. Some relationships never seem to change.

– Stanley M. Aronson, MD

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Management of HIV-Associated Lymphomas

Chia-Ching Wang, MD, and Jorge J. Castillo, MD

Since the beginning of the AIDS epidemic, HIV infection has been associated with the development of lymphomas. HIV-associated lymphomas are among the most common malignancies seen in these patients (second to Kaposi sarcoma), accounting for a substantial mortality. The pathogenesis of HIV-associated lymphomas relies on chronic antigenic stimulation, viral co-infection (e.g. EBV) and immunologic dysregulation, among others. Since the advent of **highly active antiretroviral therapy (HAART)** in the mid 1990s, the morbidity and mortality associated with HIV infection have decreased substantially, along with the incidence of HIV-associated lymphomas. In the last several years, our understanding of the biology of the disease and improvements of antiretroviral and supportive therapy have changed the treatment of patients with HIV-associated lymphoma. However, the treatment continues to represent a challenge to oncologists. The objective of this review is to highlight developments in the therapy of HIV-associated lymphomas.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of HIV-associated lymphomas, accounting for about 80-90% of cases.[1] HIV-associated DLBCL can present as either primary lymph node disease or at extranodal sites. In HIV-positive individuals, more than half of the patients have some site of extranodal involvement at diagnosis, with the most common sites being the gastrointestinal tract, bone marrow and the **central nervous system (CNS)**; but any organ may be involved. The patients affected by HIV-associated DLBCL tend to be young men with CD4 counts <200 cells/mm^3. The disease tends to be clinically aggressive, necessitating prompt treatment.

Prognostic factors in HIV-associated DLBCL can be divided into HIV-related (e.g. CD4 count, presence of opportunistic infections, HIV viral load, etc.) or lymphoma-related (e.g. stage, complete response rate, International Prognostic Index, etc). In the pre-HAART era, HIV-related and lymphoma-related factors seemed to have a prognostic value for survival. More recently in the HAART era, lymphoma-related prognostic factors, such as attainment of complete remission or high **International Prognostic Index (IPI)** scores remain as independent risk factors for survival.[1] However, an immunological response to HAART, manifested by an increase of CD4 counts and undetectable HIV viral loads, seems to confer an additional benefit in patients with HIV-associated DLBCL.

Hence, the markedly median overall survival for patients with DLBCL has gone from 6 months in the pre-HAART era to 4 years in the HAART era, an overall survival comparable to HIV-negative patients with DLBCL.[1] However, whether HAART should be used concomitantly or sequentially with chemotherapy is not well-established. One study showed virologic control of HIV infection was a significant factor in the ability to obtain complete remission of lymphoma, while another study showed that withholding HAART until completion of chemotherapy did not lead to lower overall survival.[2] Regardless, most experts agree that HAART should be given throughout the treatment of DLBCL. Zidovudine should be avoided since it is the most likely anti-retroviral to cause significant bone marrow suppression.[2]

Addition of rituximab to **CHOP (cyclophosphamide, doxorubicin, vincristine and oral prednisone)** has demonstrated a clear benefit in immunocompetent patients with DLBCL. Rituximab is a monoclonal antibody directed against CD20, a B-cell antigen expressed by normal B-lymphocytes and also by approximately 85% of NHL malignant cells. The use of rituximab in HIV-infected patients has remained controversial. Patients who received regimens containing rituximab appear to have higher rates of remission, lower rates of progressive lymphoma, but higher rates of treatment-related infection.[3] In particular, most of the infection-related deaths occurred in patients with CD4 counts <50 cells/mm^3.[2]However, several recent studies have evaluated the safety of rituximab-enhanced regimens in patients with CD4 counts >100 cells/mm^3. Nonetheless, clinicians should be vigilant about implementing appropriate antibiotic prophylaxis and promptly recognizing, diagnosing, and treating potentially life-threatening infectious complications. In the relapsed setting, **autologous hematopoietic stem cell transplantation (HSCT)** has shown feasibility, achieving similar results than in immunocompetent individuals with DLBCL.[4]

Primary Central Nervous System Lymphoma

Primary CNS lymphoma (PCNSL) accounts for approximately 1-2% of the cases of lymphoma in patients with HIV infection, but it accounts for 10% of the cases in patients with a diagnosis of AIDS. In contrast to HIV-associated Burkitt lymphoma, PCNSL is usually positive for **Epstein-Barr virus (EBV)**. The median CD4 count at the time of diagnosis is typically markedly low at <50 cells/mm^3, which may in part explain the poor prognosis for this subset of patients. With the advent of HAART, the incidence of PCNSL has decreased markedly. In fact, the incidence rate of PCNSL in HIV-positive patients has gone from 5.3 per 1000 person-years in the early 1990s (pre-HAART) to 0.3 per 1000 person-years by 1999 (post-HAART).

PCNSL generally presents with focal neurologic deficits, including cranial nerve findings, headaches, and/or seizures. The diagnosis is made by cerebrospinal fluid examination and imaging studies. The lesions on CT scans often show ring-enhancement with intravenous contrast administration and may occur at any location. PCNSL may be difficult to differentiate from cerebral toxoplasmosis, which is the most common cause of focal cerebral lesions in HIV-infected patients. Once a diagnosis of PCNSL is made, staging is not usually

necessary, since systemic involvement is rare. The survival of HIV-positive patients with PCNSL before HAART was extremely short at 3 months in patients receiving brain radiation and 1 month in patients who did not receive treatment; in the HAART era, the 2-year overall survival approaches 30%.

In terms of treatment, whole-brain radiation therapy has been used for palliation and can induce improvement in up to 50% of the patients but responses are brief. HAART is recommended in HIV-positive patients with a diagnosis of PCNSL, since there is evidence that it can improve survival concurrently with radiotherapy and steroids if an improvement in the CD4 count is achieved.[5] The role of systemic chemotherapy in HIV-associated PCNSL is unclear; however, high-dose methotrexate was associated with an overall survival of 19 months in a small pilot study.[6] In our opinion, these patients should be considered for clinical trials.

Plasmablastic lymphoma

Plasmablastic lymphoma (**PBL**) is an aggressive variant of DLBCL. The cell of origin is thought to be a mature activated B-lymphocyte in transition to become a plasma cell. The majority of cases are seen in HIV patients; however, several cases have been reported in immunocompetent individuals. PBL tends to present involving the oral cavity of HIV-positive individuals with CD4 counts <200 cells/mm^3. The association with EBV is reported at 74%. These tumors have an aggressive clinical course with a high rate of relapses and a median overall survival of 15 months.[7]

A review of 112 cases of HIV-positive PBL failed to identify prognostic indicators;[7] however, a more recent study in 70 HIV-positive PBL patients showed that clinical stage and response to chemotherapy were associated with overall survival.[8] Standard regimens such as CHOP are thought to be inadequate to treat PBL, and current guidelines recommend treating PBL with high-intensity regimens such as hyperCVAD or CODOX/M-IVAC. Due to the lack of CD20 expression by the malignant cells, the use of rituximab in PBL is unclear. Antiretrovirals should be started and administered throughout the treatment, if possible.

Primary Effusion Lymphoma

Primary effusion lymphoma (**PEL**), a rare lymphoma seen more commonly in HIV-positive patients, accounts for 3% of all the cases of HIV-associated NHL. It usually presents as an effusion without evidence of detectable masses in HIV-positive patients with severe immunodeficiency (CD4 count <150 cells/mm^3). PEL is universally associated with human herpesvirus 8 (HHV8), which is also associated with Kaposi sarcoma. The co-infection rate with EBV is reported at 70%. The median overall survival is 6 months.

Patients with HIV-associated lymphomas should be treated by HIV oncologists in settings where they can benefit from research protocols.

A study in 28 patients with HIV-positive PEL identified a poor performance status (ECOG 2 or higher) and absence of HAART prior to PEL diagnosis as prognostic factors for survival.[9] Despite its inherent chemoresistance, PEL should be treated, whenever possible, with anthracycline-based regimens, such as CHOP or dose-adjusted EPOCH with or without intrathecal chemotherapy. Rituximab should be given to the rare cases that express CD20 in the lymphoma cells, as long as their CD4 count is >100 cells/mm^3. All patients should receive G-CSF support and antiretrovirals should be started and administered throughout the treatment.

Burkitt lymphoma

Burkitt lymphoma (**BL**) is rare in adults in the United States, but is the second most common pathologic type of lymphoma in HIV-infected patients, accounting for 10-20% of the cases.[2] Most patients with HIV-associated BL present with B symptoms, peripheral lymphadenopathy, an intraabdominal mass and laboratory evidence of tumor lysis (hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis, high LDH and uric acid levels with or without renal failure).[10] BL also tend to occur in patients with relatively higher CD4 counts (>200 cells/mm^3) than other lymphomas, such as PBL or PEL.[1] Furthermore, the incidence of BL in HIV-positive patients has not decreased with the advent of HAART. Clinically, the disease is typically rapidly aggressive, developing in a matter of days or weeks, with a propensity to involve the CNS. Therefore, it is imperative to confirm the diagnosis expeditiously in order to avoid delays in initiating therapy.

In contrast with the endemic variants of BL, in which the association with EBV is virtually 100%, the presence of EBV in HIV-associated BL has been reported in 25-40% of the cases. Potential adverse prognostic factors for HIV-associated BL are CD4 counts <100 cells/mm^3 and a high IPI score. The addition of HAART does not seem to have prolonged survival in these patients; however, it will likely allow more intensive therapies and the benefit could be seen in the near future.

Unfortunately, even with the addition of HAART to chemotherapy, patients with BL still have a median survival time of only 6 months, which is unchanged from the pre-HAART era;[11] but in this study, patients did not receive modern intensive regimens. The current treatment of BL resembles that for immunocompetent patients, and involves intensive combination chemotherapy regimens such as hyperCVAD and CODOX/M-IVAC with or without rituximab. Rituximab should not be used in patients with CD4 counts <100 cells/mm^3. Importantly, CNS prophylaxis is mandatory in these patients, and for this intrathecal methotrexate is commonly used. The guidelines render R-CHOP as inadequate for HIV-associated BL, except for the patients who will not tolerate intensive chemotherapy, in which case R-CHOP can be combined with high-dose methotrexate. Support with G-CSF should be given to prevent febrile neutropenia. Since tumor lysis syndrome is common, prophylaxis with intravenous hydration, urine alkalization and allopurinol or rasburicase is sometimes required during the first cycle of chemotherapy.[10]

Hodgkin lymphoma

Hodgkin lymphoma (HL) is a very common lymphoma seen in younger immunocompetent individuals. For this reason, the association of HIV infection and HL remained unclear. The WHO classification, however, includes HL as one of the HIV-associated lymphomas, although it is not considered an AIDS-defining cancer. The risk of HL in HIV-positive individuals is approximately 20-fold when compared with the general population. Several population-based studies have shown that in the HAART era the incidence of HL seems to have increased, in comparison with the patterns observed in Kaposi sarcoma or specific subtypes of NHL such as PCNSL. HL is an EBV-associated lymphoma since 80-100% of the Reed-Sternberg cells express EBV **latent membrane protein (LMP1).**

Clinically, HIV-associated HL present with advanced stages (75-90%) and systemic B symptoms such as fever, night sweats and unintentional weight loss (70-95%). The median CD4 count at presentation is almost invariably >200 cells/mm^3. In a retrospective study of 290 cases of HIV-associated HL, absence of B symptoms, absence of extranodal involvement and prior use of HAART were associated with a better overall survival. Prior to HAART the overall survival on these patients was 18 months.

Due to the scarcity of cases, randomized controlled trials have not been done in HIV-associated HL, but the overall survival seems longer in patients treated with standard regimens, such as ABVD and Stanford V. For example, a prospective study on 59 patients with HIV-associated HL treated with Stanford V plus HAART and G-CSF support reported a 3-year overall survival of 51% [12]. More recently, a Spanish study on 62 patients treated with ABVD concurrently with HAART showed a 5-year overall survival of 75%.[13] In the latter study, an immunological response to HAART has been associated with better survival. The relapse rate in HIV patients is higher than in the general population. In this setting, autologous HSCT have shown to be well tolerated and effective, obtaining survival benefits similar to immunocompetent patients.[4] HSCT after relapse is considered a standard of care in patients with HIV-associated HL.

Conclusions

In the last 30 years, the management of HIV-associated lymphomas has evolved. Some of the most significant advances include the introduction of HAART, the ability to administer standard and high-intensity chemotherapy regimens and the improvement of supportive therapy. Despite these advances, the management of HIV-associated lymphomas remains a challenge due to potential pharmacologic interactions and an increased risk of infectious complications. Patients with HIV-associated lymphomas should be treated by HIV oncologists in settings where they can benefit from research protocols.

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Acute Myeloid Leukemia In the Elderly

Christine Ho, MD, and James N. Butera, MD

Acute myeloid leukemia (AML) is a malignant stem cell disorder characterized by a disruption in hematopoiesis resulting in accumulation of immature or blast cells in the bone marrow and the peripheral blood. This leads to bone marrow failure, severe cytopenias and death if left untreated. The incidence of AML increases with age, with the majority of patients older than age 60.[1] Elderly patients with AML have a particularly poor prognosis.

Definition

In most clinical trials, there is a clear change towards inferior prognosis in patients over age 55. However, with every decade of life beyond age 55, the prognosis decreases further. Hence, the age-demarcation between elderly and non-elderly has been a source of discussion. **The National Comprehensive Cancer Network** (NCCN) guidelines have used a cutoff of age 60 to define elderly AML.[2]

Clinical presentation and diagnosis

Patients with AML usually present with symptoms related to their cytopenias. They can develop fevers or infections as a result of neutropenia. Anemia can lead to sometimes rapidly progressing weakness and fatigue. Patients may notice petechiae or easy bruising or bleeding due to thrombocytopenia. When they present to their physician with these symptoms or when routine lab work is done (complete blood count), these abnormalities may be identified. Further testing to diagnose AML can include examination of the peripheral blood smear, bone marrow aspirate and biopsy, cytogenetic and molecular analysis, and immunophenotyping.

Prognosis

In general, the five-year survival rate of all patients with AML is between 20-25%. However, in elderly patients the survival is much worse. In some published series, patients between ages of 55-65 years have a 5 year survival of only 9%. Furthermore, the prognosis also decreases with increasing age: long-term survival is only 7% and 3.5% in age groups 66-75 years and older then 75 years, respectively.[3,4,5]

The reasons are multiple. Elderly patients frequently cannot tolerate aggressive induction chemotherapy. Some side effects that are especially toxic to elderly patients include severe myelosuppression leading to infections, cardiotoxicity, and nausea/vomiting. They typically have a higher incidence of comorbid illnesses, poor organ reserve and a poor tolerance to infections. Moreover, AML may more frequently arise from an antecedent hematologic disorder such as a myeloproliferative disorder or myelodysplasia, which is always associated with a worse outcome. There is a higher incidence of poor-risk cytogenetics in elderly AML as well as other poor outcome features ,such as a higher prevalence of multi-drug resistance proteins.[5]

Prognosis and cytogenetics of AML are tightly linked. Risk stratification can divide patients with AML among three groups: those with favorable, intermediate and unfavorable cytogenetic abnormalities. (Table 1) This stratification also applies to elderly patients with AML. However, within each cytogenetic risk group, the prognosis with standard treatments decreases with increasing age. Furthermore, with increasing age there is an increase in the proportion of patients with unfavorable risk cytogenetics and a decrease in favorable risk cytogenetics. One study found that the percentage of favorable risk cytogenetics dropped from 17% in patients ages younger than 56 years to 4% in those aged older than 75 years. Moreover, the percentage of patients with unfavorable cytogenetics increased from 35% in those younger than 56 years to 51% of patients older than 75.[2]

In addition, AML patients with a normal karytotype, who account for the majority of the cases, can make up a heterogenous group. Molecular genetics have become increasingly utilized in the characterization of patients with normal karyotypes. Three molecular markers of prognostic significance are FLT3, NPM1, and CEBPA. Table 2 summarizes the prognostic relevance of these markers.

Treatment

The conventional initial treatment of AML is induction chemotherapy with the 7+3 regimen, which consists of 7 days of continuous intravenous infusion of cytarabine 100mg/m^2 and 3 days of daunorubicin 45-60 mg/m^2. There is roughly a 64-70% chance of obtaining a complete remission with this regimen for all patients with AML. However, this success rate declines to roughly 46% in ages 56-65 years, 39% in patients 66-75 years old, and only 33% of patients older then 75 years.[2,4,6]

Some elderly patients cannot tolerate aggressive induction chemotherapy; however, there is no agreement upon the ideal age for induction chemotherapy in patients with AML. The decision to treat

Table 1. Cytogenetics and risk stratification

	Chromosomal abnormalities
Favorable risk group	t(15;17), t(8;21), inv(16) or t(16;16)
Intermediate risk group	Normal karyotype, t(9;11), del(9q), del(7q), del(20q), -Y, +8, +11, +13, +21
Unfavorable risk group	Complex karyotype, inv(3), t(6;9), t(6;11), t(11;19), del(5q), -5, -7

Table 2. Molecular markers

Marker	Characteristics	Mutation	Prognosis
NPM1	Nucleolar phosphoprotein	Delocalization of protein to the cytoplasm	Favorable prognosis with higher CR rates and lower relapse rates
CEBPA	Transcription factor involved in normal hematopoeisis	Abnormal protein leading to inability to bind to DNA	Favorable prognosis with higher CR rates and lower relapse rates
FLT3	Tyrosine kinase receptor expressed on hematopoietic cells	Activation of the receptor	Unfavorable prognosis with increased relapse risk and decreased overall survival

with induction chemotherapy depends on several factors such as age, frailty, organ function and comorbid illnesses. However, once a patient is deemed ineligible for induction chemotherapy, treatment is focused mainly on supportive measures, such as transfusions when needed and antibiotics for treatable infections. Low doses of oral chemotherapy such as hydroxyurea can reduce the leukemia burden in patients.[7] Nonetheless, ultimately, these patients will typically die of their leukemia within a matter of weeks to months from their diagnosis.

For those patients who achieve complete remission with induction chemotherapy, post remission therapy can include either consolidation chemotherapy or allogeneic bone marrow transplant in younger, well suited patients who have a match. Any of the standard post-remission therapies improve cure rates for patients with AML. The standard consolidation regimen chemotherapy for younger patients is high-dose cytarabine, but the benefit with this regimen has been noted only in patients younger than 60 years of age. Furthermore, patients over age 60 have a higher incidence of cerebellar toxicity which can be a devastating side effect of this treatment. Therefore, elderly patients may undergo 1-2 cycles of a lesser intense chemotherapy regimen for consolidation. A very reasonable consolidation regimen is to use 5 days of continuous infusion cytarabine and 2 days of daunorubicin 45-60 mg/m^2. This is typically very well tolerated in elderly patients.[1,2]

Despite some success with induction and consolidation chemotherapy in elderly patients with AML, the vast majority will relapse within 18 months and die of their disease. Several novel agents are under review for elderly patients with AML. The classes of new drugs include hypomethylating agents, nucleoside analogs, farnesyltransferase inhibitors and FLT3 inhibitors.

Elderly patients are often unable to tolerate intensive cytotoxic chemotherapy which is required to treat this aggressive malignancy.

Hypomethylating agents

DNA methylation has been known to lead to gene silencing. In AML, DNA methylation causes silencing of tumor suppressor genes. Decitabine is a drug that inhibits DNA methyltransferase, which prevents methylation and thus reactivates the tumor suppressor genes. This agent is currently FDA-approved for the treatment of myelodysplasia. A recent study used decitabine as first line therapy for AML patients older than age 60. Results were promising with an **overall response rate (ORR)** of 25% and a **complete response rate (CR)** of 24%. Further studies are being conducted comparing decitabine with standard therapies.[8] Azacitidine is another DNA methyltransferase inhibitor. A phase III randomized trial was recently conducted that compared azacitidine with intensive chemotherapy, low-dose cytarabine, or best supportive care. The results showed that azacitidine significantly prolonged overall survival by 8 months and was better tolerated compared to the other treatments in older patients with less than 25% bon marrow blast count.[9]

Nucleoside analogs

Clofarabine is a second generation purine nucleoside analog. Its mechanism of action is via inhibition of ribonucleotide reductase and DNA polymerase. A recent phase II study was conducted using clofarabine as first line treatment of elderly patients older than 60. These patients had one or more unfavorable prognostic factors. The results of the study showed that clofarabine was active against elderly AML patients with an ORR of 46% with 38% CR. This drug was overall relatively well tolerated with the most common side effect of nausea, febrile neutropenia, vomiting, diarrhea, rash, and fatigue.[10]

Farnesyltransferase inhibitors

Farnesyltransferase inhibitors are molecules that competitively inhibit farnesyltransferase; several intracellular molecules require farnesylation to function correctly. One particular molecule involved in the pathogenesis of AML is RAS. RAS functions at the plasma membrane to transduce signals to the nucleus from extracellular signals leading to cell growth. Inhibiting farnesylation results in decreased cell proliferation. There have been phase II and phase III studies with tipifarnib. Phase II studies showed a CR rate of 14% and 10% with partial response. The phase III study compared tipifarnib with supportive care and showed only 8% CR for tipifarnib versus 0% for supportive care but no overall survival benefit. However, given the modest activity seen in the phase II trial, using tipifarnib in combination with other chemotherapy drugs is being studied.[11]

FLT3 tyrosine kinase inhibitors

FLT3 is a receptor tyrosine kinase. Activating mutations lead to proliferation of blast cells. A phase II trial used lestauritnib (CEP701) as first line therapy in previously untreated older

patients ineligible to cytotoxic chemotherapy. Although no patients achieved CR, a clinical response was seen as temporary decrease in bone marrow and peripheral blood blasts. Some patients also became transiently transfusion independent. More studies are continuing with other FLT3 inhibitors as well as in combination with other chemotherapy.[12]

Hematopoietic stem cell transplantation

Many times, stem cell transplant offers another method of treatment for patients with AML. The effectiveness of stem cell transplant is through the graft versus leukemia effect. Patients who develop this phenomenon have a lower risk of relapse. In standard treatment, prior to receiving a stem cell transplant, patients undergo intensive myeloablative chemotherapy. However, the comorbidities and poor performance status of elderly patients often preclude them from getting full intensity chemotherapy.

Recently, reduced intensity chemotherapy regimens have been developed that have reintroduced stem cell transplant into the options that can be offered to elderly patients. Reduced intensity chemotherapy is capable of achieving enough host immunosuppression to allow to engraftment of the transplant without the associated toxic side effects of full intensity chemotherapy.[13]

One issue to consider with elderly patients is the timely identification of a donor. Elderly patients may not have any living, medically suitable siblings for possible donation. This makes this option less widely available for elderly patients compared to younger AML patients.

Conclusion

AML is a hematopoietic disorder that increases in incidence with age. Elderly patients are often unable to tolerate intensive cytotoxic chemotherapy which is required to treat this aggressive malignancy. Its prognosis remains poor. With ongoing clinical trials and new drug development, more options are becoming available in the treatment of elderly patients with AML.

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Pesticides and non-Hodgkin Lymphoma: An Overview for the Clinician

David Berz, MD, PhD, Jorge J. Castillo, MD, Daniela N. Quilliam, MPH, REHS, Gerald Colvin, DO

Non Hodgkin Lymphoma (NHL) represents a heterogeneous group of malignant diseases arising from the lymphatic tissues. Grossly, those disease entities can be subdivided into T-and B-cell lymphomas. Several systems have been developed over the last decades in order to further subclassify NHL. The **World Health Organization** (**WHO**) recognizes greater than 40 pathological subtypes of NHL. As molecular techniques evolve, the heterogeneity of this group of diseases is expanding further.

There were an estimated 56,390 new cases and 19,200 deaths from NHL in 2005. It was the 6th most common cancer among men and the 5th most common cancer among women.[1] The incidence of NHL increased at a rate of 3-4% per year during the 1970s and 1980s and stabilized in the 1990s.[2] Initially, better diagnostic techniques, changes in the classification patterns of NHL and the AIDS epidemic were potential explanations for this rise. However, more recent data revealed that the changes in NHL incidence are not fully explained by those phenomena and suggest that increasing exposures to not fully defined environmental factors, like diet or occupational exposures seem to be of importance.

The incidence of NHL is not homogenous throughout the **United States** (US). NHL-related mortality is higher in the central, more agricultural areas of the US. Hence, agricultural occupational exposures to pesticides have been investigated as causes for the development of NHL in numerous laboratory and epidemiological studies. Because of the large variety of potentially toxic substances, the corresponding wide spectrum of chemical structures and the sophisticated statistical techniques employed in the epidemiological investigations, the literature on the subject of the association of the development of NHL and use of pesticides is not straightforward.

What is a Pesticide?

The **United States Environmental Protection Agency** (**US EPA**) defines pesticides as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating insects, rodents or other animals, unwanted plants or weeds, fungi or microorganisms like bacteria or viruses. Approximately 890 pesticide compounds are marketed in the US in the form of more than 20,000 different products.

Methodological Difficulties with the Available Studies

Many studies tried to link farm life with the increased incidence of NHL. This does not consider whether the individual diagnosed with NHL participated in farming or was exposed to any of the toxic substances in question. Other investigations focused on the association of pesticide use and the development of NHL. Those studies often did not sufficiently address the question of the intensity of the exposure, its tenure, which pesticide was used and which type of lymphomas were observed.

Along with those more principal problems, most of those studies were retrospective cohorts or had a cross-sectional case-control design, which are generally associated with various types of biases, including coverage, sampling, selection, and recall bias.

Pesticides Frequently Used in the USA

Phenoxyacetic acid herbicides PAH

This group of pesticide compounds encompasses 2,4,5-T, which was found to contain a direct dioxin derivative that was banned in most European countries and the US in 1977, and 2,4-D, which is one of the most frequently used broadleaf pesticides in the US.

Early case control studies suggested an association between a professional PAH exposure and an increased incidence of NHL. Although most follow-up studies revealed a similar association, the findings have not always been statistically significant. An early interview-based Swedish case-control study from 1981 reported a 6-fold increase of NHL in individuals using PAH.[3] Subsequent studies from Kansas, Nebraska and New Zealand demonstrated an elevated incidence among PAH-using farmers.[4,5] Those studies also suggested that increased, unprotected and prolonged use of those pesticides seemed to increase the risk for NHL development. More recent studies showed a trend towards increased NHL incidence in the PAH using farming population without reaching statistical significance.[6] A large-scale international retrospective cohort study (SMR = 1.39, 95% CI 0.89-2.06) and a large retrospective effort from the Netherlands (RR=1.7, 95% CI 0.2-16.5) on the increase of NHL risk in occupational PAH exposure both showed trends towards an increase in NHL incidence in those populations.[7,8]

In summary, the methodological difficulties of those large scale studies notwithstanding, PAH appears to increase the development of NHL and prolonged and more intense use seems to strengthen this association.

Agent Orange

Agent Orange, used mainly for warfare, is a dioxin-contaminated mixture of PAH. It has been extensively investigated as a cause of NHL.[9,10] Although uncontrolled studies revealed an increase in NHL incidence in Vietnam veterans, ongoing large-scale Vietnam based studies are still examining the association of increased NHL incidence and exposure to Agent Orange.

Thus far, there is insufficient evidence to conclude whether there is an increased incidence of NHL in Vietnam veterans who were exposed to Agent Orange.

Chlorophenol herbicides (CPH)

The CPH are a group of nineteen different compounds which are chemically related to the PAH and which have the potential for dioxin contamination. They are mainly used in wood preservation and have been banned in many European countries since the 1970s but large amounts may still exist in soil and sedi-

ments even after the discontinuation of their use. Chlorophenols are still in use in several industries in the US. Most studies did identify a trend for increased NHL incidence in CPH exposed individuals without statistical significance and often large confidence intervals for the proposed association odds ratio.[7,11] Another international project identified a not statistically significant trend for the development of NHL with prolonged CPH exposure.[8] In addition, a recently published German study suggested an increased incidence of CPH and indolent as well as aggressive lymphoma subtypes.[12]

In conclusion, CPHs are a less well studied group of pesticides. However, their structural similarity to PAH and the possibility for contamination with carcinogenic dioxins, makes them, in the light of the evidence, potential lymphomagenic substances.

Triazine pesticides

Atrazine, cyanazine and metribuzin are members of the triazine pesticide group. These chemicals were introduced in the 1950s and are used to control germinating weeds. Atrazine is one of the most heavily used herbicides in the US, used extensively in corn, citrus, nut, sugarcane, sorghum, and cotton cultivation. Its use was restricted in the 1990s but despite the restrictions it is still significantly utilized. A Kansas case-control study demonstrated a statistically significant association of agricultural atrazine use and increased NHL incidence (OR=2.7, 95% CI 1.2-5.9). Several subsequent studies demonstrated equivocal or contradictory results.[13] A recent evaluation from the agricultural health study cohort, including 53,943 participants, could not establish an association of increased NHL incidence and agricultural atrazine use.[14]

In summary, atrazine has not been consistently associated with increased NHL incidence, whilst a synergistic effect with other pesticides, appears possible.

Glyphosate

Glyphosate (and its trade product Roundup®) is one of the most frequently used herbicides in the US. Although preclinical studies suggested an impact on the liver metabolism of prenatal rodents, a recent literature review concluded that glyphosate is not toxic to humans. Subsequent reports raised the concern that other compounds within the traded herbicide are more toxic than glyphosate itself.

One study from the Netherlands suggested an association of glyphosate exposure and hairy cell leukemia.[7] Other studies could not establish such a relationship.[11] Further, the large scale prospective agricultural health study was not able to detect an association between NHL incidence and glyphosate exposure.[15]

In summary, at this time we feel that there is no sufficient evidence that glyphosate induces NHL in farmers.

Organochlorine Insecticides (OCI)

The OCIs are a heterogenous group of insecticides that encompass DDT, DDD among others. The OCIs exert their toxic effect by virtue of opening sodium channels and hence generating steady action potentials. Due to their long half-lives the OCIs have a strong tendency for bioaccumulation in adipose tissues. Most of the OCI compounds are banned in the US because laboratory studies on rodents revealed carcinogenicity.

OCIs have been investigated for their potential to increase NHL incidence, with lindane and DDT being the most widely studied compounds. Although an early study from Kansas with few lindane exposed cases showed an increase of NHL with lindane use in the agricultural setting (OR=6.1, 95% CI 1.3-29),[8] most subsequent studies demonstrated only non-statistically significant trends towards an increase in incidence of NHL with exposure to OCI.[6,13] In conclusion, there is insufficient evidence at this time to determine if OCIs are associated with NHL.

Organophosphate Insecticides (OPI)

OPIs are the most broadly used insecticides in the US. They were originally developed as byproducts of nerve-gas production in Nazi Germany. They function as neurotoxins by virtue of irreversibly inhibiting the enzyme acetylcholinesterase. The OPIs easily degrade with sunlight, prohibiting significant bioaccumulation. However, small amounts can be detected in food and drinking water.

Several studies have investigated the impact of OPIs on the development of NHL. The Nebraska study[16] and a Canadian study[6] established a statistically significant increase in NHL incidence and the use of OPIs. Most other investigations established a similar trend, although the findings were not statistically significant.[4,13]

Overall, the OPI compounds can be regarded as potential culprits for lymphomagenesis.

Carbamates

The carbamates represent a heterogenous group of compounds that are used as herbicides and insecticides. They belong to the same class as the clinically used compounds neostigmine and rivastigmine, whose chemical structure is based on the natural alkaloid physostigmine.

A study from Nebraska described a statistically significant association of carbamate exposure and the development of NHL.[16] Several later North American studies showed a positive association, which held statistical significance for only certain subclasses of carbamate insecticides and herbicides,[16,17] which were not statistically significantly associated with the development of NHL in other studies.

Fungicides

Fungicides make up less than 10% of the pesticides used in the US. Association of fungicide use with the incidence of NHL in users has been studied over more than two decades. Although in a Canadian study[6] sulfur compound fungicides have been statistically significantly linked to an increased incidence of NHL, most other studies that studied sulfur compound and other fungicide use demonstrated either protective effects or lost statistical significance of an association when corrected for other pesticide use.[11,17]

Lymphoma subtypes

The inability of several of the above outlined studies to detect a statistically significant association between pesticide exposure and NHL development may partially be related to the fact that the incidence of NHL in general was examined as the outcome variable. As discussed previously, NHLs are a highly heterogeneous group of diseases. Even within the same subtype of NHL, the genetic profiles observed often vary widely. This prompts the question if lymphomas, harboring specific genetic abnormalities, are more likely to be associated with pesticide exposures than others.

One commonly detected genetic abnormality in NHL is a the translocation 14;18 or t(14;18). This genetic event corresponds with the activation of Bcl-2, an anti-apoptotic protein. Cells with this mutation can be immortalized by virtue of the activity of this cell cycle relevant protein and this event has been directly linked with lymphomagenesis, mainly follicular lymphoma. Several preliminary retrospective studies identified a possible link between lymphomas containing t(14;18) and pesticide exposure.[18]

Two large population-based studies have specifically evaluated the association of t(14;18)-positive lymphomas in occupational pesticide exposure. In the first study by Schroeder and colleagues,[18] the aggregate exposure OR for insecticides in t(14;18) showed a weakly positive trend without reaching statistical significance (OR 1.3, 95% CI 0.8-2.0). However, when examining specific OCI exposures, the associations observed were much stronger and reached statistical significance. A second population-based study by Chiu and colleagues found an association between pesticide exposure and t(14;18)-positive NHL.[19] The association retained statistical significance for crop insecticides (OR=3.0, 95%CI 1.1-8.2), herbicides (OR=2.9, 95% CI 1.1-7.9) and fumigants (OR=5.0, 95% CI 1.7-14.5). No association between pesticide exposure and t (14;18)-negative NHL was found.

Conclusions

Several key points can be highlighted based on our review. First, the literature on the subject is complicated by the fact that several pesticides are often used simultaneously. This might obscure pathogenic relationships between certain pesticides and NHL development. Second, most of the epidemiological studies are biased secondary to retrospective cohort and case-control designs. For better study of the exposure disease relationship further prospective studies are required. Third, in spite of several methodological shortcomings, the literature suggests an association between the exposure to several pesticides and the development of NHL. Fourth, several other compounds such as carbamates, fungicides and glyphosate have no sufficient evidence on such a relationship. Lastly, the evolving knowledge about the molecular diversity and pathogenesis of lymphomas might allow for a more specific study of associations between pesticide exposures and certain NHL subtypes.

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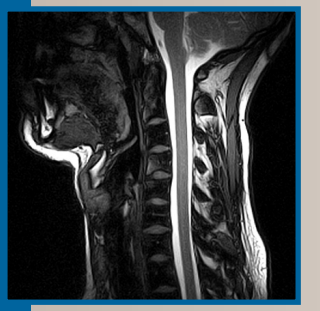

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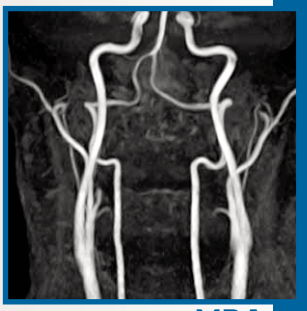

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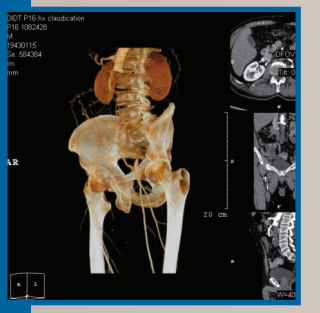

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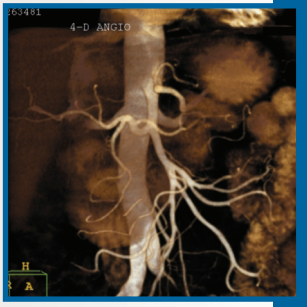

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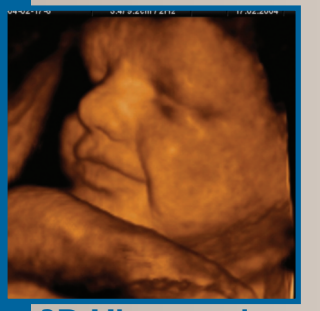

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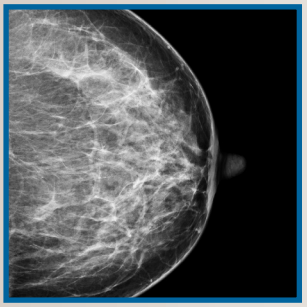
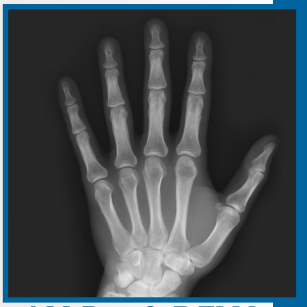


Digital Mammography



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Chronic Lymphocytic Leukemia:
Something Old, Something New and Something Borrowed...

Kimberly Perez, MD, and Eric S. Winer, MD

Chronic Lymphocytic Leukemia (CLL) is a disease of the elderly: almost 70% of diagnoses are made in patients older than 65 years. This indolent lymphoproliferative disorder, manifested by a clonal expansion of mature but functionally defective lymphocytes, is one of the most common leukemias of adults in Western countries. The incidence rate is roughly 2-6 cases per 100,000 persons per year, and increases with age reaching 12.8 cases per 100,000 at age 65 (the mean age at diagnosis).[1] The disease is more common in men, with an incidence ratio of 1.5-2:1. It also has been found to be more common in the Caucasian population, compared to African American, Hispanic, Native American or Asian populations.

There are no clear occupational or environmental risk factors for CLL. The prevalence in Caucasian populations suggests a genetic versus an environmental influence on the etiology. A recent study supports an association between blood transfusions and CLL development in 66% patients evaluated.[3] However, among the strongest risk factors for the development of CLL is a family history of CLL or other lymphoid malignancy. Retrospective studies have noted increased incidence in first degree relatives. A term coined "genetic anticipation" has also been used to describe a process in which the median age at diagnosis in an affected family decreases in younger generations.[2]

Clinical Presentation

The clinical presentation, course and outcome are extremely heterogeneous. At presentation most patients are asymptomatic; up to 25% are diagnosed when routine blood work reveals an absolute lymphocytosis. For those who present with clinical symptoms, most commonly it is in the form of painless, intermittent swelling of lymph nodes. In 5-10% of patients, clinical presentation consists of B symptoms, which include unintentional weight loss ≥10% within the previous six months, fevers >100.5°F (>38°C) for ≥2 weeks without evidence of infection, drenching night sweats without evidence of infection, or extreme fatigue (ie, ECOG Performance status 2 or worse; cannot work or perform usual activities). Other clinical findings consist of autoimmune hemolytic anemia or thrombocytopenia, recurrent infections, splenomegaly, hepatomegaly, or, rarely, extranodal infiltrates.

Histologic findings on the peripheral blood smear are typically of small lymphocytes with clumped chromatin and scanty cytoplasm. Smudge or basket cells are usually present. (Figure 1) There is usually a small proportion of immature lymphocytes, such as prolymphocytes, at a rate of <2%. Bone marrow findings are variable. Cellularity is normal or increased, and typically the architecture is disrupted, following interstitial, nodular, and/or diffuse patterns. The **International Workshop on CLL (IWCLL)** describes greater than 30% lymphoid cells as present for the diagnosis.[4]

Diagnosis

The diagnosis of CLL can be made utilizing the IWCLL guidelines, based on the identification of cells bearing the unique phenotype of CLL in peripheral blood (CD5-positive/CD19-positive). However, before the diagnosis can be made an important distinction needs to be made between CLL, **small lymphocytic lymphoma (SLL)** and **monoclonal B-cell lymphocytosis (MBL). The World Health Organization (WHO)** classifies both CLL and SLL as different clinical manifestations of the same disease: CLL is the leukemic component with genesis occurring in the marrow, whereas SLL is defined by a lymphomatous origin. To differentiate CLL and MBL, the distinction is made based on the absolute lymphocyte count. MBL is defined in patients who have an absolute increase in the number of clonal B lymphocytes in the peripheral blood that does not exceed 5000/microL and who have no lymphadenopathy, organomegaly, cytopenias, or disease-related symptoms.[5]

The diagnostic criteria for CLL include an absolute B lymphocyte count in the peripheral blood ≥5000/microL for more than 3 months, with a preponderant population of morphologically mature-appearing small lymphocytes and the demonstration of clonality of the circulating B lymphocytes by flow cytometry of peripheral blood. Clonality is determined by extremely low levels of surface immunoglobulin M and IgD with either kappa or lambda (but not both) light chains; expression of B-cell associated antigens (CD19, dim CD20, CD23, CD43 and CD79a); and expression of the T-cell associated antigen CD5.

In CLL, the bone marrow demonstrates infiltration by the clonal population in the range of 30-100%. Prior to the development of cytogenetic markers, bone marrow biopsy was utilized for diagnostic and prognostic indications. However, with the use of cell surface markers for clonality determination, the use of bone marrow aspirate and biopsy has become unnecessary for diagnosis. The same is true in regards to its prognostic use.

After the diagnosis, two clinical staging systems can be utilized: the Rai stage or the Binet system. (Table 1) Both take into account end-organ involvement due to progressive accumulation of neoplastic cells and the development of lymphadenopathy, organomegaly and cytopenias. The Rai system based their classification on the disease process, whereas the Binet system stages based on sites of involvement.[6,7] For both systems, a thorough clinical exam and complete blood count are necessary. The guidelines do not recommend the use of **computed tomography (CT)** scans at diagnosis for assessment of end-organ involvement. Some oncologists may order a CT scan if the patient has poor prognostic features, which can result in upstaging.

Determining Prognosis

The advent of molecular profiling revealed characteristics of CLL as a disease process. The profile consists of cytogenetic

Table 1. Staging systems in chronic lymphocytic leukemia

	Definition	Risk stratum	Median survival
Rai System			
0	Sustained lymphocytosis >10,000mcL	Low	150 months
1	Lymphocytosis with adenopathy	Intermediate	70-100 months
2	Lymphocytosis with splenomegaly		
3	Lymphocytosis with anemia	High	20 months
4	lymphocytosis with thrombocytopenia		
Binet System			
A	Less than 3 areas of lymphadenopathy; no anemia or thrombocytopenia	Low	Comparable to age-matched controls
B	More than 3 involved node areas; no anemia or thrombocytopenia	Intermediate	84 months
C	hemoglobin <10g/dL and/ or platelets <100 cells/mm^3	High	24 months

analysis by **fluorescence in situ hybridization (FISH)** (del 13q24; trisomy 12; deletions or mutations of 11q22-23; deletions or mutations of 6q21 or 17p13) and mutational status of the **immunoglobulin heavy chain variable gene locus (IgVH).** Due to the lack of access to IgVH mutational testing, attempts at securing surrogate markers have been developed. Examples of surrogate markers are ZAP70 and CD38 expression. On final analysis, poor prognostic features consist of IgVH unmutated status, which in turn the expression of ZAP70 or CD38 can act as a surrogate. Some major limitations in these molecular profile markers are the limited access of IgVH, mutational status testing sites, the unreliability of the assays used to determine ZAP70 status, and the question of stability in regards to CD38. Therefore, the use of the biomarkers is limited: they may help predict the behavior of a cohort of patients will behave, but they are not yet precise in predicting the outcome in individual patients.

Treatment – Something Old, Something New, Something Borrowed...and the kitchen sink

Since CLL tends to be an indolent disease and also a disease predominantly of older people, the most important decision to make is when to initiate treatment. Previous meta-analyses have shown that there is no survival benefit for patients who have early intervention versus deferred chemotherapy; in fact there was a slight trend towards worse survival in the early treatment category.[8] The updated IWCLL guidelines offer the following criteria:[4] 1) progressive marrow failure demonstrated by new or progressive anemia or thrombocytopenia, 2) massive or symptomatic splenomegaly, 3) massive of symptomatic lymphadenopathy, 4) a lymphocyte increase of more than 50% over a two-month period or a lymphocyte doubling time of <6 months, 5) autoimmune anemia and or thrombocytopenia poorly responsive to steroids, and 6) presence of B symptoms. If no treatment is indicated, the patient is followed by clinical exam and complete blood counts every 3 months for the first year. These intervals can be modified depending on aggressiveness of disease.

Once the decision to treat has been made, the clinician and patient must decide the goals of treatment. It is uncommon for patients to be cured from their CLL with conventional chemotherapy. While the goal of treatment in a younger patient may be to induce a complete remission of maximum duration, the goal for the older patient may be to manage the disease, such as minimizing anemia and thrombocytopenia. Numerous regimens have been used in CLL, many of which are shown in Table 2.

Something Old: Chlorambucil and purine analogues

Chlorambucil was the first chemotherapeutic to be effectively used in the treatment of CLL. It is given orally as either a low dose daily regimen or pulsed with prednisone on a monthly basis. It is very well tolerated with minimal myelosuppression, nausea, or alopecia. The limitation is that it has a low **complete response (CR)** rate of 0-4%, with an **overall response (OR)** rate of 31-55% when evaluated in multiple modern comparative studies ranging.[9-11] However, despite the lower response rate, very few drugs have conferred a survival advantage when compared to chlorambucil. It remains the treatment of choice for elderly or poor performance status patients due to its efficacy and its excellent side effect profile.

Three purine analogues (fludarabine, pentostatin, and cladribine) are currently used for the treatment of CLL, with the most common being **fludarabine (F).** When compared as a single agent with chlorambucil, fludarabine demonstrated a significantly higher CR (7-20%) and OR (63-72%) rates. However, there was no significant difference in overall survival. The side effect profile shows higher rates of grade 3-4 cytopenias, and therefore more complications with immunosuppression. Similarly, cladribine also produced higher OR rates, but no improvement in overall survival.

Something New: Monoclonal Antibodies

The monoclonal antibodies have revolutionized the treatment of lymphomas. These antibodies directly bind to the surface of the malignant cell and induce cell killing by **antigen dependent cellular cytotoxicity (ADCC), cellular dependent cytotoxicity (CDC)** and/or direct induction of apoptosis. The first mab in

clinical use was rituximab, an anti-CD20 mab used to treat B-cell lymphomas, is now standard in nearly all of the B-cell lymphoma-directed regimens. The CD20 antigen can also be found on 95% of CLL cases. In single agent studies of rituximab in CLL, which used doses of rituximab much higher than conventionally used in other lymphomas, the overall response rates were 36% and 45%. Ofatumumab, a second-generation anti-CD20 mab, has also recently been studied in CLL. In a group of fludarabine refractory CLL patients, the overall response rate was 47-58%.[12]

Another monoclonal antibody widely used in the treatment of CLL is alemtuzumab, an anti-CD52 mab. Alemtuzumab has been compared to chlorambucil and has shown to have higher CR (24%) and OR (83%) rates, but has not demonstrated an overall survival benefit.[20] Initially the most common side effects were severe transfusion reactions with hypotension; however, with the conversion from intravenous to subcutaneous administration, these have been replaced by injection site reactions. Persistent side effects are immunosuppression, particularly viral reactivation (VZV, CMV). Alemtuzumab has proven efficacy in patients considered high-risk with cytogenetic abnormalities such as deletion of chromosome 11 (del 11q) or chromosome 17 (del 17p) and the p53 mutation. Lumiliximab, a novel anti-CD23 mab, was recently evaluated in a phase I trial, but demonstrated limited clinical activity as a single agent.

In treating CLL patients, the first question to ask is "Does this patient need to be treated?"

Something Borrowed: Bendamustine

Bendamustine, an alkylator in the nitrogen mustard family, was first discovered in the former East German Democratic Republic in the early 1960s. Although extensively studied in East Germany, bendamustine had few validation studies and therefore did not gain worldwide acceptance until well after the unification of Germany. One of the initial bendamustine trials in patients with refractory CLL demonstrated an overall response rate of 56%,[13] while the phase III trial against chlorambucil demonstrated a CR rate of 31% and an OR rate of 68%. Bendamustine has a very well tolerated side effect profile notable for mild cytopenias, moderate nausea, and minimal alopecia.

...and the Kitchen Sink

With multiple agents available, the logical progression is the combination of chemotherapeutic agents. The first combination studied extensively was the combination of **fludarabine (F),** a purine analogue, with **cyclophosphamide (C),** an alkylator. Two studies compared F to FC, and one study compared these two regimens to standard chlorambucil.[14-16] FC showed a significant improvement in efficacy, with a CR rate of 23-38% and an overall response rate of 74-94%. Although there was an increase in grade 3-4 neutropenia with this regimen, there was no increase in the rate of severe infections.

The natural progression after this study was the combination of conventional chemotherapy with monoclonal antibodies. **Fludarabine (F)** combined with **rituximab (R)** in the front-line setting yielded a CR rate of 47% and OR of 90%. Impressively,

Table 2. Selected randomized first-line studies in chronic lymphocytic leukemia

Study	Regimen	CR rate (%)	OR rate (%)	PFS (Months)
Rai [9]	Fludarabine	20 (p< 0.001)	63 (p< 0.001)	20 (p< 0.001)
	Chlorambucil	4	37	14
Hillmen [11]	Alemtuzumab	24 (p< 0.001)	83 (p< 0.001)	15 (p<0.001)
	Chlorambucil	2	55	12
Knauf [10]	Bendamustine	31 (p< 0.001)	68 (p< 0.001)	22 (p< 0.001)
	Chlorambucil	2	2	8
Catovsky [15]	Chlorambucil	7	72	5 years-10%
	Fludarabine	15	80	5 Years-10%
	Fludarabine + cyclophosphamide	38 (p<0.0001)	94 (p< 0.001)	5 Years-10% (p<0.00005)
Finn [14]	Fludarabine	5	59	19
	Fludarabine + cyclophosphamide	23 (p< 0.001)	74 (p< 0.001)	32 (p< 0.0001)
Eichhorst [16]	Fludarabine	7	83	20
	Fludarabine + cyclophosphamide	24 (p< 0.001)	94 (p= 0.001)	48 (p=0.001)
Hallek [18]	Fludarabine + cyclophosphamide	23	88	2 Years-76.6%
	Fludarabine + cyclophosphamide + rituximab	44 (p<0.0001)	95 (p= 0.001)	2 Years-62.5% (p<0.0001)

phase II data using FCR in front-line CLL demonstrated a CR rate of 72% and an OR rate of 95%.[17] Phase III data comparing FC to FCR also showed superiority of FCR with similar results, however there was no significant difference in progression free survival or overall survival in the patients with the chromosomal deletion of 17 (del 17p). The addition of rituximab to the fludarabine and cytoxan demonstrated a survival benefit over FC alone.[18] Other purine analogues have been substituted for fludarabine in an attempt to reduce the myelotoxicity, such as the combination of **pentostatin, cyclophosphamide and rituximab (PCR)** but this showed no significant improvement in response rates or decrease in rate of infection. Trials have also studied the addition of alemtuzumab to FC or FCR, but these did not show improved efficacy and had a higher incidence of myelosuppression. Other chemotherapeutic regimens have been attempted with fludarabine but none showed improved efficacy to FCR.

One intriguing combination that demonstrated efficacy was the combination of **bendamustine and rituximab (BR).**[19] This regimen demonstrated a CR rate of 15% and OR rate of 77%. Because of the favorable side effect profile and high response rate, BR is being compared to FCR in a large phase III clinical trial. Similarly, **lumiliximab (L)**, the anti-CD23 antibody, has also been found to be synergistic with FCR;[20] a large phase III trial is ongoing comparing L-FCR with FCR. Other novel agents, such as lenalidomide, flavopiridol and ABT-263, are being studied; it is unclear what role these agents will play in the treatment of CLL.

Relapsed Disease

It is common for patients to relapse after a period of time in a CR. There are few guidelines as to the best second-line treatment. Patients who have high risk disease or relapse in less than one year from treatment and are eligible for high-dose chemotherapy and should be offered allogeneic stem cell transplantation, which has shown to be curative,[21] in a clinical trial setting. Patients with chemosensitive disease who obtain long remissions from their initial treatment are usually treated in the relapse setting with chemotherapy different than that received previously; or, if the remission was longstanding, patients often receive the same regimen.

Recommendations and Summary

In treating CLL patients, the first question to ask is: "Does this patient need to be treated?" Although it is often difficult for patients to gain comfort with "watch and wait," it is important to emphasize that there is no benefit to early intervention. Once criteria have been met for treatment, patients are stratified by performance status and presence of "high risk" molecular features (del 17p or del 11q mutations). Although clinical trials are the preferred treatment, they are not available in all locations. Therefore, older, poor performance patients should be started on chlorambucil, whereas younger patients should be treated with FCR. The treatment for CLL patients with 17p deletion (high-risk) should start with FCR, and include alemtuzumab and allogeneic stem cell transplantation.

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Images In Medicine

Adenosquamous Cell Carcinoma of the Gallbladder

Robert Bagdasaryan, MD, and Helen Miroshnichenko

A 76-year-old woman with abdominal pain underwent CAT scan evaluation which demonstrated cholelithiasis and gallbladder wall thickening.

Cholecystectomy, in addition to cholelithiasis, revealed 2.5 cm transmurally invasive ulcerated adenosquamous carcinoma.

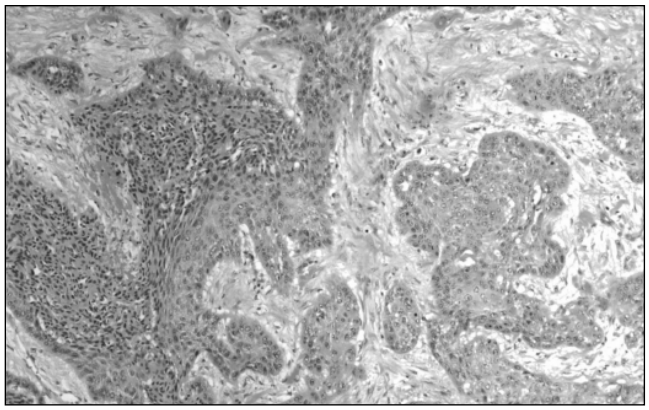
Gallbladder carcinoma is an uncommon disease, with an incidence ranging from 0.72 to 21 cases per 100,000 worldwide, a male-female ration of 1:3 and an average age at the diagnosis of 72.2 years (median age is 73 years).[3,7]

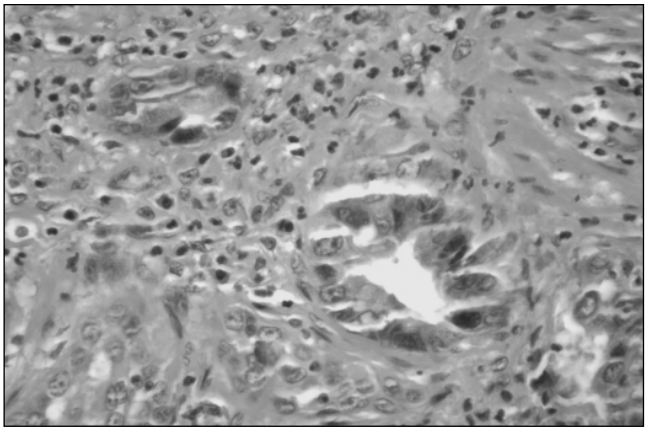
Adenosquamous cell (ASC) carcinoma of the gallbladder is a rare subtype of gallbladder cancer, accounting for 1.4-10.6% of all incidences, while the majority of cases are adenocarcinoma of the gallbladder.[1] Adenosquamous cell carcinoma is characterized by the formation of a large tumor with local invasiveness of neighboring organs, but lacks metastasis in lymph nodes or viscera. The primary spread of ASC of the gallbladder was reported by direct extension (4,5,6), that is, less lymph node invasion and lower metastatic potential compared with adenocarcinoma of the gallbladder (1).

ASC of the gallbladder lacks specific presentations in signs and symptoms until the tumor has grown substantially and the carcinoma is at advanced stages.[1-3] Usually by this time, abdominal pain leads to the discovery of the tumor. After surgery, the median life expectancy is 5.2 months.[3] Prognosis seems to improve with the resection of involved organs as part of a radical operation, which can be justified in cases where the lesion tends to remain localized with no metastasis or peritoneal seeding.[1-3]

It is important to differentiate between squamous and adenosquamous cases because when the two cases are considered together, they are characterized as a whole, by rapid growth and wide infiltration. This inaccurately portrays squamous cell carcinoma with characteristics of ASC carcinoma. In some cases squamous carcinoma is characterized by a well-localized growth and a rarity or lack of metastasis, while ASC infiltrates extensively.[2]

The nature of adenosquamous/squamous carcinoma of the gallbladder increases the opportunities of an extended surgical approach to the squamous carcinomas, in absence of lymphatic or hematogenic metastasis, even in advanced stages, as compared to ASC of the gallbladder.[3]





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Primary Care Physicians' Role in Promoting Children's Oral Health

Junhie Oh, BDS, MPH, Deborah Fuller, DMD, MS, Laurie Leonard, MS, and Katherine Miller

Despite the fact that dental caries are preventable with age-appropriate and effective caries management through periodic dental visits, many children experience dental decay. Based on The National Health and Nutrition Examination Survey, more than a quarter of US children age 2 to 5 years and more than half of the children age 6 to 8 years had dental caries in the period of 1999–2004.[1] The 2007-08 Rhode Island Third Grade Oral Health Survey reported that about half of third graders had experienced dental decay.[2]

Affordable dental insurance that covers preventive and restorative dental services increases the likelihood of obtaining dental care[3,4] and is important to provide prevention, education, and early identification and treatment of oral diseases. In addition, many states including Rhode Island recognize primary care medical providers as key resources to improve access to preventive oral health services for children.

The objectives of this report are to (a) document the percentage of Rhode Island children who received preventive oral health care within a year, (b) assess the association of dental insurance with children's preventive dental care, and (c) describe the importance of RIte Care/Medicaid reimbursement to primary care providers for oral health services.

Methods

The data used for this analysis were obtained from the 2008 Rhode Island **Behavioral Risk Factor Surveillance System (BRFSS),**[5] an ongoing telephone health interview survey of non-institutionalized US adults age 18 years or older. In 2008, Rhode Island expanded its data collection to include 1,315 children under age 18. For this age group, parents were asked whether their child received preventive dental care in the past 12 months (having visited a dentist or dental hygienist for checkup or cleaning), whether the child had dental insurance, and the parents' perceived oral health status of their child. Since the preventive dental visit question was asked for children age 1 year and older, 1,263 children age 1 to 17 years were included in the analysis. The outcome variable, receipt of preventive dental care in the past 12 months, was examined along with the child's sociodemographic and dental insurance variables.

Data were weighted to the probability of selection and adjusted to reflect the age, gender, and race/ethnicity of Rhode Island's child population. Bivariate analyses using the chi-square test were done to identify any significant differences between the various groups, with respect to children's receipt of pre-

Table 1. Rhode Island Children Age 1–17 Years Old Who Reportedly Received a Preventive Dental Care (Dental Checkup or Cleaning) in the Past 12 Months, 2008 BRFSS

Variable Category	Sample size*	Weighted % (95% CI†)	P-value
All	1,263	81.1 (78.5–83.8)	–
Gender			
Male	596	81.5 (77.9–85.0)	NS
Female	517	80.8 (77.0–84.7)	
Age (Years)			
1–5	284	48.8 (42.3–55.4)	
6–11	354	95.5 (93.4–97.6)	<.0001
12–17	475	93.9 (91.6–96.1)	
Race/Ethnicity			
Non-Hispanic White	815	84.1 (81.3–87.0)	0.0001
Other	278	71.9 (65.7–78.2)	
Parent's education			
≤ High School	348	77.6 (72.5–82.7)	NS
> High School	764	82.7 (79.7–85.7)	
Family income			
≤ $35,000	252	72.0 (65.4–78.7)	0.0004
> $35,000	773	83.8 (80.9–86.7)	
Dental coverage			
Yes	987	82.7 (80.0–85.4)	0.0002
No	116	66.3 (56.6–76.0)	

* Unweighted sample sizes for each category may not add up to 1,263 because of missing and excluded data (responses of "don't know," "not sure," or refused).
† CI = confidence interval
NS = not significant at P=0.05

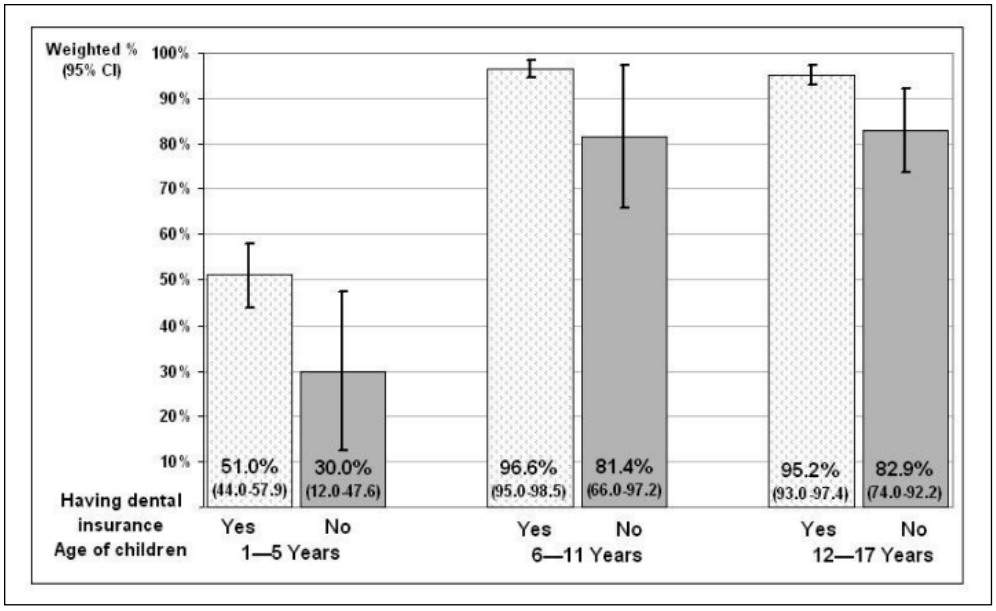

Figure 1. Preventative Dental Visits among RI Children ages 1–17 by Dental Insurance Coverage and Age Group. Source: BRFSS 2008.

ventive dental care in the past year. The statistical significance was tested at P<0.05. SAS survey procedures were used for the analyses to account for the complex sampling design.

Results

Overall, 81.1% (95% CI=78.5–83.8) of children age 1–17 years reportedly had a preventive dental visit within the previous 12 months. (Table 1) Only half of children age 1–5 years had a preventive visit in the past year. This percentage was the lowest of all children's age groups. (Table 1: 48.8% *vs.* 95.5% for children age 6–11 years, and 93.9% for children age 12–17 years) Disparities in the receipt of preventive dental care by child's race/ethnicity, family income, and dental insurance status were also observed. (Table 1)

The authors examined whether the low level of preventive dental visits among young children was associated with dental insurance status. Among the different age groups, however, no significant differences in children's dental insurance coverage were observed (89.8% [CI=86.1-93.5], 92.3% [CI=89.2-95.4], and 87.9% [CI=85.1-90.7] for children age 1–5 years, 6–11 years, and 12–17 years, respectively (P=0.16)).

Figure 1 summarizes the prevalence of preventive dental visits among different age group of children by dental insurance status. Young children age 1–5 years were the least likely to receive preventive dental care; half of the children did not obtain any preventive dental care even though they had dental insurance coverage. No significant differences were observed in the percentages of preventive dental visits by dental insurance status for children age 1–5 years and 6–11 years, mostly because only small number of children did not have dental insurance.

Discussion

Opportunities to Improve Young Children's Access to Oral Health Services

In 2008, most Rhode Island children, regardless of age, reportedly had dental insurance through private insurers or publicly funded programs (RIte Smiles or Medicaid fee-for-service), even though the rates of dental coverage were still lower than medical coverage for all age groups of children. (90% *vs.* 97%: statistics from the authors' separate analyses on dental and medical coverage using the same data source in this study).

This study's findings suggest that having dental insurance did not effectively facilitate access to preventive oral health services, particularly for young children age 1–5 years. Multiple reasons plausibly explain why so many children have not benefited from an early preventive oral health care. Many RI parents may not be aware of the need to access early oral health services and the recommended age for child's first dental visit. In addition, barriers can be associated with Medicaid program funding and administration, the oral health workforce distribution, and their ability to care for very young children.

The American Academy of Pediatric Dentistry, the American Academy of Pediatrics, the American Dental Association, and the American Association of Public Health Dentistry all recommend establishing a dental home and initiating preventive interventions by age 1 year.[5,6,7] Especially for the 1–5 years olds, because of the low level of dental visits even with dental insurance, it is imperative that pediatric primary care providers promote children's oral health.

In RI, the pediatric well-child care setting is ideal to introduce the concept of a dental home to young children and initiate dental referrals at age 1 year for a number of reasons:

1. Half of young children do not visit a dentist until after 5 years of age,

2. Many children from low-income families are unable to access dental services, and

3. Pediatricians and pediatric primary care providers (family physicians, physician assistants, nurse practitioners, etc) have already established medical homes for this vulnerable population.

The RI Department of Health Oral Health Program acknowledges the important role that pediatric primary care providers can assume in promoting children's oral health. Integration of the pediatric well-child visit with oral disease risk assessment and the referral process to a dentist office for young children has been successful in other states and studies.[8,9,10]

To facilitate this integration, RI primary care providers can receive RIte Care/Medicaid reimbursement for preventive oral health services such as risk assessment and fluoride varnish application that are provided during well-child care visits.

The integration of oral health into overall health is vital. Through early intervention, pediatric health care providers are positioned to prevent serious health consequences that can result from oral disease. Oral health risk assessment, anticipatory guidance, oral health screenings, timely referral to a dental home, and the provision of preventive services, such as fluoride varnish, can result in successful health outcomes in children.

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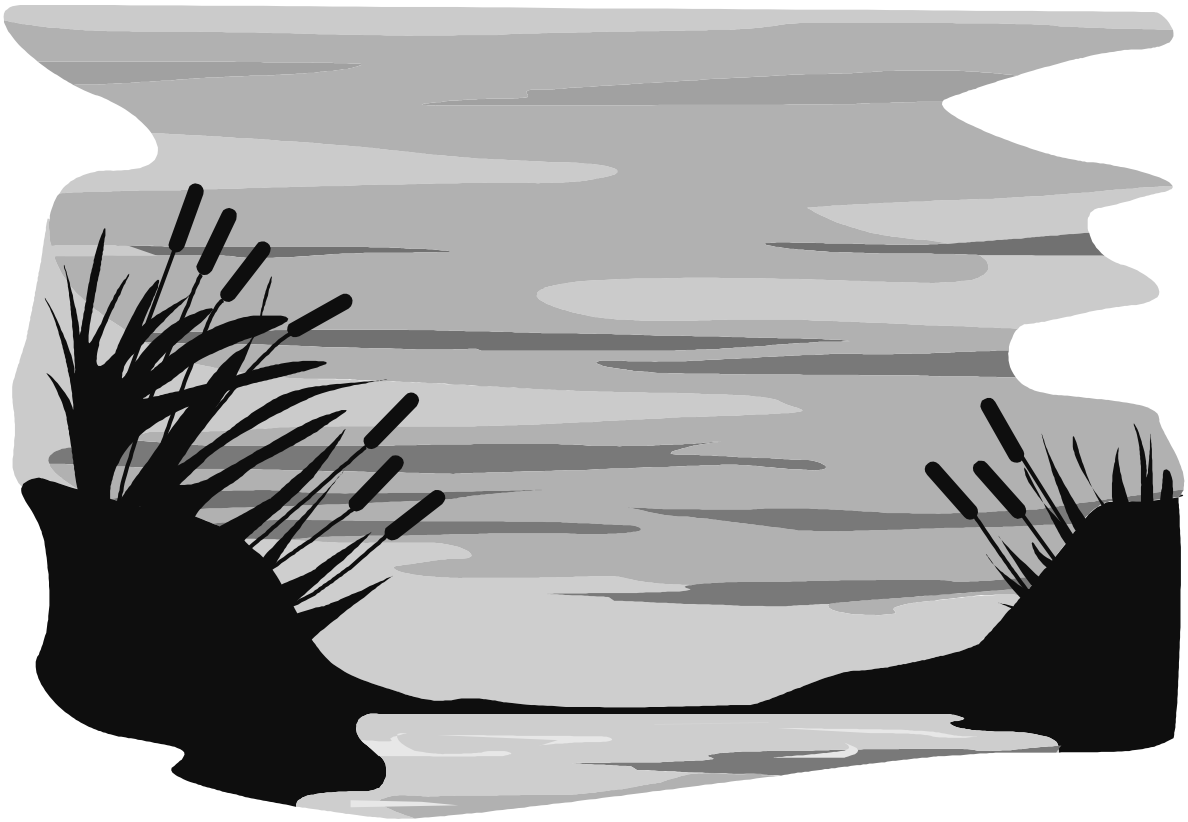
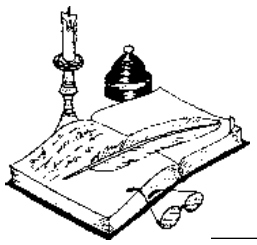
The authors and/or spouses/significant others have no financial interests to disclose.





Physician's Lexicon

A Prescription for Atonement

A contrite person is one who is overcome with guilt, a penitent individual seeking atonement. The word stems from the Latin, *contritus*, meaning to grind, to bruise, to wear away. The same Latin word, without a hint of atonement, is used in standard medical prescriptions (*contritus*, or its abbreviation, *contrit.*) to instruct the pharmacist to grind up or pulverize the medication.

Few physicians today provide detailed instructions to the pharmacist on written prescriptions since virtually all medications are now factory-prepared in both weight and composition. And fewer newly graduated physicians have formal instructions on the use of medical Latin and the five segments of the standard prescription (*superscriptio, recipio, inscriptio, subscriptio* and *signatura*.)

Some instructions persist as distant memories of a time when physicians and pharmacists conversed with each other in Latin. In addition to the *b.i.d., t.i.d., q.i.d.* abbreviations still employed, there is *alternis diebus* (*alt.dieb*.) meaning every other day, *u.d.* (*ut dictum*) meaning as directed, and *ad nauseam* (*ad naus*.) meaning to be taken until nausea supervenes. A simple, *n.r.* (*non repetatur*) signifies to the pharmacist: do not repeat. And *s.o.s.* (*si opus sit*) means if necessary.

Virtually all phrases used in prescriptions are of Latin origin. An occasional word, still Latin, is descended from an earlier Greek term. Thus the Latin, *nauseam,* comes from a Greek word, *nausia,* meaning sea-sickness, literally ship-sickness. English words of similar derivation include nautical and nautilus. A family of mollusks is also referred to as *Nautilus*.

In Homer's *Odyssey*, the daughter of Alcinous, king of the Phaeacians, is Nausicaa, a name that means, literally, "burner of ships."

In compounding prescriptions, pharmacists would be directed to make the medication agreeable to taste, *ad gratum gustum*, (abbreviated as *ad grat. gust.*), of proper and pleasing consistency: *debita spissitudine*, abbreviated as *deb. spis.*

The root, *contritus,* also finds its way in the English noun, trituration, the act of reducing a medication to a fine powder. And the Latin word, *triticum*, means a grain of wheat, suggesting that edible wheat-flour is obtained by threshing or grinding the harvested plant.

– Stanley M. Aronson, MD

Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	January 2010	12 Months Ending with January 2010		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	209	2,355	223.6	3,282.0
Malignant Neoplasms	184	2,271	215.6	6,387.5
Cerebrovascular Diseases	42	435	41.3	889.5
Injuries (Accidents/Suicide/Homicde)	58	599	56.9	10,368.5
COPD	48	507	48.1	450.0

Vital Events	Reporting Period		
	July 2010	12 Months Ending with July 2010	
	Number	Number	Rates
Live Births	1,017	12,099	11.3*
Deaths	761	9,133	8.6*
Infant Deaths	(7)	(89)	7.4#
Neonatal Deaths	(7)	(74)	6.1#
Marriages	805	6,081	5.7*
Divorces	238	3,233	3.0*
Induced Terminations	301	4,203	347.4#
Spontaneous Fetal Deaths	68	663	54.8#
Under 20 weeks gestation	(62)	(597)	65.4#
20+ weeks gestation	(6)	(66)	5.5#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,053,209.

(c) Years of Potential Life Lost (YPLL).

Note: *Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population
\# Rates per 1,000 live births

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Ninety Years Ago, January 1921

Francis P. Emerson, MD, in "Introductory Remarks on Focal Relation to Chronic Diseases," urged readers to note the "conditions of teeth and submerged tonsils." He explained: "There was, at one time, among the dentists, enthusiasm in regard to the relation of apical abscesses to rheumatism. This has somewhat subsided because they found that all cases of rheumatism were not cured by extraction of teeth and the healing of those necrosed areas." Still, he urged physicians to "see the films of these teeth yourself and know that they are looked after by a dentist who will cooperate with you in relieving foci of infection, even if the teeth have to be extracted."

The same author, Francis P. Emerson, MD, also contributed "The Major Role of the Conduction Apparatus in Slowly Progressive Deafness." He remarked: "In some cases of long-standing deafness, it would seem necessary to re-educate the vertical perception areas by exercises, after all sources of infection have been eliminated."

An Editorial, "The Modern Library Building," urged greater use of the building. "While the Medical Library building should be more of a scientific center, it should also be made a social center for the programs in Rhode Island"; for example, musical programs. Also, the Society should make the building available to the District Nursing Association for its programs.

Fifty Years Ago, January 1961

Paul C. Adkins, MD, Associate Professor of Surgery, George Washington University School of Medicine, contributed "Management of Thoracic Trauma" at the John F. Kenney Memorial Clinic Day at Memorial Hospital. The Journal reprinted his talk.

J. John Yasar, MD, and Thomas Micolonghi, MD, in "Ten Year Review of Bronchogenic Carcinoma in a Community Hospital," traced 10 years of data from 103 ward and private patients diagnosed with lung cancer at Memorial Hospital. "The majority…were characterized by insidious onset, paucity of symptoms and rapid growth with early metastases…. Twenty-one percent of cases were inoperable at the time of their initial complaint. Only 17 cases…were resectable."

Francis D. Moore, MD, Mosely Professor of Surgery, Harvard Medical School, contributed a historical essay: "Masters in Medicine: Leonardo and Versalius. Surgery and Science."

An Editorial, "The Charles V. Chapin Hospital," congratulated the new superintendent, Dr. Edward J. West, and praised "a most valuable institution."

Twenty-Five Years Ago, January 1985

Seebert Goldowsky, MD, editor, in "Deinstitutionalization in Rhode Island," noted the poor results in much of the country: "It is now realized that the concept of community mental health was oversold. " Specifically, he cited the clustering of people into substandard housing, slums, and welfare hotels. In Rhode Island, however, he praised the efforts of Dr. Joseph Bevilacqua, director of the state initiative, and his successor Tom Romeo. "Rhode Island is shining example of a successful experience in deinstitutionalization.

Wendy J. Smith, managing editor, in "The Future of Medical Practice," commented on the report by the American Medical Association Council, "The Environment of Medicine," which noted the emergence of "Doc in the Boxes" at shopping malls.

Charles E. Kaufman, MD, and Elliot M. Perlman, MD, in "Optical Causes of Red Eye,"discussed five patients, ages 7 to 79 years, who demonstrated the varied causes, including autoimmune disorder, infectious disease, vascular disorder, and a primary or metastic orbital neoplasm.

In the Clinicopathological Conference, Case Report: Rhode Island Hospital, edited by Maurice M. Albala, MD, George F. Messner, MD, Tom J. Wachtel, MD, and Mark Fagan, MD, the topic was a 60-year old woman with a history of hypertension and alcohol abuse admitted for abdominal pain. Nine days after admission, she died. The anatomic diagnosis: "Aortoduodenal fistula with massive gastrointestinal hemorrhage status post-operative right renal artery reconstruction with bypass graft."

2010 Index

Authors

Title

Key:

abs:	abstract
CC:	Creative Clinician Case
GPP:	Geriatrics for the Practicing Physician
HBN:	Health by Numbers
IM:	Image in Medicine
PL:	Physician's Lexicon

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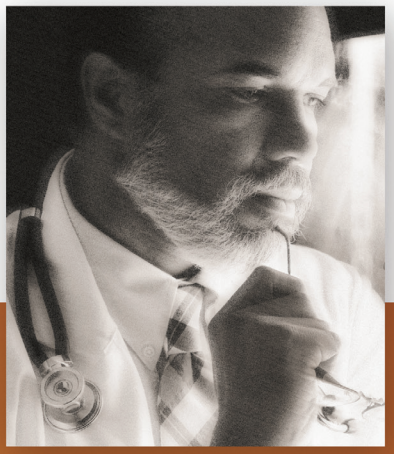

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