Sidney Farber (1903-1973) was an Polish-American pediatric pathologist. He is regarded as the father of modern chemotherapy, after whom the Dana-Farber Cancer Institute is named. He carried out both the preclinical and clinical evaluation of aminopterin (synthesized by Yella Subbarow), a folate antagonist in pediatric acute lymphoblastic leukemia, and demonstrated for the first time that induction of clinical and hematological remission in this disease was achievable.

Pediatric ALL now has a 5-year survival rate >90%!
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EKG Challenge

Dr. Joseph Wang

A 31 year-old female with unknown past medical history presents with altered mental status. EMS was called after the patient's roommate found her to be confused, non-verbal, and quite lethargic. On arrival to the ED, the patient was intubated and the patient's initial ECG was noted as follows:

**Describe the EKG.**
Sinus tachycardia with heart rate at ~115bpm. Right axis deviation. Widened QRS with deep S waves in I and aVL, large terminal R wave (R’) in aVR. Right bundle branch block pattern with downsloping ST-segment elevation most prominent in V2.

**What is the diagnosis?**
A. Digoxin toxicity
B. Hyperkalemia
C. Hypocalcemia
D. STEMI
**Answer**

E. TCA overdose

**What is the next best step in management?**

Sodium bicarbonate is the standard initial therapy in the setting of arrhythmia due to TCA toxicity, particularly in those with widening of the QRS interval >100 msec or a ventricular arrhythmia. The initial dose is 1-2 mEq/kg given as rapid IV push through a large bore catheter followed by IV infusion of 150 mEq of sodium bicarbonate mixed in 1L D5W given at 250mL/hr. Continue to obtain frequent EKGs until patient is free of symptoms or cardiac toxicity has resolved.

**Discussion**

TCA toxicity should be suspect in patients with prolonged QRS complexes, delayed right ventricular activation, and evidence of intraventricular conduction delay (rightward shift in the terminal 40 msec in the frontal plane) manifested as the following ECG characteristics:

1) QRS >100 msec
2) Deep, slurred S wave in leads I and aVL
3) R wave in aVR >3 mm or R to S ratio in aVR >0.7
These findings are suggestive of a sodium channel blockade, similar to patients with Brugada syndrome, which is a sodium channelopathy. Sinus tachycardia is also a common finding due to the anticholinergic effects of TCAs along with hemodynamic compromise leading to reflex tachycardia. The benefit of sodium bicarbonate is likely due to both increases in extracellular sodium and serum pH, which aids in increasing the electrochemical gradient across the cardiac membrane and shifts TCA to the non-ionized neutral form, respectively. In one study, those with QRS > 100 msec had 26% chance of seizure and QRS > 160 msec had 50% chance of ventricular arrhythmia. No seizures or ventricular arrhythmias were observed in those with QRS < 100 msec, leading to the above recommendation to treat with sodium bicarbonate when the QRS > 100 msec.

REFERENCES
Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Dr. Anurag Mehta reviewing Sabatine et al., NEJM March 17, 2017 DOI: 10.1056/NEJMoa1615664

SUMMARY

The FOURIER was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of evolocumab (a PCSK9 inhibitor) for decreasing future cardiovascular events among 27,564 patients (aged 40 to 85 years) with clinical ASCVD (history of MI, non-hemorrhagic stroke, or symptomatic peripheral artery disease) who were receiving moderate- or high-intensity statins and had LDL-C ≥70 mg/dL. PCSK9 inhibitors are agents that lower serum LDL-C levels by promoting LDL receptor recycling that leads to enhanced LDL-C clearance. The FDA has approved evolocumab as an adjunct to diet and maximally-tolerated statin therapy in adult patients with familial hypercholesterolemia (heterozygous/homozygous) and clinical ASCVD who require additional lowering of LDL cholesterol.

The trial patients were randomized in a 1:1 ratio to receive subcutaneous injections of evolocumab (140 mg every 2 weeks or 420 mg every month) or placebo and were followed for 2.2 years for the development of major cardiovascular events – primary composite outcome of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary outcome of interest was a composite of cardiovascular death, myocardial infarction, or stroke. Evolocumab therapy resulted in a rapid and sustained decrease in LDL-C levels. The baseline median LDL-C in both treatment arms was 92 mg/dL. At 48 weeks, the median LDL-C level in the evolocumab arm was 30 mg/dL and the least-squares mean percentage reduction in LDL-C with evolocumab as compared to placebo was 59% (p<0.001). Treatment with evolocumab significantly reduced the risk of primary outcome as compared to placebo (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio 0.85; 95% CI 0.79 to 0.92, p<0.001) (Figure 1). Also, the risk of secondary outcome was significantly lower in the evolocumab arm as compared to placebo (816 patients [5.9%] vs. 1013 patients [7.4%]; hazard ratio 0.80; 95% CI 0.73 to 0.88, p<0.001). The effects of evolocumab were consistent across major subgroups based on sex, age, ASCVD subtype, baseline LDL-C quartiles, intensity of statin therapy, and both evolocumab dosing regimens. Notably, evolocumab had no effect on cardiovascular mortality as compared to placebo. The two treatment arms did not differ in terms of adverse events. EBBINGHAUS, a sub-study of the FOURIER trial revealed that there was no increased risk of memory or other cognitive problems with evolocumab as compared to placebo. [1]

COMMENTARY
The FOURIER trial demonstrated the benefit of using the PCSK9 inhibitor evolocumab in addition to statin therapy for secondary prevention of adverse cardiovascular events in patients with prior ASCVD. The results of this large trial lend credence to the hypothesis that reducing LDL-C to a level lower than what was achieved in prior secondary prevention trials evaluating statins might be more helpful for preventing recurrent cardiovascular events. It is worth noting that the relative risk reduction observed in this trial (15% for the primary endpoint and 20% for the secondary endpoint) was lower than what was anticipated with the degree of LDL-C level lowering achieved. Interestingly, there was a larger relative risk reduction in the second year as compared to the first year, suggesting that had the trial gone longer a larger event reduction would have been seen (Figure 1). At present, the prohibitive cost of evolocumab and no effect on cardiovascular mortality make it a less attractive option as compared to the cheaper alternative of using a high-intensity statin with ezetimibe for secondary prevention. Hopefully, improved insurance coverage in the future will help increase its use among patients at high risk of cardiovascular disease.

**Figure 1**

![Graph showing cumulative incidence of primary efficacy end point](image)

**No. at Risk**
- Placebo: 13,780, 13,278, 12,825, 11,871, 7610, 3690, 686
- Evolocumab: 13,784, 13,351, 12,939, 12,070, 7771, 3746, 689

**References**

1. No cognitive impairment on evolocumab in EBBINGHAUS study.

**UTSW link**
Early Invasive Versus Selective Strategy for Non–ST-Segment Elevation Acute Coronary Syndrome


SUMMARY
While there is a clear, emergent indication for coronary angiography and PCI in patients presenting with STEMI, the need for and optimal timing of angiography in unstable angina (USA) and NSTEMI is more ambiguous. The ICTUS trial is one among several randomized control trials designed to answer whether patients presenting with USA or NSTEMI should routinely have coronary angiography +/- PCI within 24-72 hours of incident event. In this trial, 1200 patients admitted to 42 Dutch hospitals with USA or NSTEMI were randomly assigned to either receive early invasive angiography within 24-48 hours of admission or ‘selective angiography’ only in settings of continued chest pain or inducible ischemia on stress test prior to discharge. All patients received optimal medical therapy with aspirin, clopidogrel, enoxaparin, beta blockers, nitrates, and statin. This trial describes the 10 year follow up results. The primary outcome was a composite of all-cause death or incident myocardial infarction. The two arms of the trial were well-balanced. In the early invasive group, 97% of patients underwent coronary angiography +/- PCI during the hospitalization, compared to 53% in the selective invasive group. The primary outcome of all-cause death or MI occurred in 37.6% of patients in the early invasive group compared to 30.4% in the selective invasive group (HR 1.3 (1.07-1.58) p=0.009). The selective advantage for the selective invasive group may have been driven by a higher rate or procedure-related MI in the early invasive group (6.5% vs 2.4% p=0.0001). There was no difference in 10-year death or spontaneous MI between the early invasive and selective invasive arms.

COMMENTARY
This trial showed no benefit in the early invasive strategy of performing coronary angiography within 24-48 hours of presentation with USA or NSTEMI. There was no difference in 10 year death or spontaneous MI in the early invasive or selective invasive groups, although the early invasive group suffered from more procedure-related MIs. It should be noted, however, that over half the patients in the selective invasive group underwent coronary angiography during the incident hospitalization. Every patient in the selective invasive group underwent stress testing prior to discharge, which may not be feasible at a hospital like Parkland. Nevertheless, this study shows that in patients with NSTEMI or USA, it is reasonable to treat medically unless they exhibit high risk features such as peaking troponins, hemodynamic changes, inducible ischemia, or refractory angina.

UTSW Link
Figure 1: **CENTRAL ILLUSTRATION:** Early Invasive Strategy Versus a Selective Invasive Strategy in High-Risk Patients: 10-Year Clinical Outcomes

A. Death or spontaneous myocardial infarction

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

B. Death or myocardial infarction

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

No. at risk:
- Early Invasive: 604 566 549 523 505 492 482 440 419 398 380
- Selectively Invasive: 596 556 538 524 505 489 457 442 424 413 395

- Early Invasive: 596 542 535 517 493 478 447 422 414 404 391


Figure 2: Rates of death and MI between early invasive and selective invasive groups

A. Death

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

B. Myocardial infarction

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

C. Cardiovascular death

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

D. Noncardiovascular death

- **Early Invasive**
  - Time Since Randomization (Years): 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10
  - Cumulative Event Rate (%)
  - **Selectively Invasive**

No. at risk:
- Early Invasive: 604 588 577 560 550 544 534 496 475 455 436
- Selectively Invasive: 596 581 570 561 547 536 506 486 469 453 437
- Early Invasive: 596 581 570 561 547 536 506 486 469 453 437

**Early invasive**

**Selectively invasive**
Endocrinology

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

Dr. Mehwish Ismaily reviewing Stott N et al. N Engl J Med 2017

SUMMARY

Subclinical Hypothyroidism is defined as an elevated TSH and a free T4 within normal limits. Patients with this entity usually do not have symptoms of hypothyroidism such as fatigue. However given the broad range of effects of the thyroid hormone on multiple organ systems such as the heart, the bone, the brain and skeletal muscle, this study was undertaken to understand the role of supplementation in the elderly population.

This trial was a randomized, double-blinded, parallel group trial that involved patients over the age of 65 years old (n=797) with subclinical hypothyroidism. The control group involved patients (n= 369) receiving a placebo and the experimental group involved patients (n=368) receiving levothyroxine with up-titration from a starting dose of 50ug (or 25 ug depending on history of heart failure and weight). Excluded patients included those using antithyroid medication, patients with ACS, adrenal insufficiency and recent thyroid surgery. The primary end points over the course of a year were changes in scores on a “Hypothyroid Symptoms” questionnaire and a “Tiredness” questionnaire. These questionnaires are well-studied measurement tools to assess quality of life in those with subclinical hypothyroidism. The scores range from 0 to 100 and a score of 0 denotes no symptoms from subclinical hypothyroidism.

In regards to thyroid function tests, the mean baseline TSH was 6.40±2.01 mIU per liter. After 1 year, the TSH was lower in the group on levothyroxine therapy with a mean of 3.63 mIU per liter (median dose 50 ug) vs. 5.48 mIU per liter in the placebo group (p<0.001). In regards to the primary outcomes, there was no statistically significant difference at 1 year in the Hypothyroid Symptoms and Tiredness scores. The mean scores on the Hypothyroid Symptoms questionnaire was 16.7±17.5 placebo group vs. 16.6±16.9 levothyroxine group (p=0.99). The mean Tiredness score was 28.6±19.5 placebo group vs. 28.7±20.2 levothyroxine group (p =0.77). The adverse events in the placebo and levothyroxine group were similar including new onset atrial fibrillation, heart failure, fracture, and new diagnosis of osteoporosis.
COMMENTARY

Despite the lack of difference in symptomatic scores among the elderly population in this study, the current literature suggests treating a TSH level above 10 mIU/L in patients who either test positive for antithyroid antibodies or are symptomatic have the benefit of preventing progression to hypothyroidism. A limitation of this particular study was that the mean baseline TSH was 6.40±2.01 mIU per liter and that antithyroid antibodies were not checked in each of the groups. In addition the baseline symptom scores were on the low end to start with, which may make it difficult to detect any significant symptom differences with levothyroxine treatment.

Proper diagnosis of subclinical hypothyroidism can also be challenging and require reassessment at 6 -12 months as there are several factors that can affect TSH level including natural increase with age (age adjusted TSH levels are often not reported in the lab results), lithium use, amiodarone use, those recently receiving iodine contrast etc. In addition, there are also adverse events associated with those that are overtreated leading to a low TSH and a hyperthyroid state.

UTSW Link
Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis


**SUMMARY**
This study is a compilation of 3 double blind placebo-control trials meant to determine the efficacy of tofacitinib, a JAK inhibitor, as induction or maintenance therapy for ulcerative colitis (UC). Tofacitinib was previously shown in a phase 2 trial to have some efficacy as induction therapy for UC. For this study, the target population was patients with moderate to severe UC who have failed conventional therapy or tumor necrosis factor (TNF) antagonists. The goal was to see if remission could be achieved after 8 or 52-weeks of therapy. In the 8-week trial, remission was achieved in 18.5% versus 8.2% in the placebo group. For the 52-week trial, patients were either given 5 mg or 10 mg of tofacitinib. Remission was achieved in 34.3% with 5 mg and 40.6% with 10 mg, compared to 11.1% in the placebo arm. All these differences were statistically significant. Furthermore, compared to placebo, patients on tofacitinib had slightly higher rates of herpes infection, non-melanoma skin cancer, hyperlipidemia, and cardiovascular events.

**COMMENTARY**
Ulcerative colitis (UC) is a serious illness that is characterized by abdominal discomfort and bloody diarrhea. A large number of patients do not achieve remission with conventional therapy or with antagonist to TNF α, and have to consider colectomy with its associated morbidity. Tofacitinib is a relatively new drug that has shown promise either as induction or maintenance therapy for patients with moderate to severe UC. Tofacitinib works as a small molecule inhibitor of Janus Kinases (JAK), which play a role in inflammatory responses. Specifically, JAK proteins are involved in the JAK-STAT signal transduction pathways that are activated by cytokines in order to affect lymphocyte differentiation, function and proliferation. The FDA already approved tofacitinib for the treatment of rheumatoid arthritis 5 years ago. In this study, UC patients on tofacitinib achieved significantly higher rates of remission in a dose- and time-dependent manner when compared to placebo. Since this was a placebo trial, it is unclear how efficacious tofacitinib is compared to conventional therapy or TNF α antagonists. It is possible that even higher rates of remission could be achieved with the use of tofacitinib as an adjunct therapy, an area that warrants further investigation.

[UTSW Link]
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Dr. Branden Tarlow reviewing El-Khoueiry et al. Lancet 2017 April 20 online

**SUMMARY**

Hepatocellular carcinoma carries a bleak prognosis and the current approved systemic treatment has only a modest benefit. This study examined the safety and efficacy of the monoclonal antibody nivolumab (a PD-1 immune checkpoint inhibitor) in patients with advanced hepatocellular carcinoma. This large open-label trial included a diverse set of patients who received nivolumab every 2 weeks (no placebo or alternative treatment). The phase 1 portion included 48 patients and phase 2 portion included 214 patients treated at 39 academic sites. The study was funded by Bristol-Myers, who was responsible for the data analysis along with the authors. At inclusion, nearly all patients had Childs-Pugh class A cirrhosis, all had an ECOG 1 performance status or less, and none were eligible for local or surgical therapy. At enrollment, 68% had extrahepatic spread of their tumor, half had chronic viral hepatitis, and 68% had previously received sorafenib.

The results showed that nivolumab was well tolerated with no new safety issues. The incidence of rash and diverse collection autoimmune manifestations was similar to prior studies in other tumor types. In the phase 2 trial, grade 3/4 adverse events occurred in 20% of patients (mostly elevation liver enzymes) and led to drug discontinuation in 24/214 (11%). Disease control (stable disease + objective response) occurred in 64% of patients. An objective response was observed in 20% of patients and 3/214 patients had a complete response. 9-month survival was 74% at time of publication and 27% of patients were continuing treatment. Response occurred independent of individual tumor PD-L1 expression.

**COMMENTARY**

Despite the non-randomized design, the rates of overall survival and duration of response in this study have not previously been seen in phase 1/2 trials for HCC. Other drugs tested in phase 3 trials have failed to improve on sorafenib—which provides an extremely modest 2-3 month increase in median overall survival (10.7 vs 7.9 months in the landmark phase 3 study). Because HCC usually occurs within the context of liver cirrhosis, therapies must consider both tumor properties and underlying liver disease—and many compounds have failed due to toxicity. Although HCC is an inflammatory tumor, tumor-infiltrating
lymphocytes are exhausted or inactive but retain PD-1 expression\textsuperscript{iii}. The authors hypothesized that nivolumab reactivates the exhausted PD1-expressing T-cells and allows them to overcome the strong immunosuppressive signals provided by tumor and stroma. Three phase 3 randomized controlled trials comparing nivolumab with sorafenib for 1\textsuperscript{st} line HCC treatment are underway. It remains to be seen whether a 20% response rate will translate into a survival advantage over standard of care. But this first study with nivolumab in viral hepatitis and cirrhosis paves the way for future immune checkpoint inhibitor studies in HCC.

\textbf{UTSW Link}

\section*{REFERENCES:}


Hepatitis B (HBV) Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions


SUMMARY

Definitions: 1) HBV reactivation = HBV-DNA level rise by ≥100-fold in patients with formerly detectable viremia, or HBV-DNA level re-appearance in patients who had undetectable viremia before starting immunosuppressant or biological modifier therapy. 2) Chronic HBV = HBsAg+, HBV-DNA≥2000 IU/mL, and elevated ALT

Onset of HBV Reactivation: 2 weeks after beginning therapy, and up to 1 year after termination of treatment

Risk Factors: 1) Host factors: male sex, older age, presence of cirrhosis, type of disease needing immunosuppression, 2) Virologic factors: high baseline HBV-DNA level, HBeAg positive, chronic HBV, 3) Type and degree of immunosuppression: see Table 1 for risk stratification.

Screening: All patients recently diagnosed with cancer and/or receiving high or moderate risk therapies should be screened with HBsAg, anti-HBc and anti-HBs serologies. All those who are negative should receive complete vaccination.

Management and Prophylaxis: All patients who are high or moderate risk should receive prophylactic antiviral therapy. Treatment should start 2-4 weeks before immunosuppressive therapy with baseline and monitoring laboratories every 3 months (CMP, CBC, PT and serum HBV-DNA levels). Low risk treatments should be monitored only. Patients with chronic HBV (as above) should be identified and treated per guidelines (see Figure 1).

Anti-HBV Regimen for Prophylaxis: Entecavir or tenofovir are first line. Other options (with lower barriers to resistance) are lamivudine, telbivudine or adefovir. Interferon-based treatments are not used for prophylaxis.

Duration of Prophylaxis: at least 6 months after last dose of immunosuppressive or biological modifier therapy. In the case of B-cell depleting therapies, it should be 12 months after last dose. Also, ALT/AST, and HBV-DNA should be done every 3-6 months after discontinuation of prophylaxis to monitor HBV reactivation (up to 2 years in the case of B-cell depleting treatments).
**COMMENTARY**

Considering the high prevalence of HBV worldwide and the lack of curative therapy, adequate screening and prophylaxis is of the utmost importance in all patients receiving immunosuppressant, biologic or chemotherapy not only for the management of malignancies, but also for rheumatologic conditions, inflammatory bowel disease, dermatologic conditions, and solid-organ or bone marrow transplants.

**UTSW Link**

**Figure 1: Management algorithm**

**Table 1: Risk of HBV Reactivation.** High (>10%), moderate (1-10%), and low (<1%). Note that patients treated with prednisone (or equivalent)>20 mg/day for more than 4 weeks are considered high-risk for HBV reactivation if they are HBsAg-positive, and moderate risk for reactivation if they are HBsAg-negative/anti-HBc-positive.
### Immunosuppressive therapies

**Risk of reactivation in HBsAg-positive patients**

<table>
<thead>
<tr>
<th>High risk of reactivation</th>
<th>B-cell-depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, and ibritumomab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines including doxorubicin and epirubicin</td>
</tr>
<tr>
<td></td>
<td>More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab</td>
</tr>
<tr>
<td>Moderate risk of reactivation</td>
<td>Local therapy for HCC including TACE</td>
</tr>
<tr>
<td></td>
<td>Systemic chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Less potent TNF-α inhibitors including etanercept</td>
</tr>
<tr>
<td></td>
<td>Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab</td>
</tr>
<tr>
<td></td>
<td>Immunophilin inhibitors including cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Tyrosine-kinase inhibitors including imatinib and nilotinib</td>
</tr>
<tr>
<td>Low risk of reactivation</td>
<td>Proteasome inhibitors such as bortezomib</td>
</tr>
<tr>
<td></td>
<td>Moderate-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate</td>
</tr>
<tr>
<td></td>
<td>Short-term low-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Intra-articular steroid injections (extremely low risk)</td>
</tr>
</tbody>
</table>

**Risk of reactivation in HBsAg-negative and anti-HBe positive patients**

<table>
<thead>
<tr>
<th>High risk of reactivation</th>
<th>B-cell-depleting agents including rituximab, ofatumumab, natalizumab, alemtuzumab, and ibritumomab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-dose corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines including doxorubicin and epirubicin</td>
</tr>
<tr>
<td></td>
<td>More potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab</td>
</tr>
<tr>
<td>Moderate risk of reactivation</td>
<td>Systemic cancer chemotherapy including HCC</td>
</tr>
<tr>
<td></td>
<td>Cytokine-based therapies including abatacept, ustekinumab, mogamulizumab, natalizumab, and vedolizumab</td>
</tr>
<tr>
<td>Low risk of reactivation</td>
<td>Immunophilin inhibitors including cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Tyrosine-kinase inhibitors including imatinib and nilotinib</td>
</tr>
<tr>
<td></td>
<td>Proteasome inhibitors such as bortezomib</td>
</tr>
<tr>
<td></td>
<td>Moderate- and low-dose prednisone</td>
</tr>
<tr>
<td></td>
<td>Antimetabolites, azathioprine, 6-mercaptopurine, and methotrexate</td>
</tr>
</tbody>
</table>
Effect of Intensive Blood Pressure Control on Gait Speed and Mobility Limitation in Adults 75 Years or Older


SUMMARY

The data from this study comes from the Systolic Blood Pressure Intervention Trial (SPRINT) which randomized adults over the age of 50 with hypertension but without diabetes or history of stroke to either an intensive systolic blood pressure target of less than 120 mm Hg or to a target of less than 140 mm Hg and found a lower rate of cardiovascular events and death in the intensive target group. The benefit was also demonstrated in the subgroup of patients over the age of 75. This study looks specifically at gait speed and mobility limitation in 2,629 SPRINT participants over age 75. Gait speed was measured using a 4 meter walk test. The definition of mobility limitation was a gait speed of less than 0.6 m/s or self-reported difficulty with walking or climbing stairs. These variables were measured at baseline and then annually during the five years of the trial. There was an overall mean decline in gait speed of 0.026 m/s per year and an overall mean rate of transition from no mobility limitation to mobility limitation of 12.5 per 100 person years. These rates were not statistically significantly different between the intensive blood pressure target group and the standard treatment group.

COMMENTARY

Gait speed is a marker of physical function and independence in older adults, and declines in gait speed may herald declines in functional status. The SPRINT data suggests that older adults without diabetes may benefit from more aggressive blood pressure targets, but there has also been concern about the potential adverse effects of over-aggressive blood pressure control on functional status. This study suggests that at least one marker of functional status in older adults, gait speed, is not adversely affected by more intensive blood pressure control. Of note, SPRINT excluded patients with orthostatic hypotension or dementia and did not enroll patients from nursing homes. Based on the results of SPRINT, it seems reasonable to individualize blood pressure goals in our older adult patients, keeping in mind that even patients over the age of 75 may see the cardiovascular and mortality benefit of more intensive blood pressure control without associated decline in functional status.

UTSW Link
Table 2. Linear Mixed-Effect Model Estimates of Annual Change in Gait Speed by Treatment Group and for Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants</th>
<th>Intensive-Treatment Group</th>
<th>Standard-Treatment Group</th>
<th>Difference (95% CI), m/s</th>
<th>pValue</th>
<th>p Value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2514</td>
<td>-0.028 (-0.029 to -0.027)</td>
<td>-0.026 (-0.029 to -0.022)</td>
<td>0.0004 (-0.005 to 0.006)</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1461</td>
<td>-0.023 (-0.029 to -0.019)</td>
<td>-0.021 (-0.026 to -0.017)</td>
<td>0.002 (-0.008 to 0.005)</td>
<td>0.57</td>
<td>1.99</td>
</tr>
<tr>
<td>≥60</td>
<td>1153</td>
<td>-0.029 (-0.035 to -0.024)</td>
<td>-0.033 (-0.038 to -0.028)</td>
<td>0.004 (-0.004 to 0.011)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1527</td>
<td>-0.025 (-0.029 to -0.020)</td>
<td>-0.028 (-0.032 to -0.023)</td>
<td>0.003 (-0.004 to 0.009)</td>
<td>0.37</td>
<td>2.11</td>
</tr>
<tr>
<td>Female</td>
<td>987</td>
<td>-0.027 (-0.032 to -0.021)</td>
<td>-0.023 (-0.028 to -0.018)</td>
<td>0.004 (-0.011 to 0.004)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>3153</td>
<td>-0.027 (-0.030 to -0.023)</td>
<td>-0.027 (-0.031 to -0.023)</td>
<td>0.005 (-0.005 to 0.006)</td>
<td>0.87</td>
<td>0.91</td>
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<tr>
<td>Black</td>
<td>464</td>
<td>-0.021 (-0.029 to -0.013)</td>
<td>-0.021 (-0.029 to -0.013)</td>
<td>0.006 (-0.012 to 0.011)</td>
<td>0.96</td>
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<tr>
<td>SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;140</td>
<td>1227</td>
<td>-0.024 (-0.029 to -0.019)</td>
<td>-0.024 (-0.029 to -0.019)</td>
<td>0.0001 (-0.007 to 0.007)</td>
<td>0.97</td>
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</tr>
<tr>
<td>140-159</td>
<td>1056</td>
<td>-0.025 (-0.031 to -0.019)</td>
<td>-0.028 (-0.034 to -0.023)</td>
<td>0.003 (-0.005 to 0.011)</td>
<td>0.44</td>
<td>0.44</td>
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<tr>
<td>≥160</td>
<td>331</td>
<td>-0.031 (-0.041 to -0.024)</td>
<td>-0.026 (-0.035 to -0.017)</td>
<td>0.007 (-0.020 to 0.006)</td>
<td>0.27</td>
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<tr>
<td>Previous CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1446</td>
<td>-0.023 (-0.027 to -0.018)</td>
<td>-0.025 (-0.030 to -0.020)</td>
<td>0.002 (-0.004 to 0.009)</td>
<td>0.53</td>
<td>0.52</td>
</tr>
<tr>
<td>Yes</td>
<td>1156</td>
<td>-0.025 (-0.030 to -0.019)</td>
<td>-0.029 (-0.033 to -0.023)</td>
<td>0.001 (-0.009 to 0.006)</td>
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<td>Previous CVD</td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1972</td>
<td>-0.026 (-0.031 to -0.021)</td>
<td>-0.024 (-0.028 to -0.020)</td>
<td>0.002 (-0.008 to 0.004)</td>
<td>0.50</td>
<td>0.09</td>
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<td>942</td>
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<td>-0.031 (-0.038 to -0.024)</td>
<td>0.008 (-0.001 to 0.017)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>VF-12 PCS score</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤240</td>
<td>1769</td>
<td>-0.023 (-0.027 to -0.018)</td>
<td>-0.027 (-0.031 to -0.022)</td>
<td>0.004 (-0.002 to 0.010)</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;240</td>
<td>815</td>
<td>-0.032 (-0.038 to -0.026)</td>
<td>-0.024 (-0.030 to -0.018)</td>
<td>0.008 (-0.016 to 0.001)</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; m/s, meters per second; PCS, Physical Component Summary; SBP, systolic blood pressure.

*For the treatment group differences, negative values indicate a faster rate of decline in gait speed for the intensive-treatment group. Standard treatment indicates a blood pressure target of less than 140 mm Hg. Intensive treatment, less than 120 mm Hg.

* Denotes the number of participants with at least 1 assessment of gait speed (at baseline or during the course of follow-up).

A score of 50 represents the US population mean; 10 points represent 1 SD, and higher scores denote better quality of life.**

Figure 2. Least Squares Means for Gait Speed by Treatment Group During the Course of Follow-up

Circles denote estimated least-squares mean for gait speed based on linear mixed model; treating time discretely (0, 12, 24, 36, and 48 months). Error bars represent 95% CIs. Standard treatment indicates a blood pressure target of less than 140 mm Hg. Intensive treatment, less than 120 mm Hg.
Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-years Survivors of Childhood Cancer, 1970-2015


SUMMARY
The objective of the Childhood Cancer Survivor Study (CCSS) was to assess temporal changes in development of subsequent neoplasms in patients treated for childhood cancer. The CCSS was a retrospective cohort study with longitudinal follow up of 5-year survivors of childhood cancers treated at 27 centers across the United States. Patients included in the study were diagnosed between January 1, 1970 and December 31, 1999. The participants were younger than 21 at the age of initial diagnosis. The medical record was reviewed to obtain information regarding prior cancer therapy including surgery, chemotherapy, and radiation.

Twenty three thousand six hundred and three patients were identified. The most common initial diagnoses included acute lymphoblastic leukemia (35.1%), Hodgkin lymphoma (11.1%), and astrocytoma (9.6%). At 15 years after the initial diagnosis, the cumulative incidence of subsequent neoplasm was 2.9% (95% CI, 2.5%-3.3%) among patients diagnosed in the 1970s, 2.4% (95% CI, 2.1%-2.7%) in the 1980s, and 1.5% (95% CI, 1.3%-1.8%) for those diagnosed in the 1990s. A majority (58.5%) of these neoplasms were nonmelanoma skin cancer, however 34% were subsequent malignancies. There was a significantly lower incidence of secondary malignancies in patients diagnosed in 1990s of 1.3% (95% CI, 1.1%-1.5%), compared to 1.7% in the 1980s (95% CI, 1.5%-2.0%), and 2.1% in the 1970s (95% CI, 1.7%-2.4%). The most frequent secondary malignancy was breast and thyroid cancer.

Significant changes in cancer treatment were also observed between 1970-1999. Radiation therapy decreased from 77% in 1970s to 33% in the 1990s. The use of alkylating agents and anthracyclines increased over time, but the median dosages have decreased. The proportion of children treated with platinum agents have also increased along with an increase in median cumulative dose.

COMMENTARY
As the treatment of childhood cancer continues to improve, focus has turned to management of health consequences of cancer therapy. Late effects of treatment include infertility, cognitive dysfunction, pulmonary disease, cardiotoxicity, renal dysfunction, and endocrine abnormalities. The risk of subsequent neoplasms after aggressive chemotherapy
and radiation has been well described. Over the past 30 years, there has been significant effort to eliminate or reduce the exposure to radiation requiring intensification of some chemotherapy regimens. This study demonstrates that with temporal changes in childhood cancer treatment, there has been a subsequent decrease in secondary neoplasms as well as malignancies. Due to the increasing number of cancer survivors, it is a growing challenge for physicians to provide appropriate care for this high-risk population. A health care plan that involves lifelong screening, surveillance, and prevention that integrates risks based on the previous cancer, cancer treatment, genetic susceptibilities, lifestyle behaviors, and comorbid conditions should be developed for all cancer survivors.

**UTSW Link**
What Is the More Effective Antibiotic Stewardship Intervention: Pre-prescription Authorization or Post-prescription Review With Feedback?


SUMMARY
Current guidelines strongly recommend the implementation of antimicrobial stewardship programs to promote judicious use of antibiotics in acute care hospitals. In this study, the authors compared the use of two different antibiotic stewardship interventions: pre-prescription authorization (PPA), in which prescribers are required to seek input from the stewardship program prior to prescribing certain antibiotics, and post-prescription review with feedback (PPRF), in which empiric prescription of these antibiotics is allowed but is followed by stewardship review within 48-72 hours.

A crossover trial was conducted in which 4 medical teams in a large teaching hospital (Johns Hopkins Hospital) were assigned to either PPA or PPRF for a 4-month period of data collection, with crossover of study arms after a 1-month washout in between study periods (5379 total patients, 1508 patients on antibiotics). The primary outcome was days of therapy per individual antibiotic per patient (DOT); secondary outcomes were (i) total length of therapy (LOT) that included all antibiotics used per patient, (ii) incidence of Clostridium difficile infection within 60 days, (iii) length of hospital stay, and (iv) in-hospital mortality.

The study found that median patient DOT in the PPA arm was higher than that in the PPRF arm (8 vs 6 DOT per 1000 patient days, respectively; p=0.03). The median LOT in the PPA arm was also higher (7 vs 5 per 1000 patient days in PPRF arm; p<0.01), and although more patients in the PPRF arm were on non-guideline compliant antibiotics on day 1 (41% vs 24% in PPA arm, p<0.01), more patients in the PPA arm were on non-guideline compliant antibiotics at day 3 (36% in PPA vs 24% in PPRF arm, p=0.03). There was no significant difference in rates of C difficile infection, duration of hospital stay, or in-hospital mortality between the two study arms. Overall antibiotic usage did not change significantly over the study period.

COMMENTARY
The Centers for Disease Control and Prevention estimates that approximately 20-50% of antibiotic prescriptions in U.S. hospitals are either unnecessary or inappropriate. These alarming statistics, together with growing concerns over the rapid rise in antibiotic resistance worldwide, have prompted the development of interventions to promote
antimicrobial stewardship. Current guidelines recommend the integration of PPA and/or PPRF-type strategies into hospital stewardship programs. Various trials to date have demonstrated that both strategies are associated with decreased antibiotic use overall as well as improved clinical outcomes including fewer instances of antimicrobial failure, decreased prevalence of multidrug resistant organisms, reduction in C difficile infection, fewer drug-associated adverse events, and reduced duration of hospital stay and healthcare-associated expenditure.

This study by Tamma et al found that a postprescription review strategy was more effective than preauthorization in restricting non-guideline antibiotic therapy within the teaching services at John Hopkins Hospital, whereas another study described findings to the contrary. These conflicting results may be attributable to differences in study design (the latter used a sequential model with interventions occurring at different times; the current study included antibiotics prescribed at discharge in the DOT), and facility-specific attributes including hospital infrastructure and resources, institutional culture, and patient population. No significant differences in clinical outcomes were described in this small study with a relatively short study period of only 8 months.

There remains a paucity of trials directly comparing the efficacy of PPA and PPRF strategies. Future studies describing other outcomes such as drug-related adverse events, prevalence of multi-drug resistant organisms, ICU admission and hospital readmission rates, and physician/patient satisfaction, are needed to guide the development of tailored hospital stewardship programs and ultimately help reduce the inappropriate use of antimicrobials in acute care hospitals.

**UTSW Link**

**REFERENCES**

Nephrology

Dementia and Alzheimer’s Disease among Older Kidney Transplant Recipients
Dr. Stephanie Chiao reviewing McAdams-DeMarco et al. JASN. 2017; 28(5):1575-1583

SUMMARY
As access to kidney transplantation has improved for older patients and patients are living longer with multiple medical problems prior to KT, KT recipients are becoming increasingly at risk for age-related conditions, such as dementia. This study was therefore performed to examine the rates of post-KT dementia as well as the effects of dementia on transplant outcomes.

The study examined data from Medicare claims on 40,918 KT recipients aged ≥55 years. It found that the 10-year risk of post-KT dementia was 5.1% for KT patients aged 55-60, 7.2% for those 60-65, 11.0% for those 65-70, 15.6% for those 70-75, and 17% for those 75 and older. For those who developed dementia, the 10-year risk of mortality was 86.7% and death-censored graft loss was 43.1%. This translates to a 1.5 fold increased risk of graft loss and a 2.4 fold increased risk of mortality compared to KT recipients who did not develop dementia. Predictors of dementia included older age, female sex, black race, fewer years of education, and diabetes at the time of transplantation. Participants were less likely to develop dementia if they had a calcineurin inhibitor-free maintenance immunosuppression regimen.

COMMENTARY
For a reference, the Framingham study found an incidence of dementia of 1-1.5% in adults aged 65, 7.4-7.6% in adults aged 75. KT recipients, therefore, are at a significantly increased risk of dementia compared to the general older adult population. This may be related to the significant burden of vascular pathology often found in ESRD patients in combination with the neurotoxic side effects of immunosuppression post-KT. KT recipients who develop dementia have significantly worse outcomes in terms of mortality and graft loss, which may be related to the debilitating effects of dementia. Impaired self-care, medication management, nutrition, and ability to communicate can lead to increased post-KT complications, such as infection or rejection, facilitating the process of graft loss and mortality. When considering kidney transplantation, the risks of dementia must be weighed against the burden of continuing dialysis, and once transplantation has occurred, providers must be vigilant about screening for cognitive impairment and assessing ADLs in order to optimize patient survival and quality of life.
Figure 1. The risk of dementia by age at transplantation. The risk (cumulative incidence) was estimated for 40,918 older KT recipients using a competing risks survival analysis. Dementia represents the ICD-reported diagnoses of dementia.
Impact of Palliative Care Screening and Consultation in the ICU: A multi-hospital Quality Improvement Project

Dr. Lauren Smith reviewing Zalenski R, et al. J Pain Symptom Manage Jan 2017;53:5-12

SUMMARY

In the last decade, we have seen increased intensive care unit(ICU) utilization in the last 30 days of life, more so for people with chronic terminal illnesses such as cancer or dementia. This article is a retrospective analysis of a prospective quality assurance intervention that involved screening patients admitted to the ICU for palliative care consultation(PCC). The study was conducted over 1 year at seven hospitals in the Midwest and Texas that comprised both closed and open ICUs as well as academic and community centers. Each hospital participated for a 16-week period. Patients were screened within 24 hours of admission to the ICU and if their screen was positive the information was presented to the attending who ultimately decided whether or not to order a PCC. Notable criteria for positive screen included: admitted from SNF, LTAC or patient with several ADL dependencies; admitted after a cardiac/respiratory arrest with neurological compromise; end-stage cancer; dementia, ALS, MS, etc; admitted after hospital stay 5+ days; or readmitted to ICU within 30 days. Primary outcomes of the study included: change in code status to “DNR”, hospice referrals, 30-day readmissions, length of stay and hospital cost. During the study period, 1923 patients were admitted to the ICU of which 1134(60%) were screened for PCC and 431(40% of those screened) met one or more criteria for a palliative care consultation. Only 405 were included for analysis because of missing data to assess primary outcomes and of these 161(40%) received a PCC. The most common diagnosis in this group was sepsis at 33% followed by 15% having some sort of respiratory failure. Results showed a statistically significant increase in code status change to “DNR” and discharges to hospice in the PCC group. There was a reduction in 30-day readmissions in patients receiving palliative care consults but it was not statistically significant. With regards to hospital length of stay(LOS) it was noted that patients who received PCC on or before hospital day 4 had a lower LOS by ~2 days compared to no PCC. Contrastingly, patients who received PCC after day 7 had a longer LOS by 6.2 days than someone who did not receive consultation at all.

COMMENTARY

Palliative care is of particular importance in the ICU. Patients are subject to invasive procedures or interventions and understanding the patients’ and families’ beliefs, goals and
values can guide appropriate treatment. This study shows several benefits of palliative care consultation in the ICU for complex patients with severe disease particularly when utilized early in an ICU admission. However, this study was limited by the fact that only 60% of patients admitted to the ICU were screened so the results may have some bias. Given the significant reduction in hospital utilization, decrease in CPR or other invasive procedures utilizing a screening tool for palliative care consultation seen in this paper further studies should be done to confirm these findings. As there is potential for widespread benefit within the health care system.

**UTSW Link**

**Figure 1**: Difference in Length of Stay Based on Timing of Palliative Care Consult

Table 1: Unadjusted Odds for Major Outcome Variables

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>PCC (161)</th>
<th>No PCC (244)</th>
<th>Odds Ratio (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged to hospice</td>
<td>45 (28.0%)</td>
<td>10 (4.10%)</td>
<td>$P &lt; 0.0001$, OR = 9.08 (95% CI: 4.41–18.66)</td>
</tr>
<tr>
<td>Not discharged to hospice</td>
<td>116 (72.0%)</td>
<td>234 (95.9%)</td>
<td></td>
</tr>
</tbody>
</table>

PCC and full code (147) vs. No PCC and full code (230)

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>PCC and full code</th>
<th>No PCC and full code</th>
<th>Odds Ratio (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code change to DNR</td>
<td>109 (74.1%)</td>
<td>45 (19.6%)</td>
<td>$P &lt; 0.0001$, OR = 11.79 (95% CI: 7.21–19.30)</td>
</tr>
<tr>
<td>No code change</td>
<td>38 (25.9%)</td>
<td>185 (80.4%)</td>
<td></td>
</tr>
</tbody>
</table>

PCC and discharged (90) vs. No PCC and discharged (182)

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>PCC and discharged</th>
<th>No PCC and discharged</th>
<th>Odds Ratio (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission</td>
<td>17 (18.9%)</td>
<td>49 (26.9%)</td>
<td>$P = 0.15$, OR = 0.63 (95% CI: 0.34–1.18)</td>
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<tr>
<td>No readmission</td>
<td>73 (81.1%)</td>
<td>133 (73.1%)</td>
<td></td>
</tr>
</tbody>
</table>

PCC = palliative care consult; OR = odds ratio; DNR = do not resuscitate.

*Reduced N as patients not full code on admission were excluded.

*Reduced N as patients not discharged alive from hospital were excluded.
Association Between Time to Colonoscopy After a Positive Fecal Test Result and Risk of Colorectal Cancer and Cancer Stage at Diagnosis

*Dr. Shreya Rao reviewing Corley et al. JAMA. 2017 April 25; 317(16): 1631-1641.*

**Summary**

Routine colon cancer screening has been demonstrated to reduce mortality caused by colorectal cancer by means of early detection and treatment. A 2008 Cochrane review for the United States Preventative Task Force demonstrated similar life-years gained with annual FIT testing and colonoscopy performed every ten years. USPSTF recommends follow up of positive FIT testing with definitive screening by colonoscopy, but does not specify a time frame for doing so, resulting in variations in time to follow up in primary care practices. This retrospective study seeks to determine the optimum time frame for follow up of positive FIT testing.

Participants in this study were formed from a cohort of the Kaiser Permanente Northern California and Southern California health plan. In all 70,124 patients with a positive FIT test received follow up colonoscopy, diagnosing 2,191 cases of any colorectal cancer and 601 late stage malignancies. The median time to colonoscopy follow up was 37 days (IQR, 23-62 days), with 33.3% receiving a colonoscopy within the first 30 days, 63.6% in 2 months, 80.6% within 6 months and 83.2% within one year. Each additional month after the first 30-day window increased the risk of detecting any colorectal cancer by 3% and the risk of detecting advanced disease by 5%. There was, however, no significant increased risk in cancer outcomes up to 6 months from initial positive FIT testing, with risk of stage II cancer increasing between 7 to 9 months and risk for any colorectal cancer increasing between 10 and 12 months with an OR of 1.48 (1.05-2.08). After one year, the risk of all colorectal cancer outcomes was increased.

**Commentary**

Guidelines regarding appropriate time to follow up of positive FIT testing are currently lacking, with average wait times often demonstrating systems limitations rather than evidence based practice. The authors of this study note that studies conducted in the VA and public health systems that more closely resemble resident primary care practices at this institution demonstrate median times to follow up of 103 and 174 days, respectively (between 3 and 6 months). Institution-specific guidelines are largely lacking in supporting
The findings of this study, though useful in guiding practice, are not widely generalizable. High-risk patients, including those with a prior history of diagnosed colorectal cancer, and those who were new to the healthcare system or with a history gaps in follow up were excluded from analysis. Individuals enrolled in the Kaiser program were also predominantly white, with frequent (1 or more per year) visits with their PCP, prior FIT screening, and a low incidence of anemia in the prior year (3.4%). The risk to higher risk populations, with diminished access to healthcare, remains to be determined and will provide much needed guidance in the execution of commonly practiced USPSTF recommendations.

UTSW Link


Association of Primary Care Practice Location and Ownership with the Provision of Low-Value Care in the United States

Dr. Sarah Kiani reviewing Mafi, MD, MPH et al. JAMA Intern Med.

**Summary**

This large retrospective study was carried out to evaluate the effect of location and ownership on the value of care delivered at primary care centers. Comparisons were made between hospital based practices vs community based practices. Further comparisons were made within the community-based practices between hospital-owned vs physician-owned practices. Value of care was evaluated as the primary outcome for 3 common conditions namely upper respiratory tract infection (URTI), back pain, and headache. Care was considered low value when the following were ordered: antibiotics for URTI, CT/MRI for back pain or headache and radiographs for patients with URTI or back pain. Referral to another physician for the three conditions was evaluated as a secondary outcome. 31,162 visits were studied. Analysis revealed that hospital-based visits had higher number of orders for CT and MRI (8.3% vs 6.3%, \( P = .01 \)), radiographs (12.8% vs 9.9%, \( P < .001 \)), and specialty referrals (19.0% vs 7.6%, \( P < .001 \)) than community-based visits. Antibiotic orders were found to be similar in both cases. All the primary outcomes in the hospital owned and physician owned community based clinics were similar. However, specialty referrals were higher in hospital owned practices. Additionally, it was found that a visit to physician other than the primary care physician (PCP) resulted in increased delivery of low value care, mainly in the hospital based setting. The study also showed patients visiting the community based physicians to be younger (mean age, 44.5 vs 49.1 years; \( P < .001 \)) and less frequent visitors to their PCPs (52.7% vs 81.9%, \( P < .001 \)) than their hospital based counterparts.
Within the last few decades there has been a remarkable increase in the growth of hospital owned primary care practices. Many smaller physician owned community practices have been absorbed into the hospital system. While this system offers many conveniences (such as common electronic medical record, ease of referral and rapid availability of diagnostic testing) this study demonstrates avoidable use of imaging and referrals in the hospital based practices. Also, it was shown that overutilization of services may be higher if the patient was seen by a provided other than the primary care physician, a key finding that is particularly relevant for institutions where a shared practice model is employed. Based on the results of this study, it appears likely, that accessibility to services such as imaging and specialists may affect ordering patterns. However, the authors did not adjust for a difference in payment model; age and level of training of physician; process of referral and clinical outcomes between the groups. Although no significant difference was seen in complexity of patients’ illness between the groups, it is possible that the difference was underestimated since patients diagnosed with serious medical conditions upon work up were excluded from the study. It is certainly possible that the patient population presenting to the hospital based clinics is different in disease severity than community based clinics, for example, there may be a higher number of cancer diagnosis in patients presenting to hospital based clinic with back pain, in which case the decision to order imaging to work up these common presenting conditions may be associated with fewer missed fatal diagnosis and hence may not be consider low value. Ultimately, the discussion comes down to the age-old dilemma of the definition of health care quality and value. Comprehensive head to head randomized control trials are needed that compare the appropriateness of test utilization by stratifying patients based on disease complexity, outcomes and costs to better determine the healthcare quality and value in hospital vs community based primary care practices.

REFERENCES

Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders


SUMMARY

Methods:
- Objectives: To study the effectiveness of extended-release naltrexone in criminal justice offenders
- Five-site, open-label, randomized trial. 24-week course of extended-release (ER) naltrexone (380mg, intramuscular, every 4 weeks) in 153 patients compared to usual treatment (brief counseling, community program referral) in 155 patients. All participants were community dwellers with a history of criminal justice involvement had a history of opioid dependence and were abstinent at randomization time
- Primary outcome: time to an opioid-relapse event (defined as 10 or more days of opioid use in a 28-day period assessed by self-reporting or urine samples every 2 weeks).
- Secondary outcomes: rates of opioid-negative urine samples, percentage of 2-week intervals without opioid use (by self-reporting or urine samples)

Results:
- The mean age was 44 years, 85% were male, 77% were black or Hispanic, 74% were on parole or probation and 65% had not used any other opioid in the previous 30 days
- Participants in the ER-naltrexone arm had a longer median time to relapse compared to the usual treatment arm (10.5 vs 5.0 weeks, p<0.001, HR 0.49; 95% CI 0.36-0.68), a lower rate of relapse (43% vs 64%, p<0.001, OR 0.43; 95% CI 0.28-0.65), and a higher rate of opioid-negative urine samples (74% vs 56%, p<0.001; OR 2.30; CI 1.48-3.54)
- 1 year after treatment (week 78), rates of opioid-negative urine samples were similar (46% in each group, p=0.91), and there were no overdose-events in the ER-naltrexone arm and 7 in the usual treatment arm (p=0.02)

COMMENTARY

In this study, ER-naltrexone was associated with a lower relapse rate when compared to usual treatment. The absolute difference in risk was 21% and the number needed to treat was 5. This effect disappeared after treatment discontinuation and there was no effect on secondary outcomes (cocaine, heavy alcohol, injection drug use). Since opioid abuse disproportionately affects individuals involved in the criminal justice system, who often
have limited access to opioid-agonist maintenance treatment such as methadone or buprenorphine, ER-naltrexone is a good treatment option for this population.

**UTSW Link**

**Figure 1**: Kaplan-Meier Curves showing Relapse-free Survival in both groups.

![Kaplan-Meier Curves](image)

**Figure 2**: Kaplan–Meier Curves for Relapse-free Survival.
Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation with Sepsis


SUMMARY

Dexmedetomidine (brand name Precedex) is a highly selective alpha 2 agonist commonly used in the intensive care unit (ICU) setting for its light sedative properties. Along with its ability to improve patient communication compared to other commonly used sedatives such as midazolam and propofol, certain animal studies have shown it to suppress inflammatory reactions, and therefore, may have an organo protective effect. Interestingly, the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial suggested an improvement in mortality rate when using dexmedetomidine versus lorazepam in a subgroup analysis of patients with sepsis. In this study, the Dexmedetomidine for Sepsis in the Intensive Care Unit Randomized Evaluation (DESIRE trial) aimed to investigate whether early initiation of dexmedetomidine among ICU patients with sepsis could improve mortality and ventilator-free days.

This was an open-label, multicenter randomized clinical trial conducted in 8 ICUs in Japan with a total population size of 201 adult patients meeting criteria for sepsis; sedation with dexmedetomidine (n = 100) or without (control group; n = 101). The primary outcomes included mortality and ventilator-free days over a 28 day period.

The mean age of patients were 69 years old with 63% being male. Mortality was not significantly different between the dexmedetomidine (22.8%) and control group (30.8%) [hazard ratio, 0.69; 95% CI, 0.38 – 1.22, P = 0.20). Ventilator-free days were not significantly different between the two groups as well (dexmedetomidine group median 20 days and control group; P = 0.20).

COMMENTARY

In total, the results of this study showed no improvement in mortality or ventilator-free days in using dexmedetomidine versus other traditional sedatives in patients with sepsis. This is in contrast to suggestions made by subgroup analyses from the MENDS trial. However, it is notable that the MENDS trial compared dexmedetomidine to lorazepam whereas the current trial compared the experimental drug to either propofol or versed; in fact, by day 5, only 29% of the control group was subjected to a benzodiazepine. Furthermore, the open label methodology creates an inherent bias in assessing critical end-
points, but as noted in the paper, mortality was less likely to be influenced by physician judgement and there was a strict criterion in place for determining ventilation weaning.

What does this mean for future practice? It is difficult to make generalizations regarding dexmedetomidine and other traditional sedatives as this study was not sufficiently powered to detect a significant difference, which is an area future studies will need to address. Moreover, Jakob et al 2012 reviewed two randomized controlled trials showing dexmedetomidine to be non-inferior to propofol or midazolam in maintaining light sedation in all ventilated patients, but noticed a reduced duration of ventilator days compared to the other two medications [1]. Despite the implications of this study, the actual applicability of it to practice may be less impactful as the benefits of dexmedetomidine have been shown time and time again.

UTSW Link

Rheumatology

Intradiscal Glucocorticoid Injection for Patients with Chronic Low Back Pain Associated with Active Discopathy


Summary

Dr. Nguyen and colleagues conducted a randomized double-blind, placebo-controlled trial on patients with active discopathy (confirmed by MRI) to determine if a single intradiscal glucocorticoid injection can improve symptoms of low back pain (LBP). 135 patients with active discopathy were enrolled in the trial; half received a single injection of 25 mg prednisolone acetate and half received a placebo injection. The primary outcome of interest was pain intensity (assessed as percentage of patients within the group with LBP rated less than 40 on a 0-100 scale) at one month; a secondary outcome was pain intensity and discopathy at 12 months. Outcomes were assessed in an intent-to-treat analysis. Subjects were on average 46 years of age, 60% women with mean LBP duration of more than 6 years who had failed conservative management including NSAIDS. At one month, pain intensity improved with glucocorticoid injection (55.4% of the glucocorticoid group reported LBP intensity <40, compared to 33.3% of the placebo group \(p=0.009\)). At 12 months 97% of the intervention group and 94% in the control group reported adverse events, with 78 serious adverse events, many of which were not related to the intervention in this trial (including subsequent need for lumbar surgery, further hospitalization attributed to usual LBP care and events deemed unrelated to the injections received in this trial) being reported.

Commentary

Modic 1 discopathy, defined by vertebral endplate subchondral bone edema on MRI, is associated with an inflammatory-like pattern of back pain. Several previous trials have attempted intradiscal glucocorticoids with equivocal results in a more heterogeneous population, but the present trial enrolled only patients with Modic-1 discopathy. This trial was conducted at 3 tertiary care centers in France that specialize in spine care. The authors of this paper describe a robust blinding protocol wherein only the radiologists injecting the material were aware of the patient allocation. Randomization was performed via computer-generated list with permuted blocks stratified by center. The trial was well-designed; with outcome assessments constructed to allow for analysis of responders versus non-responders, consistent with NIH recommendations in the study of LBP. The high incidence of reported adverse events is alarming, however further analysis shows that many of the reported adverse events were not related to the intervention. Of the patients receiving glucocorticoid injection, 88% would agree to a second procedure and 83% of the placebo patients would agree to a second procedure, indicating high
acceptability amongst the patients. The overall management of discopathy following conservative management remains controversial. The present study indicates clinical improvement is feasible in one month, but longer-term pain improvement strategies are needed.

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