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# EDITOR'S MESSAGE

## Winter of Discontent

Ronald Januchowski, DO, FACOFP, Editor, *Osteopathic Family Physician*

*Now is the winter of our discontent*

*Made glorious summer by this sun of York;*

*And all the clouds that lour'd upon our house*

*In the deep bosom of the ocean buried.*

Those words, spoken as the opening lines of William Shakespeare's *Richard III*, have been widely quoted to tag political and social unrest in any season, using winter as metaphor for a bleak, discouraging time; John Steinbeck even borrowed the words as a title of his novel that addressed the moral degeneration of American culture during the 1950s and 1960s. As Richard III continues his monologue, he is outraged about what appears to be outwardly positive events occurring in England. Focusing on his frailties, he consciously creates chaos and struggle to disrupt peace, prosperity and health without any looming threats to limit the pleasures of life.

Jump a little over half a millennium later and we perhaps stand again looking forward to warming away the winter of our discontent, whether it is politics, pandemic or the true winter storms seen this time of year. Remaining conscious to our surroundings will help reduce false and treacherous thoughts while falling into the role of the villain as Richard III had done. Do not descant upon your deformities; rather, enjoy the gifts and common ground that the universe presents to you. You may truly be able to see beyond the winter of discontent.

Enclosed in this issue are review articles with strong osteopathic components, a novel research article related to post-operative cardiac patients and a very interesting clinical image. I hope your 2022 continues in fine fashion! Enjoy the read.

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*Jean Beaufort has released this "Winter Scene" image under public domain license.*

## FROM THE PRESIDENT'S DESK

# A Family Reunion to Remember

Nicole Heath Bixler, DO, MBA, FACOFP
ACOFP President

As we embark on a new year with renewed hope that our scientific knowledge and public health awareness will continue to bring us closer to a sense of normalcy, it is time to reunite! We are excited to convene a "family reunion" of colleagues and friends at the ACOFP 59th Annual Convention & Scientific Seminars in Dallas, Texas, March 17–20.

We have all had unique and challenging experiences since our last in-person ACOFP convention in Chicago in 2019, and we are long overdue to share osteopathic hugs, conversations about our growing families, updates regarding our careers and some good laughs. With this as our focus, ACOFP has reimagined your convention experience to prioritize in-person engagement while delivering exceptional educational content.

In response to feedback from previous conventions and membership surveys, as well as the work of the Task Force on Convention Innovation, we are poised to enjoy a convention experience that is hybrid in many ways. From a CME standpoint, this year's event will feature more than 30 hours of live 30- and 45-minute sessions across two tracks. Plus, attendees will have access to all sessions they missed on-demand—for up to one year after the event. Can't make it in person? If your schedule doesn't allow, please know that a virtual option will also be available, offering access to all the high-quality CME that ACOFP is known for providing.

To maximize the on-site experience, ACOFP '22 will feature new and improved networking opportunities and more time to make meaningful connections, including a Welcome Reception to kick off the event and a re-envisioned President's Banquet that will be open to all attendees without the need for a separate ticket. These experiences will be more reminiscent of "ACOFP fun nights" of the past while incorporating the needs of our diverse membership at this time. Our goal is to make this convention the highlight of 2022—and one that you will talk about for years to come.

When I reflect on my favorite ACOFP memories, they are often the ones shared at our past conventions. I have attended a rodeo in Phoenix, enjoyed the beach view in San Juan, been in Chicago when the river is green for St. Patrick's Day and celebrated the presidential election of my mentors in Philadelphia and Las Vegas. There have been ice cream socials, casino nights, family breakfasts, entertainment from our own colleagues and my seven-year-old daughter dancing to "Single Ladies" at Dr. Robert DeLuca's President's Reception. All these moments have allowed me to build new connections in new places.

My three daughters have practically grown up with ACOFP as their extended family since I was elected to the Board of Governors in 2013, and our family is grateful for the love, kindness and opportunity to serve in this capacity. Our collective hope was to add an exciting celebration in New Orleans to our list of fond memories before those plans were derailed by COVID-19.

It was then—and still is now—important to me to foster the incorporation of family in all that we do at our convention. Whether that is your nuclear family, your extended family, your work family or your ACOFP family, we want to come together in a welcoming and inclusive environment for everyone to learn, engage and make new memories.

I am excited for what we have planned in March. Our venue and schedule will provide the perfect backdrop for expanding your clinical knowledge while attending a true family reunion. We will celebrate the installation of Dr. Bruce Williams as your new ACOFP president, quite possibly with some Texas BBQ. With fun, food and family, what could possibly go wrong? Don't answer that! Instead, make plans to join us as we celebrate being together again as the largest and strongest osteopathic specialty.

See y'all in Dallas!

Nicole Bixler DO, FACOFP

Nicole Heath Bixler, DO, MBA, FACOFP

RESEARCH ARTICLE

# DETERMINANTS OF POSTOPERATIVE ATRIAL FIBRILLATION: A RETROSPECTIVE EVALUATION OF POSTOPERATIVE ATRIAL FIBRILLATION IN CARDIAC SURGERY

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**KEYWORDS:**

Arrhythmia

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**Introduction:** Atrial fibrillation is the most common postoperative arrhythmia and is associated with increased length of stay, cost, morbidity and mortality.[1–4] The incidence of postoperative atrial fibrillation for noncardiac, nonthoracic surgeries ranges from 0.4% to 26%.[5] The incidence increases to 20%–50% in cardiac surgery, occurring in approximately 30% of isolated coronary artery bypass grafting (CABG), approximately 40% of isolated valve surgeries and up to 50% of CABG plus valve surgeries.[6–8] Our aim was to identify risk factors that may predispose patients to postoperative atrial fibrillation and compare the efficacy of previously developed prediction tools to a new bedside prediction tool. We sought to develop a bedside screening tool using 4 easily identifiable variables: body mass index, age, congestive heart failure and hypertension (BACH). We predicted that our model would compare similarly to previously developed and validated prediction models but would be easier to use.

**Methods:** We retrospectively identified 672 patients without a history of atrial fibrillation who had undergone cardiac surgery from July 2011 to December 2018. The risk factors for atrial fibrillation were evaluated alongside previously developed prediction tools. Using logistic regression, *t* tests and receiver operator characteristic (ROC) analysis, we compared previously used risk stratification scores of $CHA_2DS_2$-VASc, CHARGE-AF and age. We also compared our proposed BACH risk prediction tool to our population and compared it against $CHA_2DS_2$-VASc, CHARGE-AF and age. In a subpopulation analysis of 259 people, we evaluated if left atrial size was an independent risk factor for the development of postoperative atrial fibrillation.

**Results:** A total of 131 patients—approximately 20%—developed postoperative atrial fibrillation. $CHA_2DS_2$-VASc had the lowest area under the curve (AUC) and did not perform as well at classifying patients with postoperative atrial fibrillation as the other 3 predictors. CHARGE-AF, age by itself and age per 5 years performed relatively similarly to one another. ROC was greatest for age alone (ROC area .634, 95% CI: .581–.688), followed by CHARGE-AF (ROC area .631, 95% CI: .577–.684), and finally $CHA_2DS_2$-VASc (ROC area .564, 95% CI: .509–.619). A logistic model was fit for the BACH variables (continuous versions of body mass index, age, congestive heart failure and hypertension). The model achieved good fit, $\chi^2(671, N=672)=633.029$, $P=.816$, Nagelkerke $R^2=.070$. However, only the predictors of age and prior heart failure were found to be significant. For BACH, the C-statistic (and AUC) for the model was .645 (95% CI: .601, .707), which was marginally better than age alone. All the models that were fit using ROC analyses were not statistically different from one another in terms of performance. No statistical significance was found between the 2 groups for preoperative left atrial size.

**Conclusion:** These findings suggest that age may be the highest risk factor for postoperative atrial fibrillation. The bedside prediction tool BACH compared slightly better than age alone but was not statistically different from the other prediction tools' performance. The BACH prediction tool is easy to use, includes only 4 factors that are readily available at the bedside and improves prediction over age alone.

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## INTRODUCTION

Atrial fibrillation is the most common postoperative arrhythmia and is associated with increased mortality and significant morbidity including increased risk of stroke, myocardial infarction and persistent congestive heart failure.[1–3] Additionally, it leads to an increase in healthcare resources including cost, prolonged intensive care unit stay and length of hospital stay.[2,4] In various studies it has been linked to an average increased length of stay of 3 days and an increase in total hospital cost of nearly $10,000.[9] The incidence of postoperative atrial fibrillation for noncardiac, nonthoracic surgeries ranges from 0.4% to 26%.[5] The incidence increases to 20%–50% in cardiac surgery, occurring in up to 30% of isolated coronary artery bypass grafting (CABG), approximately 40% of isolated valve surgeries, and up to 50% of CABG plus valve surgeries.[6–8,10]

Given the high frequency of postoperative atrial fibrillation combined with the associated increase in mortality, morbidity and healthcare costs, significant efforts have been made to predict patients who are at the highest risk. These efforts are to attempt to decrease postoperative atrial fibrillation occurrence by using prophylactic antiarrhythmics. Over the past 2 decades, numerous studies have attempted to decrease the occurrence of postoperative atrial fibrillation with beta blockers, amiodarone, sotalol, magnesium, digoxin and non-dihydropyridine calcium channel blockers with inconsistent results. Beta blockers and amiodarone have shown the most promising results in decreasing postoperative atrial fibrillation.[9,11–16] Unfortunately these treatments are associated with increased side effects. Prophylactic use of beta blockers has been associated with hypotension, bradycardia, and pulmonary edema due to its suppression of myocardial inotropy. These risks are amplified in beta blocker–naive patients.[17,18] Amiodarone is also associated with hypotension and bradycardia in addition to QT prolongation and pulmonary, hepatic and thyroid toxicity.[14,19] In the past few years, Skiba *et al* completed a prospective, randomized, single-blind, controlled pilot study in patients undergoing elective cardiac surgery to receive either standard therapy, metoprolol or amiodarone. They were able to identify that perioperative metoprolol but not amiodarone was associated with a significant reduction in postoperative atrial fibrillation.[20] This blanket prophylactic study also demonstrated the significance of bradycardia, as 40% were unable to be assigned treatment due to bradycardia.[20]

Although these studies have demonstrated the possibility of decreasing postoperative atrial fibrillation, they have also shown risks and decreased efficacy when using a blanket prophylaxis strategy. As a result, many studies have attempted to identify predictors of post–cardiac surgery atrial fibrillation. These have been developed in attempts to determine which patients would have the greatest benefit of a prophylaxis strategy while mitigating the possible medication side effects.[21–27] Ferreira *et al* also found that larger left atrial diameter is an independent risk factor for postoperative atrial fibrillation. This was also supported by Osranek *et al*, who suggested that left atrial volume was a strong and independent predictor of postoperative atrial fibrillation.[28] Although supported by few studies, the left atrial size or volume has not consistently been demonstrated to be an independent risk factor. Left atrial size or volume has not been included in any of the previously published risk calculators. Despite the high number of trials and development of multiple risk calculators, advanced age has consistently been shown to be the most significant risk factor for increased risk of postoperative atrial fibrillation.[4,6–9,21,22,27] Other predictive tools have been studied and shown to be somewhat predictive; however, few have shown to be better than age alone. In a recent large study comparing the $CHA_2DS_2$-VASc score, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF score, and a risk model for predicting postoperative atrial fibrillation following cardiac operations (POAF score) with age, only CHARGE-AF performed better than age alone in the prediction of postoperative atrial fibrillation. Despite the large number of studies, there remains no consensus of who or how to prophylactically treat in order to decrease occurrence of postoperative atrial fibrillation. In this study, we investigated the ability of CHARGE-AF, $CHA_2DS_2$-VASc, BACH (body mass index [BMI], age, congestive heart failure and hypertension) and age to predict new-onset postoperative atrial fibrillation in a community setting after cardiac surgery.

## METHODS

This single center retrospective study identified 672 patients without a prior history of atrial fibrillation who underwent cardiac surgery including CABG, aortic or mitral valve surgery, or any combination of these from July 2011 to December 2018 in a community hospital in California. The study used electronic health information combined with data from the Society of Thoracic Surgeons cardiothoracic database. Postoperative atrial fibrillation development was determined by ICD billing codes. This included development of atrial fibrillation any time in the postoperative inpatient treatment period. Any length or burden of atrial fibrillation was included. Additional subpopulation was developed using ICD billing codes for atrial fibrillation, and manual chart review was completed on 259 patients to obtain echocardiogram metrics for left atrial size.

The data was then used to identify age in addition to calculating the CHARGE-AF and $CHA_2DS_2$-VASc scores.[29,30] Preoperative intra-aortic balloon pump utilization (IABP) was not available on many patients and was unable to be included in the analysis for risk factor. This precluded the ability to evaluate POAF score against the prior studies and our proposed bedside tool, BACH. BACH was developed as a historical tool that could be used at the bedside prior to surgery to determine if these factors combined could be used to predict new-onset postoperative atrial fibrillation. The CHARGE-AF tool uses 10 different variables and barely outperforms age alone; this is more cumbersome in beside use. We hypothesized that we could use BACH variables with similar performance. This study was approved by the institutional review board.

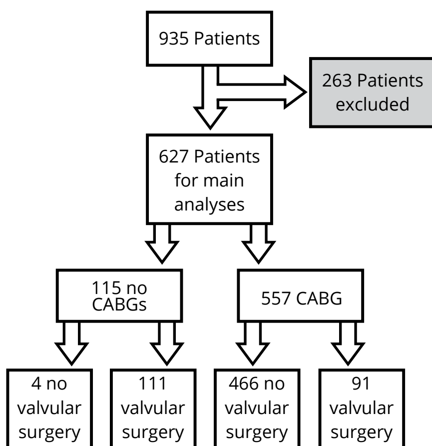
## Study data

Patient data was obtained from a single hospital's electronic health record (EHR) system combined with data provided to the Society of Thoracic Surgeons cardiothoracic database. The data was then used to identify age, in addition to calculating CHARGE-AF and $CHA_2DS_2$-VASc scores.[29,30]

### INCLUSION AND EXCLUSION

Inclusion criteria were all patients older than 18 who underwent cardiac surgery including CABG, valvular or both, July 2011–December 2018. Exclusion criteria included those with any history of atrial fibrillation preoperatively. In total, there were 263 of 935 patients excluded from the cohort analysis due to missing information or prior history of atrial fibrillation. Of the remaining 672 patients, 115 did not undergo CABG, while 557 did, and 202 patients had valvular surgery, while 470 did not. Of the patients who did not undergo CABG, 4 had no valvular surgery, while 111 did, and of the patients who did undergo CABG, 466 had no valvular surgery, while 91 did. A visual breakdown of patients is provided in Figure 1.

FIGURE 1:




### STATISTICAL ANALYSES

To investigate demographic differences, chi-square tests of independence were performed to test for differences in the discrete variables of patients: sex; diabetes; current smoker status; hypertension; whether patients were taking antihypertension medication; and whether patients had a stroke, congestive heart failure or myocardial infarction in the past. Independent-samples *t* tests were performed to test for differences in continuous demographic variables of patients: age, BMI, height, weight, preoperative blood pressure (systolic and diastolic), the 2 risk scores ($CHA_2DS_2$-VASc, CHARGE-AF), and preoperative left atrial size (pre-op LA size). Pre-op LA size was measured for only a portion of the sample: 259 patients.

To investigate how well different scores could identify postoperative atrial fibrillation, receiver operator characteristic (ROC) curve analyses were performed for age, $CCHA_2DS_2$-VASc and CHARGE-AF. Logistic regression was performed with the variables used in the formation of CHARGE-AF scores to determine how well the prediction model worked in the current sample. Afterward, another logistic regression was performed using uncategorized versions of the categorical variables used in the CHARGE-AF model (age, weight, height, systolic blood pressure and diastolic blood pressure). Finally, the BACH model proposed in this study (age, BMI, congestive heart failure and hypertension defined using systolic and diastolic blood pressure) was fit to the data to investigate its predictive power.

A combination of the variables used to create CHARGE-AF and $CHA_2DS_2$-VASc scores were included in ROC analyses to determine whether better classification could be achieved in the current sample. In addition to the ROC analyses, logistic regression models were fit on the variables included in $CHA_2DS_2$-VASc and CHARGE-AF, as well as a combination of the variables, including potential confounding variables, used to create the risk scores to determine the most important predictors of postoperative atrial fibrillation.

# RESULTS

## Demographic analyses

Demographics of the 672 patients in the study cohort were summarized in Table 1. Incidence of postoperative atrial fibrillation was 19.5%. A total of 131 patients developed postoperative atrial fibrillation and 541 did not. The 2 groups of patients were quite similar to one another, only statistically differing on a few variables. Regarding discrete variables, only history of prior congestive heart failure significantly differed between groups, $\chi^2(1, N=672)=4.028$, $P=0.045$, $\Phi=0.07$. Despite being statistically significant, the relationship between heart failure and postoperative atrial fibrillation was rather weak.

For the continuous variables, age and the 2 risk scores were statistically significant. For age, $t(670)=-4.694$, $P<.001$, $d=0.46$, and Levene's test of homogeneity of variance was non-significant, $P=.577$, suggesting the variances were the same in both groups. The groups differed by 4.761 years (95% CI: −6.749, −2.773) on average. The effect size of the difference between the 2 groups was medium in size.[25] For $CHA_2DS_2$-VASc, $t(670)=-2.175$, $P=.030$, $d=0.21$, and Levene's test was nonsignificant, $P=.753$. The groups differed by 0.502 points (95% CI: −0.723, −0.280), a small effect size. Finally, for CHARGE-AF, $t(670)=-4.450$, $P<.001$, $d=0.44$, and Levene's test was nonsignificant, $P=.513$. The groups differed by 0.502 points (95% CI: −0.723, −0.280), a medium effect size.

No statistical significance was found between the 2 groups for pre-op LA size, $t(96.85)=-0.276$, $P=.730$, $d=0$. Levene's test of homogeneity of variance was significant, $P=.004$, suggesting the variances were different between groups, so a correction for heterogeneity of variance was performed. Additionally, an independent-samples Mann-Whitney *U* test also found nonsignificance, $P=.709$. The difference of 0.035 cm (95% CI: −0.233, −0.164) was negligible.

## TABLE 1:

Patient characteristics

| CHARACTERISTIC | POST-OP AFIB (N=131, 19.5%) | NO POST-OP AFIB (N=541, 80.5%) | *P* VALUE |
|---|---|---|---|
| Age, mean + SD, years | 70.9±10.33 | 66.2±10.437 | <.0001* |
| Body mass index, mean ± SD, kg/m$^2$ | 28.6±5.1 | 28.6±5.0 | .968 |
| Height, mean ± SD, cm | 173.4±10.4 | 171.4±10.3 | .057 |
| Weight, mean ± SD, kg | 86.2±18.0 | 84.2±17.1 | .242 |
| Sex | | | .680 |
| Female | 32 (24.4) | 123 (22.7) | |
| Male | 99 (75.6) | 418 (77.3) | |
| Diabetes | 46 (35.1) | 230 (42.5) | .122 |
| Current smoker | 16 (12.2) | 82 (15.2) | .392 |
| Hypertension | 98 (74.8) | 440 (81.3) | .094 |
| Antihypertensive medication | 110 (84.0) | 484 (89.5) | .078 |
| Stroke TIA | 9 (0.07) | 41 (0.08) | .782 |
| Congestive heart failure | 19 (0.15) | 47 (0.09) | .045* |
| Prior MI | 56 (42.7) | 206 (38.1) | .325 |
| Preoperative blood pressure, mean ± SD, mm Hg | | | |
| Systolic | 135.9±23.5 | 136.4 ± 22.7 | .819 |
| Diastolic | 71.1±15.0 | 73.6 ± 14.4 | .064 |
| Pre-op LA size (n=259) | | | .730 |
| N | 48 | 211 | |
| Mean ± SD, cm | 4.1±0.6 | 4.0±0.8 | |
| Risk scores | | | |
| $CHA_2DS_2$-VASc | | | .030* |
| Mean ± SD | 3.8±1.9 | 3.4±1.8 | |
| Median (IQR) | 4.0 (3.0) | 3.0 (3.0) | |
| CHARGE-AF | | < .0001* | |
| Mean ± SD | 13.4±1.1 | 12.9±1.2 | |
| Median (IQR) | 13.6 (1.6) | 13.0 (1.6) | |

Note: * denotes *P*<.05. For continuous variables, the *P* value represents that of an independent-samples t-test.
For discrete variables, the *P* value represents that of a chi-square test of independence.

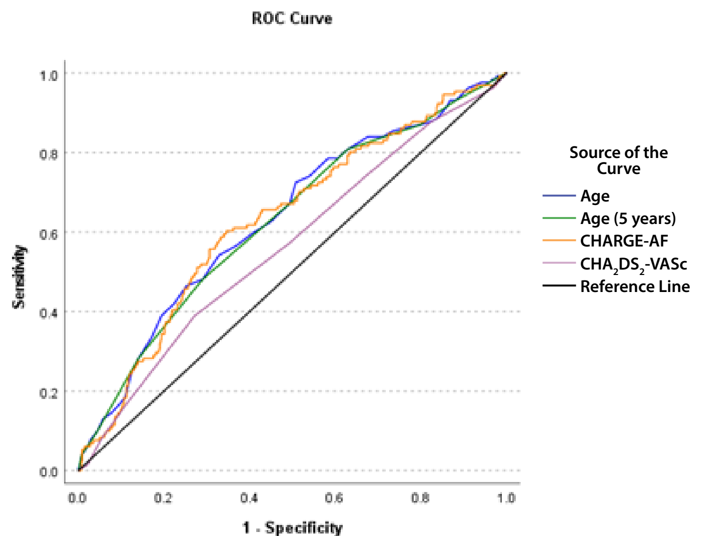
Abbreviations: afib, atrial fibrillation; SD, standard deviation; TIA, transient ischemic attack; MI, myocardial infarction; LA, left atrial; IQR, interquartile range.

## Receiver operator characteristic curve analyses

To investigate whether the scores accurately classified patients, ROC analyses using $CHA_2DS_2$-VASc and CHARGE-AF scores, age by itself, and age per 5 years were entered into the area under the curve (AUC) analyses using 131 individuals who experienced postoperative atrial fibrillation and 541 who did not. A comparison of the ROC curves for each of these 4 analyses can be found in Figure 2. AUC was significant for all 4 analyses. For $CHA_2DS_2$-VASc, the AUC was .564 (*P*=.24, 95% CI: .509, .619), for CHARGE-AF, the AUC was .631 (*P*<.001, 95% CI: .577, .684), for age by 5 years the AUC was .627 (*P*<.001, 95% CI: .573, .681), and for age by itself, the AUC was .634 (*P*<.001, 95% CI: .581, .688). AUC=.5 represents chance accuracy, while AUC=1 indicates perfect accuracy.[31] $CHA_2DS_2$-VASc had the lowest AUC and did not perform as well at classifying patients with postoperative atrial fibrillation status as the other 3 predictors. CHARGE-AF, age by itself and age per 5 years performed relatively similarly to one another.

## FIGURE 2:

Graphic representation of ROC analyses




## Logistic regression analyses

### CHARGE-AF

A logistic regression analysis was performed using the predictors from the CHARGE-AF score to determine how the model fit for the sample in the current study, and its results are displayed in Table 2. The model achieved good fit, $\chi^2(661, N=672)=622.126$, *P*=.884, Nagelkerke $R^2$=.094. The C-statistic for the model was .675 (95% CI: .624, .726). Although the model achieved good fit, many predictors were found to be nonsignificant. Only age, antihypertensive medication use and prior congestive heart failure were significant predictors.

## TABLE 2:

Logistic regression with CHARGE-AF

| PREDICTOR | ß | S.E. | SIG. | OR |
|---|---|---|---|---|
| Age (5 yr) | 0.247 | 0.056 | .000** | 1.280 |
| Height (10 cm) | 0.095 | 0.114 | .404 | 1.100 |
| Weight (15 kg) | 0.181 | 0.101 | .075 | 1.198 |
| Systolic BP (20 mm Hg) | 0.035 | 0.102 | .732 | 1.035 |
| Diastolic BP (10 mm Hg) | −0.109 | 0.880 | .212 | 0.897 |
| Current smoker | 0.63 | 0.315 | .842 | 1.065 |
| Antihypertensive medication use | −0.669 | 0.305 | .028* | 0.512 |
| Diabetes | −0.299 | 0.223 | .181 | .742 |
| Congestive heart failure | 0.711 | 0.310 | .022* | 2.036 |
| Myocardial infarction | 0.351 | 0.212 | .099 | 1.420 |
| Constant | −6.447 | 2.112 | .002 | .002 |

Note. * is significant at the .05 level and ** at .001.

### CHARGE-AF UNCATEGORIZED

A logistic regression analysis was also performed using uncategorized predictors from the CHARGE-AF score (using continuous versions of age, weight, height, systolic blood pressure, and diastolic blood pressure rather than categorized versions) to attempt to form a better prediction model for postoperative atrial fibrillation. Results from this model are displayed in Table 3. Using the CHARGE-AF model achieved good fit, $\chi^2(661, N=672)=617.833$, $P=.884$, Nagelkerke $R^2=.104$. The C-statistic for the model was .689 (95% CI: .638, .739). However, only the predictors of antihypertensive medication, prior heart failure and age were found to be significant.

### BACH

A logistic model was fit for the BACH variables (using continuous versions of age, BMI, systolic blood pressure, and diastolic blood pressure along with congestive heart failure), to attempt to create a better bedside prediction model for postoperative atrial fibrillation. Results from this model are displayed in Table 4. The model achieved good fit, $\chi^2(671, N=672)=633.029$, $P=.816$, Nagelkerke $R^2=.070$. However, only the predictors of age and prior heart failure were found to be significant. Figure 3 displays an ROC analysis comparing the BACH model to just using age. For BACH, the C-statistic (and AUC) for the model was .645 (95% CI: .601, .707), which was marginally better than age alone, but again all of the models fit using ROC analyses were not statistically different from one another in terms of performance.

## TABLE 3:

Logistic regression using uncategorized CHARGE-AF predictors

| PREDICTOR | ß | S.E. | SIG. | OR |
|---|---|---|---|---|
| **Age** | 0.053 | 0.011 | .000** | 1.054 |
| **Height** | 0.013 | 0.012 | .257 | 1.014 |
| **Weight** | 0.013 | 0.007 | .075 | 1.013 |
| **Systolic BP** | 0.001 | 0.005 | .791 | 1.001 |
| **Diastolic BP** | −0.012 | 0.009 | .187 | 0.988 |
| Current smoker | 0.086 | 0.316 | .785 | 1.090 |
| Antihypertensive medication use | −0.688 | 0.307 | .025* | 0.502 |
| Diabetes | −0.297 | 0.225 | .186 | 0.743 |
| Congestive heart failure | 0.740 | 0.313 | .018* | 2.096 |
| Myocardial infarction | 0.362 | 0.213 | .090 | 1.437 |
| Constant | −7.304 | 2.156 | .001 | .001 |

Note. * is significant at the .05 level and ** at .001. Variables in bold differ from the previous model in that they were included as continuous rather than discrete.

Abbreviations: BP, blood pressure.

## TABLE 4:

Logistic regression using BACH predictors

| PREDICTOR | ß | S.E. | SIG. | OR |
|---|---|---|---|---|
| Age | 0.048 | 0.011 | .000** | 1.049 |
| BMI | 0.017 | 0.020 | .377 | 1.018 |
| Systolic BP | −0.001 | 0.005 | .914 | 0.999 |
| Diastolic BP | −0.009 | 0.009 | .308 | 0.991 |
| Congestive heart failure | 0.701 | 0.302 | .021* | 2.105 |
| Constant | −4.535 | 1.173 | .000** | 0.011 |

Note. * is significant at the .05 level and ** at .001.

Abbreviations: BMI, body mass index; BP, blood pressure.

FIGURE 3:

ROC curves comparing age and BACH

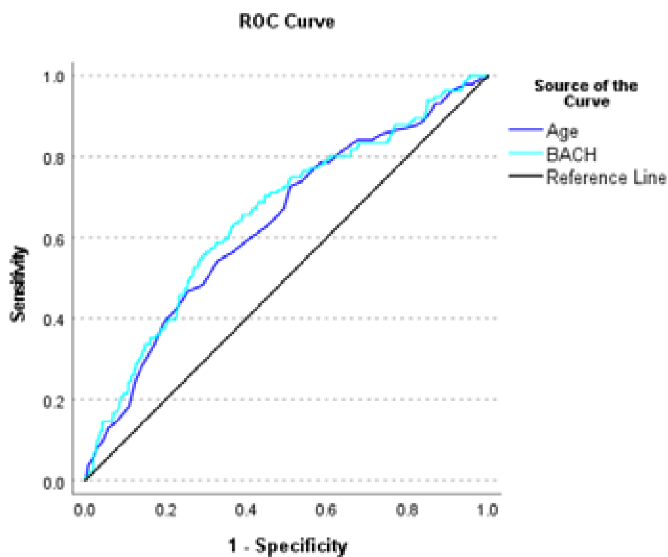
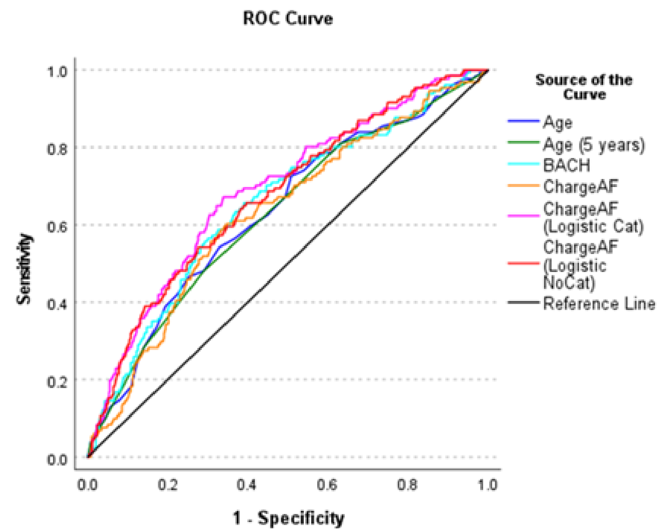



FIGURE 4:

ROC curves comparing prediction model




## Investigating a better model

Using the CHARGE-AF model with continuous versions of each variable, additional predictors were investigated to determine whether a better predictive model could be built using readily available variables. The inclusion of $CHA_2DS_2$-VASc predictors such as prior stroke/transient ischemic attack ($\chi^2(1)=0.259$, $P=.611$), vascular disease ($\chi^2((1)=0.048$, $P=.827$), and gender ($\chi^2(1)=1.271$, $P=.260$), failed to statistically improve the model based on chi-square difference tests.

To determine whether the model would benefit from the inclusion of BMI instead of having height and weight separately, model comparisons were performed between nested models. First, a base model including all variables from Table 3 besides height and weight was fit. Next, BMI was introduced as a predictor. The inclusion of BMI did not significantly improve the model, $\chi^2(1)=2.129$, $P=.145$. Height and weight were added into the base model, which resulted in a significant improvement to the model, $\chi^2(2)=9.369$, $P=.009$. This suggests that despite not being significant predictors, height and weight were important for the overall performance of the model. This was true for height and weight by themselves, but not when combined into BMI.

ROC analyses using CHARGE-AF, age, age by 5 years, the logistic model using CHARGE-AF variables, the logistic model using CHARGE-AF variables without categorizing age, weight, height, systolic blood pressure and diastolic blood pressure, and BACH showed that overall the final model, utilizing uncategorized variables, was more successful than others. However, all models performed quite similarly to one another as seen in Figure 4.

The ROC analysis for age along with the computation of Youden's *J* to balance sensitivity and specificity found that the age of 66 was the ideal cut point between those at greater risk for developing postoperative atrial fibrillation.[32] Similarly, the use of Youden's *J* with age by 5 years found the age of 65 as an ideal cut point.

Overall, the $CHA_2DS_2$-VASc and CHARGE-AF criteria performed relatively poorly in this sample compared to previous studies.[26] The BACH model did not significantly improve over CHARGE-AF, and age by itself performed similarly to the more complex models. Although prediction could be improved by fitting a logistic regression to obtain new coefficients for CHARGE-AF, and prediction could be further improved by using continuous variables rather than categorized ones, the improvements were considered marginal.

## DISCUSSION

The incidence of postoperative atrial fibrillation for this cohort was 19.5%, which is similar to previously published literature. This information is supportive and also helps illustrate the burden of this arrhythmia postoperatively. The overall goal of this investigation was to determine predictors of atrial fibrillation and evaluate prediction tools in a community setting. During this process we evaluated if left atrial size would be an independent risk factor. Based on this review using a subpopulation of patients, we determined left atrial size was not an independent risk factor. This is similar to some prior studies but contrary to others.[28,33]

Our primary investigation compared the performance of well-known predictive tools CHARGE-AF, $CHA_2DS_2$-VASc and age in a community hospital patient population undergoing cardiac surgery. We also developed a bedside prediction tool using historical data that is readily available and easy to use, consisting of only 4 factors. Unfortunately, the previously developed POAF

calculator was excluded from our study due to inadequate numbers/missing data of preoperative intra-aortic balloon pump placement in our cohort.[24] However, the POAF calculator has been compared to CHARGE-AF and age alone in a study of 9416 consecutive patients by Pollock *et al*, revealing it to be less predictive of postoperative atrial fibrillation than CHARGE-AF and age but slightly better than $CHA_2DS_2$-VASc.[27] Additionally, preoperative intra-aortic balloon pump placement does not apply to patients undergoing elective cardiac surgery.

Our evaluation and comparison of CHARGE-AF, age and $CHA_2DS_2$-VASc revealed each of these risk stratification tools showed statistically significant differences in the group of patients who developed postoperative atrial fibrillation. The difference was larger in CHARGE-AF and age when compared to $CHA_2DS_2$-VASc. Interestingly, age was a better predictor of postoperative atrial fibrillation when compared to the aforementioned tools in our cohort. The findings of Pollock *et al* were similar in that they found age and CHARGE-AF to be the best predictors. In their evaluation, however, they found that CHARGE-AF was slightly better than age alone. Logistic regression showed a history of congestive heart failure and increasing age in this sample resulted in increased risk of postoperative atrial fibrillation. These predictors alone, or in combination, did not prove to be a better predictive model when compared to age alone, CHARGE-AF or BACH.

Our bedside prediction tool, BACH, compared similarly to the previously developed prediction tools. ROC analyses using CHARGE-AF; age; age by 5 years; the logistic model using CHARGE-AF variables; the logistic model using CHARGE-AF variables without categorizing age, weight, height, systolic blood pressure and diastolic blood pressure; and BACH all showed that overall, the final model—utilizing uncategorized variables—was more successful than others. For BACH, the C-statistic (and AUC) for the model was .645 (95% CI: .601, .707), which was marginally better than age alone. When compared using all the models that were fit using ROC analysis, BACH was not statistically different in terms of performance. In review of the BACH model, age and prior heart failure were the strongest predictors. Although the BACH model did not improve the prediction, surprisingly, it had similar success with fewer variables. Although the variables needed to calculate the CHARGE-AF score are readily available in the electronic health record, simplifying the prediction score to the 4 variables in the BACH score may improve physician utilization and standardization.

Based on our findings and the importance of age in all of the previously studied prediction tools, including our BACH tool, we attempted to further clarify what age would be the ideal cutoff for classification of patients as high risk. An ROC analysis for age, along with the computation of Youden's *J* to balance sensitivity and specificity, found that the age of 66 was the ideal cut point between those at greater risk for developing postoperative atrial fibrillation and those who are not.[32] Further studies are needed to look at the potential use of age alone in predicting postoperative atrial fibrillation; the ideal age cutoff that would make a patient "high risk"; and continued efforts to identify a better predictive model, which can then possibly lead to firm guidelines of who should be considered high risk and receive prophylactic arrhythmias per the 2019 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines.

A consensus postoperative atrial fibrillation prediction tool remains elusive. Multiple prediction tools have been developed with varying predictive capabilities and consistency. Given the findings in both our study and the larger recent study by Pollock *et al*, it seems that age may be the most useful predictor of postoperative atrial fibrillation.[27] Additionally, adding variables does not improve prediction, and in our setting, the 4 variables of BACH performed similarly.

## STRENGTHS AND LIMITATIONS

As with other retrospective analysis, there is risk for confounding as well as selection bias, which are the limitations of such study design. Some patients had to be excluded from analysis due to lacking data in IABP use and sex. Thus, the POAF score had to be excluded from this analysis. Researchers attempted to limit the effects of confounding variables by using case matched controls with an equal number of all variables in both groups. This study's cohort was relatively small when compared to a CHARGE-AF derivation cohort of over 26,000 participants, and it was geographically limited to a single center in Southern California, whereas CHARGE-AF utilized 3 separate cohorts.[29] The percentage of women included was 23.1%, which reflects the clinical practice of a single surgical group and somewhat limits generalizability. Our findings are similar to Pollock *et al*, which demonstrated CHARGE-AF and age as better predictors than the POAF bedside score.[29]

Strengths of the study include that patients who had pre-existing atrial arrhythmias were excluded from analysis. Some of the previously published prediction models included patients with preoperative history of atrial fibrillation, which calls into question the incidence of new-onset atrial fibrillation in these study cohorts.[24] Our study cohort included only patients without known preoperative atrial fibrillation who developed it during hospital stay, which is the population who have been shown to have longer length of stay and are at higher risk of perioperative stroke.[1–4] Our ROC analysis independently validates BACH, CHARGE-AF and age alone as potential tools for prediction of atrial fibrillation, adding evidence to previously reported studies.

Despite many studies, postoperative atrial fibrillation remains difficult to predict. As per the 2019 AHA/ACC/HRS guidelines, beta blockers should be continued if already prescribed, and preoperative administration of amiodarone is reasonable for prophylactic therapy in patients at high risk for developing postoperative atrial fibrillation.[34] The lack of a consensus on how to quantify high risk highlights the need for a reliable and easy-to-use method of identifying those at high risk. This is particularly important to prevent blanket prophylaxis with medical therapies that have been shown to have significant adverse side effects.[14,17–19]

## CONCLUSION

Our analysis suggests increasing age, BACH and CHARGE-AF are the best predictors of determining patients at higher risk of postoperative atrial fibrillation. Increasing age alone carried the most weight in our study and thus may be considered to identify high-risk patients preoperatively. Further studies need to be performed to confirm these findings as well as utilize the BACH method in a randomized controlled trial for prevention of this dangerous and costly arrhythmia.

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**Data Availability Statement:** The data utilized for this research is part of the Society of Thoracic Surgeons Cardiothoracic Database and included the specific data contributed from our community hospital July 2011–December 2018. The specific data can be obtained from contacting our corresponding author to have access to the de-identified information if access is granted by the institutional review board at Community Memorial Hospital.

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REVIEW ARTICLE

# ACUTE GIARDIASIS AND CHAPMAN REFLEXES: MUSCULOSKELETAL SYMPTOMS PRECEDING, DURING AND AFTER INFECTION

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**KEYWORDS:**

Giardiasis

Osteopathic manipulative medicine

Osteopathic manipulative treatment

Giardiasis is an acute infection caused by *Giardia lamblia*, which produces profuse secretory diarrhea that can lead to dehydration and electrolyte derangement. Musculoskeletal manifestations resulting because of giardiasis occur due to prolonged inflammation and viscero-somatic reflexes of the pathophysiology for this disease process. By treating the parasitic infection with an antiparasitic agent, as well as treating the somatic dysfunctions with osteopathic manipulative treatment, analgesics and a home exercise program, the patient in the following article experienced an uneventful course of treatment and a complete recovery including resolution of the pain.

## INTRODUCTION

The organism *Giardia lamblia* is most often transmitted through contaminated water or food, or by the fecal-oral route.[1] Clinical presentation of giardiasis can vary; approximately 50% of patients exposed remain asymptomatic, and the other 50% will develop gastrointestinal symptoms.[2] Gastrointestinal symptoms include loose diarrhea with foul-smelling, non-bloody stools, in addition to flatulence, abdominal cramps, bloating, loss of appetite, nausea and weight loss within 1–2 weeks of exposure.[2] Malabsorption, dehydration and substantial weight loss are hallmarks of the infection, in addition to the infectious diarrhea.[2] Approximately half of infections resolve without treatment within 4 weeks of onset, and the other half require antibiotic and/or antiparasitic therapy. The diagnosis of giardiasis is made by stool analysis revealing cysts. *Giardia* antigens can be detected in stool specimens using monoclonal antibodies or direct fluorescent assays; serologic studies are not useful because they cannot distinguish between active and recovered infection.

The prevention of infection with *G. lamblia* should focus primarily on the avoidance of contaminated water. Outbreaks of giardiasis have usually been associated with contaminated surface water or shallow wells. Vigorous hand-washing and proper disposal of soiled diapers should be practiced in day care settings. Boiling water that may be contaminated with *Giardia* cysts is useful for eradication, but chlorination of the water is not effective. The cysts associated with *Giardia* transform into the trophozoite form in the gastrointestinal tract. The *Giardia* genus will lead to decreased expression of brush border enzymes, structure changes to the microvilli, increased intestinal permeability to water and death of small intestinal epithelial cells. Cysts and trophozoites are unable to survive outside of the gastrointestinal tract.[2,3]

## EPIDEMIOLOGY

Giardiasis is present all over the world, affecting nearly 8% of children and 2% of adults in developed countries, and 33% of persons living in developing countries have had giardiasis. In the United States, *Giardia* infection is the most common intestinal parasitic disease affecting humans. Those at greatest risk include those who travel to countries where giardiasis is common, those in child care settings with exposure to soiled diapers, those who work in the vicinity of or ingest contaminated water, and those engaged with anal intercourse (including men who have anal sex with men).[2]

## CASE REPORT

A 43-year-old male developed musculoskeletal symptoms of the bilateral hips, back pain, abdominal pain and thigh pain. He experienced 2 days of sharp bilateral pain along the greater trochanteric region, as well as radiation to the lateral thighs bilaterally. He did not have any specific or identifiable triggers to cause the pain, nor had he sustained an acute injury, although he did report swimming in 2 different lakes and had visited 2 different water parks 2 weeks prior to the onset of symptoms. He

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reported that the pain was insidious at the onset and gradually became more severe, to the point where he experienced difficulty sleeping at night due to significant pain when lying on either side. He initially attributed his symptoms to a musculoskeletal cause and used over-the-counter analgesics without relief.

Two days after the onset of symptoms, he noted the onset of severe watery diarrhea. He reported experiencing at least 12–15 episodes of this secretory diarrhea within the first 24 hours after onset as well as a fever of 102.2°F (39°C) at home. Associated symptoms included generalized weakness and malaise. He tolerated oral fluids and mild bland food but felt that post-meal transit time was accelerated. He attempted fluid resuscitation at home and was unsuccessful, becoming near-syncopal and requiring evaluation at the emergency department. He was treated with intravenous hydration and had labs performed, including a complete blood count and a basic metabolic panel. Other than slight hypokalemia with a potassium level of 3.4, the remainder of the labs were unremarkable. Stool studies were not ordered at this initial visit. His past medical history was notable for gastroesophageal reflux disease, chronic gastritis and *Helicobacter pylori* infection. His past surgical history was remarkable for an appendectomy. His family history is non-contributory. Social history was unremarkable for alcohol, tobacco or drug use. Home medications included one 30 mg lansoprazole tab daily and one 10 mg loratadine tab daily. He denied any medication allergies. His vital signs and physical exam were unremarkable, though his mucous membranes were dry at the time of presentation. He was discharged home and diagnosed with a viral gastrointestinal illness.

On the first post-discharge day he continued to experience several episodes of watery diarrhea. He reported another 10–15 episodes within these 24 hours. As a result of his ongoing symptoms, he was directly admitted to the hospital by his gastroenterologist. Upon admission, laboratory values were repeated and were not significantly different from the prior emergency department visit. Imaging of the bilateral hips with x-ray was unremarkable. A computed tomography scan of the abdomen and pelvis was also unremarkable. He demonstrated no acute peritoneal signs. However, at this time, stool samples were obtained for studies. Stool culture was negative for enteric pathogens. Toxin studies were negative for *C. difficile*. Ova and parasite studies were positive for *G. lamblia*. There were live parasites noted within the stool. *Giardia* enzyme-linked immunosorbent assay in the stool was positive, and the *Cryptosporidium* screen was positive as well, but his HIV antibody test was negative. He was treated with a course of nitazoxanide. Though he clinically improved, the musculoskeletal symptoms persisted.

## DISCUSSION

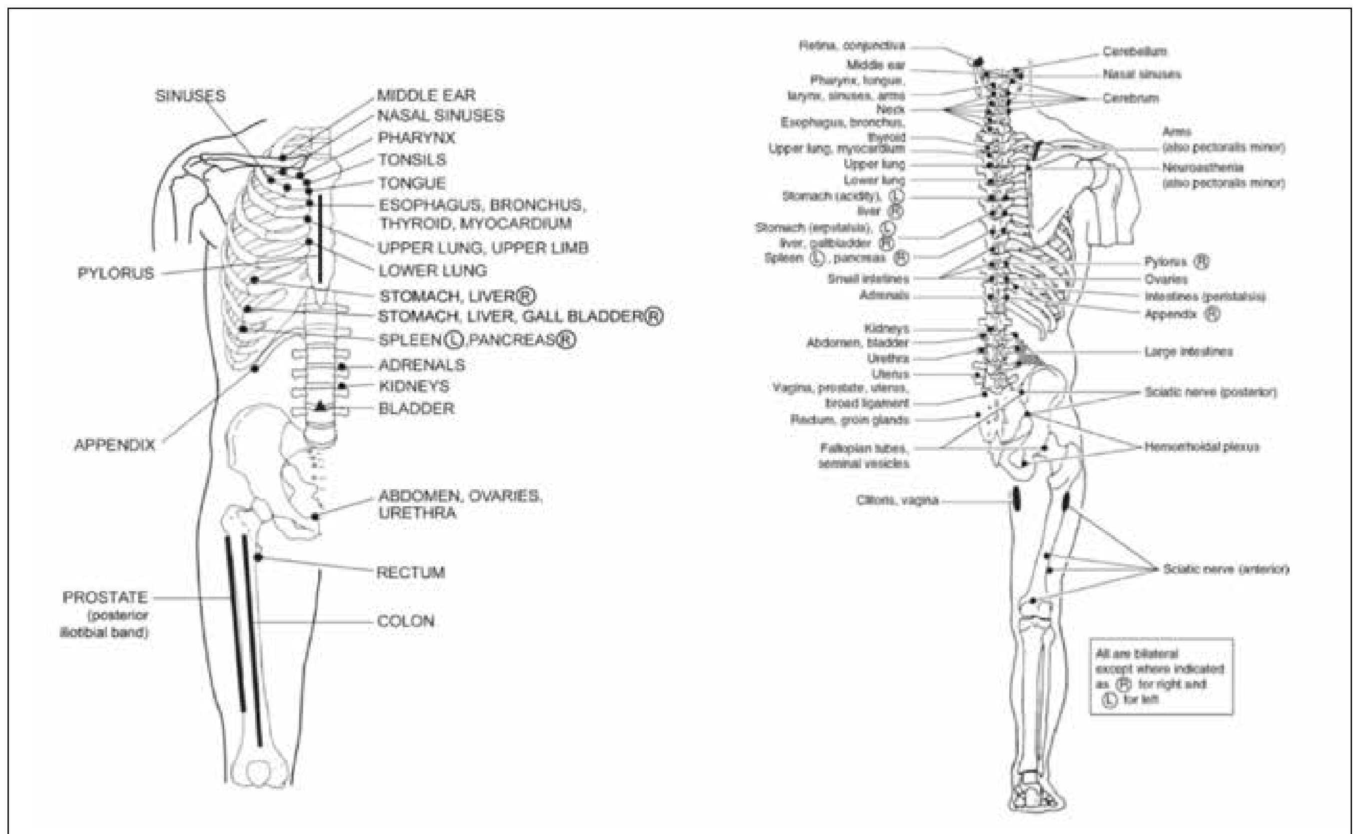
The musculoskeletal findings that preceded and accompanied the symptoms of this disease process provide the osteopathic physician with an additional clue to the underlying disorder. A consideration of the physiologic and pathophysiologic mechanisms involved is appropriate. The autonomic nervous system mediates the interactions between the paravertebral ganglia and the prevertebral ganglia, as well as somatic structures leading to viscero-somatic reflexes. The paravertebral ganglia, also known as the sympathetic trunk, are found paraspinally to the sympathetic trunk of the spinal levels of T1–L2. The prevertebral ganglia are associated with the large vessels of the abdominal cavity: the celiac ganglia, the superior mesenteric ganglia and the inferior mesenteric ganglia. A viscero-somatic reflex is caused by irritation of the viscera, causing a signal to be sent to somatic structures in the local area as the result of a referred pain. Signal pathways by which these reflexes occur originate from afferent signals entering through the dorsal horn of the spinal cord (posteriorly) and efferent signals leaving through the ventral horn (anteriorly).[4] When signals enter through the visceral afferent pathway, nerves are very close to each other, resulting in signals being carried to higher brain centers, which then 1) travel back down to the efferent output, 2) form an immediate signal arc from the dorsal horn to the ventral horn in the brain matter, or 3) both. This can result in referred pain. It is often difficult to determine the origin of the input (ie, muscle versus viscera); therefore, the result is referred to muscular tissue. Specifically, an imbalance of sympathetic versus parasympathetic dominance can exacerbate expected symptoms associated with the respective autonomic division. Chapman reflexes are a type of viscero-somatic reflex mediated by sympathetic nerves. These reflexes represent lymphatic stasis secondary to diseased, stressed or irritated organs. Chapman points are located on both the anterior surface and the posterior surface. Anterior Chapman points are typically located in intercostal spaces, with the rib segments corresponding to the sympathetic innervations of the involved viscera, and are utilized for diagnosis. Posterior Chapman points are found in the soft tissue between the spinous process of a vertebrae above and a transverse process of a vertebra below and are utilized for treatment.[4,5]

*Giardia* affects primarily the lower gastrointestinal tract because of epithelial dysfunction in the small intestine. The posterior Chapman points associated with the gastrointestinal tract are located at T1–L2 levels at the spinous and transverse processes of the corresponding levels of the spine. The anterior Chapman point for the lower gastrointestinal tract occurs along the anterior iliotibial band bilaterally. The patient's hip and thigh pain occurred due to spinal facilitation, which is the maintenance of a pool of neurons in a state of partial or sub-threshold excitation. The prolonged inflammation of the small intestine due to resolving infection will certainly manifest in the musculoskeletal symptoms this patient was experiencing.

Innervation of the GI tract should be considered in addition to viscero-somatic reflexes and Chapman reflexes. The prevertebral ganglia are associated with the large vessels of the abdominal cavity: the celiac ganglia, the superior mesenteric ganglia and the inferior mesenteric ganglia. The GI tract and nearby structures can be grouped into the following regions based on the corresponding ganglia and nerves:

FIGURE 1:

Anterior and posterior Chapman points[4,5]




1) Upper GI tract: T5–T9 levels (celiac ganglion and greater splanchnic nerve): stomach, liver, gallbladder, spleen, and portions of the pancreas and duodenum.

2) Middle GI tract: T10–T11 levels (superior mesenteric ganglion and lesser splanchnic nerve): portions of the pancreas and duodenum, jejunum, ileum, ascending colon and proximal 2/3 of the transverse colon (the right colon). Also classified here are the kidneys and the upper ureters.

3) Lower GI tract: T12–L2 levels (inferior mesenteric ganglion and least splanchnic nerve): distal 1/3 of the transverse colon, descending colon and sigmoid colon (the left colon), as well as the rectum. Also classified here are the lower ureters. The transverse colon does not fit neatly into the above classification; the sympathetic innervation of the transverse colon for the proximal 2/3 is by the T10–T11 spinal levels and the distal 1/3 by the T12–L2 spinal levels. The parasympathetic innervation of the proximal two-thirds of the transverse colon is by the vagus nerve and the distal 1/3 by the pelvic splanchnic nerves.[4,6] The viscero-somatic reflexes will show tissue texture changes at the T5–T10 levels for the small intestine and T12–L2 for the length of the colon with respect to sympathetic autonomic innervation. The vagus and pelvic splanchnic nerves supply parasympathetic autonomic innervation to the GI tract.[4,6]

Of interest are the musculoskeletal manifestations of viscero-somatic reflexes occurring because of giardiasis. A literature search did not reveal any prior examples of either diagnosis of giardiasis using Chapman points or treatment of symptoms or sequelae using osteopathic manipulation. The patient continued to experience intermittent abdominal cramping for up to 4 weeks after completing the initial treatment. He continued to experience persistent bilateral hip and lateral thigh pain. The pain was more severe nocturnally and frequent sleep interruption was experienced. Acetaminophen was utilized for pain.

A comprehensive examination of the 10 body regions of somatic dysfunction—cranial, cervical, thoracic, ribs/sternum/clavicle, lumbar, sacrum, hips/pelvis/innominates, upper extremity, lower extremity and abdomen—was performed. Affected regions included thoracic, lumbar, sacrum, abdomen and hips/pelvis/innominate. The following somatic dysfunctions and structural abnormalities were identified:

1) T5–T7 neutral, side bent left, rotated right

2) Anterior Chapman points on the right in the fifth and sixth intercostal spaces and along the bilateral iliotibial bands

3) L2–L4 neutral, side bent right, rotated left

4) L5 neutral, side bent left, rotated right

5) A left-on-left sacral torsion

6) A hypertonic left piriformis muscle

7) A hypertonic right psoas muscle

8) A right anterior innominate

9) Hypertonic celiac collateral ganglion musculature

On a 10-point scale, the patient noted pain of 7.

Osteopathic manipulative medicine was engaged as an adjunctive treatment modality, and these treatments provided relief and were targeted to the affected biomechanical, autonomic and lymphatic dysfunctions. Treatments were performed twice at 2 consecutive visits. The autonomic dysfunction was treated with release and OA release (to normalize parasympathetic tone, in particular, the vagus nerve), rib raising (to normalize sympathetic tone) and sacral rocking (to normalize parasympathetic tone, in particular, the pelvic splanchnic nerves S2–S4). Collateral ganglia myofascial release (MFR) techniques were used to target the respective ganglion, particularly the superior (T10–T11) and inferior (T12–L2) mesenteric ganglia for this patient. MFR and muscle energy techniques were applied to the thoracic spine, lumbar spine, sacrum, piriformis and psoas muscles, with treatment of posterior Chapman points invoked. In addition, the patient was prescribed a home exercise program with lateral hip stretches. After the initial treatment, only the bilateral hip and thigh pain remained and was diminished, compared to the initial presentation. All the gastrointestinal and musculoskeletal symptoms took a total of 6 weeks to entirely resolve. The pain gradually improved, and the patient has had no residual effects. At the end of the 6 weeks, his pain reduced to 1/10. The resolution of posterior Chapman points additionally demonstrated a successful treatment. Lymphatic considerations and treatments were insignificant in this scenario; thus, those techniques were not performed here.[6]

## CONCLUSION

Infection with *Giardia lamblia* leading to acute giardiasis and secretory diarrhea shows associated musculoskeletal manifestations, including bilateral hip and thigh pain. Considerations of the underlying biomechanical and autonomic dysfunctions can suggest osteopathic manipulative treatment as an adjunctive to treating the underlying parasitic infection during convalescence and potentially help to shorten the course of disease if employed at onset of musculoskeletal symptoms. Due to the persistent inflammation, a multifaceted treatment modality would be beneficial in such situations. The patient was treated with an antiparasitic, analgesics and osteopathic manipulative treatment. He recovered without further sequelae.

### AUTHOR DISCLOSURE(S)

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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REVIEW ARTICLE

# PROSTATE DISORDERS DIAGNOSIS AND MANAGEMENT REVIEW WITH AN OSTEOPATHIC COMPONENT

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**KEYWORDS:**

Benign prostatic hypertrophy

Prostate

Prostatitis

PSA

Physicians commonly encounter disorders of the prostate in the primary care setting, where shared decision making for prostate cancer screening should also occur. Hence, it is important for physicians to understand and differentiate the diagnoses of prostate disease. Initial evaluation should include a thorough history, physical examination, laboratory examination and imaging, if necessary. This article aims to provide a diagnostic and management approach for prostate disease.

## INTRODUCTION

Found in biological males, the prostate is a gland the size of a walnut located below the bladder and anterior to the rectum, surrounding the urethra at the neck of the bladder. The prostate functions in controlling and preventing urine entry during ejaculation, expelling sperm during ejaculation, and secreting fluid that aids in sperm motility and survival.

Prostate disease can occur secondary to infection (acute vs. chronic vs. granulomatous prostatitis), enlargement of the prostate or malignancy of the prostate.

## ACUTE BACTERIAL PROSTATITIS

Acute bacterial prostatitis is an infection of the prostate that is most commonly caused by gram-negative rods (*pseudomonas* species) and less commonly by gram-positive organisms (*enterococci*).[1,2] Routes of infection are attributed to ascent in the urethra and reflux of infected urine into the prostatic ducts; lymphatic and hematogenous routes are rare.

Symptoms of acute bacterial prostatitis include fever; irritative voiding symptoms; and perineal, sacral or suprapubic pain. Urinary retention can result from swelling or inflammation of the prostate leading to obstruction.[3]

Physical examination will reveal exquisite tenderness on digital rectal exam (DRE). However, care should be taken not to perform vigorous or multiple exams of the prostate since there is a risk of septicemia with such examinations.

Laboratory examination will reveal leukocytosis with left shift. Urinalysis (UA) will reveal pyuria, bacteriuria and varying degrees of hematuria. A positive urine culture will reveal the pathogen causing infection. Patients who fail to respond to antibiotic therapy within 24–48 hours should undergo a pelvic computed tomography (CT) scan or a transrectal ultrasound (US) to rule out prostatic abscess.

Patients who are afebrile and without signs of sepsis can be treated with empiric antibiotic therapy with either trimethoprim-sulfamethoxazole (1 double-strength orally every 12 hours) or a fluoroquinolone (ciprofloxacin 500 mg every 12 hours or levofloxacin 500 mg daily). It is important to note that men younger than 35 years of age who are sexually active and those older than 35 with high-risk sexual behavior should also be treated for *N. gonorrhoeae* and *C. trachomatis*.[4]

While awaiting sensitivities from the urine culture, patients may require hospitalization for intravenous (IV) antibiotics, which should be considered if the patient is febrile or if bacteremia is suspected. If the patient has been afebrile for 24–48 hours and sensitivities are available, then you can transition to oral antibiotics to complete a total of 4–6 weeks of antibiotic therapy. If there are obstructive symptoms, the patient can undergo straight catheterization to relieve retention, and an indwelling catheter can be maintained for fewer than 12 hours if needed.

Bacteria identified in the culture can be eradicated with the appropriate use of antibiotics. Progression to chronic bacterial prostatitis is rare if acute bacterial prostatitis is treated appropriately. However, family physicians should consider referring their patient to urology when there are signs of urinary retention or chronic prostatitis.

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## PROSTATE ABSCESS

Abscess of the prostate occurs following acute bacterial prostatitis that is left untreated or inappropriately treated.[5] A higher incidence is noted in patients with an immunocompromised state, such as diabetes mellitus or end-stage renal disease on hemodialysis. Patients with indwelling catheters or recent urethral instrumentation are also at higher risk of acute prostatitis.[6]

Patients will typically present initially with fever; irritative voiding symptoms; perineal, sacral or suprapubic pain; and urinary retention. A diagnosis of acute bacterial prostatitis is usually made (inaccurately) and the patient is treated with antibiotics. If symptoms return or persist during treatment, then prostatic abscess should be suspected.

DRE will often reveal tenderness and swelling of the prostate, and a workup should include a transrectal US and pelvic CT scan to confirm diagnosis.

Treatment of a prostate abscess requires drainage of the abscess. This drainage can be accomplished by using transrectal US guidance. If this does not provide adequate drainage, transurethral drainage is used, especially if the abscess is >1 cm.

## CHRONIC BACTERIAL PROSTATITIS

Chronic bacterial prostatitis is a bacterial infection of the prostate that can occur secondary to acute bacterial prostatitis or recurrent urinary tract infections. Only half of those who present with chronic bacterial prostatitis have a history of acute bacterial prostatitis. As with acute bacterial prostatitis, the most common etiology is secondary to gram-negative rods and gram-positive *enterococci*.[7]

Symptoms of this condition are more variable than with acute infection. Patients can present with varying degrees of voiding symptoms, urethral pain and obstructive urinary symptoms, or they may present with perineal pain and low-back pain.

Unlike in acute bacterial prostatitis, the physical examination is often unremarkable. DRE of the prostate may be normal, boggy or indurated. Urinary retention should be ruled out with a post-void residual urine volume.

Laboratory examination will often reveal a normal UA (unless secondary cystitis is present). Post-prostatic massage voided urine will reveal increased leukocytes in urine and positive urine culture (a culture is required to make a diagnosis). The number of leukocytes is not indicative of the severity of disease. Imaging studies are generally not helpful in diagnosis.

The treatment for chronic bacterial prostatitis is similar to acute bacterial prostatitis in that if patients are febrile or systemically ill, they may require admission, and initial IV antibiotic therapy with broad-spectrum antibiotics is often necessary. Once patients are afebrile for 24–48 hours, they can continue oral therapy for 4–6 weeks. Symptomatic relief can be achieved with anti-inflammatory agents, hot sitz baths and alpha blockers. Prostatitis may be recurrent and difficult to cure, often requiring multiple courses of antibiotics. It is important to refer the patient to a urologist when a patient has persistent symptoms.

## GRANULOMATOUS PROSTATITIS

Two forms of nonspecific granulomatous prostatitis have been identified as non-eosinophilic and eosinophilic. Non-eosinophilic granulomatous prostatitis occurs secondary to extravasated prostatic fluid, which causes a prostate tissue response. Eosinophilic granulomatous prostatitis (usually more severe) is secondary to an allergic response of the prostate to an unknown antigen. Viral, fungal or bacterial infections; use of the Bacillus Calmette-Guerin (BCG) vaccine; malakoplakia; and systemic granulomatous disease can all cause granulomatous prostatitis. More than 2/3 of cases have no specific cause that is found.[6]

Patients with acute granulomatous prostatitis can present with fever; chills; hematuria; obstructive, irritative voiding symptoms; and/or urinary retention. Patients with chronic granulomatous prostatitis (secondary to BCG) are usually asymptomatic.

DRE will reveal a hard, indurated, fixed prostate. Diagnosis confirmation requires prostate biopsy. UA and urine culture are non-revealing. A complete blood count will typically reveal a leukocytosis and marked eosinophilia (in eosinophilic granulomatous prostatitis).

The treatment for acute granulomatous prostatitis includes antibiotic therapy, corticosteroids and temporary bladder drainage. If patients do not respond to medical treatment, transurethral resection of the prostate (TURP) may be necessary to relieve any obstruction. Asymptomatic chronic granulomatous prostatitis does not typically require treatment.

## NONBACTERIAL CHRONIC PROSTATITIS/ CHRONIC PELVIC PAIN SYNDROME

Both chronic nonbacterial prostatitis and chronic pelvic pain syndrome feature a combination of inflammatory, immunologic, endocrine, muscular, neuropathic and physiologic symptoms.[8]

The most common presenting symptoms include chronic perineal pain, suprapubic pain, pelvic pain, pain during or after ejaculation, testicular pain, groin pain, and low-back pain. Chronic pelvic pain syndrome is often aggravated by depression, anxiety and stress. The diagnosis is usually one of exclusion because the cause of chronic pelvic pain syndrome/nonbacterial chronic prostatitis is unknown.[9]

Nonbacterial chronic prostatitis and chronic pelvic pain syndrome differ in the laboratory examination. The laboratory examination in chronic nonbacterial prostatitis typically reveals increased leukocytes in expressed prostatic secretions. Cultures of urine and prostatic secretions are often negative. In chronic pelvic pain syndrome, laboratory examination often reveals negative leukocytes and negative cultures of expressed prostate secretions.

Treatment is dependent on presenting symptoms. Surgery is not recommended in these patients.[10,11]

### TABLE 1:

Treatment of nonbacterial chronic prostatitis and chronic pelvic pain syndrome

| PRESENTING SYMPTOM | TREATMENT |
|---|---|
| **Voiding Symptoms** | Alpha blockers (tamsulosin, alfuzosin, sildosin) |
| **Psychosocial** | Behavioral therapy, antidepressants, anxiolytics, referral to mental health specialist |
| **Neuropathic Pain** | Gabapentin, amitriptyline, referral to pain management |
| **Pelvic Floor Muscle Dysfunction** | Diazepam, pelvic floor physical therapy (Kegel exercises), pelvic shock wave lithotripsy, heat therapy |
| **Sexual Dysfunction with Pain** | Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) |

## BENIGN PROSTATIC HYPERTROPHY

The incidence of benign prostatic hypertrophy (BPH)—the most common benign tumor in men—is related to age. The prevalence of the tumor increases with age, with a 90% prevalence in men 80 years or older. Risk factors are poorly understood, but genetic predisposition has been suggested.[12]

Patients can present with obstructive urinary symptoms including hesitancy, decreased force/caliber of stream, sensation of incomplete bladder emptying, double voiding, straining to urinate and post-void dribbling. Patients may also present with irritative symptoms including urgency, frequency or nocturia.

Physical examination should comprise a DRE and a focused neurologic evaluation. DRE often reveals smooth, firm, elastic enlargement of the prostate. Prostate size does not have a known correlation with the degree of symptoms. Elevated prostate specific antigen (PSA) can be secondary to BPH, but malignancy should also remain on the differential.

Laboratory testing should include UA to rule out infection. A PSA should also be obtained, especially in those with a life expectancy of more than 10 years. Note that there is overlap between levels seen in BPH and prostate cancer.

Imaging with CT or US of the kidney is recommended if there is concurrent urinary tract disease or complications, such as hematuria, urinary tract infection, chronic kidney disease or nephrolithiasis. Surgery is often recommended in the setting of these complications. Imaging should not routinely be ordered and should be considered on a case-by-case basis. Cystoscopy is also not routinely recommended but may be helpful in those seeking invasive therapy.

Patients can be treated with medical therapy (alpha blockers, 5-alpha-reductase inhibitors, phosphodiesterase-5 inhibitors, combination therapy, phytotherapy), surgical intervention (TURP, transurethral incision of the prostate, simple prostatectomy) or minimally invasive therapy (laser therapy, transurethral electrovaporization of the prostate, hyperthermia, implant to open prostatic urethra or water vapor thermal therapy).

## PROSTATE CANCER

Prostate cancer is the second most common cancer in men worldwide, with more than 31,000 men dying from the illness annually, as well as the second-highest cause of death due to malignancy.[13] In the United States, there is a 11% lifetime risk of being diagnosed with prostate cancer and a 2.5% lifetime risk of dying from prostate cancer.[14] There have been significant improvements in mortality in recent years due to screening, but this comes at the cost of overdiagnosis and overtreatment. Some of the risk factors for prostate cancer include advanced age, African American race, family history, smoking and obesity. BPH is not a known risk factor.

Screening for prostate cancer includes DRE, PSA testing and/or transrectal US. Prostate cancer detected through DRE is often in an advanced state. Recommendations for prostate cancer screening vary across different organizations. However, shared decision making with the patient is agreed upon in most guidelines.

Patients with early-stage prostate cancer are often asymptomatic. Advanced prostate cancer can present with weight loss and loss of appetite. Obstructive or irritative voiding symptoms, including hematuria from local growth of the tumor into the urethra or bladder, may also occur. Metastatic disease into the vertebral column may present with bone pain. If cord compression is present, the patient may have paresthesia, weakness of the lower extremities, and fecal or urinary incontinence.

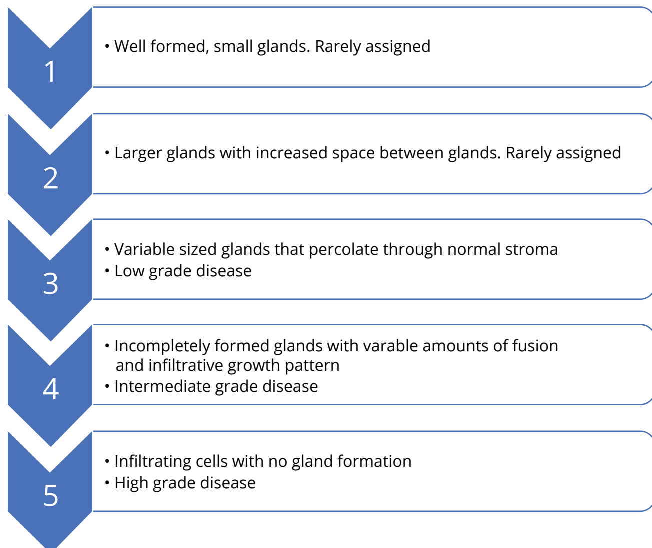
Physical examination may reveal induration and nodularity of the prostate on DRE; however, a negative DRE does not rule out prostate cancer. Locally advanced disease may present with lymphadenopathy, lymphedema of the lower extremities and a hyperreflexic bulbocavernosus reflex.

Laboratory examination not only may include an elevated PSA but also may reveal azotemia from bilateral ureteral obstruction due to extension into the trigone of the bladder or retroperitoneal adenopathy. Anemia can be present in cases of metastatic disease along with increased alkaline phosphatase in the setting of metastasis to the bone.

Prostate biopsy should be considered using joint decision making in men with abnormal DRE and/or elevated PSA. More than 95% of prostate cancers are adenocarcinomas. Based on the glandular architecture, a grade is assigned to the primary and secondary patterns in the specimen.[15]

FIGURE 1:

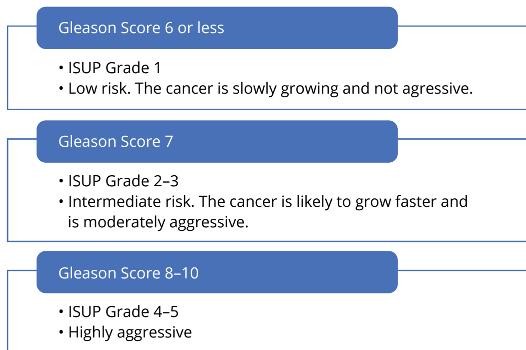
Gleason grades explained[13]




The Gleason score is obtained by adding the two grades together, from which an International Society of Urological Pathology (ISUP) grade group can be assigned to stratify risk.[16,17]

FIGURE 2:

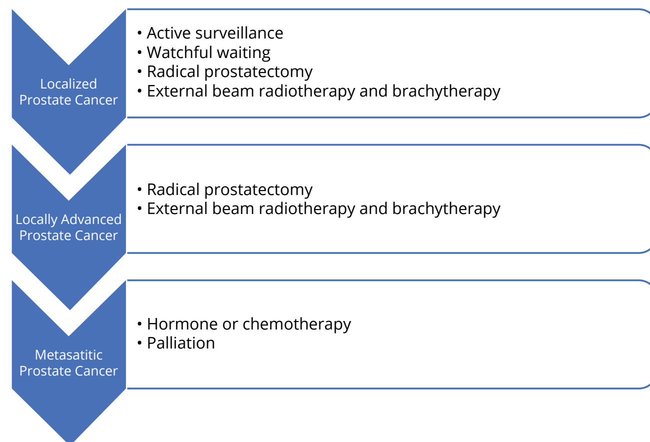
Gleason score and ISUP grade group[14]




There are multiple options for the treatment of prostate cancer based on staging, including watchful waiting, active surveillance, radical prostatectomy, external beam radiotherapy/brachytherapy and chemotherapy. Watchful waiting is a less aggressive form of monitoring cancer without treating it. It differs from active surveillance in that it does not involve frequent biopsies and testing. Active surveillance may require patients to have many biopsies to track cancer growth but avoids overtreatment and is non-invasive and non-radical. Curative treatment can be given if there are signs of disease progression. During the period of active surveillance, metastatic cancer can develop, removing the option for curative treatment. Watchful waiting also avoids overtreatment and is non-invasive; however, there is an increased risk of death due to prostate cancer, and metastatic cancer may develop in the interim. Radical prostatectomy aims to cure or control disease; however, approximately 20% of patients have residual tumors and around half of those patients will develop biochemical or clinical recurrence of prostate cancer. In addition, side effects of the procedure include infertility, erectile dysfunction and urinary incontinence. External beam radiotherapy and brachytherapy aim to cure or control disease. However, side effects include erectile dysfunction, urinary symptoms, bowel problems and infertility.[17]

FIGURE 3:

Treatment options for prostate cancer[15]




## OSTEOPATHIC PRINCIPLES

The prostate is innervated from the prostatic plexus of the autonomic nervous system, which arises from the inferior hypogastric plexus. The preganglionic efferent sympathetic fibers of this plexus are derived from T10 to L2 spinal levels. The parasympathetic preganglionic fibers originate from S2 to S4. Somatic dysfunctions of the prostate are most often found in the T12–L1 region. Dysfunctions of the pubic symphysis and congestion of the ischiorectal fossa are also likely. Any somatic dysfunctions in this area should be treated to relieve or prevent discomfort secondary to prostate disease.[18]

## SUMMARY

Management of symptoms and diagnoses of the prostate is an important aspect of primary care. In order to diagnose diseases of the prostate, the physician must start with a thorough history and physical examination. The laboratory examination, imaging and biopsy will help further narrow the differential. Treatment should be guided by history, clinical examination and lab results in joint decision making with the patient.

## TABLE 2:

Summary of prostate diseases

| | SYMPTOMS | PHYSICAL | LABS/IMAGING | TREATMENT |
|---|---|---|---|---|
| **Acute Bacterial Prostatitis** | Fever<br><br>Irritative voiding symptoms, urinary retention<br><br>Perineal, sacral, suprapubic pain | DRE: Exquisite tenderness | CBC: Leukocytosis with left shift<br><br>UA: Pyuria, bacteriuria, hematuria<br><br>UC: pos, MCC G-rods, pseudomonas | IV antibiotics pending cultures<br><br>Oral antibiotics 4–6 weeks<br><br>Straight catheter |
| **Prostate Abscess** | Recurring symptoms from acute bacterial prostatitis not responsive to antibiotics | DRE: Tenderness and swelling of prostate | Transrectal ultrasound<br><br>Pelvic CT | Abscess drainage |
| **Chronic Bacterial Prostatitis** | Varying degrees of voiding symptoms<br><br>Urethral pain<br><br>Obstructive urinary symptoms | Physical exam unremarkable<br><br>DRE: Normal, boggy, indurated | UA: Normal<br><br>UC: Positive<br><br>Post-prostatic massage voided urine: Increased leukocytes in urine | If febrile, treat like acute bacterial prostatitis<br><br>May require multiple courses of antibiotics<br><br>Symptom relief with anti-inflammatories, sitz baths and alpha blockers |
| **Acute Granulomatous Prostatitis (AGP) and Chronic Granulomatous Prostatitis (CGP)**<br><br>**Subtypes: Eosinophilic and Non-Eosinophilic)** | **AGP**: Fever, chills, hematuria, obstructive and irritative urinary symptoms (eosinophilic is more severe the non-eosinophilic)<br><br>**CGP**: Asymptomatic | DRE: Hard, indurated, fixed prostate | CBC: Leukocytosis and marked eosinophilia (in eosinophilic granulomatous prostatitis)<br><br>UA: Normal<br><br>UC: Negative<br><br>Prostate biopsy | **AGP**: Antibiotic therapy, corticosteroids, bladder drainage, TURP<br><br>**CGP**: No treatment necessary |
| **Nonbacterial Chronic Prostatitis (NBCP)/ Chronic Pelvic Pain Syndrome (CPPS)** | Chronic perineal, suprapubic, pelvic, testicular, groin or low back pain<br><br>Pain during or after ejaculation<br><br>Aggravated by psychosocial factors | Unrevealing | **NBCP**: pos WBC and negative culture of expressed prostate<br><br>**CPPS**: neg WBC and neg culture of expressed prostate<br><br>Both have neg post-prostatic massage urine cultures | See Table 1 |
| **Benign Prostatic Hypertrophy** | Obstructive and irritative urinary symptoms | DRE: Smooth, firm, elastic enlargement of prostate | UA: To rule out UTI, PSA<br><br>CT or renal ultrasound if UTI or complication | **Medical Therapy**:<br><br>Alpha blockers, 5-alpha-reductase inhibitors, phosphodiesterase-5 inhibitors<br><br>**Invasive Therapy**: TURP, simple prostatectomy, etc. |
| **Prostate Cancer** | Early stage: asymptomatic<br><br>Advanced prostate cancer: obstructive or irritative voiding symptoms, weight loss, loss of appetite<br><br>Metastatic disease: bone pain | DRE: Induration and nodularity of prostate. Negative DRE does not rule out prostate cancer<br><br>Locally advanced disease with lymphadenopathy/ lymphedema | Elevated PSA, azotemia, anemia, elevated alkaline phosphatase<br><br>Prostate biopsy (MCC adenocarcinoma) | See Figure 3 |

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REVIEW ARTICLE

# EMERGING NON-INVASIVE NEUROPLASTIC-TARGETING THERAPIES FOR SUBSTANCE USE DISORDER TREATMENT

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**KEYWORDS:**

Addiction

Dopamine

Neuroplasticity

Opioid

Substance use disorder

**Context:** America is in the midst of a substance use disorder (SUD) epidemic, which has only worsened in the current COVID-19 pandemic. SUD is a public health crisis that affects an ever-increasing proportion of the population and is extraordinarily difficult to treat. Misused substances induce neuroplastic changes that not only predispose individuals to relapse but also persist after completing treatment recommendations.

**Objective:** To establish the phenomenon of neuroplasticity in relation to SUD and summarize non-invasive neuroplastic therapies designed to return the brain to its pre-dependency state.

**Methods:** On October 29, 2019, the search term "neuroplasticity addiction" was entered into PubMed. Articles were selected based on description of neuroplastic changes occurring in SUD and treatment modalities that foster neuroplastic improvements for SUD treatment.

**Results:** 1241 articles were excluded based on irrelevance to the specific topic, language or redundancy. 41 articles met inclusion criteria, with 18 illustrating neuroplastic effects induced by SUD and 23 describing therapeutic interventions.

**Conclusions:** SUD induces neuroplastic changes that predispose an individual to relapse and persist after completing SUD recommendations. Transcranial magnetic stimulation, environmental enrichment and exercise are shown to affect altered brain composition and reduce SUD-related negative behavior, while motor training appears to block neurophysiological changes normally caused by substance use. This illustrates that therapies targeting neuroplastic changes reduce adverse behaviors in those with SUD. The implementation of these modalities with current standard-of-care treatment may increase treatment success. Additional research into these modalities and their potential to enhance current treatments is warranted.

## BACKGROUND

Substance use disorder (SUD) is a devastating disease that is both common and exceedingly difficult to treat. The American Psychiatric Association DSM-5 defines SUD as substance use in association with at least 2 of 11 criteria including impaired control, social impairment, risky use and pharmacologic indicators (withdrawal and tolerance).[1] In 2017, nearly 20 million Americans aged 12 or older (10% of the population) suffered from SUD, costing the United States $740 billion in health care, crime and decreased work productivity annually.[2]

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SUD treatment programs generally employ a combination of medication-assisted withdrawal management and detoxification, medication-assisted treatment, and psychotherapy.[3] Medication-assisted withdrawal management uses drugs, such as anxiolytics, antiepileptics, beta blockers,[4] antiemetics, antidiarrheals and anti-inflammatories, for withdrawal symptom relief. Medication-assisted treatment relies on prescription drugs that act on the same targets in the brain as the substance that was being abused to relieve cravings,[3] allowing the patient and their healthcare provider to manage dosing in a safer manner. Psychotherapy consists of regular visits with behavioral health counselors in individual or group settings with the goal of managing the exposure to environments, situations and emotional states that may contribute to SUD.[3] While the above modalities address different aspects of SUD, the return-to-use rate (even with treatment) remains 40%–60%,[5] illustrating the potential for improvement in the treatment of SUD.

In the field of SUD treatment, focus is increasing on the structural and functional changes that occur in the brain during substance use—termed neuroplasticity.[6] Neuroplastic changes influence an individual's drive for continued substance use and may increase their likelihood of return to use after years of abstinence.[6] Structural change that defines neuroplasticity occurs throughout the cortex,[7] with dopamine acting as a catalyst to increase the production of new synapses.[8] As certain substances can cause large increases in dopamine release,[9] it follows that substance use has the capacity to induce neuroplastic changes. This dopamine release occurs via the increase of dopaminergic transmission from ventral tegmental area neurons into the striatum, the location of the nucleus accumbens.[8] The nucleus accumbens is casually referred to as the "pleasure center" of the brain. The significance of dopamine in this context is its ability to prioritize memories. Dopamine levels increase and produce pleasure if an action yields a reward or decrease and produce less pleasure if no reward is perceived.[10] Thus, certain substances may cause SUD not only because they are pleasurable (note that nicotine is not euphorigenic), but also due to the coupling of the experience of taking the substance with a large dopamine release, which imprints the memory as highly salient.[4]

Mice that were administered a single dose of cocaine exhibited long-term potentiation, or synaptic strengthening, of the "AMPA-receptor-mediated currents at excitatory synapses onto dopamine cells in the ventral tegmental area" that lasted for 5 days.[11] Similar studies using amphetamine, morphine, nicotine, ethanol[12] and benzodiazepines[13] revealed nearly identical neural changes. Notably, these substances have differing mechanisms of action,[14] supporting the theory that neuroplastic changes induced by these substances are related to their addictive nature and not their mechanisms of action. Furthermore, non-addictive psychoactive drugs, such as fluoxetine and carbamazepine, do not appear to cause long-term potentiation in ventral tegmental area AMPA receptors.[12] It also appears that the extended amygdala, which influences the hypothalamic-pituitary-adrenal (HPA) axis, a key component in the stress response, is altered with chronic substance use.[15] Researchers believe elevated levels of a FKBP5 protein in the extended amygdala, as seen in rats following chronic cocaine use,[15] may lead to a loss of negative feedback yielding overactivity of the HPA axis,[16] resulting in more severe negative affective symptoms of cocaine withdrawal.[15] This may lead to an increased drive for relapse.[15]

While these studies illustrate the nature of the brain's response to substances of abuse, others demonstrate how long these effects last. Rats exposed to a single dose of nicotine displayed upregulation of AMPA receptors 72 hours after administration.[17] In a different study, rats that self-administered cocaine for 14 days displayed neuroplastic changes after 3 months of abstinence.[18] Similar results were seen in humans, where chronic cocaine use sustained substance-induced neuroplastic changes after 4 months of abstinence[19] and chronic alcohol use showed persistent neuroplastic changes at 11 weeks post-detoxification.[20] These structural changes are significant, as they may predispose an individual to relapse.[21] These studies establish that substances of abuse lead to increased dopamine release onto the nucleus accumbens and increase the production of synapses. These dopamine-catalyzed[8] changes alter the wiring of the brain and may last for an extended period.[20] Moreover, they prime an individual to be more likely to use these substances[21] even after prolonged abstinence.[20] Thus, to achieve the highest success in the treatment of SUD, patients must not only detoxify and have their withdrawal symptoms managed, but also receive treatment to restore their brain to a pre-substance use state. The motivation for this paper is to explore non-invasive, nonpharmacological treatments that may reset the brain's composition to the pre-substance use state with a goal of improving treatment success.

## METHODS

In this narrative review, we aim to establish the phenomenon of neuroplasticity in relation to SUD and summarize emerging non-invasive therapies that may alter SUD-induced neuroplastic changes with the goal of returning the brain to its pre-addicted state. On October 29, 2019, the search term "neuroplasticity addiction" was entered into PubMed. Inclusion criteria consisted of articles that illustrated neuroplastic changes occurring in SUD and studies that explored potential therapeutic interventions yielding neuroplastic improvements in the context of SUD. Exclusion criteria included articles not written in English, irrelevance to the topics of neuroplastic changes induced by SUD and therapies to address these neuroplastic changes, and redundancy to selected studies. Furthermore, studies evaluating therapeutic interventions that were not directly transferable to human application were excluded.

## RESULTS

The results of this database search yielded 1282 articles. After applying the aforementioned exclusion criteria, 41 articles were selected. Of that total, 18 articles illustrated neuroplastic effects induced by SUD, and 23 of the articles evaluated various therapeutic interventions.

## DISCUSSION

### Promising non-invasive neuroplastic treatment modalities

#### TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a therapy in which a coil placed on the scalp generates a magnetic field directed at specific locations of brain tissue to induce intracranial currents.[22] The induction of energy both excites and inhibits neurons and axons, with repetitive TMS (rTMS) producing a neuroplastic effect that persists following stimulation.[23] These neuroplastic changes may modulate behaviors that incite drug cravings and relapse.[22]

In a trial studying rTMS and cocaine use disorder, rTMS was targeted to the dorsolateral prefrontal cortex to attempt to reduce addiction and craving behavior.[24] Individuals received 8 rTMS sessions over 29 days, resulting in a significant decrease in cocaine use and craving scores.[24] To assess rTMS in the context of alcohol use disorder, individuals who fit the DSM-5 criteria for alcohol use disorder received 10 sessions of rTMS targeted

to the medial prefrontal cortex.[25] It was observed that rTMS yielded a decrease in the mean number of alcoholic drinks per day. Decreased craving levels persisted for one month following treatment.[25] The most compelling evidence for rTMS regarding SUD is seen in its treatment of nicotine use disorder. Smokers who consumed 20 cigarettes per day and were previously unsuccessful in treatment received rTMS directed to the lateral prefrontal cortex and insula for 13 sessions.[26] This treatment design resulted in significant decreases in nicotine dependence and cigarette use, with an abstinence rate of 44% following treatment and 33% at 6 months post-treatment.[26]

While the specific mechanism of TMS varies with the substance of abuse it is treating (as different areas of the brain are targeted for different substances of abuse treated), it is theorized that rTMS modulates SUD-altered dopamine release and homeostasis.[24–27] rTMS has been shown to increase dopamine levels in the mesolimbic and mesostriatal pathways[26] and in the caudate nucleus,[27] mimicking the dopamine release induced by substances of abuse.[28] This may prompt the uncoupling of the conditioned response of drug cue and drug use as summarized above. However, despite the successes observed, it must be noted that there are concerns about potential complications from microstructural changes in ferrous-containing structures[29] and that more research is needed.

### ENVIRONMENTAL ENRICHMENT

Environmental enrichment (EE) consists of exposing subjects to stimulating environments[30] and has been shown to produce favorable changes in the brain in the setting of compulsive substance use.[31,32] Regarding EE and primates, a study utilized environments containing large, complex cages with straw nests, vegetation, branches and many unique objects that allowed for foraging, including “branches with holes filled with dried fruit and live worms,” in contrast to a control environment of plain cages with no enriching stimuli.[33]

In a study examining cocaine use disorder and EE, mice were exposed to cocaine, then housed in either an enriched environment or a standard environment without access to cocaine.[31] After 30 days in the enriched environment, dependency-related behaviors were eliminated (ie, cues and environments that previously induced cocaine use no longer compelled the mice to self-administer).[31] A similar study investigated EE’s effects on methamphetamine, heroin and nicotine use disorder.[32] Across all 3 substances, drug-seeking behavior was decreased following EE, with no change in drug-seeking behavior in the control environment.[32]

The mechanisms for EE’s effects on SUD and neuroplasticity remain up for debate.[32] Multiple studies have reported that EE may increase dendritic size, number of dendritic spines[33,34] and dendritic complexity in the hippocampus and prefrontal cortex of subjects, as well as increase the levels of proteins such as GluR2, a subunit of the AMPA receptor.[33] As dendritic spines are the location of excitatory synapses,[35] the combination of an increase in dendritic spines and synaptic receptor subunits has led researchers to conclude that EE induces the formation of new excitatory synapses.[31] Additionally, research has shown that EE increases the rate of destruction of dendritic spines.[34] As the receptors modulated by EE are the same receptors altered by dependency (AMPA receptors), it is possible that through the effects of EE building up new dendritic trees while pruning others, the synapses previously altered by dependency are replaced with new, “nondependent” synapses. In other words, individuals in EE-related situations may make new memories quicker while leaving behind their dependency-associated memories. One could argue that much of standard behavioral therapy, including vocational training and 12-step programs that expand social networks, is a form of EE and works in part because of its neuroplastic changes. More research is needed to understand what an expanded emphasis on human EE would include and accomplish; some considerations may include utilizing meditation, art and music therapy and improving general life conditions.[32]

### MOTOR-SKILL LEARNING

Motor-skill learning is the increased accuracy of specific movements with repetition.[36] It has been explored in the context of SUD treatment because motor-skill learning rewires the brain in the same manner as nicotine use.[37] Smoking tobacco induces neuroplastic changes in the dorsomedial striatum and nucleus accumbens core in the acute smoking phase.[37] During withdrawal the dorsolateral striatum, nucleus accumbens shell and central nucleus of the amygdala are affected.[37] The potential utility of motor-skill learning in the treatment of nicotine use disorder is the prevention of rewiring in the acute smoking phase and, most importantly for nicotine use disorder treatment, during the withdrawal phase.

To test the effect of motor-skill learning on neuroplastic changes induced by nicotine, researchers administered nicotine to rats over 15 sessions in a three-week period, followed by 5 days of rotarod training.[37] A rotarod is a device that contains a horizontal, rotating rod that may be accelerated.[38] The mouse must learn to walk on the moving rod to remain upright.[38] To determine neuroplastic changes and functionality, researchers performed post-mortem electrophysiological field potential recordings.[37] It was found that training on the rotarod extinguished neurophysiological changes induced by nicotine use in the acute phase, and blocked neurophysiological rewiring that occurs during the withdrawal phase.[37] Intriguingly, rotarod training restored plasticity to the endocannabinoid system,[37] a lipid signaling system[39] that has been theorized to contribute to SUD in general.[40] This finding is significant as it broadens the potential utility of motor-skill learning from the treatment of nicotine use disorder to the treatment of other SUDs.

### EXERCISE

With the knowledge that individuals may become addicted to exercise itself,[41] it is not surprising that both exercise and substances of abuse fire the same reward pathways and alter the same neural substrates in the brain.[42] These findings led to the exploration of exercise as a treatment for SUD, with encouraging results.

In a study evaluating exercise's effect on cocaine-seeking behavior, rats were trained to self-administer cocaine, exposed to 10 days of free access to the substance, then restricted from cocaine for 14 days.[43] During the abstinent period, rats were given access to a running wheel for 2 hours daily.[43] Researchers discovered that prefrontal cortex levels of phosphorylated extracellular signal-regulated kinase (pERK), a biomarker positively correlated with the development of cocaine cravings,[44] significantly decreased in the exercise group and concluded that exercise may halt prefrontal cortex neuroadaptations that develop in the cocaine abstinence period.[43] Conflicting results were found in a trial that evaluated ethanol use and running.[45] Rats maintained high ethanol intake for 5 weeks, then made abstinent.[45] Rats with access to a running wheel after 1 or 2 weeks of ethanol withdrawal had an increased craving and consumption of ethanol following exercise, while rats that had access to the running wheel only after week 4 of ethanol withdrawal did not show increased craving and consumption.[45] This study brought to light the potentially complex nature of exercise and SUD treatment and possible timing sensitivities.

A study evaluating the effects of exercise on methamphetamine-related cravings in humans subjected methamphetamine users undergoing detoxification to three 30-minute sessions of exercise for 12 weeks. Craving levels were evaluated every 3 weeks. The exercise group began to experience reduced craving levels after 6 weeks of exercise, which persisted to the end of the study.[46] Nicotine use disorder and exercise have also been evaluated with similar success. Smokers assigned to a smoking cessation program were fitted with a pedometer. These individuals were recommended to increase their steps by 10% biweekly, with a goal of reaching 10,000 steps per day. After 24 weeks it was found that increases in physical activity were an accurate predictor of abstinence, while smoking relapse was associated with a decrease in exercise.[47]

The mechanism for exercise improving SUD treatment outcomes is a subject of debate. Knowledge that both exercise and substances of abuse activate the same reward pathways[42] may provide an answer. Prolonged substance use results in increased

## TABLE 1:

Comparison of neuroplastic therapies used in the treatment of various substance use disorders

| NEUROPLASTIC THERAPIES | SUBSTANCES | OUTCOMES | STATISTICAL SIGNIFICANCE (P VALUE AND N) |
|---|---|---|---|
| **Transcranial Magnetic Stimulation** | Cocaine[24] | Humans. Significantly decreased levels of craving. | *P*=.038<br>n=16 |
| | Alcohol[25] | Humans. Significantly decreased levels of craving and mean number of drinks per day. | *P*=.0315, *P*=.021<br>n=9 |
| | Tobacco[26] | Humans. Achieved an abstinence rate of 44% at end of treatment and 33% 6 months post-treatment. | *P*=.039, *P*=.0026<br>n=32 |
| **Environmental Enrichment** | Cocaine[31] | Mice. Substance use disorder–related behaviors eliminated after 30 days of environmental enrichment. | *P* <.0001<br>n=64 |
| | Methamphetamine, heroin, nicotine[32] | Rats. In contrast to standard environments, exposure to enriched environments reduced drug-seeking behavior. | *P*=.0062<br>n=unavailable |
| **Motor Training** | Nicotine[37] | Mice. Training of mice on a rotarod following the establishment of nicotine dependence extinguished nicotine-induced striatal neuroadaptations and restored synaptic plasticity. | *P*=.03, *P*<.01<br>n=16 |
| **Exercise** | Cocaine[43] | Rats. Wheel-running reduced cocaine-seeking in rats who were previously exposed to cocaine. | *P*=.015<br>N=21 |
| | Ethanol[45] | Rats. Wheel-running during 1 or 2 but not 4 weeks of ethanol withdrawal increased ethanol intake and preference. | *P*<.01, *P*<.01<br>Wk1: n=8<br>Wk2: n=6<br>Wk3: n=8 |
| | Methamphetamine[46] | Humans. Reduced methamphetamine craving levels and increased behavioral inhibitory control after 6 weeks of the exercise program. | *P*<.01<br>n=25 |
| | Tobacco[47] | Humans. Increased moderate-to-vigorous physical activity predicted sustained smoking abstinence at 24 weeks and decreased perceived difficulty staying smoke-free. | *P*=.028 (sustained smoking abstinence) and *P*=.038 (decreased perceived difficulty remaining smoke-free)<br>n=163 |

dopamine signaling,[48] a component of the reward pathway.[49] As dopamine signaling results in increased levels of glutamate[50] (produced from glutamine[51]), the finding that striatal glutamine levels are decreased after running[52] suggests exercise as offsetting the increased sensitivity of dopamine signaling. This is in addition to exercise's effect on the extracellular signal-regulated kinase system.[43] Exercise also promotes increased executive control.[53] This may point toward exercise as reversing the damaging effects of substances of abuse.

## CONCLUSION

While many advancements have been made in the field of addiction medicine, the substance use epidemic is far from over, and there is a continued call for the exploration of additional therapeutic modalities. To ensure greater success, further research needs to be done on the neuroplastic changes that occur with substance misuse as well as changes that occur during the recovery state. SUD treatment should include therapies that are targeted at returning the brain to its pre-dependent state. While the non-invasive neuroplastic-directed therapies summarized above are in the infancy of their exploration, they hold promise. In the subjects studied in each of the studies reviewed, many of the nontraditional therapeutic approaches resulted in not just observable changes in behavior, but also measurable, objective changes in brain signaling. Interventions like enriching a patient's environment, exercise and mindfulness training are all consistent with the holistic approach of osteopathic medicine. These interventions deserve to be studied further, with the goal of complementing current SUD treatment practices.

### AUTHOR DISCLOSURE(S)

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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REVIEW ARTICLE

# GLAUCOMA: A REVIEW FOR THE FAMILY PHYSICIAN

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**KEYWORDS:**

Angle-closure glaucoma

Glaucoma

Intraocular pressure

Normal tension glaucoma

Primary open-angle glaucoma

Retinal nerve fiber layer

Glaucoma is an insidious disease process that causes damage to the optic nerve head and retinal nerve fiber layer, resulting in progressive vision loss. Multiple factors play a role in its pathophysiology, but intraocular pressure is a significant yet modifiable risk factor and therefore is targeted by all current treatment modalities. Its high prevalence and potential for irreversible damage necessitate an understanding of the condition by primary care physicians, who will undoubtedly be managing conditions and medications that can influence glaucomatous progression. This article will explore the pathophysiologic basis of glaucoma, discuss some of the common subtypes and highlight important clinical considerations.

## INTRODUCTION

Glaucoma is one of the foremost causes of vision loss globally, with a staggering 111.8 million people worldwide projected to be affected by it in 2040.[1] In the United States, glaucoma is second only to cataracts among the leading causes of vision loss.[2,3] Unlike cataracts, the damage incurred from glaucoma is irreversible and cannot be improved with surgery, although surgery may limit further damage. Given the indolent nature of the disease, there is often substantial damage present before a patient is aware of vision changes. The retinal nerve fiber layer (RNFL) may be 28%–50% damaged before a visual field defect is documented.[4,5] Therefore, timely diagnosis and treatment are imperative.

Although there are various forms of glaucoma, they are unified and defined by characteristic changes to the optic nerve head (ONH) and RNFL.[6] Such changes clinically manifest as a gradual reduction in peripheral vision, which can progress to central vision loss in severe cases. Due to the multifactorial nature of the disease, its pathogenesis is influenced by a myriad of common conditions, medications and other risk factors. As family physicians are often the ones managing these conditions and medications, they play a vital role in caring for glaucoma patients. In addition to being familiar with factors that hasten glaucomatous progression, it is in the patient's best interest for physicians to remain cognizant of systemic effects of various glaucoma medications and their potential impact on comorbidities.

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## CLASSIC PRESENTATION

In the most common type of glaucoma—primary open-angle glaucoma—the disease course is slowly progressive and painless. Patients undergo a gradual reduction in peripheral vision bilaterally that is usually imperceptible until later stages. In the primary care setting, this may be detected during a patient's physical exam by testing confrontation visual fields. Central vision is often preserved, thus visual acuity (as measured with a Snellen chart) may appear to be unchanged. Patients frequently have elevated intraocular pressure, although this is not a prerequisite feature for the diagnosis of glaucoma. On fundoscopic exam, one should expect to see pathological cupping of the optic disc, characterized by an increased cup-to-disc ratio.[6]

## PATHOPHYSIOLOGY

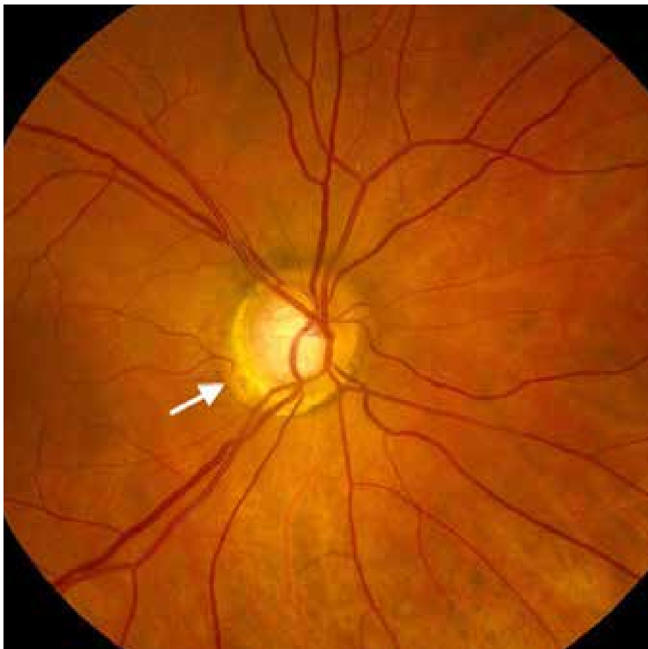
Despite significant advances in the understanding and treatment of glaucoma, its pathophysiology has yet to be fully elucidated. This has given rise to several theories, two of which have received more attention than others: the mechanical theory, which pertains to deformation of retinal nerve fibers as they traverse the lamina cribrosa, and the vascular theory, which pertains to alterations in optic nerve blood supply. It is probable that both scenarios play a role in the disease process, together inducing apoptosis of retinal ganglion cells by disrupting axoplasmic transport of nutrients and waste as well as by causing ischemia.[7,8] An important, well-established contributor is elevated intraocular pressure (IOP). IOP is dependent upon the dynamics of aqueous humor in the eye.[9]

Within the posterior chamber of the eye, the ciliary body produces aqueous humor, a fluid that nourishes avascular structures (eg, lens and cornea) and contributes to the structural integrity of the eye.[9] Under normal conditions, aqueous humor flows from the posterior chamber to the anterior chamber via the pupil, eventually reaching the iridocorneal angle. From here, 90% of aqueous humor traverses the trabecular meshwork to reach Schlemm's canal, where episcleral veins return the fluid to circulation. The remaining aqueous exits the eye primarily through the uveoscleral pathway, aided by the venous system of the ciliary body, choroid and sclera.[6] Secretion and outflow of aqueous humor are modulated through various autonomic receptors and structural factors, ultimately striking a balance that determines IOP. If there is a disturbance in secretion exceeding outflow, the resultant elevation in IOP can predispose the ciliary body to glaucomatous damage.

During fundoscopic examination, glaucomatous damage is evidenced by an increased cup-to-disc ratio that continues to increase as more nerve fibers are lost (Figure 1). Peripapillary atrophy may be noted adjacent to the optic disc (Figure 1). As shown in Figure 2, a healthy optic nerve is characterized by a normal cup-to-disc ratio. In glaucoma patients, additional features that may be present include disc hemorrhages, bayoneting of vessels and notching of the neuro-retinal rim (Figure 3).[6] A disc hemorrhage, also known as a Drance hemorrhage, is suggestive of inadequate IOP control or disease progression when seen in a glaucoma patient.[9]

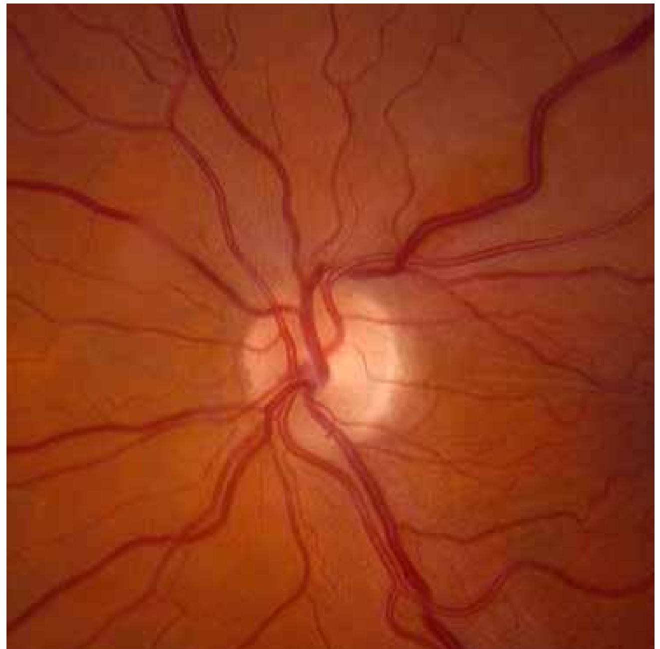
### FIGURE 1:

Increased cup-to-disc ratio with adjacent peripapillary atrophy (arrow)



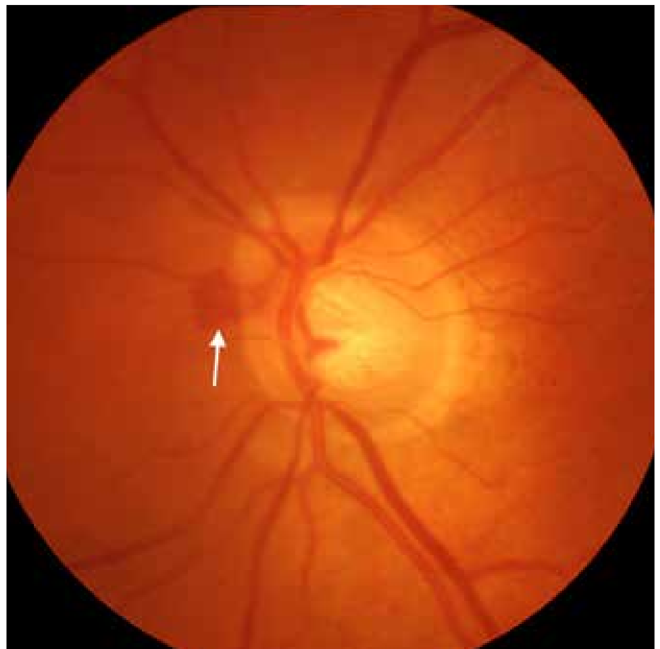
### FIGURE 2:

Healthy optic nerve with a normal cup-to-disc ratio



### FIGURE 3:

Disc hemorrhage, also known as a Drance hemorrhage (arrow)

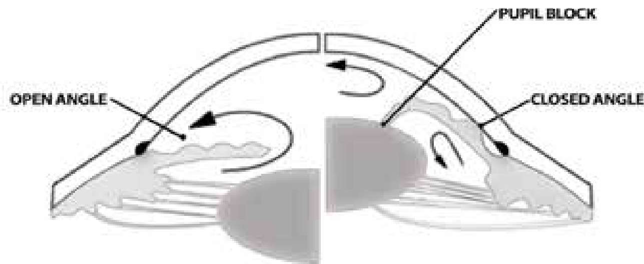


## COMMON TYPES

Glaucoma may be broadly categorized as open-angle glaucoma or angle-closure glaucoma, depending upon the openness of the iridocorneal angle (Figure 4). Further distinction may be made if the process is determined to be idiopathic (primary) or attributable to an identifiable etiology (secondary).[10]

FIGURE 4:

Aqueous flow from posterior to anterior chambers. The cross-section on the right depicts the pupillary block mechanism of angle closure. Reproduced with permission from *The Indian Optician*, September–October 2016.




**Primary open-angle glaucoma (POAG)** is the most common form of glaucoma in the United States.[11] Some estimate the number of Americans with POAG may increase from 52.7 million in 2020 to 79.8 million in 2040.[1] As the name suggests, the iridocorneal angle in the anterior chamber appears open; however, aqueous outflow is nonetheless impeded by debris that obstructs the trabecular meshwork. As intraocular pressure rises due to impaired drainage, damage to the optic nerve ensues.

Beyond elevated IOP, there are additional risk factors that should alert the primary care physician to patients who may be asymptomatic but at higher risk of developing POAG. Advanced age is a well-established risk factor, particularly beyond the fifth decade of life.[9,12] Race plays a role, as prevalence is roughly three times higher in African American and Hispanic patients than in white patients.[13] Family history is another factor, given that first-degree relatives of those with POAG are much more likely to be affected.[14–16] The multifactorial nature of the disease is supported by the fact that only about 5% of POAG cases display Mendelian inheritance, most commonly in association with MYOC gene variants.[17] This gene encodes myocilin, and mutations cause accumulation of the protein within cells of the trabecular meshwork, compromising its function as a drainage pathway.[18]

Although data does not currently support widespread screening, Medicare and Medicaid cover annual glaucoma evaluations for diabetics, patients with a family history of glaucoma, African Americans aged 50 years or older, and Hispanics aged 65 or older.[19,20] Such evaluations should involve IOP measurement, ophthalmoscopy and visual field testing.

**Normal tension glaucoma (NTG)** is a less common form of glaucoma and may be considered a variant of POAG. Although there is substantial overlap between the two, NTG is distinguished by glaucomatous damage that occurs at a normal IOP within the range of 11–21 mm Hg.[6] This lends credence to the idea that other IOP-independent mechanisms—particularly structural or vascular anomalies—contribute to the pathogenesis. Despite this fact, reducing IOP has shown efficacy in treating NTG and remains a cornerstone of therapy.

Anatomic variation may partially explain why some eyes are seemingly less tolerant of normal IOP. For example, larger eye size or a larger optic disc can amplify the mechanical strain incurred from a given pressure within the eye.[21] Central corneal thickness is lower in NTG patients than in POAG patients.[22] This can result in underestimation of IOP, as a thin cornea exerts less resistance against a tonometer tip. It is also possible that a thin cornea corresponds to a thin lamina cribrosa—another finding seen in patients with NTG.[9,23]

Adequate control of certain comorbidities may help attenuate NTG, as several conditions lead to reduced ocular blood flow and predispose the ONH to injury. Vascular dysregulation occurring in Raynaud's phenomenon or migraine is more common with NTG than with POAG.[24,25] In obstructive sleep apnea (OSA), transient hypoxemia results in vasospasm that predisposes the ONH to ischemic injury.[26] OSA has been noted in patients with NTG.[26] Evidence suggests that continuous positive airway pressure is a useful adjunct to conventional glaucoma therapy in such cases.[27,28]

**Primary angle-closure glaucoma (PACG)** differs from POAG and NTG in that it involves a narrow iridocorneal angle with the peripheral iris impeding aqueous outflow. Although POAG is more common, PACG accounts for a larger amount of glaucoma-related blindness.[29] The most common mechanism—pupillary block—occurs when aqueous cannot flow around the lens and through the pupil, forming a pressure gradient that causes the iris to billow forward and obstruct the anterior chamber angle.[6] The non–pupillary block mechanism usually involves an abnormally thick peripheral iris that blocks aqueous drainage. Demographic features that predispose individuals to PACG include advanced age; female sex; and being of Vietnamese, Chinese, Inuit or Pakistani descent.[30]

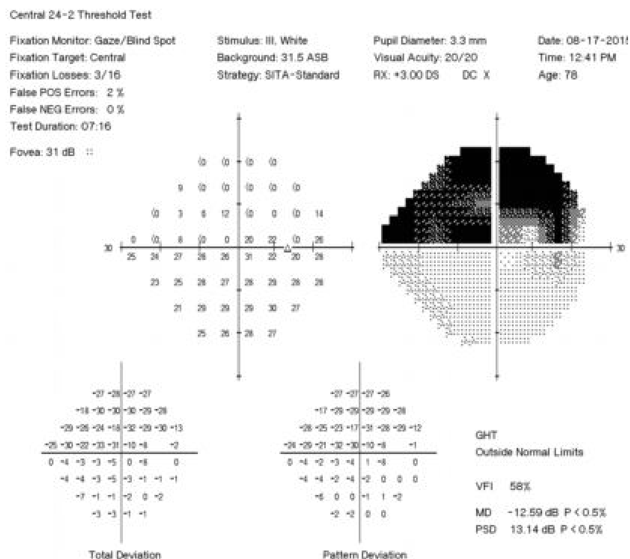
In most cases, the disease follows a chronic course like that of POAG.[6] Symptomatic attacks of acute angle closure can be precipitated by factors that induce pupillary dilation (eg, watching a movie in a darkened room). These patients may present to their primary care provider with ocular pain, blurred vision, nausea, vomiting and headache. In such cases, examination often reveals a markedly elevated IOP (ie, 50–80 mm Hg); a tense globe; and a mid-dilated, poorly reactive pupil.[6] Immediate referral and prompt reduction of IOP are crucial to prevent blindness. Administration of topical and oral medication is performed to quickly lower IOP and alleviate pain.[30] Definitive treatment is obtained with a laser iridotomy, which involves forming a small hole in the iris with a laser and allowing aqueous to bypass the obstruction and maintain outflow. Laser iridotomy is also performed prophylactically in the other eye because roughly half of these patients may experience an attack in the fellow eye within five years.[30]

## MANAGEMENT

Management of glaucoma is based upon two primary goals: preservation of vision and maintenance of quality of life. Patients should see an ophthalmologist regularly for fundoscopic examination and diagnostic assessments, such as visual field testing (Figure 5) and optical coherence tomography (Figure 6), which help monitor disease progression. By comparing current with previous visits, these assessments help determine if glaucoma is well-controlled.

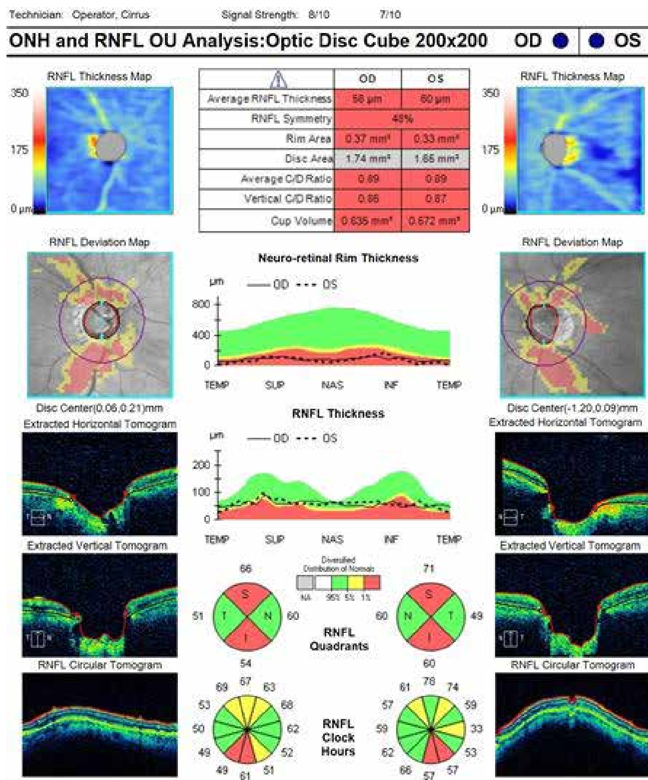
## FIGURE 5:

Superior arcuate visual field defect of the right eye as detected by automated perimetry.




## FIGURE 6:

Optical coherence tomography that depicts thinning of the retinal nerve fiber layer (RNFL). RNFL quadrants/clock hours indicate thinning in red color. Green color indicates stable RNFL. Yellow color indicates borderline changes.




## TREATMENT

Topical prostaglandin analogues are typically used as first-line agents due to their once-daily dosing and few systemic adverse effects. These agents reduce IOP primarily by enhancing aqueous outflow via the uveoscleral pathway.[31] Examples include latanoprost, travoprost and bimatoprost. Patients often remember them by their turquoise-colored cap. The most common adverse effects with this class are local and include conjunctival hyperemia, eyelash growth, irreversible darkening of the iris, and periorbital fat loss.[31] Less commonly, prostaglandin analogues may precipitate migraines in some patients.[32]

Topical beta-blockers are also commonly used, but their adverse effect profile can be problematic for many patients. These agents reduce IOP by decreasing aqueous humor production.[33] Examples include timolol and levobunolol. These have a yellow-colored cap. Most notably, beta blockers can cause bronchospasm and should be avoided in patients with existing pulmonary disease. Cardiovascular effects may include bradycardia, heart block and hypotension. Hypotension may be of particular concern in the elderly because it may further increase their risk of falls.[9] Less common effects include exacerbation of Raynaud's phenomenon, reduced exercise tolerance, sexual dysfunction, depression, dyslipidemia and reversible alopecia.[33] Advising patients to keep their eyes closed for a few minutes after eyedrop administration or performing manual nasolacrimal occlusion can help limit systemic absorption.

Topical alpha-2 agonists, such as brimonidine, lower IOP by reducing aqueous production and by increasing uveoscleral outflow.[34] Additionally, some evidence suggests a neuroprotective effect on retinal ganglion cells.[34] These agents typically have a purple-colored cap. Ocular irritation is a local adverse effect that is sometimes observed. Systemically, however, alpha-2 agonists are known to cause fatigue, xerostomia and worsened vascular insufficiency.[6] These agents are contraindicated in patients under 2 years old because of their potential to cause central nervous system depression and apnea.[11,34] If a patient with Parkinson's disease or depression has been prescribed a monoamine oxidase inhibitor, concurrent use of an alpha-2 agonist can precipitate hypertensive crisis.[6]

Carbonic anhydrase inhibitors (CAIs) come in topical and oral forms, both of which inhibit aqueous production.[6] Topical CAIs, which have an orange-colored cap, include dorzolamide and brinzolamide. An oral CAI, such as acetazolamide, is used when a rapid reduction in IOP is needed, as in acute angle-closure glaucoma. Systemic effects are more common with oral formulations and include hypokalemia, paresthesia, Stevens-Johnson syndrome and bone marrow suppression.[6] Although evidence is primarily limited to case reports, topical dorzolamide has been associated with thrombocytopenia and nephrolithiasis in some patients.[35,36]

Miotics, such as pilocarpine, are cholinergic agonists primarily used in the management of acute angle closure, although they can also be used in POAG. Pilocarpine has a green-colored cap. By inducing pupillary constriction and ciliary muscle contraction, miotics open the anterior chamber angle to promote aqueous

outflow.[33] Patients may complain of blurry vision (particularly at night) or brow ache after use.[9] Rarely, cholinergic agonism may result in bradycardia, diarrhea, urinary frequency and increased sweating.[33]

Topical rho kinase inhibitors are a new class of glaucoma medication. Netarsudil has been shown to reduce IOP by facilitating outflow through the trabecular meshwork, reducing episcleral venous pressure and decreasing aqueous production.[37] Netarsudil is available with a white-colored cap. Adverse effects seem to be primarily local, with conjunctival hyperemia being the most commonly reported problem.[37] Less commonly, patients may develop small conjunctival hemorrhages or cornea verticillata (whorl-like opacities).[37]

Although described as stand-alone classes, several combined preparations are available for the treatment of glaucoma. In certain circumstances, laser or surgical modalities may be warranted. Some options include laser trabeculoplasty, cycloablation, trabeculectomy, minimally invasive glaucoma surgery and placement of drainage shunts.[6] Despite the variety of procedures available, the goal of each intervention is a reduction in IOP.

## ADDITIONAL CONSIDERATIONS

In addition to the demographic factors and medical conditions previously discussed, certain systemic medications pose the risk of worsening glaucomatous progression. Patients requiring long-term corticosteroid therapy should undergo evaluation by an ophthalmologist, as these drugs can increase IOP and predispose some patients to glaucoma. These individuals are considered steroid responders, and they often have a first-degree relative with POAG.[38] This risk is magnified by high potency, long duration of use and proximity of administration to the eye. Recent studies have also identified prolonged use of oral contraceptives as a potential risk factor for glaucoma.[39,40]

Medications with anticholinergic effects can dilate the pupil and precipitate acute angle closure in patients with narrow angles. It is inadvisable to prescribe antimuscarinics—such as ipratropium for chronic obstructive pulmonary disease, scopolamine for motion sickness or oxybutynin for overactive bladder—for these patients. Other drugs that can exacerbate PACG include antihistamines, tricyclic antidepressants, selective serotonin/norepinephrine reuptake inhibitors and topiramate (Table 1).[41,42] As this can potentially result in blindness, family physicians should be vigilant in the event that a patient on one of these medications presents with symptoms of acute angle closure. These agents are mostly problematic in those susceptible to pupillary block; therefore, patients that have undergone laser iridotomy should be able to take these drugs without precipitating angle closure.

TABLE 1:

Commonly prescribed medications that may exacerbate glaucoma.

| Common medications that may exacerbate glaucoma |
|---|
| **Antidepressants** |
| *Citalopram, Fluoxetine, Duloxetine, Imipramine, Paroxetine* |
| **Antihistamines and Antiemetics** |
| *Hydroxyzine, Promethazine, Scopolamine* |
| **Antimuscarinic bronchodilators** |
| *Ipratropium, Tiotropium* |
| **Antispasmodics** |
| *Oxybutynin, Tolterodine* |
| **Other** |
| *Corticosteroids, Topiramate* |

## CONCLUSION

Glaucoma is a slowly progressive disease with various subtypes and etiologies, each resulting in gradual vision loss as the optic nerve head and retinal nerve fiber layer are damaged. One should be suspicious of glaucoma when patients with risk factors (eg, family history or advanced age) complain of impaired peripheral vision. In such cases, further evaluation by an ophthalmologist can establish the diagnosis and allow initiation of the appropriate therapy. Family physicians play a crucial role in minimizing vision loss, as they can encourage adherence to anti-glaucoma regimens as well as recognize conditions or medications that can exacerbate glaucoma.

**AUTHOR DISCLOSURE(S)**

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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# CALENDAR OF EVENTS

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Boyne Falls, MI
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**JANUARY 27–30, 2022**
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CLINICAL IMAGE

# HYPERPIGMENTED NODULAR RASH IN A 61-YEAR-OLD AFRICAN AMERICAN FEMALE

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**KEYWORDS:**

Cutaneous sarcoidosis

Hyperpigmented rash

Sarcoidosis

A 61-year-old African American female presents to an outpatient family health center with a hyperpigmented nodular rash of 2 months' duration. The rash first appeared on her abdomen before spreading across her upper arms, lower leg, back, face and scalp. She has a history of controlled type 2 diabetes mellitus, cerebral aneurysm rupture, Sjögren's syndrome, asthma and a left below-the-knee amputation due to osteomyelitis. She smokes cigarettes but does not use alcohol or illicit substances. She has also noticed a dry cough with mild dyspnea on exertion over the past 6 months. On physical exam, hyperpigmented nodules are palpable in both the intradermal and subcutaneous layers of the skin. Nodules are firm, mobile and nontender. Alopecia is noted where scalp nodules are present. Her lungs exhibit diminished air movement throughout, with scattered, end-expiratory wheezing.

A 6 mm punch biopsy performed of a skin nodule demonstrates non-necrotizing granulomatous dermatitis.

## QUESTIONS:

### 1. What is the most likely diagnosis?

A. Granuloma annulare

B. Sarcoidosis

C. Tuberculosis

D. Foreign body reaction

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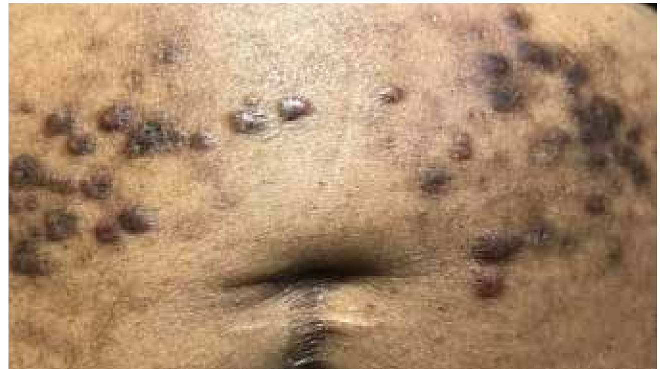

### 2. What initial imaging study should be performed to help confirm this diagnosis?

A. Ultrasound of skin lesion

B. Brain magnetic resonance imaging (MRI)

C. Chest radiograph

D. Positron emission tomography/computed tomography (PET/CT) scan

## ANSWERS:

### 1. What is the most likely diagnosis?

**Correct Answer:**
*B. Sarcoidosis*

Cutaneous lesions are found in 20%–35% of patients with sarcoidosis.[1] Skin manifestations of sarcoidosis come in many different forms, including papules, plaques, nodules (including subcutaneous), alopecia, scar lesions and hyperpigmented patches.[1] Given the variable presentation of sarcoidosis, the diagnosis is often difficult to reach. It is important to consider any suspicious cutaneous lesion as part of a systemic process, as lesions can be utilized to easily obtain a tissue diagnosis. No single test is confirmatory for the diagnosis of sarcoidosis, but histologic evidence of noncaseating granulomas is important supporting evidence.

This patient is exhibiting nodular sarcoid lesions on her abdomen, which is a common cutaneous manifestation.[1] She also had deeper subcutaneous nodules present on the upper arms and posterior lower legs that are far less common. The differential for nodular granulomatous skin lesions includes granuloma annulare, tuberculosis, rheumatoid nodules, primary neoplastic or metastatic lesions, and foreign body reactions. Granuloma annulare is a

relatively common and self-limited primary skin disorder that traditionally involves annular plaques on extremities but can also present as subcutaneous nodules.[2] Tuberculosis skin lesions have subtle histologic differences compared to sarcoidosis.[3] Whereas tuberculoid granulomas exhibit a dense lymphocytic infiltrate, this is notably absent in granulomas in sarcoidosis.[3] A negative acid-fast stain does not rule out tuberculosis; therefore, further workup should determine whether there is a high index of suspicion for mycobacterium infection.[3] Granulomas can form as a reaction to foreign bodies in the skin, and a thorough history should help guide this diagnosis.[3]

### 2. What initial imaging study should be performed to help confirm this diagnosis?

**Correct Answer:**
*C. Chest radiograph*

Although there is no definitive imaging for diagnosis of sarcoidosis, chest radiographs should be obtained to assess for the classic bilateral hilar lymphadenopathy seen in pulmonary sarcoidosis.[4] At least 90% of patients with sarcoidosis have evidence of lung involvement.[5] Findings on radiography should be followed up with high-resolution chest computed tomography and pulmonary function testing to further assess lung structure and function.[5] Ultrasound can be helpful in assessment of a skin lesion but is not helpful as a diagnostic tool in this case. Brain MRI is the imaging modality of choice in patients with suspected sarcoidosis and neurologic symptoms. There is growing literature on the utility of PET/CT in diagnosis and management of sarcoidosis. PET/CT with fluorine 18 fluorodeoxyglucose (FDG) can assess the inflammatory activity of sarcoid lesions throughout the body and is being studied as a means to identify occult lesions that would otherwise be difficult to obtain tissue diagnosis.[6] The clinical usefulness of PET/CT in sarcoidosis is still unclear and is not currently recommended for routine use.

## DISCUSSION:

Sarcoidosis is a multisystem inflammatory disorder characterized by tissue infiltration of noncaseating granulomas. Although the exact cause is unknown, research suggests a genetic predisposition to formation of an exaggerated immune response to environmental exposures.[7] A twin cohort study out of Denmark and Finland estimated the heritability to be around 66%.[7] In this study, at least one twin with sarcoidosis was identified in 210 twin pairs.[7] Interestingly, the statistical analysis revealed an 80-fold increased risk of developing sarcoidosis in the co-twin of monozygotic twins compared with a mere 7-fold increase in dizygotic twins.[7]

The prevalence of sarcoidosis is estimated to be 10–20 per 100,000 and is more common in those of middle age, female gender and Black race.[8] Geographical patterns have also identified increased incidence in the United States and Scandinavia.[8] Epidemiologic factors also appear to influence disease presentation. Clinical presentation is highly variable, and up to one-half of all cases are incidentally discovered.[5] Asymptomatic disease is more common in whites, whereas severe musculoskeletal or constitutional symptoms arise more frequently in African Americans.[8] In symptomatic disease, intrathoracic structures are most frequently affected and generally present as persistent cough, dyspnea or chest pain.[5] Cutaneous involvement is the next most common and can take many forms.[5] Fever, fatigue, anorexia, weight loss and weakness are commonly associated symptoms.[9] Additional manifestations can arise from involvement of other organ systems, such as neurologic impairment (central and peripheral), uveitis, vision loss, cardiomyopathy, cardiac dysrhythmia, biliary disease or renal failure.

The diagnosis of sarcoidosis is made through a combination of findings through laboratory testing, imaging and histologic examination. Other possible etiologies for presenting symptoms must be excluded, namely tuberculosis, which can present in a similar manner. The most helpful supporting evidence is histologic evidence of noncaseating granulomas in affected tissue.[5] Although nonspecific, elevated angiotensin-converting enzyme (ACE) is found in 75% of patients.[10] Other associated lab abnormalities include hypercalcemia, hypercalciuria, hypergammaglobulinemia and elevated inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein.[8] Imaging of the chest can reveal the classic bilateral hilar lymphadenopathy, additional adenopathy and/or interstitial lung disease.[4] The diagnosis can be made without histology in two distinct clinical presentations. Löfgren syndrome presents with the triad of hilar lymphadenopathy, erythema nodosum and polyarthralgia, and can have associated fevers and lung parenchymal involvement. Heerfordt-Waldenström syndrome presents with acute parotitis, fever, uveitis and facial nerve palsy. At time of diagnosis, patients should be evaluated for additional organ involvement with electrocardiography (EKG), pulmonary function testing, ophthalmologic evaluation and baseline renal and hepatic function tests.

There is no cure for sarcoidosis, but treatment with immunosuppressive therapy can slow the granulomatous process. First-line treatment is corticosteroids, with methotrexate as second-line.[11] Cutaneous sarcoid has demonstrated a positive response to intralesional corticosteroids, tetracyclines and hydroxychloroquine.[11] A growing body of evidence supports monoclonal antibody therapies (specifically infliximab and adalimumab) as potential third-line treatments for resistant cases.[11] Interestingly, spontaneous remission can occur in up to half of all cases. Sarcoidosis can affect any organ system to incite dysregulation and lead to a host of complications. Although most cases of sarcoidosis are mild or asymptomatic, chronic disease persists in 10%–30% and mortality has been estimated at up to 6%.[12] Keeping sarcoidosis in our differential diagnosis is important for timely identification and treatment to prevent the associated morbidity and potentially deadly complications.

## CASE SUMMARY:

In this case, skin biopsy of a suspicious rash led to the diagnosis of sarcoidosis. The patient's associated symptoms of dry cough and dyspnea on exertion were concerning for pulmonary involvement, and a chest radiograph confirmed bilateral hilar adenopathy. Subsequent computed tomography demonstrated peripheral fibrotic changes and ground glass opacities with bilateral axillary,

mediastinal, and hilar lymphadenopathy. Lab studies were significant for an elevated ACE level and hypergammaglobulinemia, and the EKG demonstrated a right bundle branch block. The patient was started on prednisone 20 mg by mouth daily. At 3 months, her rash had completely resolved, and respiratory symptoms had significantly improved. Her chest CT was repeated 6 months after initiation of treatment and showed regression of ground glass opacities and near-resolution of lymphadenopathy.

**AUTHOR DISCLOSURE(S)**

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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# Foot care for people with diabetes

**Austen Smith, DO**

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Diabetes mellitus (DM) is a disease associated with increased glucose, or sugar, in blood vessels. High blood sugar can damage blood vessels, causing vascular disease, and can damage nerves, causing neuropathy. Individuals with vascular disease have reduced blood flow that can impair healing. Individuals with neuropathy have difficulty sensing pain and pressure, which can lead to skin and subcutaneous (below the skin) damage where nerves are affected. Neuropathy and vascular disease often affect the feet and can lead to the following problems:

- Corns and calluses, or areas of thickened rough skin
- Blisters caused by friction and a collection of fluid
- Ulcers, or open sores, that can extend to the deeper tissues of the foot
- Cellulitis, or infection of the skin and subcutaneous tissue
- Osteomyelitis, or infection of the bones
- Amputation, or the surgical removal of toes, a foot or portions of the leg
- Charcot foot, a condition associated with weak bones that can break

Individuals with DM types 1 and 2 should have a foot exam performed by their family doctor or a foot doctor, known as a podiatrist, at least once per year. During this visit, the doctor will examine the skin and bones, assess the function of the nerves using different tools, and feel for the strength of blood flow through arteries. In addition, they may help you trim your toenails and treat the problems listed above if found. In between visits, you can keep your feet healthy by:

- Examining your feet daily for cuts, sores, blisters, warm spots, redness and thickened skin
- Wearing shoes and socks, both outdoors and indoors
- Wearing comfortable shoes that are supportive and "breathable"
- Washing feet daily with soap and warm water not exceeding 95°F (35°C)
- Smoothing corns and calluses as recommended by your doctor
- Trimming toenails straight across, following the shape of the toe
- Taking all medications and checking blood sugars as advised by your doctor
- Not smoking
- Exercising and eating healthy

Foot problems associated with DM can greatly impact your life and can cause further issues down the road. Following the advice of your doctor and the recommendations listed above can prevent or delay these problems. If you have concerns about DM or your feet, please contact your doctor.

**RESOURCES:**

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# Acute back pain: How OMT can help

**Matthew Wolbert, DO; Tonya Kozminski, DO**
*Ronald Januchowski, DO, FACOFP, Editor • Paula Gregory, DO, MBA, CHCQM, FACOFP, Health Literacy Editor*

Acute back pain is a common condition that most people will experience at some point in their lives. Back pain is considered acute if it has been going on for fewer than 4 weeks. While there are many potential causes, most cases are due to muscle strain and unrelated to an underlying medical condition. A complete history and physical examination should be given to rule out any serious causes of back pain.

There are different approaches to the treatment of acute back pain, all with the goal of short-term symptom relief. Osteopathic manipulative treatment (OMT) is one option that can be used alone or along with heat, ice, physical therapy and medication.

## WHAT IS OMT?

OMT is a hands-on technique performed by a doctor of osteopathic medicine (DO) to diagnose and treat several conditions. OMT aims to restore normal structure and function, which encourages the body's natural ability to heal itself. Multiple techniques can be used depending on the condition being treated and OMT should not be painful.

## HOW CAN OMT HELP WITH ACUTE BACK PAIN?

**Myofascial Release OMT:** Your physician will attempt to release both tight back muscles and the surrounding fascia with manual stretching and pressure.

**Muscle Energy OMT:** Your physician will position your back to apply a controlled force in a specific direction. You will be asked to counter that force in the opposite direction for 3–5 seconds, then relax, while your physician extends the stretch.

**Counterstrain OMT:** Your physician might find a tenderpoint for which they will move your body until that point becomes painless. That position is held for 90 or more seconds before your physician gently returns you to a neutral position. There can be multiple tenderpoints that are treated individually.

**High-Velocity, Low-Amplitude OMT:**Your physician will focus on the spine's alignment with this technique that involves small, quick thrusts. You might experience a therapeutic pop during treatment, which should be painless.

## WHERE CAN YOU GET OMT?

Locate a DO to obtain OMT. Use *osteopathic.org* to find an osteopathic physician in your area.

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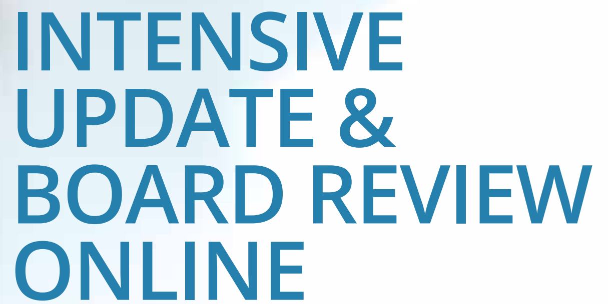


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