ORIGINAL RESEARCH:
Wii Fit™ Age in Older Adults Undergoing Total Hip Arthroplasty: A Preliminary Study

CLINICAL REVIEW:
Lung Cancer Screening: A Clinical Review

COMMENTARY:
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Wii Fit™ Age in older adults undergoing total hip arthroplasty: a preliminary study

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ABSTRACT:

Background:
Wii Fit has potential applications in rehabilitative and preventative medicine; however, the prognostic value of the Wii Fit Age (WFA) parameter has not been explored. WFA is derived from the player’s weight, height, age, and balance scores. This study assesses changes in WFA in total hip arthroplasty (THA) patients as a gross estimate of hip function.

Methods:
THA participants were aged ≥50 undergoing THA with no experience using Wii Fit. The control group met identical criteria without hip pathology. Both groups were assessed at 3 temporally spaced sessions. Each session consisted of a baseline Wii Fit Age (WFA1) assessment, followed by 3 Wii Fit Exercises (Soccer Heading, Penguin Slide, Hula-Hoop) and then a post-exercise Wii Fit Age assessment (WFA2). Past medical history and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) were completed.

Results:
Seventeen participants were recruited for the study (8 THA group and 9 control). Five THA participants were lost to follow-up by Session 3. WFA1 decreased across sessions for both THA and control groups, but the decrease was not significant. WFA2 was consistently lower than WFA1 for both groups. There were no significant inter-sessional differences in WFA1 or WFA2 for either group. Multiple regression analysis revealed WOMAC scores were never a significant predictor of WFA for either group at any time. There were no significant differences in Soccer Heading or Penguin Slide scores between or within groups. Scores for Super Hula-Hoop were significantly higher in the control group in Session 1 (p=0.042) but not in Sessions 2 or 3 (p=0.792; p=0.105).

Conclusion:
This pilot study does not support the use of Wii Fit Age nor any of the undertaken exercises as definitive prognostic tools. Further research with larger cohorts is needed.
INTRODUCTION

In 2010, 42,713 Canadians underwent a hip arthroplasty procedure, representing an increase of ~11% compared with 2006 [1]. Of these hip replacements, 10% were revision arthroplasties performed mostly for aseptic loosening [1]. The majority of hip arthroplasty patients are aged 65 to 74; however, the rates of hip surgery in younger patients are increasing with 29.6% of all hip arthroplasties currently performed in patients aged 45 to 64 [10]. These increases in national hip replacement surgery necessitate appropriate longitudinal post-operative follow-up.

At Queen’s University affiliated hospitals, routine postoperative follow-up for hip arthroplasty occurs at 6 weeks and 3 months. However, these patients often rely on others for transportation. Attending follow-up appointments presents a challenge, especially for individuals in remote settings. Additionally, the tools to assess post-operative hip function, such as comprehensive physiotherapy evaluations and gait analysis, are time and resource intensive. An inexpensive and portable means of evaluating post-operative hip function is desirable for implementation in rural and primary care settings.

Active video game systems controlled through movement, such as the Nintendo Wii™ gaming console, have gained popularity in the health sector. Created in 2006, the Wii™ gaming system revolutionized virtual reality by allowing interactive gameplay via an infrared motion-detection system combined with a handheld remote control device with built-in 3D accelerometer technology. The system responds to changes in the handheld controller’s direction, speed and acceleration. The Nintendo Wii Fit™ Plus game is paired with a wireless Bluetooth™ balance board allowing 60 hours of play time with 4 AA batteries. The balance board has 4 strain gauge load sensors (1 positioned in each corner) to estimate centre of gravity and track movements via weight shifting. At a basic level, the Wii Fit™ balance board resembles pressure plate systems currently used in gait labs.

The Wii Fit™ Plus system has been evaluated for its use in depression [15], neurogenic [3-7] and muscular [8,9] rehabilitation, fall risk assessment [16] and fall risk reduction [11-13]. However, few have investigated its use in joint replacement surgery. [14,15]. One preliminary randomized controlled trial investigated Wii Fit™ as an adjunct or replacement to physiotherapy in total knee replacements [14]. Wii Fit™ was found to be an acceptable adjunct – but not replacement – for guided physiotherapy in this population [14]. Even fewer studies have assessed the validity and reliability of Wii Fit™ scores [10,16,17]. One such study found the Basic Step exercise to demonstrate reliability and discriminant validity in the assessment of fall-related risk [14].

Within the Nintendo Wii Fit™ Plus system is a measurement called the Wii Fit Age (WFA). WFA is a computed virtual age based upon the player’s actual age, body mass index (BMI) and balance. Balance is scored after performing a Basic Body Test. This study assesses whether there is a correlation between WFA and postoperative changes in hip function after total hip arthroplasty (THA). The study also evaluated select exercises including Soccer Heading, Penguin Slide, and Super Hula-Hoop.

METHODS

i. Patient Selection

This study was approved by the Queen’s University Research Ethics Board. Informed consent was obtained from all participants. The study was conducted from June 2013 to November 2013 in the outpatient clinic at Hotel Dieu Hospital in Kingston, Canada under the supervision of a medical student or orthopaedic surgery resident. Total hip arthroplasty patients, representing the THA group (n=8), were recruited during their preoperative anesthesia visit. Patients were eligible if they were over the age of 50 with adequate vision and hearing, and no experience using the Wii Fit™ Plus system within the past year. Control participants, recruited through local organizations, were age-matched and had no known history of hip pathology. THA participants were withdrawn if they developed post-operative medical or infectious complications.

ii. Instrumentation

The Nintendo Wii Fit™ Plus system (Nintendo of Canada, Inc) and its balance board were used to assess balance function. The THA group was first assessed pre-operatively (Session 1) and then at 6 weeks and 5 months post-operatively (Sessions 2 and 3, respectively). The control group completed three sessions at 1-week intervals to prevent training and repetition-related improvement. The sequence of exercises is shown in Figure 1. All participants initially performed a Basic Body Test, used to compute the first Wii Fit Age (WFA1). Next, participants performed three Wii Fit exercises selected for their motion at the hip joints and balance requirements: Soccer Heading, Penguin Slide, and Super Hula-Hoop. In Soccer Heading, participants move their centre of gravity to strike oncoming soccer balls while avoiding distractors. Penguin slide involves laterally shifting one’s centre of gravity to catch fish jumping on to an iceberg. In Super Hula-Hoop, participants must rotate their hips in large clean circles at a fair pace while occasionally leaning left or right to catch additional hula-hoops. Soccer Heading and Penguin Slide exercises were completed 3 times each and scores averaged. Super Hula-Hoop was done once because it was more physically demanding. After all exercises were completed, the Basic Body Test was repeated and the second Wii Fit Age (WFA2) was recorded. Following each session, participants completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
Hip Score. The WOMAC is a standardized questionnaire used to assess osteoarthritis by asking participants to subjective rank pain, stiffness, and functional limitation. It is sometimes used to assess the need for arthroplasty. The total assessment was 45 minutes in duration.

### iii. Statistical Analyses

The data was analyzed using Statistical Package for Social Sciences Version 21 (IBM Corp., New York, USA). Chi-square, Mann-Whitney U and independent sample T-tests were run to compare descriptive statistics (age, height, weight, physical activity) between THA and control groups. Sample T-tests compared Wii Fit Age and exercise scores between groups. A multiple regression analysis was performed to determine if changes in Wii Fit Age correlated with WOMAC scores. An alpha <0.05 was considered significant.

## RESULTS

### i. Patient Demographics

Eight participants (6 female, 2 male) with an average age of 72 (range 60-88) were recruited as THA participants. Two were lost to follow-up for Session 2 and an additional 3 were lost for Session 3. Study participants withdrew due to transportation restrictions and difficulty accommodating the length of the session into their schedule. Nine individuals (5 female, 4 male) with an average age of 68 (range 51-81) volunteered as control participants, and none were lost to follow-up. The groups did not differ significantly in demographics.

### ii. Wii-Fit Age

For the control group, mean WFA2 was lower than WFA1 in all 3 sessions (Fig. 2A). These decreases were not significant except for Session 1 where the mean WFA1 was 68.9 ± 2.5 (mean ± SE) and WFA2 was 62.6 ± 5.2 (p=0.01). WFA1 did not differ significantly between Sessions 1 and 2 (p=0.98), or Sessions 2 and 3 (p=0.55).

For the THA group, mean WFA2 was lower than WFA1 both pre- and post-operatively (Fig. 2B). However, this trend was only significant at Session 2 where the mean WFA1 was 65.2 ± 3.1 and mean WFA2 was 53.8 ± 7.2 (p=0.02). There were no significant differences in WFA1 from Sessions 1 to 2 (p=0.22), or between Sessions 2 and 3 (p=0.98).

Comparing WFA results between the THA and control groups using independent samples T-tests revealed no significant differences in WFA1 or WFA2 at any time.

### iii. WOMAC Scores

The mean WOMAC score for the control group was 92.6 ± 4.3 (Fig. 3). Inter-sessional WOMAC scores did not change for the control group, as participants noted no change in hip function. THA group WOMAC scores increased with each session. Session 1, 2 and 3 WOMAC scores for the study group were 72.4 ± 4.5, 84.2 ± 4.5, and 85.7 ± 8.5 respectively. No increases in mean WOMAC scores were significant for the THA group (p=0.21; p=0.99). WOMAC scores were significantly different between THA and control groups at Session 1 (p=0.01), but this significance was lost for Sessions 2 and 3 (p=0.22; p=0.46). A multiple regression analysis revealed that the WOMAC score was never a significant predictor of WFA in either group at any session (p=0.26; p=0.53; p=0.79).
iv. In-Game Exercises

In the Soccer Heading exercise, mean scores increased with each session for both the THA and control groups (Fig. 4). The largest increase was seen in Session 3 for the control group, where the mean score increased from 16.7 ± 3.7 in Session 2 to 32.3 ± 11.0 in Session 3; however, this increase was not significant (p=0.27). No other differences in mean Soccer Heading scores between sessions were significant for either the THA or control groups, respectively. Mean Soccer Heading scores were not significantly different between groups at any session (p=0.09; p=0.40; p=0.09 for Sessions 1-3 respectively).

Figure 4. Mean Soccer Heading scores (± SE) for the study and control groups at Sessions 1, 2 and 3.

For the Penguin Slide exercise, mean scores increased with each session for both the THA and control groups (Fig. 5). These inter-session increases were never significant in either group. In addition, comparative analysis between THA and control group at each session failed to detect statistical differences in Mean Penguin Slide scores (p=0.61; p=0.15; p=0.65 for Sessions 1-3 respectively).

Figure 5. Mean Penguin Slide scores (± SE) for the study and control groups at Sessions 1, 2 and 3.

For the Super Hula-Hoop exercise, mean scores increased between sessions for the THA group (Fig. 6A). However, these increases were not significant (p=0.60 [Session 1 vs. 2]; p=0.81 [Session 2 vs. 3]). Control group Super Hula-Hoop scores decreased from 71.0 ± 16.8 in Session 1 to 55.8 ± 28.2 in Session 2 (below that of the THA group), only to increase in Session 3 to 85.2 ± 36.1. The fluctuation in control group Super Hula-Hoop scores was never significant (p=0.92; p=0.74). The control group's mean Super Hula-Hoop scores were significantly higher than the THA group's scores in Session 1 (p=0.04) but not in Sessions 2 or 3 (p=0.79; p=0.10). Figure 6B shows the individual and mean pre-operative Super Hula-Hoop scores for the THA and control groups.

Figure 6A. Mean Super Hula-Hoop scores (± SE) for the study and control groups at Sessions 1, 2 and 3. (* denotes P<0.05).

DISCUSSION

The Wii Fit™ Plus system allows direct visualization and objective quantification of hip function post-THA. Gait labs accomplish this with great accuracy, however, lengthy wait times, cost and limited access are deterrents. The Wii Fit™ Plus system is an appealing option given its affordability, portability, and applicability to various healthcare sectors [17]. Wii Fit™ is also feasible and enjoyable in the older adult population [19,20].

The primary outcome WFA encompasses age, BMI and balance results from the Basic Body Test. In this study, WFA was measured before and after other exercises to determine the parameter's reproducibility and objectivity. WFA2 always trended lower than WFA1 in both groups, though only significantly in Session 1 for the control group. Since age and BMI are constant variables, this suggests balance improved after completing the additional exercises. WFA2 is likely amenable to training and is an unsuitable objective measure of hip function. Furthermore, the process of obtaining WFA2 is not standardized. Whereas all participants complete a common Basic Balance test in the first Basic Body Test, the repeat test randomizes participants to 2 out of 10 activities. Some assess parameters other than balance like memory and visual acuity.
WFA1 was expected to remain relatively constant in the control group since hip function was stable. A decreasing WFA1 would suggest training-related improvement. WFA1 was constant at a mean of 68 years for Sessions 1 and 2 in the control group, and then decreased to 63 years for Session 3. These were not significant changes so WFA1 shows potential as an objective measure for hip function. In the THA group, WFA1 decreased from 73.5 years to 66 years post-operatively by Session 3. While also not significant, this downward trend may suggest WFA1 potential to detect balance improvements following THA. Further evaluation with a larger cohort is required.

To assess the validity of the WFA1 score, a multiple regression analysis assessed the correlation between changes in WOMAC scores with THA group changes in WFA across sessions. It was found that WOMAC scores were not a predictor of WFA1 at any point. This may be related to the study’s low power. At this point, WFA1 does not show adequate delineation of hip function either pre- or post-operatively. In a study of 45 active adults, Wikstrom (2012) similarly found that Wii Fit activities, including the basic balance test, had poor intra-session and inter-session reliability with minimal detectable change in scores relative to the mean [12]. Wikstrom did not recommend the use of Wii Fit balance scores as objective measures of progress [12]. However, modifications in study design may more accurately assess balance scores as objective measures. Such modifications include a larger sample size with a lower minimum age and earlier post-operative follow-up to better characterize trends in WFA.

Of the undertaken exercises, Soccer Heading and Penguin Slide appear least useful. An ideal objective exercise shows post-operative increase in THA group scores with only conservative increases (if any) in control group scores. Both exercises show steadily increasing scores for both groups. Most notable is the near doubling of the mean Soccer Heading score in Session 3 for the control group. This sharp increase, and narrow standard error, suggests Soccer Heading is highly susceptible to training. The Soccer Heading activity also depends more on visual acuity and reaction time rather than balance. Participants often could not differentiate between soccer balls and the “distracters”. They also complained the game was too fast. As vision and reaction time are not products hip function, Soccer Heading and Penguin Slide should not be used. Super Hula-Hoop shows great promise as a prognostic exercise given the significantly higher Session 1 scores of the control group. Similar to the WOMAC survey, Super Hula-Hoop differentiates participants with hip pathology from those without. This difference is lost once the pathology is corrected. With further investigations, a cutoff point similar to that in Yamada et al. (2011) might be derived [10]. Our preliminary data suggests the cutoff for Super Hula-Hoop might lie between 33 and 48 points. Limitations include the small sample size, the randomized assessment of WFA2, and loss-to-follow-up in the THA group. It should be noted that most participants withdrew because of scheduling and transportation issues. This emphasizes the importance of local assessment convenient for THA patients.

Anecdotal comments about the use of the Wii Fit™ Plus system in this population include enjoyment using the system and communicated interest in self-purchasing a console for home use. Participant enjoyment was noted in other studies [7,13,19,20]. Although, a different study by Laver et al. (2011) found their population of hospitalized older adults to prefer conventional physiotherapy over Wii Fit [21]. In our study, there was some difficulty completing the 45-minute session due to fatigue.

In conclusion, this pilot study does not currently support the use of WFA1 or any of the undertaken exercises as measures of hip function. However, WFA1 and Super Hula-Hoop show potential in delineating hip function. Further evaluation with a larger cohort is required. Recommendations for continuation include scheduling study group follow-up sessions before 9-weeks post-operation, and eliminating WFA2, Penguin Slide and Soccer Heading. This would greatly reduce the duration of the assessment, reducing participant fatigue and increasing its feasibility for clinic implementation.
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ABSTRACT:

Purpose:
To evaluate the freedom from biochemical failure (FFF) and acute toxicity for patients with prostate cancer treated with curative intent radiotherapy (RT) at Grand River Regional Cancer Centre (GRRCC) from 2007 to 2012 inclusive.

Methods and Materials:
A retrospective review of electronic patient charts at GRRCC was conducted, and 246 prostate cancer patients receiving curative intent radiotherapy between the years 2007 and 2012 were identified. The median follow-up was 24 months (2007-2012). Contingency tables, logistic regression, and actuarial analysis were used to compare the incidence of biochemical failure (BF = prostate specific antigen [PSA] of nadir + 2 ng/ml) and the incidence of combined gastrointestinal (GI) and genitourinary (GU) acute toxicity symptoms ≥ Radiation Therapy Oncology Group (RTOG) grade 2 in low-dose (<78 Gy) and high-dose (≥78 Gy) groups.

Results:
Contingency tables showed that there was no significant association between dose group and acute toxicity symptoms ≥ RTOG grade 2, but there was a significant association between dose and biochemical failure (P = 0.03), with 11.5% in the <78 Gy group and 4.2% of patients in the ≥78 Gy group experiencing BF. Logistic regression supported these conclusions: the ≥78 Gy group had reduced odds of experiencing BF (P = 0.04); the patients in the <78 Gy group had 5.8 greater odds of experiencing BF compared to the ≥78 Gy group. Actuarial analysis for the rate of BF revealed a non-significant difference between the <78 Gy and ≥78 Gy groups.

Conclusion:
There has been a gradual adoption of dose-escalated RT for the treatment of prostate cancer patients at GRRCC from the years 2007-2012 inclusive. Analysis of biochemical failure rates and rates of toxicity suggests a moderate improvement in biochemical failure corresponding to dose escalation, without any increase in the incidence of acute GU or GI toxicity.
INTRODUCTION:
Randomized controlled studies have demonstrated a radiation dose-response relationship for localized prostate cancer. Increased radiation dose, however, carries the risk of increased toxicity. The development and implementation of more precise radiation techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) has the potential to reduce toxicity, and may allow dose escalation without an increase in toxicity1.

The M.D. Anderson Cancer Center randomized control study of 301 patients demonstrated a significant improvement in freedom from failure (FFF) with a dose increase of 8 Gy, from 70 Gy to 78 Gy. Significant improvement in FFF was only found in intermediate-to-high risk patient groups (prostate-specific antigen [PSA] ≥10 ng/ml), and there were reported increases in gastrointestinal (GI) toxicity in the 78 Gy arm2. Long term follow-up at 8 years post-treatment confirmed the superiority of higher doses, with the high dose arm exhibiting significantly improved FFF3.

The Dutch multicenter randomized controlled study of 669 patients reported a significant increase in FFF in the higher dose arm. Compared to the M.D. Anderson trial, the Dutch multicenter study found fewer cases of GI toxicity1. Another study by Peeters et al. showed that patients who develop late GI complications may be predisposed to such toxicities due to a history of abdominal surgery or pre-treatment GI symptoms; these factors were not considered in the M.D. Anderson trial1. In 2002, Cancer Care Ontario released practice guidelines recommending that 75-78 Gy be delivered using RT for intermediate risk group prostate cancer4.

The purpose of this retrospective review was to evaluate the FFF and acute toxicity for patients with prostate cancer treated with curative intent RT at Grand River Regional Cancer Centre (GRRCC) from 2007 to 2012 inclusive.

MATERIALS AND METHODS
This is a retrospective quality assurance review of electronic patient records. A search of the radiation therapy database at GRRCC was conducted to identify all prostate cancer patients receiving curative-intent RT between the years 2007-2012 inclusive. We excluded men that were treated post-prostatectomy or were enrolled in clinical trials. The electronic patient charts were reviewed for demographic information, disease characteristics, and treatment information. Tumour staging information collected included Gleason score, T-stage, and pre-treatment PSA values. Tumour staging was performed according to the criteria established by the American Joint Committee on Cancer (AJCC 6th/7th edition). These characteristics were used to stratify patients into D’Amico risk categories1. Low risk patients had a combined Gleason score ≤7, T-stage of T1a-T2a, and pre-treatment PSA <10 ng/ml. Intermediate risk patients were those with a Gleason score of 7, T-stage of T1a-T2a, and pre-treatment PSA ≥10 ng/ml but <20 ng/ml. High risk patients had Gleason scores >7, T-stage of T2c-T4c, or a pre-treatment PSA ≥20 ng/ml.

A standard planning target volume (PTV) expansion of 1 cm (but 7mm posteriorly) was used throughout. All patients were treated with conventional fractionation, with 2 Gy daily fractions. Patients were assessed weekly by clinicians during RT for signs and symptoms of acute toxicity. GI and GU toxicity symptoms were graded according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria (RTOG/EORTC grades). The acute toxicity information was collected prospectively at each visit during RT and stored in a database, which was accessed and collected retrospectively for this review. Acute GU and GI toxicity was available for 2007-2011 inclusive (N=184). Late toxicity information was not available. Patients typically had a clinical follow-up exam with a serum PSA 3 months post-RT and then every 6 months for 5 years. BF is defined according to the Phoenix definition (nadir + 2 ng/ml)5,6.

Statistical analyses were performed using SAS® Version 9.2 (SAS® Institute, Inc., Cary, NC), IBM® SPSS® Statistics Version 21.0 (IBM Corporation, North Castle, NY), or Microsoft® Office Excel® 2007 (Microsoft, Redmond, WA). For all tests, the critical value used was α = 0.05. RT treatment doses (70 Gy, 72 Gy, 74 Gy, 76 Gy, or 78 Gy) were divided into two mutually exclusive categories: <78 Gy vs. 78 Gy. Cross tabulation (contingency) tables were generated using the SAS® Software FREQ procedure. These tables were used to assess: 1) whether or not the incidence of GI or GU toxicity of RTOG grade ≥2 was contingent upon dose group; 2) whether or not the incidence of BF was contingent upon dose group. Pearson’s chi-square test was used to assess statistical significance.

Using the LOGISTICS procedure of SAS®, logistic regression models were generated for the data collected from patients treated in 2007-2011. The binary logistic regression models included either toxicity or BF as the dependent variable; dose, year of treatment, age at the time of treatment, risk group, and androgen deprivation therapy (ADT) status were used as independent categorical variables. The dose groups were <78 Gy and 78 Gy. The likelihood ratio test was used to test the global null hypotheses that none of the independent variables had a predictive effect on the dependent variable (i.e. β = 0). The chi-square statistic was used to assess significance. Maximum likelihood estimates and adjusted odds ratios (OR) were calculated for each independent variable to establish the effect that each particular variable had on the dependent variable, controlling for the effects of the other independent variables. Chi-square tests were used to determine whether the effects were significant (Table 2).

Using SSPP® actuarial analysis was performed comparing freedom from BF following RT with doses <78 Gy vs. 78 Gy (Figure 2). Time 0 was defined as the date of first follow up visit (i.e. 3 months post RT). If BF did not occur, patients were censored at the last available PSA determination (i.e. right censored). Freedom from BF was estimated for the patients in the dose groups using the Kaplan-Meier (K-M) method7. The tests were also performed with stratification by D’Amico risk groups. The freedom from BF rates between dose groups were compared using the log-rank statistic.
RESULTS

Patient Demographics and Disease Characteristics

The demographics and clinical characteristics of the 246 prostate cancer patients treated with curative intent RT between the years 2007-2012 are summarized in Table 1. Follow-up data for one patient, treated in 2008 with 76 Gy, were not available. This patient was excluded from most of the analysis (where N=184 or N=245). The mean approximate age at the time of RT was 73 years (range 55-87 years, SD 6 years). The mean pre-treatment serum PSA was 9.74 ng/ml (range 1.1-70.0 ng/ml, SD 7.1 ng/ml). Patients were stratified into D’Amico risk groups with 47 (19%), 182 (74%), and 16 (7%) patients in the low, intermediate, and high risk groups, respectively.

Treatment and Follow-up

The median follow-up time for the patients treated between the years 2007-2012 was 24 months (range 0-72 months, mean 26.9 months, SD 18 months). Sixteen patients had experienced BF, with a mean time to BF of 25.5 months (range 0-48 months, SD 16 months). Nine patients died of any cause, and two of these deaths were attributed to prostate cancer. The mean time to death was 19 months (range 6-42 months, SD 11 months).

The mean dose of radiation delivered to the prostate tissue was 76.7 Gy (range 70.0 Gy - 78.0 Gy, SD 2 Gy) for the overall study sample. Every patient fell into one of 5 dose groups: 70 Gy, 72 Gy, 74 Gy, 76 Gy, or 78 Gy. Between the years 2007-2012, the numbers of patients in each group were 16, 2, 25, 34, and 168, respectively (Figure 1). The mean dose delivered to the prostate tissue of the patients in the <78 Gy group was 74.0 Gy (range 70.0-76.0 Gy, SD 2 Gy), compared to the 78 Gy group in which all patients received the same dose of 78 Gy. The median follow-up time for the <78 Gy group was 42 months (range 0-72 months, mean 40.9 months, SD 21 months) and the median follow-up time for the 78 Gy group was 24 months (range 0-72 months, mean 24.4 months, SD 16 months). The number of patients receiving ADT in the low, intermediate, and high risk groups were 3 (6%), 14 (8%), and 9 (56%), respectively. In the <78 Gy group, 8 (10%) patients received ADT and in the 78 Gy group, 19 (11%) patients received ADT. The number of patients experiencing toxicity symptoms ≥ RTOG grade 2 each year from 2007-2011 were 5, 0, 2, 3, and 8, respectively.

Comparing the Proportion of Patients with RTOG Grade ≥2 Toxicity to Dose Received

Contingency tables comparing toxicity to dose were constructed. The doses were divided into two mutually exclusive dose groups of <78 Gy and 78 Gy. The number of patients within each group was 75 and 109, respectively. The frequencies of toxicity ≥2 are compared between the dose groups in Table 2. The proportion of patients experiencing toxicity symptoms ≥2 was slightly smaller in the <78 Gy group (9.3%) compared to the 78 Gy group (10.1%), but the difference was not significant (P = 0.8).

Comparing the Proportion of Patients Experiencing Biochemical Failure to Dose Received

Contingency tables were created to determine whether there was an association between the dose group of patients and the proportion of patients experiencing BF. Patients treated between the years 2007-2012 were included. The dose groups <78 Gy and 78 Gy included 77 and 168 patients, respectively. The frequencies of BF are compared between the dose groups in Table 2. There was a significant difference (P = 0.03) between the percentage of patients experiencing BF in the <78 Gy group (11.5%) compared to the 78 Gy group (4.2%).

Logistic Regression Models to Test for Any Variables with Predictive Effects on Either the Occurrence of Toxicity or Occurrence of Biochemical Failure

In the toxicity logistic regression model with the dose groups <78 Gy and 78 Gy, the use of androgen deprivation therapy (ADT) in the treatment regimen was a significant predictor of toxicity (P = 0.04). In addition, the logistic regression model for BF had a significant chi-square value (P = 0.04). Specifically, dose had a significant effect on the occurrence of BF (P = 0.04). The chi-square probability values are summarized in Table 3.

Table 3 also summarizes the ORs determined for the predictive independent variables in the toxicity and BF logistic regression models. The patients treated with RT and neo-adjuvant and/or concurrent ADT had 4.7 greater odds of experiencing toxicity symptoms of RTOG grade ≥2 than those not treated with any ADT (95% CI 1.080-20.506, P = 0.04). In the toxicity regression model, dose group (<78 Gy or 78 Gy) did not have a significant predictive effect on whether or not patients would experience toxicity symptoms ≥2. All variables included in the logistic regression model and their effects on the occurrence of toxicity are summarized in Table 4.

In the BF regression model, patients in the 78 Gy dose group had an OR of 0.17 compared to the patients in the <78 Gy group (95% CI 0.032-0.915, P = 0.04). In other words, the odds of a patient treated with >78 Gy experiencing BF were 5.9 times higher than those treated with 78 Gy. In the BF regression model, use of ADT did not have a significant predictive effect on BF. All variables included in the logistic regression model and the effects that they have on the occurrence of BF are summarized in Table 5.

Actuarial Analysis

K-M analysis for the BF data are presented in Figure 2. Comparison of the K-M curves for <78 Gy and 78 Gy dose groups without stratification were not significantly different (Figure 2A, P = 0.7). However, the <78 Gy group had moderately superior biochemical FFF at the end of the follow-up period. When the group was stratified into D’Amico risk groups, only a K-M curve for the intermediate risk group could be generated because the low and high risk groups did not have any events of BF. The number of patients in the intermediate risk group treated with doses <78 Gy and 78 Gy were 38 (49%) and 99 (59%), respectively. The proportion of intermediate risk patients with freedom from BF was higher in the 78 Gy dose group, although the difference was not significant (Figure 2B, P = 0.07).
DISCUSSION

Several studies have reported improvements in FFF with dose-escalated radiotherapy\[^{1-3,10}\]. There has been gradual adoption of dose escalation at GRRCC from 2007-2012 (Figure 1). Here, we performed a retrospective quality assurance review to investigate whether or not prostate cancer patients at GRRCC have benefitted as expected from the adoption of dose-escalated RT.

The M.D. Anderson dose escalation trial followed patients treated with either 70 Gy or 78 Gy. K-M analysis at 5 years found a significant difference in biochemical and clinical FFF between 70 Gy and 78 Gy; 84% of patients treated with 78 Gy and 78% of patients treated with 70 Gy had biochemical and clinical FFF at 5 years\[^{2-3}\]. Our analysis has found that patients treated with 78 Gy at GRRCC have benefitted from dose escalation. The overall percentage of GRRCC patients experiencing BF in the 78 Gy group was lower (4.2%) than the percentage of patients with BF in the <78 Gy group (11.5%) and the 78 Gy group had 5.9 lesser odds of experiencing BF compared to the <78 Gy group (95% CI 1.1-31.3, \(P = 0.04\)). The K-M analysis, on the other hand, fails to provide evidence that dose escalation to 78 Gy leads to significantly improved biochemical control (Table 2; Figure 2).

It is necessary to be cautious interpreting the results of the contingency and regression analyses, due to the presence of several confounding factors and a discrepancy in the follow-up periods between the dose groups. The <78 Gy group had a median follow-up of 42 months, whereas the 78 Gy group had a median follow-up of 24 months. This is because of the trend in the adoption of dose escalation (Figure 1) where treatment with 78 Gy began in recent years. Considering that the mean time to BF for the combined <78 Gy and 78 Gy study group was 25.5 months (range 0.0-48.0 months, SD 16 months), it seems probable that the 78 Gy group has not been followed long enough to observe a number of imminent failures. This argument is supported by the trend of the K-M curve (Figure 2A). During the period from 0 months to 48 months post-treatment, the 78 Gy group had only slightly superior biochemical FFF. At 48 months post-treatment, however, the 78 Gy group had a number of late failures and <78 Gy became superior in FFF. Unlike our K-M curves, the M.D. Anderson K-M displayed a divergence with time between the low-dose arm (70 Gy) and high-dose arm (78 Gy) in terms of FFF\[^{3}\], with the high-dose arm doing progressively better than the low-dose arm. It will be interesting to see what trends emerge in our data as follow-up increases.

Considering only intermediate risk patients (Figure 2B), those in the 78 Gy group appeared to have had improved FFF compared to the <78 Gy group, but the difference was not significant. It is interesting to note that there were no patients in the low- or high-risk groups who had BF between the years 2007-2012. Due to the less aggressive nature of low risk disease these patients are inherently less likely to have BF\[^{3}\]. Compared to the intermediate risk group, the high risk patients may have been protected from BF because the majority received neoadjuvant ADT. Contingency tables showed that there was no significant difference in the incidence of acute toxicity of RTOG grade ≥2 between those patients receiving <78 Gy (9.3%) versus 78 Gy (10.1%) (Table 2). The occurrence of toxicity of RTOG grade ≥2 was not contingent upon dose. Logistic regression also indicated that dose received had no significant effect on the occurrence of acute toxicity (Table 3).

Our findings are in agreement with the results of the Dutch multicenter dose escalation trial, where the incidence of RTOG grade 2 or greater toxicity symptoms was not statistically different in the high-dose arm (78 Gy) compared to the low-dose arm (68 Gy). The proportion of patients with acute GI toxicity symptoms ≥2 were 41% in the 68 Gy arm and 47% in the 78 Gy arm. For GU symptoms these proportions were 40% and 42%, respectively\[^{3}\]. Our analysis revealed a much lower proportion of patients experiencing combined GU and GI grade ≥2 toxicity symptoms, with 10.1% in the 78 Gy group and 9.3% in the <78 Gy group. Acute toxicity data was collected prospectively and retrieved for this review; as such the lower rates of toxicity may be a result of adoption of more precise radiation techniques. Other studies of external beam radiotherapy have reported incidences of toxicity more similar to those values found in our review\[^{15-17}\]. A review of patients treated at the British Columbia Cancer Agency (BCCA) found toxicity values similar to ours. Reported toxicities of RTOG grade ≥2 from this Liu et al. study were 12% (GI) and 20% (GU) at 5 years post-treatment\[^{14}\].

The M.D. Anderson, Dutch multicenter, and Zietman et al. dose escalation studies all reported late GI and GU toxicity symptoms as well\[^{1-3,10}\]. There were variable results between these studies for late GI toxicity symptoms, but none of the above trials found a significant difference in late GU toxicity symptoms of RTOG grade ≥2 between the high-dose and low-dose arms. It is important to continue to implement further follow-up with the GRRCC prostate cancer patients treated with dose-escalated RT, as severe late complications may appear\[^{16}\].

The inclusion of patients treated with ADT introduces a confounding factor to our review which was not present in the large randomized, controlled dose-escalation trials\[^{1-3,10}\]. The use of ADT may have had an effect on the apparent differences between the rates of BF in the <78 Gy vs. 78 Gy groups. In earlier years, when treatment with <78 Gy was more common, a larger proportion of low and intermediate risk patients were treated with neoadjuvant ADT. This may have contributed to improved FFF in the <78 Gy group. In the years 2011 and 2012 most (82%) of the high-risk patients were treated with ADT and RT. However, fewer low- and intermediate- risk patients were treated with ADT during this period. This period (2011-2012) coincides with an increasing proportion of patients being treated with 78 Gy (Figure 1). The decrease in ADT for low and intermediate risk patients in 2011-2012 may have contributed to the large number of late biochemical failures in the 78 Gy group (Figure 2A). The inclusion of patients treated with ADT means that we must be careful not to attribute any apparent differences in FFF entirely to dose effects. It seems likely that dose does, however, have some predictive effect on BF because the use of ADT was controlled for in the logistic regression models.
Regression analysis found that the incidence of toxicity was significantly predicted by the inclusion of ADT in the treatment regimen. Those patients treated with ADT had odds of experiencing toxicity ≥RTOG grade 2 that were 4.7 times greater than the odds of patients that were not treated with ADT (95% CI 1.1-20.5, P = 0.04). This OR is remarkably high, and surprising considering the results of other studies. Three groups found that the use of adjuvant ADT in combination with RT led to small yet significant increases in GI toxicity14-15,17, and an analysis of three RTOG trials found that the addition of ADT to RT decreased the incidence of toxicity18. Given the wide 95% confidence interval from our regression analysis, it is possible that the true odds ratio is closer to the lower limit of the interval. It is also plausible that patients treated with ADT were not more susceptible to toxicity because of the ADT, but instead because those patients treated with ADT are usually high risk patients; these patients are typically treated with RT that includes the pelvis nodes. Pelvic RT increases the probability of toxicity symptoms and was not included as a variable in the logistic regression12-14,19.

There are several limitations to consider when interpreting our results. Many of the limitations are due, in part, to the retrospective nature of this review. The patient population was relatively small, especially for the toxicity analyses (2007-2011, N =184). The small sample size affected the statistical power of our tests, and most of our findings were non-significant. The significant p-values also hovered around the α value of 0.05. We must be cautious with the interpretation of these results due to the possibility of false-positive results.

Differences in sample size also affected our ability to make meaningful comparisons between the dose groups. The number of patients in the 78 Gy group was larger than the number of patients treated with <78 Gy, and the groups had different median follow-up times. The follow-up for the 78 Gy group (24 months) was shorter than the follow-up for the <78 Gy group (42 months). The discrepancy between the groups in follow-up further hindered our ability to make comparisons. Continued follow-up with patients treated with 78 Gy may allow for equivalent follow-up between the groups in any future analyses. Overall, the median follow-up time for the entire patient sample was less-than-optimal at 24 months. The short overall follow-up may be due, in part, to many patients being followed in the community. Elderly patients, in particular, are often followed in the community. Patients are also followed outside of the Cancer Centre for geographical reasons. This data could not be accessed for the purpose of this review.

CONCLUSION

The proportion of prostate cancer patients treated with dose-escalated radiotherapy at Grand River Regional Cancer Centre has gradually increased from the years 2007-2012 inclusive. Our analysis suggests a corresponding improvement in biochemical control, without any increase in the incidence of acute GU or GI toxicity. Prospectively collected late radiation toxicity data would be valuable, because limitations in dose are more commonly related to late/chronic complications rather than acute symptoms. Longer follow-up and efforts to capture follow up data for patients being followed in the community are needed to improve our ability to make comparisons and further improve confidence in our results. Nonetheless, the results of our analysis suggest that the continuation of dose-escalated radiotherapy at GRRCC should be recommended for the benefit of our patients.
Figure 1. Trend in dose-escalated radiotherapy for prostate cancer patients treated at Grand River Regional Cancer Centre between the years 2007-2012.

The total number of patients treated at Grand River Regional Cancer Centre within each year, further divided into dose groups. The doses indicated represent the total dose of radiation delivered with 2 Gy daily fractions the prostate. N = 246

Figure 2. Freedom from biochemical failure (BF) during the post-radiotherapy follow-up period for patients treated between the years 2007-2011 inclusive, using Kaplan-Meier analysis.

A) Comparing the freedom from BF between <78 Gy and 78 Gy dose groups, without stratification. Log-rank statistic, P = 0.7. B) Comparing the freedom from BF between <78 Gy and 78 Gy dose groups, intermediate risk group only. Log-rank statistic, P = 0.07. Note that Kaplan-Meier Analyses were not performed for the low and high D’Amico risk groups because there were not any BF events in these groups during the post-RT follow-up periods for patients treated between the years 2007-2011.
### Table 1: Demographics of Population

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<table>
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<tr>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
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</tr>
<tr>
<td>Mean</td>
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</tr>
<tr>
<td>Standard Deviation</td>
<td>6</td>
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<tr>
<td>Minimum</td>
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<tr>
<td>Maximum</td>
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<td><strong>Dose (Gy)</strong></td>
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<td>Mean</td>
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<tr>
<td>Standard Deviation</td>
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<td>Minimum</td>
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<tr>
<td>Maximum</td>
<td>78.0</td>
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<td><strong>PSA (ng/ml)</strong></td>
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<tr>
<td>Mean</td>
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<td>High</td>
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<td>Mean Months to BF</td>
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<td>Standard Deviation</td>
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<td>Maximum Months</td>
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<tr>
<td><strong>Death</strong></td>
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<td>Mean Months to Death</td>
<td>19</td>
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<tr>
<td>Standard Deviation</td>
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<td>Minimum</td>
<td>6</td>
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<tr>
<td>Maximum</td>
<td>42</td>
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<tr>
<td>Total Number of Cases</td>
<td>9</td>
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**BF = PSA of nadir + 2**

**PSA = Prostate serum antigen**

**Risk = D’Amico risk category - see text for criteria**

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<table>
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<tr>
<td><strong>Median Follow-Up Months</strong></td>
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<td>&lt;78 Gy group</td>
<td>42</td>
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<tr>
<td>[N = 77]</td>
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<tr>
<td>79 Gy group</td>
<td>24</td>
</tr>
<tr>
<td>[N = 168]</td>
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<tr>
<td>All patients</td>
<td>24</td>
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<td>Total Population</td>
<td>246</td>
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Table 2: Cross-tabulation Results of 78 Gy vs. <78 Gy in Terms of Biochemical Failure and Toxicity

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Toxicity</th>
<th>P- Value</th>
<th>Biochemical Failure</th>
<th>P- Value</th>
<th>ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>78 Gy</td>
<td>10.1%</td>
<td>0.8</td>
<td>4.2%</td>
<td>0.03†</td>
<td>11%</td>
</tr>
<tr>
<td>&lt;78 Gy</td>
<td>9.3%</td>
<td></td>
<td>11.5%</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

Biochemical Failure = nadir + 2
Toxicity = GI or GU toxicity symptoms of RTOG grade ≥ 2
P-Value = calculated using Pearson’s chi-square test
† A significant Pearson’s chi-square value.

Table 3: Logistic Regression Results of 78 Gy vs. <78 Gy for Biochemical Failure and Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio*</th>
<th>95% CI*</th>
<th>P&lt;0.05*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical Failure (BF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>78 Gy (&lt;78 Gy)</td>
<td>0.17</td>
<td>0.032-0.915</td>
<td>0.04†</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>78 Gy (&lt;78 Gy)</td>
<td>1.67</td>
<td>0.294-9.517</td>
<td>0.6</td>
</tr>
<tr>
<td>ADT (No ADT)</td>
<td>4.71</td>
<td>1.080-20.506</td>
<td>0.04†</td>
</tr>
</tbody>
</table>

Total Population: 184
Reference group included in parentheses
BF = nadir + 2
Toxicity = GI or GU toxicity symptoms of RTOG grade ≥ 2
ADT = Androgen Deprivation Therapy
95% CI = 95% Confidence Interval for odds ratio estimate
P<0.05 = calculated using chi-square test

*Statistics included in table are for the higher dose groups (i.e. 78 Gy).
Odds ratios of reference groups are the inverse of the values presented in the above.
†A significant chi-square value for the maximum likelihood estimate used to calculate odds ratio.

Table 4: Logistic Regression with Toxicity as Outcome - Odds Ratio Estimates

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference Group</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P&lt;0.05</th>
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<tbody>
<tr>
<td>Age</td>
<td>N/A</td>
<td>0.975</td>
<td>0.894-1.064</td>
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<tr>
<td>2011</td>
<td>2007</td>
<td>0.365</td>
<td>0.053-2.508</td>
<td>0.31</td>
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<td>0.146</td>
<td>0.021-1.032</td>
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<td>2009</td>
<td>2007</td>
<td>0.172</td>
<td>0.022-1.368</td>
<td>0.10</td>
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<td>2008</td>
<td>2007</td>
<td>&lt;0.001</td>
<td>&lt;0.001-&gt;999.99</td>
<td>0.96</td>
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<tr>
<td>78 Gy</td>
<td>&lt;78 Gy</td>
<td>1.674</td>
<td>0.294-9.517</td>
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<tr>
<td>ADT</td>
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<td>1.080-20.506</td>
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<td>Low Risk</td>
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<td>0.184-3.203</td>
<td>0.72</td>
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</table>

ADT = Androgen Deprivation Therapy
95% CI = 95% Confidence Interval for odds ratio estimate
P<0.05 = calculated using chi-square test

*Statistics included in table are for the Effect groups [e.g. 78 Gy].
Odds ratios of reference groups are the inverse of the values presented in the above.
†A significant chi-square value for the maximum likelihood estimate used to calculate odds ratio.
### Table 5: Logistic Regression with Biochemical Failure as Outcome - Odds Ratio Estimates

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference Group</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P&lt;0.05</th>
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<td>1.897</td>
<td>0.190-18.968</td>
<td>0.59</td>
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<tr>
<td>2011</td>
<td>2007</td>
<td>1.057</td>
<td>0.128-8.76</td>
<td>0.96</td>
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<tr>
<td>2010</td>
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<td>1.502</td>
<td>0.198-11.389</td>
<td>0.69</td>
</tr>
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<td>0.137-5.661</td>
<td>0.89</td>
</tr>
<tr>
<td>2008</td>
<td>2007</td>
<td>1.006</td>
<td>0.911-1.112</td>
<td>0.89</td>
</tr>
<tr>
<td>78 Gy</td>
<td>&lt;78 Gy</td>
<td>0.172</td>
<td>0.032-0.915</td>
<td>0.039†</td>
</tr>
<tr>
<td>ADT</td>
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<td>0.515</td>
<td>0.052-5.129</td>
<td>0.57</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Low Risk</td>
<td>1.980</td>
<td>&lt;0.001-&gt;999.99</td>
<td>0.99</td>
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<tr>
<td>High risk</td>
<td>Low Risk</td>
<td>N/A</td>
<td>N/A</td>
<td>0.95</td>
</tr>
</tbody>
</table>

ADT = Androgen Deprivation Therapy  
95% CI = 95% Confidence Interval for odds ratio estimate  
P<0.05 = calculated using chi-square test

*Statistics included in table are for the Effect groups [e.g. 78 Gy].  
Odds ratios of reference groups are the inverse of the values presented in the above.  
†A significant chi-square value for the maximum likelihood estimate used to calculate odds ratio.
References


Lung cancer is a predominant cause of cancer-related morbidity and mortality. Early detection of lung cancer can result in much better outcomes. Thus, there is widespread demand for the development of a screening program to identify lung cancer in chronic smokers. Clinical trials and meta-analyses were compared in order to evaluate the utility of screening interventions. Initial trials using chest radiography and sputum cytology screening did not reveal a significant improvement in mortality outcomes.

The National Lung Screening Trial (NLST) was the first to demonstrate a significant reduction in the relative risk of death among subjects who were screened with low-dose computed tomography (CT) compared to chest radiographs alone (RR 0.8, 95% CI 0.70 to 0.92). The NLST has sparked significant interest because it showed the potential benefit of a useful screening program that could be implemented on a large-scale. With a common goal towards reducing lung cancer-related mortality, clinical trials further exploring CT screening have started globally. The results of these trials, along with further studies, are necessary to determine which patient subgroups will benefit most from screening with low-dose CT.

Screening with chest radiographs have been studied at great length in high risk individuals. A meta-analysis looking at nine separate trials assessing the utility of chest radiographs for lung cancer screening, eight of which were randomized controlled trials, included a total of 453,965 subjects. Several of these trials compared outcomes based on screening frequency while others compared screening against no screening. No significant mortality benefit was detected for screening regimens using chest radiography.

Research has been undertaken to determine if the addition of sputum cytology to chest radiography would improve lung cancer detection and survival. Sputum provides the added benefit of obtaining a sample of potentially malignant cells. Several trials across North America and Europe evaluated this screening regimen in high-risk individuals. A meta-analysis reviewed each of these studies, which included a total sample size of over 50,000 individuals. Again, no significant mortality benefit was detected.
Recently, researchers have started exploring low-dose computed tomography (CT) as a possible screening method. The purpose of this review is to provide a thorough overview of the current evidence for CT screening.

**METHODS**

Data for this review were identified by reviewing the latest expert consensus guidelines on lung cancer screening (Table 1). Bibliographies from the guidelines were also reviewed to identify relevant studies.

**CT SCREENING National Lung Screening Trial**

Initially prohibited for screening purposes due to excessive radiation, recent advances in radiation dose reduction techniques have allowed for low-dose CT to be performed safely.

The National Lung Screening Trial (NLST) hosted in the United States was the largest study ever performed to explore CT screening for lung cancer. Its primary outcome was lung cancer-specific mortality. In total, 53,454 high-risk individuals, between the ages of 55 to 74, who had smoked at least 30-pack years, or had quit less than 15 years ago were included. Patients with a prior diagnosis of lung cancer or who had previously received a CT scan within the last 1.5 years were excluded.

The study population was randomized into two arms. The screening intervention group was assigned to a total of three low-dose CT scans at annual intervals. The control group did not receive CT scans throughout the trial and instead received three chest radiographs at annual intervals. Baseline characteristics, including smoking history, were similar between the study arms.

Fellowship-trained thoracic radiologists interpreted the results of each scan. Several possible pre-defined findings led to a ‘positive’ screen for suspicion of cancer. Any CT scan or radiograph with a non-calcified node with a diameter of at least 4 mm was considered a positive result. Other possible image findings including lymph node enlargement and pleural effusions were also designated as positive. Individuals with positive results were given further diagnostic follow-up and medical care based on the recommendations of the radiologist and other healthcare providers.

The NLST was stopped early when interim analysis identified that CT screening led to a significant reduction in lung cancer specific mortality (RR=20%; 95% CI, 6.8% to 26.7%; P=0.004). The CT arm resulted in lung cancer death rate of 247 per 100 000 person-years compared to 309 deaths per 100 000 person-years in the control arm. Consequently, the NLST showed that a screening intervention could lead to measurable improvements in lung cancer-related mortality.

In each of the three screening tests performed on study participants, the low-dose CT arm had a much higher incidence of positive image findings. In the first screen, 27.3% of participants receiving CT scans had a positive result compared to only 9.2% in the chest radiograph arm. Subsequent screens for the next two years showed a similar trend at 27.9% vs 6.2% and 16.8% vs 5.0%. After compiling the results from all three screening tests, an overall 39.1% of participants in the low dose-CT arm had at least one positive result compared to 16.0% in the control arm after three years. Further assessment revealed a positive screen results in a false positive rate of 96.4% in the low-dose CT group and 94.5% in the chest radiograph group. Overall, the rate of false positives was similar in both arms of the trial, but participants in the CT group had true positive test results almost three times as often.

**Limitations and Concerns**

When interpreting results of the NLST, several limitations must be considered. Image interpretation was performed by thoracic fellowship-trained radiologists. Additionally, lung cancer therapy was performed by highly-specialized surgeons, respirologists, oncologists, and radiation oncologists. If screening were to be implemented in a general community setting, it is unknown how varying proficiency among specialists could affect outcomes. This raises doubt with respect to the reproducibility of the NLST results on a national scale.

Other concerns with the NLST include overdiagnosis and healthy volunteer biases. Overdiagnosis bias refers to the detection and diagnosis of asymptomatic cancers that would not have affected life expectancy. By confirming a cancer diagnosis that would have not have had an impact on mortality outcome, the potential benefits of a screening intervention may be artificially inflated. Healthy volunteer bias is based on the premise that individuals who typically volunteer for clinical studies are usually healthier.

Another limitation associated with CT screening is the high rate of false positives. Elevated false positives lead to more unnecessary diagnostic follow-up that is often invasive and poses its own risks. For example, transbronchial biopsy carries the potential risks of hemorrhage, pneumothorax, and pneumothorax requiring a chest tube. Additionally, the high false positive rate can lead to negative psychosocial consequences including anxiety and depression. Finally, there is the potential for CT screening to lead to radiation-induced cancers. It is estimated that 1.5% to 2% of all cancers in the United States will be attributed to the use of CT scans in the near future. Having continuous screening scans can lead to an excessive cumulative radiation dose.

With any intervention in healthcare, it is critical to consider cost effectiveness to ensure sustainability. Preliminary studies in the American setting have estimated the cost of annual lung cancer screening to be 81,000 United States Dollars (USD) per quality-adjusted life year (QALY) gained. 100,000 USD per QALY is typically considered the threshold for cost-effectiveness in a screening program. Relevant changes pertaining to screening eligibility, frequency, diagnostic thresholds, and follow-up treatments can have a major effect on the cost model. Additionally, studies evaluating the potential cost-efficacy in a public healthcare model, such as the Canadian model, are still required.
Lung Cancer Screening: A Clinical Review

**Current Recommendations**

Current consensus guideline recommendation statements from various North American medical societies and governmental agencies can be found in Table 1.

**Ongoing and Future Trials**

In addition to the NLST, there are several other trials assessing the utility of low-dose CT screening for lung cancer.

To date, the NLST is the only trial specifically powered to detect a mortality benefit for CT screening. Other much smaller and insufficiently powered studies, such as DANTE, have found no significant mortality difference between screening and non-screening groups. Subsequent ongoing studies have compared varying frequencies of CT screening as well as CT screening versus usual care, as opposed to chest radiography. Plans are underway to amalgamate the results of all European studies on completion in order to reach sufficient power to detect a significant difference in mortality. The patient population, results, strengths and weaknesses of all other studies on CT screening are summarized in Table 2.

**Table 1**

<table>
<thead>
<tr>
<th>Agency or Society</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF17</td>
<td>The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.</td>
</tr>
<tr>
<td>CancerCare Ontario18</td>
<td>Screening for lung cancer with LDCT is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years who currently smoke or have quit within the past 15 years and are disease free at the time of screening.</td>
</tr>
<tr>
<td>American College of Radiology19</td>
<td>The United States Preventive Services Task Force (USPSTF) has issued a recommendation (Grade B) for low-dose computed tomography (CT) lung cancer screening of adults aged 55 to 80 years who have a 30-pack-per-year smoking history and currently smoke or have quit within the past 15 years. The ACR supports this recommendation.</td>
</tr>
<tr>
<td>American Cancer Society20</td>
<td>The American Cancer Society recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with patients aged 55 to 74 years who have at least a 30-pack-year smoking history, currently smoke or have quit within the past 15 years, and who are in relatively good health.</td>
</tr>
<tr>
<td>American Association of Thoracic Surgeons21</td>
<td>The American Association for Thoracic Surgery guidelines call for annual lung cancer screening with low-dose computed tomography screening for North Americans from age 55 to 79 years with a 30 pack-year history of smoking. Long-term lung cancer survivors should have annual low-dose computed tomography to detect second primary lung cancer until the age of 79 years. Annual low-dose computed tomography lung cancer screening should be offered starting at age 50 years with a 20 pack-year history if there is an additional cumulative risk of developing lung cancer of 5% or greater over the following 5 years. Lung cancer screening requires participation by a subspecialty-qualified team.</td>
</tr>
<tr>
<td>American College of Chest Physicians22</td>
<td>For smokers and former smokers ages 55 to 74 who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, ASCO suggests that annual screening with LDCT should be offered over both annual screening with chest radiograph or no screening, but only in settings that can deliver the comprehensive care provided to NLST participants. For individuals who have accumulated fewer than 30 pack-years of smoking, are either younger than 55 or older than 74, or who quit smoking more than 15 years ago, as well as for individuals with severe comorbidities that would preclude potentially curative treatment and/or limited life expectancy, ASCO suggests that CT screening should not be performed.</td>
</tr>
</tbody>
</table>

In addition to chest radiographs and CT scans, there have been other proposed imaging modalities that may have potential as a screening intervention such as endobronchial ultrasounds and positron emission tomography. However, there have not been clinical trials exploring the screening utility of these tests.11

**CONCLUSIONS**

Current evidence suggests that low-dose CT screening leads to a significant reduction of mortality in high-risk patients. Various North American governmental and non-governmental medical societies have advocated national screening programs. The results of several ongoing trials may resolve the potential limitations of CT screening which would enable implementation of a more widely accepted national screening program.
### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population and Design</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Main Results</th>
<th>Strengths and Weaknesses</th>
</tr>
</thead>
</table>
| NLST9                         | 53,454                      | Inclusion:  
- Male and female between 55-74 years old 
- 30+ pack-year history 
- Quit smoking <15 years ago 
- Can lie on back with arms raised over head  
Exclusion:  
- Metallic implants in chest or back 
- History of lung cancer 
- History of lung removal 
- Unexplained weight loss of over 15 pounds in the last 12 months 
- CT Chest in the last 18 months 
- Participation in another cancer screening trial 
- Recent hemoptysis | Significant lung-cancer specific mortality reduction with LDCT compared to the chest radiograph group. RR = 20% (95% CI, 6.8 to 26.7; P=0.004) | Strengths:  
- Large study powered to detect mortality 
- High adherence rate 
- High followup rate 
- Well-defined rigorous inclusion criteria  
Weaknesses:  
- Concern over reproducibility 
- Overdiagnosis bias 
- Healthy volunteer bias 
- Using chest radiography as control group limits the ability of this trial to answer the question of whether low-dose CT provides a mortality benefit over no screening |
| DANTE7                        | 2,811                       | Inclusion:  
- Minimum 60 years of age 
- Males only 
- Current or former smokers with a 20+ pack-year history  
Exclusion:  
- A history of any cancer within the last 10 years 
- Comorbid conditions with a life expectancy of under 5 years 
- Inability to comply with any component of the screening or follow-up protocol | Twenty patients in the LDCT group (1.6%) and 20 controls (1.7%) died of lung cancer 
Non-significant difference led authors to conclude mortality benefit from lung cancer screening by LDCT might be much smaller than anticipated | Strengths:  
- Control arm had no screening, which is an accurate representation of the effects of low-dose CT compared to usual care  
Weaknesses:  
- Small study population not powered to detect mortality 
- Study population male only |
| Danish Lung Cancer Screening Trial14 | 4,104                      | Inclusion:  
- 20+ pack-year history and currently smoking 
- Or, former smokers 20+ pack-year history that quit after the age of 50 and <10 years ago 
- Men or women aged 50-70 
- Be able to climb 2 flights of stairs (36 steps) without pausing 
- FEV-1 at least 30% of normal predicted value  
Exclusion:  
- Body weight above 130 kg 
- Previous treatment for lung cancer, breast cancer, or hypernephroma 
- History of any cancer within the last 5 years 
- History of tuberculosis within the last 2 years 
- Any comorbidity that would shorten life expectancy to under 10 years 
- CT scan within the last 12 months | More lung cancers were diagnosed in the screening group [69 vs. 24, p=0.001] 
More lung cancers were low stage (48 vs. 21 stage I-IIIB non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC), p=0.002) in screening group 
High-stage lung cancer was the same [21 vs 16 stage IIIA-IV NSCLC and extensive stage SCLC, p=0.509] between the two groups 
No mortality difference | Strengths:  
- High followup rate 
- Control arm had no screening, which is an accurate representation of the effects of low-dose CT compared to usual care  
Weaknesses:  
- Overdiagnosis bias 
- Small study population not powered to detect mortality |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
</table>
| MILD  | 4,099        | Male or Female smoker with a 20+ pack-year history  
• Former smoker with 20+ pack-year history that quit <10 years ago | None reported | Lung cancer mortality rates were 109, 109 and 216/100 000 between the control, biennial and annual low-dose CT groups, respectively  
No significant mortality benefit of LDCT screening | Included an additional group that looked at any possible benefits of having an annual vs biennial CT screen |
| LUSI  | Ongoing      | Male or female between the ages of 50-79 and with 'heavy' smoking history | Not Available | Ongoing |
| UKLS  | 32,000       | Male or female between the ages of 50-75  
• Target population with 5% risk of developing lung cancer in 5 years selected using Liverpool Lung Project risk prediction model | Inability to give consent  
• Comorbidity that would counteract either screening or treatment if lung cancer were detected.  
• Technical reasons including a weight >200 kg and inability to lie flat  
• CT performed within 1 year of the invitation to be screened | Ongoing |
| NELSON| 15,822       | Males aged 50-75  
• Current smokers who smoked more than 15 cigarettes daily for over 25 years or more than 10 cigarettes daily for over 30 years  
• Former smokers with 10 years or less of cessation, and above criteria | Inability to climb two flights of stairs  
• Body weight ≥140 kg  
• Lung cancer less than 5 years ago or still under treatment  
• Current or past renal cancer, melanoma or breast cancer  
• Chest CT within the last 12 months | Of the 7500 screened, 196 had a positive result, with 70 having lung cancer. The lung cancer detection rate among the screened population was 0.9%. Screening sensitivity 84.6% and specificity at 98.6%  
10-year lung cancer mortality results yet to be released | Instead of defined inclusion criteria, NELSON used a questionnaire to determine the optimum criteria for balance between risk profile, sample size, and required rates of participation and retention  
NELSON participants are followed up over a long period of 10 years  
Used multiple readers to improve accuracy |
ITALUNG15 3,206
RCT
Comparison: LDCT vs Usual Care

Inclusion
• Male or female between the ages of 55–69
• Current smokers with a 20+ pack-year history
• Former smoker with 20+ pack-year history that quit <10 years ago

Exclusion
• History of previous cancer
• General conditions precluding thoracic surgery
• Inability to give consent

Not available

Strengths
• Control arm had no screening, allowing for comparison of low-dose CT to usual care

Weaknesses
• Small overall study population, not powered to detect significant mortality benefit

CXR: Chest Radiography; LDCT: Low-dose computed tomography; RCT: Randomized Controlled Trial

References
Clinical Reviews

Cell Transplant Therapy for Parkinson’s Disease: Triumphs and Challenges in Clinical Research

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Conflicts of Interest: The author has no conflict of interest to declare.

ABSTRACT:

Parkinson’s disease (PD) is a progressive neurodegenerative disorder resulting from the depletion of dopaminergic neurons of the midbrain. The dopamine precursor levodopa (L-Dopa) is often prescribed as the first line of treatment to alleviate symptoms. Extended L-Dopa therapy is associated with significant side effects that impact quality of life. The search for a treatment that targets the etiology of PD has lead to clinical trials of cell transplant therapy aimed at regenerating a functional dopaminergic midbrain. The appropriate cell type to use for PD transplant therapy is under investigation. The optimal cell type will have a minimal risk of tumorigenicity and will not require the use of immunosuppressive agents, while having the potential to show significant benefits in motor functioning and quality of life. Clinical trials have shown cell transplant therapy to be a safe intervention that can be tolerated well by patients. Sham-surgery clinical trials demonstrate a significant placebo effect and show a need for more double-blind controlled clinical trials in this field.

INTRODUCTION

Parkinson’s Disease (PD) is a progressive neurodegenerative disease characterized by impairments in motor control. The disease is understood to result from the degeneration of the dopaminergic neurons of the substantia nigra pars compacta. The nigrostriatal tract projects from the substantia nigra to the striatum of the basal ganglia, and is involved in both motor and emotional processing within the limbic system. PD patients suffer difficulty in both executing motor tasks and controlling movement. Symptoms of PD include bradykinesia, rigidity, resting tremor and postural abnormality. Additional changes in emotion and cognitive functioning may present. PD is a progressive disease that is non-life threatening, although life expectancy may be shortened due to complications of the disease.

To date there is no cure that can halt the progression of PD. The standard treatment approach is to replace the loss of dopamine in the brain. Since dopamine cannot cross the blood-brain barrier, the dopamine precursor levodopa (L-Dopa) is prescribed orally. L-Dopa therapy can alleviate symptoms of PD most effectively in the early stages of the disease. Long-term use of L-Dopa therapy is associated with a wide range of side effects that may significantly impact quality of life. A particularly concerning side effect of L-Dopa is dyskinesia, a movement disorder characterized by the loss of voluntary movements and the presence of involuntary movements. Most common is peak-dose dyskinesia that occurs shortly after patients have taken a high dose of L-Dopa medication. Patients may also experience diphasic dyskinesia as the concentration of L-Dopa in the body changes.

The experience of these side effects causes the L-Dopa treatment regimen to be unsatisfactory for many patients. Dopamine agonists are also used as a first line treatment option, and show less dyskinesia but have a different side effect profile. Current research efforts focus on finding alternative treatments that target the PD etiology rather than symptomatology. Stem cell therapy is a possible treatment option under investigation. The goal of stem cell therapy for PD is to recreate a functional dopaminergic midbrain. In theory, pluripotent stem cells transplanted into the midbrain will become incorporated into the surrounding neural connections and will differentiate into dopaminergic neurons in response to environmental cues. The historical risk of any stem cell transplant is failure of the implanted cells to integrate into the host environment. These rapidly dividing
cells are then at risk of progressing into tumor growth. Another possible option in cell transplant therapy for PD is to transplant fully differentiated cells that are dopaminergic in nature. In this scenario the transplanted cells would have a much lower risk of developing into tumor growth. The ability of these cells to become functionally integrated is still under study.

Clinical trials to date have shown controversial results for both the safety and efficacy of stem cell treatment for PD. The typical surgical procedure is to deliver multiple injections of cells to the striatum trans-cortically via a stereotactically guided straight cannula. Possible complications of this procedure include intracranial hemorrhage and cortical damage. The standard approach to clinical trials has been to compare a treatment group, in which participants receive cell transplant surgery, to a control group in which participants undergo sham-surgery. Clinical outcomes following surgery are typically quantified by the Unified Parkinson’s Disease Rating Scale (UPDRS), which includes measures of motor functioning, mental functioning, mood, behavior, and activities of daily living. Clinical trial participants usually remain on their regular antiparkinsonian medications following the surgical procedure. Clinical outcomes are recorded in both “off-medication” and “on-medication” states. The off-medication state is defined as no less than 12 hours following a patient’s previous dose of L-Dopa. This is usually first in the morning before the patient takes their medication. The on-medication state is defined as a patient’s highest level of functioning during the daytime after they have taken their medication. In double-blind clinical trials, participants are typically followed by a physician who is blinded to their assigned treatment group. Medication adjustments are made as needed according to the patient’s functioning, and changes are recorded as tertiary clinical outcomes. Molecular outcomes following cell transplant can be measured by fluorodopa (F-Dopa) positron emission tomography (PET). This technique involves IV administration of F-Dopa, a radiolabelled dopamine precursor. F-Dopa crosses the blood-brain barrier and is converted to fluorodopamine by midbrain neurons. PET detection of increased F-Dopa uptake following cell transplant suggests an improved functional dopaminergic midbrain and success of the transplant at the molecular level.

The need to use immunosuppressive agents in neurological stem cell transplant remains undetermined. The brain is considered an immune privileged site that can typically withstand the introduction of antigens without eliciting an immune response. However, neural cell transplant research has found T lymphocytes and natural killer cells to be capable of targeting stem cells implanted in the brain. The possibility of rejection is a serious concern as it will diminish the possible benefits of cell transplant treatment. The risk of transplanted cells inducing graft-versus-host disease will depend on the cell type, but is less likely in immunologically immature cells such as human embryonic stem cells. Since the benefits of cell transplant therapy for PD may not outweigh the risks associated with systemic immunosuppression, the search for a cell type that will not require immunosuppression is critical if the treatment is to be introduced into clinical practice.

Embryonic and Fetal Stem Cell Transplant

Early PD stem cell experimentation involved the use of embryonic and fetal stem cells from human and animal sources. The first clinical trials began in the late 1980’s after promising evidence emerged from rodent and primate studies. Embryonic xenografts, stem cells from non-human species, have been trialed. In one study unilateral transplantation of embryonic ventral mesenteric porcine tissue was trialed in 12 PD patients. A local immunosuppression technique was used in this study in order to avoid systemic immunosuppression. The immunosuppressant cyclosporine was implanted in combination with the stem cells and also given pre- and post-operatively to 6 patients. Alternatively, in the other 6 patients the transplanted cells were treated with a monoclonal antibody directed against major histocompatibility complex I (MHC I). Surgery was tolerated well by all patients. Outcomes were measured by the UPDRS for 1 year post-surgery. A few patients showed notable improvement in functioning by 3 months following the intervention, while most patients showed little to no change in symptoms. Important to note is the lack of a control group in this pilot study. The patients showed only marginal improvements, which could be attributed to a placebo effect.

Extensive work has been done using human embryonic stem cell sources. One group of researchers has performed human embryonic stem cell transplants in more than 60 patients in total. In these clinical trials patients did not receive immunosuppressants. In the largest double-blind clinical trial performed by this research team, 40 patients were randomized to receive either cell transplant into the putamen or sham surgery. One year after surgery clinical improvement and an increase in putamen F-Dopa uptake was found compared to controls in patients who were younger than 60 years of age. The greatest improvement was seen in young male patients with less severe disease. After completion of the blinded study, 14 of 20 patients in the control group chose to undergo cell transplant. In a long-term study patients who received cell transplant were found to show continued improvement up to four years post-surgery. At this time the effect of age and sex was no longer significant. An additional increase in F-Dopa uptake was found at this time, indicating continual functional integration of transplanted cells in the putamen. Clinical outcomes were shown to correlate with F-Dopa uptake as detected by PET scanning. Pre-surgery neurotrophic factor treatment is recommended to increase the survival of implanted cells and maximize success. Through many years of work, the researchers have concluded that response to stem cell therapy correlates with an individual’s response to L-Dopa therapy prior to surgery. They have also concluded that transplant patients who show improvement in motor function have a tendency to develop dyskinesias after discontinuing L-Dopa medication.

In a long-term case study, two patients who received human mesencephalic embryonic stem cell transplantation were followed for eight years post-surgery. The patients’ response to treatment was monitored over time using single-photon emission computed tomography (SPECT) of radioligands for striatal dopamine transporters (DAT). This is an alternative method to measuring striatal uptake of F-Dopa with PET scanning. The patients showed clinically significant improvement in motor function over the eight
years, correlating with increased DAT binding. However, both patients developed moderate-severe off-medication dyskinesia.

Another group of researchers has performed double-blind control trials using human fetal cell transplant. In one study 34 patients were randomized to receive bilateral fetal nigral cell transplant from one donor, bilateral transplant from four donors, or bilateral sham surgery. Outcomes were measured by PET detection of F-Dopa uptake and UPDRS for 2 years after the intervention. Patients were treated with the immunosuppressant cyclosporine and tolerated it well. PET detection showed an increase in putamen F-Dopa uptake in patients who received transplantation, the largest increase being in patients who received transplant from four donors. Adverse events occurred more commonly in subjects who underwent transplant than those who received sham surgery. The most common side effect was off-medication dyskinesia. Results showed that there was no overall significant benefit of receiving transplant compared to sham surgery. The patients who had the least severe symptoms prior to intervention showed a benefit compared to control patients, suggesting the intervention worked to slow disease progression but did not alleviate symptoms in patients with severe PD.

A common theme in the results of embryonic and fetal stem cell treatment for PD is the presence of off-medication dyskinesias in transplant recipients. This finding is very concerning to the future of stem cell therapies as dyskinesias can negatively and significantly impact quality of life. The 34 participants of a double-blind controlled study described above were assessed specifically for off-medication dyskinesias for up to two years following fetal nigral cell transplant. Videorecordings were taken of the patients during on- and off-medication periods, and were analyzed by a movement disorders specialist who was blinded to the patient groups. The results showed 13 of the 23 transplant patients developed off-medication dyskinesias, whereas none of the patients in the placebo group showed this side effect. Patients who developed off-medication dyskinesia had been taking lower doses of L-Dopa than the transplant patients who did not. Interestingly, the patients who showed off-medication dyskinesia also showed greater improvement in UPDRS motor scores in the months following surgery. The researchers speculate these patients were more sensitive to both the benefits and side-effects of dopaminergic therapy.

In addition to the clinical findings of off-medication dyskinesias, other scientific and ethical issues inhibit the advancement of embryonic stem cell transplant for patients suffering from PD. Fetal and embryonic cells show more potential for tumorigenicity than other stem cell types. Animal studies that initially showed promising results from embryonic stem cell transplant later showed discouraging findings of tumor growth. The tumorigenicity of pluripotent embryonic stem cells is due to their potential to rapidly proliferate. Embryonic stem cells have a much greater capacity to divide and differentiate than adult-derived stem cells. Beyond the technical challenges of using embryonic stem cells are the ethical restrictions that limit the research possibilities in this area. Access to embryonic stem cell tissue for research purposes remains restricted and public support for the use of these tissues is limited. The use of adult-derived stem cells is much less controversial. For these reasons, researchers have been exploring the possibility of using stem cells from adult tissues in the treatment of PD.

### Adult Cell Sources

Several adult cell sources have been trialed. Autologous transplant is ideal to eliminate the need to administer immunosuppressant therapy. Patient-derived induced pluripotent stem cells (iPSCs) have held great promise in theory due to their capacity to divide and differentiate without any risk of rejection or inducing graft-versus-host disease. The technique involves culturing patient-derived somatic cells, such as skin cells, in vitro with growth and transcription factors that promote differentiation into dopaminergic neurons. Transplantation of iPSC-derived dopaminergic neurons have been tested in vivo using neurotoxin-induced parkinsonian animal models. An important finding was that iPSC-derived dopaminergic neurons from patients with familial PD show a parkinsonian phenotype. This renders the technique unsuitable for patients with familial PD, about 5% of the PD population. These cell lines are instead useful as a research tool to create a cellular model of PD.

Autologous transplant using other tissue types have been tested in clinical trials. Carotid body cells were transplanted into the striatum to treat PD in one study. The reasoning behind using this cell source is the nature of the glomus cells of the carotid bodies to release dopamine in response to low arterial oxygen concentration. These cells also grow and proliferate under hypoxic conditions, making them ideal for transplant into the cell-depleted PD striatum. In a pilot study, 6 patients received autologous cell transplant using glomus cells resected unilaterally from their own carotid body tissue. Participants tolerated the surgery well without serious adverse events. Improvement was shown in UPDRS scores 18 months post-surgery, but this was less significant for older patients. Histology studies of the carotid body tissue showed less glomus cells and more fibrous carotid body tissue in older patients, correlating with clinical outcomes. It is important to note that this pilot study was uncontrolled and may be susceptible to the placebo effect.

Autologous transplant using bone-marrow derived stem cells are another option under experimentation. In a pilot study 7 patients suffering from PD received unilateral transplantation of bone marrow-derived mesenchymal stem cells. Outcomes were measured using the UPDRS in on- and off-medication phases. Patients were also examined with MRI periodically following surgery, showing no notable changes and no evidence of tumor growth. No significant adverse events occurred. Patients showed marginal improvement in symptoms over a 2-year period and described a subjective improvement in well-being. There was no control group or blinding in this pilot study, and the results are therefore subject to the placebo effect.

A final cell type under consideration is human retinal pigment epithelial (RPE) tissue. These are potential candidates for PD treatment due to their characteristic secretion of L-Dopa. However, autologous transplant is not an option for this type of tissue. In a controlled clinical trial 35 patients suffering with PD received
intrastrital implantation of human postmortem RPE cells.\textsuperscript{23} The control group of 36 PD patients received sham surgeries. A large portion of the participants in this study experienced adverse events related to the surgical procedure, and these were more serious in the cell implantation group. Overall, patients that received RPE cell transplantation did not show a significantly greater improvement in their condition compared to the control group. A substantial placebo effect appeared to have occurred, emphasizing the need to continue double-blind studies in this field.

Human RPE cells have also been tested in a more recent pilot study.\textsuperscript{24} In an uncontrolled clinical trial 12 patients received unilateral cell transplantation from human postmortem RPE cells. Outcomes were measured intermittently for up to 3 years post-implantation using the UPDRS in on- and off-medication phases. PET scanning was used to detect DAT uptake pre and post-operatively, and showed increased DAT uptake 6 months after surgery in most patients. Participants did not experience any serious adverse events. Overall the patients showed improvement in their condition and a reduction in parkinsonian symptoms following surgery. Their improvements were greatest 12 months post-surgery and were less appreciative at 36 months. Since a control group was not used in this study, a placebo effect cannot be ruled out. Importantly, the results of this study indicate the procedure can be done safely.

**Clinical Considerations**

The limited number of randomized controlled trials of stem cell transplant for PD reflects the nature of the intervention and the challenges of conducting research in this area. Stem cell transplant surgery is risky and invasive, and recruiting participants for clinical trials can be difficult. A recent article addresses these challenges and makes recommendations for the process of selecting participants for first-in-human (FIH) stem cell trials, in which new cell types or surgical techniques are tested.\textsuperscript{25} In order for an intervention to be acceptable to enter FIH trials, a level of safety, efficacy, and competitiveness relative to existing treatments must be established based on results of laboratory and animal studies. The risk-benefit ratio of enrolling a patient in an FIH trial will depend on these factors and also on the severity of the patient’s disease. The authors argue that FIH trials for stem cell therapy may be too risky and invasive to be carried out in healthy individuals or even patients in early stages of PD. However, subjects at the final stages of their disease are unlikely to show promising results in response to the FIH intervention. The authors suggest selecting patients in order to minimize risk, maximize the ability to analyze results, and enhance the benefits to individual subjects and society.\textsuperscript{25,26}

The risks associated with stem cell transplant therapy will not be justifiable in clinical practice until the benefits are found to be substantially greater than current PD treatment options. To appreciate the benefits of therapy researchers must not only analyze changes in motor functioning but also the impact of treatment on overall quality of life. In a follow-up study of a double-blind controlled trial, 30 patients were assessed for one year following stem cell transplant for the impact of the intervention on their quality of life.\textsuperscript{25,27} Patients remained blinded to whether they received cell transplant surgery or sham surgery. Overall subjective quality of life did not differ between the treatment and control group. Interestingly, quality of life was measured as significantly higher for patients who believed they had received the cell transplant surgery. This highlights the influence of the placebo effect and the need for double-blind control studies in future research.

One aspect of quality of life that could be affected by cell transplant intervention is cognitive function. There is concern that the surgical procedure of stem cell transplant could damage the cortex and negatively impact cognitive functioning post-surgery. Cognitive function of embryonic stem cell transplant recipients have been assessed through neuropsychological evaluation using a battery of tests.\textsuperscript{25} The UPDRS and PET scanning were also used to allow interpretation of the cognitive test results. No significant difference in cognition pre- and post-surgery was found. This supports evidence that stem cell transplant can be safely performed.

**CONCLUSIONS**

The clinical studies discussed in this article outline important principles of cell transplant therapy for PD. The major risks of cell transplant therapy include tumor growth and the risks associated with immunosuppression. Additional risks include surgical complications such as intracranial hemorrhage and cortical damage. A feasible cell transplant treatment for PD would utilize a cell type that would not require immunosuppression and would be highly unlikely to cause tumor growth. Clinical trials seem to show that allographic embryonic stem cell transplant is possible without immunosuppression. The tumorigenicity of embryonic cells remains a concern from animal studies, although human clinical trials have not shown this adverse event. Ethical issues also restrict the use of embryonic stem cells in research. Finally, the clinical finding of off-medication dyskinesias drastically reduces the benefits of embryonic stem cell transplant compared with L-Dopa therapy.

Autologous cell transplant held great promise for the elimination of the need to administer immunosuppressants. The surgical procedures were well tolerated. However, improvements in clinical outcomes were not overly convincing. What has instead been convincing is the role of the placebo effect in clinical outcomes. The placebo effect has been a recurring theme in cell transplant studies for PD and a focus of this review article. Notably, the placebo effect is not unique to cell transplant therapy. Research in other treatment modalities for PD has also shown a role of the placebo effect. These include medical therapies, such as dopamine agonists, and surgical interventions including deep brain stimulation and subthalamic nucleus stimulation.\textsuperscript{29,30,31} The placebo effect of PD treatment is hypothesized to result from the effects of motivation and reward on dopamine action in the brain.\textsuperscript{32} The placebo effect has also been demonstrated in the treatment of other neurological disorders including multiple sclerosis and migraines. Increased medical attention that is associated with enrollment in a clinical trial may attribute to the placebo effect shared across multiple fields in neurological research.\textsuperscript{33} Surgical interventions have been found to show a more substantial placebo effect than medical
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therapies, illustrating the necessity of using double-blind clinical trials in surgical research. Recruiting participants for these studies is a challenge, however, and clinical trials often involve small numbers of patients. There is also a need to conduct long-term studies that will follow patients for many years after undergoing cell transplant surgery. If patients from previous clinical trials are followed up in the long-term, further improvements in their UPDRS scores might be found as the transplanted cells continue to be functionally integrated into the host midbrain.

It is important to note that the majority of clinical trials conducted to date included only PD patients who had responded well to L-Dopa therapy. This was decided to increase the likelihood of success of the clinical trials. If cell transplant were to be introduced into clinical practice, it would ideally be an option for patients who did not respond to other therapies. Future research will have to extend to include these patients in order to determine if this will be possible. Past trials have also shown that the best results were found in younger patients with mild disease. We hope that cell transplant therapy will one day be able to help patients with severe symptoms.

There remains to be many unknowns about stem cell therapy that prevent its introduction into clinical practice. Importantly, the clinical studies completed to date have shown cell transplant is an intervention that can be safely performed and well tolerated by patients. This is an achievement that opens the doors for continued intervention that can be safely performed and well tolerated by clinical trials completed to date included only PD patients who had responded well to L-Dopa therapy. This was decided to increase the likelihood of success of the clinical trials. If cell transplant were to be introduced into clinical practice, it would ideally be an option for patients who did not respond to other therapies. Future research will have to extend to include these patients in order to determine if this will be possible. Past trials have also shown that the best results were found in younger patients with mild disease. We hope that cell transplant therapy will one day be able to help patients with severe symptoms.

There remains to be many unknowns about stem cell therapy that prevent its introduction into clinical practice. Importantly, the clinical studies completed to date have shown cell transplant is an intervention that can be safely performed and well tolerated by patients. This is an achievement that opens the doors for continued work in this field to tap into the optimal cell type that can be used for therapeutic transplant.

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Piliriqatigiingniq: Working Together to Stop Tuberculosis in Northern Canada

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Every clinical story has a social story. It is Christmas, and I am visiting friends and family in my hometown, an Inuit community on the north coast of Labrador. Packing my computer into my favourite gift, a sewn sealskin case, I explain that I am heading up to the school to write about tuberculosis (TB). “There’s lots of TB here”, one of my friends shares, and she’s right. In 2009, Nunatsiavut experienced its third TB outbreak of the decade, with incidence rates peaking at 550 new cases per 100,000 people (1). As I listen to my friends share stories of their experiences with infection and treatment, it becomes clear that outbreaks like these are more than acute public health crises; they reveal chronic patterns of overcrowded housing, poor nutritional status, and low incomes that shape patterns of risk. These patterns can teach us a lot about how our communities and health systems are organized, and the paths from here to a more just and healthy society.

TB is a communicable disease caused by *Mycobacterium tuberculosis*, an almost exclusively human pathogen spread by the aerosolization and respiration of droplet nuclei. Communicability is determined by the intimacy and duration of exposure to an infected person, the number of bacilli discharged, adequacy of ventilation, and exposure of bacilli to sun or UV light (2). Host susceptibility to infection and disease is heightened with immunodeficiency, poor nutritional status, diabetes mellitus, renal disease, HIV/AIDS, or a history of TB infection (4). Keeping these factors in mind, exposure to an infectious case of TB may lead to initial infection, with approximately 5% of infections developing into primary TB disease and 95% into latent TB infection (LTBI). The risk of LTBI progressing to secondary (or reactivation) TB is closely related to immunocompetence, with immunocompromised people at higher risk of reactivation (3). The Canadian Tuberculosis Standards provide an excellent evidence-based approach to screening, diagnosis, and treatment, and should be reviewed by all health professionals working with Canadian populations at high risk of TB (3).

Global Health and Circumpolar Health

TB remains a major global health challenge. The WHO estimates that more than 2 billion people, fully one third of humanity, are infected with *M. tuberculosis*. In 2013, 9 million people developed active TB, a global incidence rate of 126 new cases per 100,000 people (5). While incidence has been falling since 2002 due to improved living conditions and the efforts of the WHO Stop TB Strategy (3), we also know that 1.5 million people died from the disease in 2013 alone (5). Such avoidable deaths, and their concentration among the poor, are an injustice on a grand scale. As the WHO Commission on Social Determinants of Health put it, “social justice is a matter of life and death” (6).

In Circumpolar countries, tuberculosis reached a global peak in the 1950s. In 1955, Greenland reported an incidence of 2,300 new cases per 100,000 people, the highest incidence anywhere in the world, with similar numbers reported across northern Canada and Alaska (7). Canada’s overall TB incidence has declined since the 1950s to an all-time low of 4.6 per 100,000 people in 2010, but this promising pattern has not been shared equally by all populations (3). New cases of active TB remain concentrated among foreign-born Canadians and Indigenous populations, especially Inuit (3).

A look at the average annual TB incidence rate in Canada’s four Inuit regions between 2001 and 2011 reveals a disturbing picture, with 17.7 new cases per 100,000 people in the Inuvialuit Settlement Region (northern Northwest Territories), 151 new cases per 100,000 people in Nunavut, 107 new cases per 100,000 people in Nunavik (northern Quebec), and 129 new cases per 100,000 people in Nunatsiavut (northern Labrador) (1). These active cases are potentially the tip of the iceberg of endemic TB infection in the North. Finding and treating these hidden cases is an important part of any effective strategy of TB prevention and control, just as contact tracing, prophylaxis, and disease treatment are core tasks of outbreak response (3).
Outbreaks of this preventable and curable disease are more than acute public health crises. They reveal chronic patterns of food insecurity, overcrowded housing, and income disparity that challenge our idea of Canada as a just society, and call on us to think upstream. Upstream thinking draws on a helpful metaphor – instead of standing downstream trying to help all those drowning in a river, why not head upstream to find out why people fall in, and work together to solve problems at their source? This is what public health and community medicine is all about. So what can TB in northern Canada teach us about thinking upstream?

**Partnerships**

Healthy partnerships are part of decolonizing public health practice in the North. For many Inuit, TB has too often meant a loss of control over their lives. Early TB control efforts were governed from Ottawa, with Inuit quarantined and evacuated to southern sanatoria thousands of kilometres from their families. This trauma continues to inform how many Inuit think about TB, and makes an ethic of partnership all the more important (1). Canada’s national Inuit organization, Inuit Tapiriit Kanatami (ITK), representing 55,000 Inuit living in 53 communities across the four Inuit regions, has developed a Inuit-specific TB Strategy with five priorities for action: 1) community education and mobilization, 2) intersectoral partnership towards addressing social determinants of Inuit health 3) evidence-based, Inuit-appropriate TB prevention, control, and care programs, 4) improved surveillance and research, and 5) better evaluation and reporting (1). ITK’s emphasis on community engagement and Inuit-appropriate practice are important signals in the context of decolonization (8). Pilirigatigiingmiq, the Inuit principle of working together for a common purpose (9), is an important guiding ethic for public health practice and TB prevention and control in the North.

**Health Systems**

Strengthening our public health and primary care systems is key to stopping TB. While access to TB treatment in the North is excellent overall, epidemiological trends affirm the need to keep improving our prevention efforts. Nunavut’s Taima TB project, which means “Stop TB” in Inuktitut, offers valuable lessons to TB prevention. Taima TB is a partnership between Inuit through Nunavut Tunngavik Inc, the Government of Nunavut, and scholars from the University of Ottawa. It included an awareness campaign followed by door-to-door in-home testing and treatment for people living in areas with high rates of TB, and resulted in a 33% relative increase in treatment completion for latent TB infection in the community (10). This project shows that participatory design, community mobilization, and case finding can complement existing contact tracing efforts and improve TB prevention.

**Housing**

Built environments shape our everyday lives, creating spatial and social patterns of risk. Ventilation, exposure to sunlight, and crowding are especially important indicators of risk for TB exposure, presenting an important design challenge for TB prevention (11). During the 1950’s, the Canadian government began settling Inuit into prefabricated housing not designed for large intergenerational families or Inuit hunting and harvesting activities (12). Today, 31% of Inuit live in crowded homes compared with 3% of Canadians, while 21% of Inuit live in houses needing repair compared with 8% of Canadians (13). ITK’s Inuit-specific TB strategy proposes improved housing quality and increased housing units as key solutions for reducing TB across the North (1). Improving access to adequate and affordable housing is a smart, upstream approach to TB prevention in the North.

**Nutrition**

Nutritional status is an important indicator of host susceptibility to infection. The high price of market food and the high cost of access to country food mean that too many people in the North do not have adequate access to healthy food. Statistics Canada estimates that the cost of providing a nutritious diet for a family of four in the North ranges from $350-400/week, compared to about $200/week in southern Canada (14). The 2007-2008 Inuit Health Survey found that 62.7% of Inuit households are food insecure, a rate six times higher than the Canadian average (15), and the highest rate among any indigenous population in the world living in a high-income country (16). The Inuit Health Survey also found that people living in food insecure homes had a significantly lower Healthy Eating Index, eating less vegetables, fruits, grains, and dairy products, and more high sugar foods compared to food secure homes (15). ITK’s Inuit-specific TB strategy notes that expanding and improving nutrition education, food subsidy, and harvester support programs is an important way to improve food security and nutrition, and could have “a substantial impact on improving Inuit health and the number of Inuit who develop TB disease” (1).

**Income**

Income is an important indicator of people’s control over their lives (17). It shapes people’s ability to pay for expenses like housing, clothing, food, and supplies for harvesting country food. Recognizing the importance of income as a social determinant of health, physicians and allied health professionals are increasingly exploring ways to coordinate with public services to improve income security for patients living in poverty (18). In 2005, Inuit median income was $16,699, markedly less than the $25,955 median income reported by non-Aboriginal Canadians or the $60,047 median income of the non-Aboriginal population living in Inuit communities across the North (14). Improving income security is an important part of addressing the social determinants of health, and may lead to improved tuberculosis prevention and control outcomes (11).

**Conclusion**

The challenge of stopping TB is also an invitation to think upstream and work together to build more healthy communities. Inuit are leading the way in designing upstream solutions to improve Inuit health and protect Inuit communities from TB. An upstream approach to TB prevention and control includes intersectoral action to improve health systems, housing, nutrition, and income security. This approach transcends a...
focus on any single disease, reducing risk for a broad assortment of communicable and non-communicable diseases, and creating the conditions for healthy communities. Just as tuberculosis shows how conditions of everyday life are embodied as disease, it can also teach us to think upstream and work together to build a more just and healthy society.

References


In June 2014, the American College of Obstetricians and Gynecologists published a Committee Opinion for physicians on the ethical treatment of obese women. The six-page document directs physicians to care for obese women according to the basic concepts of ethical medical treatment such as respect for autonomy, nonmaleficence, beneficence, and justice. Because all patients should be treated with compassion and without bias, it is interesting that the American College is compelled to remind physicians of the guiding principles of ethical medical treatment in the case of obese women. Undoubtedly obesity is stigmatized across Western society; yet, no similar list of recommendations has been devised for treating the obese patient who is male, despite comparable rates of obesity among American men and women (33.3% and 35.8%, respectively). With major sections devoted to the “medical risks of obesity,” the “increased resource utilization in the care of obese women,” “counseling,” “consultation and referrals,” and “the physician relationship and barriers to good medical care,” the College largely engages with material relevant to the care of obese patients of both sexes, despite limiting their discussion to women.

If physicians really are treating female obese patients in a more judgmental manner, as the creation of this June 2014 Committee Opinion implies, it is worth examining what exactly is more complex about the female obese patient as opposed to the male obese patient. Although male obesity is a topic of importance unto itself, this commentary exclusively focuses on females in order to explore the heightened anxiety surrounding the obese woman. Of course, women fundamentally differ from men in their sexual characteristics and their ability to bear children. Indeed, more recently, researchers have focused on the range of health problems that stem from women’s obesity in the preconception and perinatal periods, a condition called “maternal obesity.” Pregnancy is both a crucial period of growth for a fetus that shapes development for years to come and a time of significant physiological changes for a mother that can impact immediate and long-term health. Ironically, maternal obesity is not explicitly brought to the forefront by the American College of Obstetricians and Gynecologists, despite the fact that concerns about the negative health effects of obesity in the preconception and perinatal periods permeate the entire article. Recently, maternal obesity has become its own topic of scientific inquiry, generating a continuously growing body of literature on its risks and dangers; yet, most publications are of a similar nature as the aforementioned statement, continuing to call for physicians to measure women’s pre-pregnancy body mass index (BMI) while only advising that women and their fetuses are at increased risk for medical complications without weight loss.

Maternal obesity negatively affects every stage of pregnancy and development. The preconception pathophysiological effects of obesity include subfertility and infertility, which primarily relate to ovulatory dysfunction, with women having a 4% lower pregnancy rate per BMI unit. Obese women have increased risks of spontaneous abortion and recurrent miscarriages, preeclampsia, gestational diabetes mellitus, infection, and thromboembolism. Additional intrapartum management considerations for obese women arise due to possible difficulties of fetal and uterine monitoring, prior to increased risks of fetal macrosomia and Caesarean section. Obesity also impacts obstetric outcomes as fetal structures may be poorly visualized using ultrasound, and administering anesthesia is more difficult with higher rates of unsuccessful tracheal intubations and epidural failure. Children with elevated BMIs experience an elevated risk of obesity throughout adolescence and into adulthood. Health regulators have not yet established clear recommendations for how the health burden of maternal obesity can be lessened. A 2010 guideline by the Society of Obstetricians and Gynaecologists of Canada directs physicians to treat the problem of maternal obesity by counseling obese women about their weight gain, nutrition, and food choices during pregnancy. In contrast, the American College of Obstetricians and Gynecologists’ 2014 Committee Opinion urges physicians to go beyond “simply counseling a woman to eat less and exercise more” by practicing a “willingness to learn about the particular causes of a patient’s obesity.” While such recommendations are idealistic, they are not realistic. If a physician invests the time to learn about the complex and multifaceted causes of a particular woman’s obesity in the preconception period, then he or she is left to devise unique treatments options without further recommendations by the Canadian Society or the American College. A lack of clinical guidance...
has characterized the problem of obesity in the preconception and perinatal periods: a 2012 review of the literature on maternal obesity finds that there are few guidelines that assist physicians in providing “the best possible care and support for this group of women.”

Given that the June 2014 publication calls for increased physician training on treating obese patients at all levels of physician education without clarifying effective strategies to treat maternal obesity, it is evident that the discussion around the management of obesity in the preconception and perinatal periods is ineffective in its current form. Considerable rates of unplanned pregnancies, workplace demands, and a lack of counseling by physicians in the preconception period all create barriers to the treatment of maternal obesity. According to self-reports, approximately 30–40% of pregnancies are unplanned in Canada. Exercise and nutrition programs specific for soon-to-be mothers thus possibly miss a significant portion of the population. For the reduced numbers who plan their pregnancies, the various challenges associated with healthy weight loss in a limited period of time may also constitute a significant barrier for conceiving at a BMI between 18.5 and 24.9 kg/m². Modern workingwomen have less flexibility in family planning than ever before as career aspirations often dictate tight timelines. It may not be realistic for a professional to plan a maternity leave for one to two years in the future; yet, this is how long healthy weight loss takes for some individuals. Physicians need to change how they engage women of childbearing age in discussions about pregnancy and maternal obesity. Because 49.8% of surveyed Ontario physicians report that their patients do not discuss pregnancy planning with them, it is evident that physicians and policymakers need to be proactive in starting the conversation about healthy family planning earlier. Physicians do not have a large window during which to counsel their patients about pregnancy; however, for those who are successful in talking to a woman in the preconception period, less than 8% identify diet and exercise as topics of counseling. It is too late to counsel patients about maternal obesity during pregnancy as the negative health sequelae that stem from obesity cannot be prevented or reversed, only curbed through the reduction of gestational weight gain. The problem in treating maternal obesity in the preconception period thus seems to be two-fold: physicians cannot always engage with patients prior to conception but, when they do, only a minority discuss factors relevant to the treatment of maternal obesity.

Alterations in insulin resistance, glucose homeostasis, fat oxidation, and amino acid synthesis in an obese woman's body affect the metabolism of her child, often times predisposing him or her to childhood and adult obesity. As a result of its effects on posterity, maternal obesity should be perceived as a trans-generational health problem. The recent demand for the ethical treatment of obese women (but not men) possibly stems from an apprehension that obese women are responsible for perpetuating obesity in our society. In actuality, policymakers, physicians, and patients all play significant roles in controlling weight; yet, collectively, we are too complacent about the obesity epidemic in our society. National strategies need to educate physicians and the lay public about curbing obesity throughout life in order to help both future generations and ourselves. The type of prenatal care discussed in papers on maternal obesity should actually begin as early as possible to give parents an opportunity to adopt healthy behaviors for their offspring. Given the difficulty that many obese patients encounter when trying to lose weight, parents should intervene when children or teenagers become overweight if they ultimately want help control the weight of their grandchildren. Canadians would be born with less of a predisposition to develop obesity themselves, and the trans-generational nature of this condition could be interrupted. Unfortunately, physicians do not sufficiently engage their patients in early discussions about maternal obesity: only 44-52% of physicians report counseling women of childbearing age about nutrition and weight management.

Maternal obesity should no longer be treated as its own facet of the obesity epidemic; the window for the preconception and pregnancy periods does not afford the time for adequate treatment. Because weight accumulates during the teenage years or even earlier, maternal obesity can only be stopped through prevention and behavioral changes when someone is obese, rather than obese and pregnant. Maternal obesity needs to tip us away from our tolerance of the obesity epidemic because we are no longer talking about our own bodies, but the health of our progeny as well.
References


I moved to a fishing and farming village in rural Cambodia in the summer of 2008. I was supposed to stay for three months; I ended up staying for six and a half years.

After finishing up my undergrad training I received a government grant to support a research project of my choosing somewhere in the developing world. My funding allowed me to partner with a local non-governmental organization that was already established in the region. Although the majority of their work focused on water and sanitation, the links to anemia and poor nutrition (intestinal parasites picked up as a result of open defecation in fields can lead iron deficiency) were evident to all. And so, I was brought on board to investigate just how problematic anemia truly was in these communities.

The problem of anemia in Cambodia was far direr than I’d ever imagined. Everywhere I went, I saw men, women and children seeking shelter from the blazing sun under the floors of their stilted houses. One of the most common symptoms of the condition is lack of energy, and while we all like to complain that we are tired, most of us really have no idea what it’s like to be truly devoid of energy. Men and women had no energy to work and generate income to support their families, and children had no energy to attend school or even play with their friends. And the worst part was, people didn’t even know they felt so badly because they couldn’t remember ever feeling any different. If you grow up anemic and spend your whole life with poor iron reserves you have no clue just how unhealthy you are.

Around the world, more than two billion people are anemic – largely women and children - with more than half of all cases caused by poor dietary intake of iron rich foods. The best national estimates in Cambodia suggested that approximately half of all women of reproductive age, and more than 60% of school-aged children were anemic. By using a 1980's era centrifuge picked up at a hospital auction and connected to an old car battery I was able to quantify the problem: more than 90% of the women in the test communities I was working in were anemic.

We often associate anemia with fatigue, possibly shortness of breath or dizziness, but outside of the confines of our Western hospitals, anemia has very real impacts on maternal and child health. Thousands of women die every year as a result of hemorrhage during childbirth caused by anemia, children grow up with cognitive delays and deficits, infections run rampant as a result of weakened immune systems, and billions of dollars are lost each year as a result of decreased worker productivity.

Anemia presents a viscous cycle a disease: women who are born anemic are almost always anemic in their adult lives, and as a result will almost certainly give birth to anemic children. The iron levels in a new mother’s breast milk are so low, and supplementary foods of such poor nutritional value, that those children who are born anemic will almost certainly remain anemic. The cycle is incredibly difficult to break and so anemia runs rampant across the region.

As my three-month stint in Cambodia wound down and I had collected hundreds of blood samples showing just how common the problem was, I was faced with a predicament: Either I return to Canada and begin graduate training in neuroscience (my plan at the time), or I stay in Cambodia and try to unearth a solution to this incredible problem. About a week before I was supposed to leave, I called my supervisor back home in Canada and I went out on a limb. I said that I wasn’t quite done with the work that I had started and that I wanted to stay. I couldn’t just uncover the enormity of the problem, write a report and move on as many before me had done. It was a bold move, but one that paid off. Rather than being berated, I was encouraged to turn the project into my thesis, ditch the rat experiments, and find a solution.

Over the past 30 years there have been a small number of studies that have looked at the use of iron cooking pots as a way to supplement an otherwise deficient diet. The concept is simple: prepare your food in a cast iron pot and some of the iron will leach from the pot and fortify each and every meal. The idea seemed promising, but for one small problem: people don’t like to use iron pots. Iron is expensive,
heavy and rusts very easily, changing the taste and colour of food that is left in them. In low-income countries, where people don’t have overflowing drawers or tupperware, food is stored in the pot it is cooked in until it’s all eaten, and is therefore very easily spoiled if a cast iron pot is used.

So in concept, the idea of cooking with iron was supported with human and lab trials. But in practice it just didn’t work out. I knew that there must be a way to add iron during the cooking process that could later be removed. The iron could be added to any cooking pot, whether it be aluminum – like the ones they use in Cambodia – steel or even clay. It would need to be light to make it easy to use, cheap so that even the most poverty-stricken family could afford to use it, and environmentally sustainable – re-usable over and over again providing the badly needed iron, but not creating unnecessary waste.

In the early months of the project a lot of time was spent on the design of the iron supplement. After developing several unsuccessful prototypes, I landed on the idea of making an iron ingot that was shaped like a small fish. Cambodia is a country that relies entirely on fish. The mighty Mekong River that provides a source of income for millions dominates the country. Fish are seen as a livelihood, a staple food, and interestingly are associated with luck.

Ultimately I decided to model the iron ingot after a species of fish called Try kantrop. The design appealed to the culture’s sense of luck – not pandering, but embracing an untapped dimension. Understanding the human link to the project was key here. Scientists often work in silos and it is easy to forget what we are doing, why we are doing it, and how it will impact someone’s life. The key to success with this project was not just acknowledging, but embracing the complexity of the problem – medicine, nutritional science, public health and anthropology – a detailed understanding of each in the Cambodian context was essential.

From day one, the fish were made in local metal factories. There, scrap iron was melted down and forged into the shape of the Lucky Iron Fish. By using scrap iron, costs can be minimized and the project can contribute to a healthy, sustainable environment. By keeping production local, rather than farming it out to a more experienced company elsewhere in Asia, we are able to contribute to the fledgling economic development of the country. By producing a single fish, we are able to both recycle waste metals and support local livelihoods.

To make sure they actually worked, the iron fish were tested in several ways. First, they were subjected to a battery of tests to make sure that they didn’t contain any heavy metal contaminants that could harm rather than help. Next, they were transported to my research lab in Canada where they were used to prepare several different types of soup and drinking water. The results were astounding – the iron fish could provide 75% of person’s daily iron requirements by consuming just one litre of fortified soup or water each day.

Once I knew they were safe and at least theoretically effective, I needed to see if people would actually use them. Discoveries promising to save the developing world are made every day, but few actually succeed. Usually they are too expensive, often too complex technically, or sometimes they just aren’t adopted at the community-level. The best public health intervention in the world is useless if people don’t accept it.

Hundreds of women in several rural villages were recruited into a series of randomized controlled trials. Blood samples were taken over a year to see if the body was actually absorbing the iron that was being leached into the food. The hard work paid off and again the results were impressive: use of the fish led to a two-fold reduction in the prevalence of anemia, and over 90% of families who were given a fish used it every day.

The anecdotal evidence was perhaps even more inspiring. Over the months of working in the villages I constantly had women come up to me and tell how much better they felt after using the iron fish. Their headaches were gone, they didn’t get dizzy, they had more energy, and they were sleeping better. It was as if I was reading a (now very familiar) medical text with a list of symptoms of anemia and ticking off each and every one. The fish were truly a success.

Today, the iron fish are being produced at a mass scale. The Lucky Iron Fish Project is now a social venture that employs a team of Cambodian representatives that travel village-by-village spreading the word. With production costs less than US$1, the fish can be produced, packaged and sold for a nominal cost to the hundreds of thousands of families across Cambodia that suffer from iron deficiency anemia.

The main lesson that I took away from my years spent trying to improve nutrition in Cambodia is that you can have the best public health solution in the world, but if people don’t buy into it, don’t use it, don’t remember it, you have nothing. Simple innovations save lives, and the Lucky Iron Fish provides a very simple solution to a complex public health problem.
INTRODUCTION

Suppurative jugular thrombophlebitis otherwise known as Lemierre’s syndrome is a life-threatening diagnosis. Previously referred to as “the forgotten disease”, the syndrome manifests with such common symptoms as fever, sore throat, and lymphadenopathy. For this reason, it is often misdiagnosed.

Lemierre’s syndrome was first characterized by Dr. Andre Lemierre in 1936 with his report of 20 cases published in the Lancet. The disease typically begins with an oropharyngeal infection and subsequently develops into septic thrombophlebitis within the internal jugular vein (IJV), with seeding to distant organs (1). While pharyngitis is commonly the first sign of infection, other primary sources have been documented including odontogenic infection, mastoiditis, otitis media, sinusitis, and parotitis (2). While the pathophysiology remains somewhat obscure, this infection is believed to cause microbial seeding of surrounding tissues via hematogenous, lymphatic, or even contiguous spread from a local abscess, resulting in thrombophlebitis of the IJV within 1-3 weeks (2). The most commonly isolated pathogen is Fusobacterium necrophorum, which has been found in as many as 81.7% of cases (3). Cases involving other pathogens such as streptococcus, bacteroides, eikenella, or MRSA as well as sterile cultures, have also been documented (2).

Without appropriate antibiotic therapy, Lemierre’s syndrome can rapidly progress to sepsis and mortality. Other complications arise from the seeding of distant organs such as the lungs, liver, bones and joints, kidneys, cardiovascular or central nervous system (3-4). If diagnosed and treated early, Lemierre’s syndrome is amenable to treatment. The issue is early diagnosis, which is made complicated by the diversity of clinical presentation and relative rarity of the disease (5-7). Lemierre’s is often diagnosed when blood cultures reveal anaerobic Gram-negative rods. This leads to investigation for evidence of septic thrombophlebitis (2). Despite an increasing number of case reports in recent years, Lemierre’s syndrome remains a mysterious disease. It is not commonly thought of when patients present, and as such, diagnosis is frequently delayed.

This report presents a case of Lemierre’s syndrome in a 7-year-old female that was diagnosed after a full course of antibiotic therapy for otitis media and query mastoiditis.

CASE REPORT:

First Presentation:
A 7 year-old previously healthy female presented with a two-week history of low-grade fever in late March 2014. She was seen by her family physician and diagnosed with right-sided otitis media. She was treated with oral amoxicillin that was discontinued after 3 days due to vomiting.

Second Presentation:
She subsequently presented to the Emergency Department (ED) on April 5th, this time with right-sided neck pain suspicious for meningismus. Again, she had a fever of 37.4°C, rising to 38.4°C. A full septic work up revealed a white blood cell count (WBC) of 16.1, hemoglobin (Hb) 124, and platelets 383. Lumbar puncture was negative. With ongoing neck pain and suspected mastoiditis, treatment with IV ceftriaxone and vancomycin was started. She was discharged home on oral cefprozil, and completed a 10-day course. Her blood culture was positive for Streptococcus intermedius after 81 hours of incubation, which was considered likely to be a contaminant. Although the diagnosis of mastoiditis was considered, an ENT consult was not obtained.

Third Presentation:
She improved with the 10-day course of antibiotics and returned to school. On April 18th, she again developed fever, vomiting, and bilateral calf and neck pain. Her vital signs were: Temp 38.7, HR 144, RR 32, O2 92%. She had a small right-sided cervical lymph node. Complete blood count showed WBC of 24 with a left shift, neutrophils of 21, bands 1.7 and platelets of 437. A nasopharyngeal swab was negative for RSV, Influenza A and B, and monospot was negative. Repeat blood cultures were positive for Streptococcus viridans after 51 hours of incubation. The patient was again discharged as cell counts normalized and her pain and subjective signs had improved.

The “Atypical Sore Throat” – a Pediatric Case of Lemierre’s Syndrome

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Case Report

Fourth Presentation:
She was readmitted on April 21st with fever, vomiting, neck pain and severe frontal headache. At this point she had been experiencing intermittent fevers for 5 weeks. She continued to have soft tissue swelling in her neck along with enlarged right-sided cervical lymph nodes. A CT head and neck Doppler showed transverse sinus thrombosis and total occlusion of the right internal jugular vein, in addition to soft tissue swelling in her neck. Lymph nodes measured 1.5cm x 1.2cm x 0.7cm. She was restarted on IV ceftriaxone and vancomycin, and a third set of blood cultures drawn. Based on the patient’s clinical course and radiologic imaging, the diagnosis of Lemierre’s syndrome was made. IV metronidazole was added to her treatment according to current recommendations. She also received subcutaneous enoxaparin (8).

After treatment was reinitiated, the patient demonstrated a slow but progressive improvement over the next 11 days of inpatient care. She did not develop significant long-term morbidity due to metastatic Lemierre’s disease. She was afebrile by day 3 of admission and began ambulating on day 9. At the time of discharge, her vital signs were stable, and she no longer required morphine for pain control. A Community Care Access Centre referral was made to complete a 6-week course of IV antibiotics at home via PICC line.

DISCUSSION
This case of Lemierre’s syndrome demonstrates both typical and atypical features. Classic features included an initial infection involving the oropharynx, followed by intermittent fever without obvious source, lymphadenopathy, and neck swelling. The definitive diagnosis was made based on clinical features, and the right internal jugular vein thrombus was seen on both computed tomography and doppler ultrasound. Although blood cultures did not isolate Fusobacterium necrophorum, the typical pathogen seen in Lemierre’s syndrome, both Streptococcus intermedius and viridans were isolated. It is not clear whether this reflected contamination or a true infection, and the role of these specific organisms in the pathogenesis of Lemierre’s is not currently well-known.

The atypical features of this case included the young age of the patient, her lack of sore throat as the single most important presenting symptom, and her relatively mild clinical course. The patient’s early treatment with amoxicillin and 10 days of broad-spectrum antibiotics could account for the clinical course in this case. It is likely that early and aggressive antibiotic therapy contributed to a milder manifestation of disease, and helped to prevent metastatic organ involvement. An alternative explanation may be a different mechanism for the spread of infection.

Our treatment of this patient was in keeping with the most recent literature including the use of long-term third generation cephalosporin and metronidazole (2)

CONCLUSION
Several case reports published over the past decade emphasize the importance of maintaining a high clinical suspicion for Lemierre’s Syndrome (5-7). This is noted in particular when patients present with pharyngitis and several days of fever. Our case occurred in a pediatric patient in whom sore throat was not a feature and blood cultures did not isolate Fusobacterium. As such it does not follow the more typical features of this syndrome, and clinical suspicion was not raised until several weeks after symptoms began.

Recent publications have suggested that the prevalence of Lemierre’s syndrome has increased due to the restricted use of antibiotics for pharyngitis (4). In our case, it is possible that a full course of antibiotics administered early prevented more serious and systemic disease. Further research is needed to better elucidate the pathogenesis of Lemierre’s syndrome and the mechanism(s) of infectious spread. This may help us to better understand this mysterious and “forgotten” disease and provide clinicians with more concrete signs to raise clinical suspicion and support early diagnosis.

Acknowledgements
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References:
1. A 65 year old female with a history of hyperlipidemia presents with unstable angina. She is medically managed and subsequently receives coronary catheterization. Her angina is under control but she is oliguric for the next 2 days in hospital. Her creatinine has doubled from her initial level on presentation and is continuing to rise by day 6. Which of the following findings is not likely to be seen?

- a. Low serum eosinophils
- b. Livedo reticularis
- c. Pyuria
- d. Confusion

**Answer:** a. Low serum eosinophils

There are two primary considerations for this patient's AKI: contrast-induced nephropathy (CIN) and cholesterol emboli syndrome (CES). Both of these syndromes are the result of coronary catheterization, although their etiologies are very different. In the case of CIN, the contrast dye can cause a pre-renal AKI or ATN through direct nephrotoxicity and vasoconstriction of renal vasculature. On the other hand, CES occurs when the catheter dislodges an atherosclerotic plaque (often when passing through the aorta) – releasing fragments that can occlude smaller vessels.

It can be challenging to distinguish CIN and CES clinically. Often the key is to trend a patient's creatinine. While it is not a firm rule, the creatinine will peak in the first 2-3 days of CIN before decreasing. Conversely, in CES, the creatinine continues to increase in a step-wise fashion and can lead to chronic kidney disease and dialysis in the less fortunate.

In this case, the patient's creatinine has continued to rise by day 6, raising the concern of CES. Common findings of CES relate to tissue-ischemia from vascular occlusion by the cholesterol emboli. Ischemia in the peripheral tissues (often the feet) will lead to livedo reticularis.

(b) 2. Altered mental status can occur secondary to a uremia as well as possible emboli in the cerebral vasculature (d). CES involves a classic inflammatory response characterized by an eosinophilia and pyuria (c) – making (a) the correct answer.

2. A 70 year old man with a 50 pack-year history (and still smoking) comes in for follow-up at your respirology clinic. Since he was last seen, he has developed a pneumonia managed as an out-patient: his 3rd of the year. His last FEV1/FVC is 0.6 and his FEV1 is 40% of predicted; there is negligible reversibility. His last DLCO was 0.5. He is complaining of worsening shortness of breath, increasing exercise intolerance and stable pedal edema. His last echocardiogram from 2 years ago shows elevated right-sided pressures with a normal EF. His last PaO2 was 58mmHg at rest. He is currently on a combination of Advair and Spiriva. What is the next best choice in his management?

- a. Repeat CXR to rule out other additional lung/heart disease
- b. Addition of a loop diuretic
- c. Consideration for home oxygen
- d. Repeat echocardiogram

**Answer:** c. Consideration for home oxygen

This is a typical presentation of Chronic Obstructive Pulmonary Disease (COPD). This is manifested by the patient's PFTs revealing an obstructive lung disease with irreversibility and reduced gas-exchanged (manifested by the reduced DLCO). He also has classical symptoms of shortness of breath and exercise intolerance. He is also demonstrating signs of cor pulmonale – pedal edema and an echocardiogram revealing right heart strain.
Although he is being managed appropriately on an ICS + LABA (Advair) and an AC (Spiriva), there is room to improve this patient’s care. Specifically, the focus at this point should be reducing the frequency of COPD exacerbations and improve long-term mortality. There are 3 evidence-based strategies for improving mortality in COPD: supplemental home oxygen, lung reduction surgery & smoking cessation. Therefore, c) is the correct answer. As per the Canadian Thoracic Society Guidelines, continuous Oxygen therapy (keeping SPO2 greater than 90% for 18 hours per day) offers a mortality benefit in hypoxic patients. This is defined as patients with a resting partial pressure of less than 55mmHg on ABG or less than 60 mmHg in the presence of bilateral ankle edema, cor pulmonale or a hematocrit greater than 56%. This patient would likely be classified as having moderate COPD – a good candidate for home oxygen as long as he quits smoking.

3. A 55 year old man presents to the emergency department after being found unconscious in a puddle of his own vomit. His friend describes the vomitus as dark brown with chunks of blood in it. This patient has no history of alcohol abuse or liver disease but was recently in line for a TAAVI for aortic stenosis. His vitals are as follows: HR = 105, BP = 100/80, SpO2 = 96%, RR = 14, T° = 37.0. On examination, his GCS is 10 and he is diaphoretic with weak pulses and an III/IV crescendo-decrescendo systolic murmur in the RUSB – otherwise, his exam is unremarkable. What is the next best step in management?

a. Call GI for urgent endoscopy
b. Draw bloodwork then start blood transfusions with the according amount of packed RBCs
c. Start IV PPI and IV octreotide infusions
d. Initiate IV fluid resuscitation

Answer: d. Initiate IV fluid resuscitation

One consideration here is Heyde's syndrome – a rare entity where the development of aortic stenosis is concurrent with vascular malformations in the GI tract. Although unconfirmed, some current theories posit that shear forces around the stenotic valve cause a form of Von Willenbrand’s Disease, leading to coagulation abnormalities that contribute to GI bleeding.

Diagnosing Heyde’s syndrome is not necessary in this case, however. The key is to recognize the GI bleed and stabilize the patient by managing its subsequent hemodynamic effects. This patient is in hypovolemic shock on the grounds of altered mental status, tachycardia and hypotension. Therefore, an urgent GI consult and endoscopy/colonoscopy (a) is inappropriate at this time until the patient is stabilized. In a similar vein, drawing bloodwork is important but the hemodynamic instability warrants prompt attention first – (b) is incorrect as well. Furthermore, while blood transfusions may be appropriate based on bloodwork, resuscitation must be started before the patient is appropriately cross and typed. Therefore, (d) is the correct answer: IV resuscitation with (likely with crystalloids) must be attempted early and aggressively to improve circulation. An UGIB secondary to PUD is a reasonable consideration here and this patient will likely receive IV PPI soon. However, there are no concerning physical exam findings or history suggestive of variceal bleeding/liver disease – IV octreotide would not be warranted in this case and (c) is therefore incorrect.

4. A 65 year old woman presents to the emergency room with a 1-day history of blue lips and shortness of breath. She has primary immunodeficiency syndrome, for which she is on dapsone for PCP prophlaxis. Her vital signs on admission are: HR = 109, BP = 104/78, SpO2 = 83%, RR = 18, T° = 36.8. Despite attempts to improve supplemental oxygen delivery, her SpO2 is unchanged. Her initial physical exam, CXR, ECG, and basic bloodwork are unremarkable. What is the next best choice in management?

a. Provision of a short-acting bronchodilator and/or loop diuretic
b. Intubation and mechanical ventilation
c. ABG
d. CT chest with pulmonary embolism protocols

Answer: c. ABG

This case is concerning for acquired methemoglobinemia because of her normal ABG, signs of peripheral cyanosis and low pulse oximetry despite attempts to improve oxygen delivery. When hemoglobin is oxidized from ferrous form to ferric form – either because of acquired or congenital causes – the affinity for oxygen is decreased. This is left-shift of the oxygen dissociation curve. Tissues are thereby deprived of oxygen, causing a spectrum of peripheral cyanosis to end-organ damage. The pulse oximetry in methemoglobinemia will usually be around 80-85%. Pulse oximetry devices only measure arterial haemoglobin absorbance at two wavelengths: 660nm and 940nm. The ratio of absorbance at these wavelengths yields the oxygen saturation value. An absorbance ratio of 0.43 corresponds to 100% saturation. Methemoglobin absorbs light equally at both wavelengths.
wavelengths resulting in consistent SpO2 readings of about 85%-90%. This patient likely developed methemoglobinemia as a side-effect of dapsone.

The most appropriate early diagnostic tool in confirming suspicion of methemoglobinemia is an ABG revealing a characteristic chocolate-brown colour sample, a normal PaO₂, and a co-oximetry demonstrating an abnormal percentage of methemoglobin (>1%). Even if methemoglobinemia is not on your radar, an ABG is the best choice in this situation because it illustrates oxygen delivery and supply at a tissue level to corroborate the pulse oximetry levels suggesting hypoxia. This is an easy test to perform and provides early and useful results to guide further diagnostic and management decisions.

In this situation, provision of a SABA and/or loop diuretic is unwarranted. There are no specific findings concerning for bronchospasm, tachypnea or respiratory distress to warrant trial of a bronchodilator. Similarly, there are no symptoms or signs of volume overload to warrant a loop diuretic. Intubation may be appropriate in the future if there is refractory hypoxemia and signs of peripheral cyanosis. However, it’s too early for this right now – this patient is maintaining her airway, is not tachypneic, and is reasonably stable despite her low SpO₂. Consideration of a pulmonary embolism is fair given the complaints of SOB, signs of hypoxemia and tachycardia. A clinical decision rule should be applied here (such as Well’s or PERC), which she should score low on in combination with a normal CXR and ECG. Therefore, a CT chest with PE protocols may be reasonable down the road but not now – there are other diagnostic tools that are easier to use with more utility.

References:
Clinical Quiz

**Dermatology: What’s Your Diagnosis?**

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**CASE 1:**
A 24-year-old female presents with a 6 month history of depigmented patches developing on the face and neck.

*What’s your diagnosis?*
- a. Pityriasis alba
- b. Vitiligo
- c. Postinflammatory hypopigmentation
- d. Nevus depigmentosus

**Answer: b. Vitiligo**
Vitiligo (answer b) is an autoimmune skin condition occurring in 0.5% to 1% of the European and American population1. It is characterized by well-demarcated depigmented macules and patches affecting the skin. There are three main types of vitiligo: localized, generalized and universal. Localized vitiligo is further subtyped into focal, segmental, and mucosal vitiligo2. Generalized vitiligo, the most common type, is subtyped into acrofacial, vulgaris, or a mixed subtype. The term “universal vitiligo” is used when more than 80% of the skin is involved3. Onset of vitiligo may be at any age, with a mean age of onset of 22 to 25 years depending on the geographic region4. On histology, a complete absence of melanocytes is seen. Treatment consists of photoprotection along with topical glucocorticoids or calcineurin inhibitors for localized cases and NB-UVB for more generalized involvement.

Pityriasis alba presents as ill-defined hypopigmented patches in atopic individuals.

Postinflammatory hypopigmentation presents as hypopigmented macules with a preceding history of inflammation, for example from psoriasis or eczema, in the same area.

Nevus depigmentosus presents as a congenital nevus at birth or in early childhood and is a misnomer, in that it is hypopigmented rather than depigmented.

**CASE 2:**
A 50 year old otherwise healthy male presents with a 6 week history of progressive asymptomatic lesions on his left hand.

*What’s your diagnosis?*
- a. Granuloma annulare
- b. Tinea corporis
- c. Lichen planus
- d. Papular sarcoid

**Answer: a. Granuloma annulare**
Granuloma annulare (GA) (answer a) is characterized by firm, smooth, shiny dermal papules and plaques most often in an annular (circular) arrangement. The lesions occur most commonly on the dorsa of the hands. However, they may also be seen on the feet, elbows and knees. Localized GA usually occurs in children and young adults, however a more generalized form can be found in older patients. Skin biopsy is not usually required, however biopsy can be performed for definitive diagnosis to rule out other, more serious skin conditions. GA is a self-limited skin disorder and in most cases the lesions will disappear within 2 years5. Associations between GA and diabetes...
Clinical Quiz

Mellitus, as well as thyroid disease, have been reported. More recently, there have been studies showing an increased risk of dyslipidemia in patients with GA. As a result, it is important to perform the adequate screening tests in patients affected with GA. Treatment is not required. However, when desired, therapies for localized disease include topical glucocorticoids or intralesional steroid injections.

Tinea corporis, commonly known as “ringworm”, is a dermatophyte infection that generally presents with enlarging annular scaly plaques. GA is most often misdiagnosed as tinea corporis and the key features of tinea corporis that are not seen in GA are pruritus and scaling. Lesions of GA are smooth and generally asymptomatic. When tinea corporis is suspected, potassium hydroxide (KOH) scrapings and culture should be performed for confirmation of fungal infection.

Lichen planus is an inflammatory dermatosis involving the skin and/or mucous membranes. Skin lesions consist of pruritic, purple, polygonal, planar papules and plaques. Often seen are overlying fine, white lines on the lesions as well as on the buccal mucosa, called Wickham striae.

Sarcoidosis is a multisystem granulomatous disease of unknown cause, primarily affecting the lungs. Skin lesions may mimic GA and if sarcoidosis is suspected, biopsy should be performed to determine the diagnosis. Clues to sarcoidosis may include dyspnea, cough, or constitutional symptoms such as fever, fatigue, and weight loss.

**CASE 3:**

A 21-year-old man presents with thin brown plaques on the upper torso, which appear every summer.

**What’s your diagnosis?**

  a. Guttate psoriasis
  b. Tinea corporis
  c. Post-inflammatory hyperpigmentation
  d. Pityriasis versicolor

**Answer: d. Pityriasis versicolor**

Pityriasis versicolor (answer d), is a noncontagious skin condition caused by the overgrowth of Malassezia species. The term “tinea versicolor” is commonly used, although this condition is not caused by a dermatophyte. Skin findings are characterized by well-demarcated patches with variable pigmentation (hypopigmented, hyperpigmented or erythematous), hence the name “versicolor”. When scraped, a fine characteristic scale appears, known as “grattinage”. The lesions are most commonly found on the trunk. Clinical findings can be confirmed by KOH preparation, showing a classic “spaghetti and meatballs” appearance of clusters of yeast cells and long hyphae.

Guttate psoriasis presents as diffuse erythematous papules and plaques with overlying silvery scale. It is often preceded by a streptococcal infection.

Post-inflammatory hyperpigmentation presents as ill-defined hyperpigmented macules and patches following a resolved cutaneous eruption, such as eczema or psoriasis. Scales will be absent.

Tinea corporis, commonly known as “ringworm”, is a dermatophyte infection that normally presents with slowly extending annular plaques with scales and central clearing. KOH preparation and fungal culture are used to confirm the presence of dermatophyte infection.
References


This book is a non-fictional piece written by Otis Webb Brawley, who is the chief medical officer and vice president of the American Cancer Society. In this book, Otis Webb Brawley revisits his past cases, experiences, and memories, from since he was a child up until the present day. He does this in order to point out the many faults in the American health care system. Specifically, he wants to make the point that sometimes doctors “Do Harm” rather than good, whether this is intentional or not. The problems that he brings into focus relate to the care that unlucky citizens without health insurance are forced to receive as well as the corruption of several doctors who take advantage of those patients who have health insurance. Additionally, he proposes some examples of ways to try to repair the broken health care system.

The book visits many locations across America, but it starts off at the Grady Memorial Hospital in Atlanta, Georgia. Although the patients who come to Grady without insurance are forced to wait an eternity to be seen and are not given access to the newest forms of treatments, Dr. Brawley argues that these patients may be receiving care from better, more honest, doctors than insured patients. The doctors at Grady (Dr. Brawley himself is one of them) know they are treating patients who cannot pay, and they are on a fixed salary. Patients with health insurance, and more money, see doctors who are paid-for-service and driven by greed. Therefore, they sometimes do not have their patients’ best interests in mind but rather their own. Otis Webb Brawley cites many examples of cases where doctors prescribed treatments to patients either when it was not necessary or when a safer treatment was available, just because it would make them more money. The unfortunate result of these incidents was a decrease in the quality of life, if not the death, of some patients.

Although he gives many examples of doctors acting in despicable ways, he also is sure to include some examples of excellent doctors who treat patients as they should be treated – with evidence-based medicine. This is the type of medicine that Dr. Brawley himself practices, where he looks at the current research and informs his patients of all the risks and rewards of every possible treatment. The corrupt doctors who are driven by greed prescribe the newest and most expensive drugs, while keeping patients in the dark about their treatment, regardless of whether these drugs are ineffective or unsafe.

Otis Webb Brawley makes a desperate cry for a complete overhaul of the corrupt medical system that is harming patients more than healing them. However, he is not optimistic about the possibility of a reform as the health care system is trending downhill. He attributes this to a lack of patient knowledge of current medical research, patients’ desire to seek out treatment for every illness, the rise of technology, and the powerful advertising of pharmaceutical companies. Thankfully, he does provide some ray of hope by giving examples of groups of patients who have come together to educate other patients on how to have an informed role in their own health care. It seems that he is trying to point out the fact that if the system is to be fixed, it must start from the ground up, with the patients themselves.

This book has many positive features. It is easy to read and it keeps the reader engaged by constantly introducing new stories and characters. It also appeals to all audiences. There is enough explanation and common terms so that a non-medical person can understand the book, but there is also enough scientific detail and intricacies about the health care system so that health care professionals can enjoy it as well. I really enjoyed the way Otis Webb Brawley introduced every one of his characters by providing the readers with some background information about their lives. This made it enjoyable when he referred back to these characters later on in the book because the reader already felt a connection to them. Finally, thanks to his use of pseudonyms, he was able to write about many interesting, controversial, and private cases while still maintaining patient confidentiality and anonymity. This allowed the readers to learn about some of the hidden flaws and secrets of the health care system.

There were some negative features about this book. I found it hard to follow the timeline since the author would jump back and forth between his childhood, his time in medical school, and his early and late professional life. Also, this book was extremely American-centric. As a Canadian with very little knowledge of the American health care system, I did not understand some of the intricacies and terms...
associated with American health care insurance. Despite the fact that this book is tailored towards an American audience, it still has value to other readers as well. I would recommend this book to anyone interested in informing themselves about the dangers associated with health care systems. By reading this book, patients may be more inclined to inquire about their health care, by asking doctors the right questions, so that they can prevent themselves from being harmed by the system. I would also recommend this book to health care students and professionals because it may be an eye opener for them to see the flaws in the healthcare system. This book may encourage some people to try to do something to change the system for the better, and it would hopefully discourage others from trying to abuse the system because they would see the harm that it can do and that their wrongdoings are not going unnoticed.
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