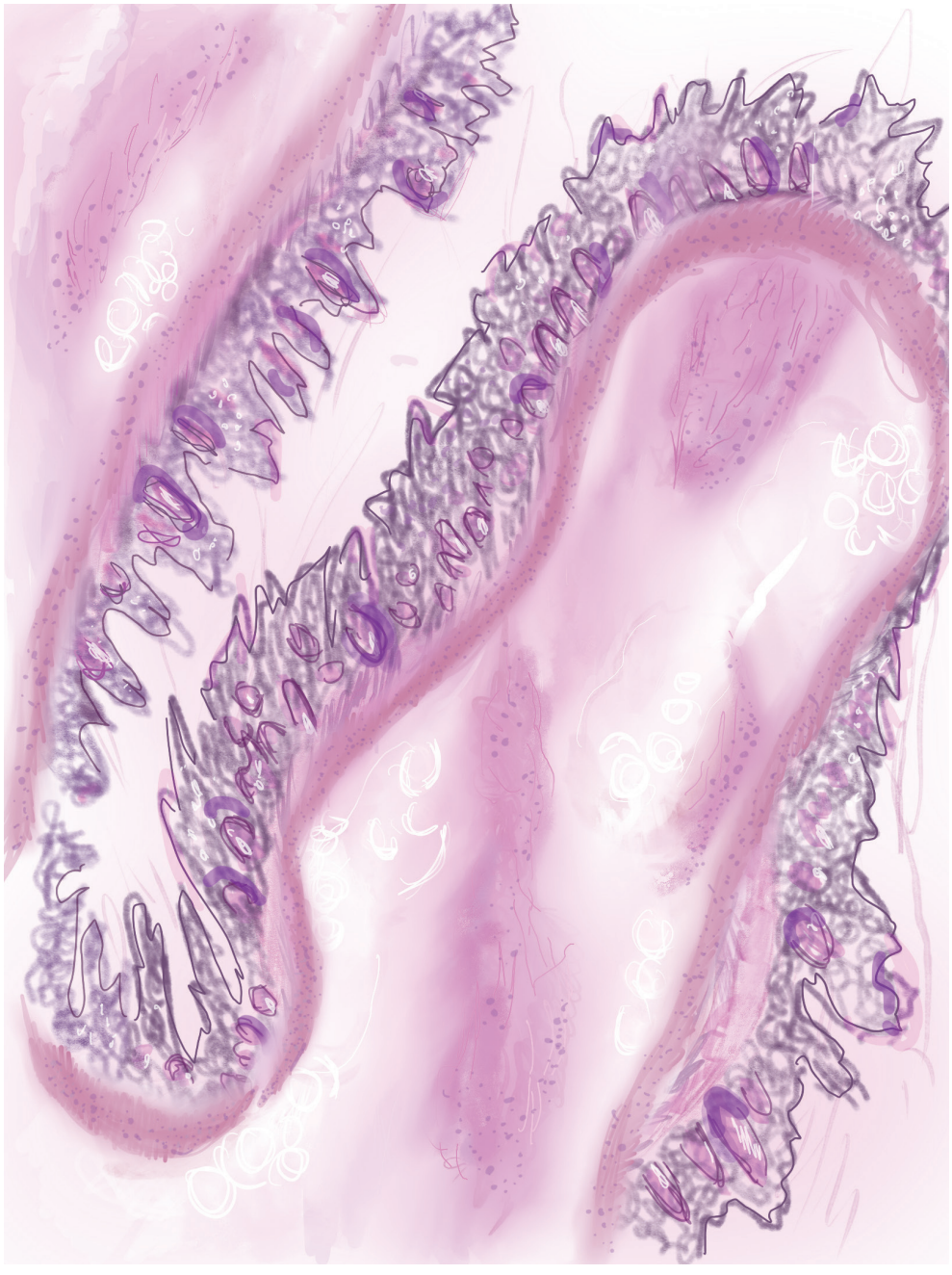
MSRJ™
Medical Student Research Journal

Spring, 2022



MICHIGAN STATE UNIVERSITY | College of Human Medicine

MSRJ

Michigan State University College of Human Medicine

Vol: 8, Issue: Spring, 2022

The Medical Student Research Journal (MSRJ) is the longest-running international academic journal in the United States authored, reviewed, edited, and published by medical students for medical students. It is dedicated to promoting the scientific achievements of medical students, teaching principles of peer and article review, and providing editorial, publishing and leadership learning experiences. Medical students worldwide are invited to submit manuscripts and serve as trained reviewers. The MSRJ publishes original research, case studies, editorials, research letters, reviews, and reflections that meet required standards, are authored by a medical student, and advance science. It is sponsored by the Michigan State University College of Human Medicine. Visit www.msrj.org and www.facebook.com/msrjchm for more information.

COVER ARTIST

Illustration of colon histology on H&E stain
Rachel Lawson, Class of 2024 College of Human Medicine, Michigan State University

SPECIAL THANKS

Aron Sousa, M.D., Interim Dean, College of Human Medicine
Dianne Wagner, M.D., Interim Senior Associate Dean for Academic Affairs
Walter Esselman, Ph.D., Senior Associate Dean for Research
Michigan State University, College of Human Medicine, Office of Research
Datapage.ie

MICHIGAN STATE UNIVERSITY | College of Human Medicine

MSRJ

Michigan State University College of Human Medicine

Vol: 8 Issue: Spring, 2022 **Pages 01–29**

Spring, 2022

REVIEWS

ORIGINAL RESEARCH

REFLECTIONS

A Narrative Review of the Current Evidence of Fecal Microbiota Transplant as Curative Therapy for Recurrent *Clostridioides difficile* Infection

Divya Lakshmi Yerramsetty*, Dipendra R. Pandeya

Medical University of the Americas, Devens, MA, USA

*Corresponding Author: Divya Lakshmi Yerramsetty, yerrams1@msu.edu

INTRODUCTION

The gastrointestinal tract is a reservoir for up to 10,000 to 100 trillion microorganisms, collectively known as the gut microbiota.[1] Among these colonizers, the dominant genera include *Bacteroides, Clostridioides, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus*, and *Bifidobacterium*.[1] Although these microbes are mostly confined to the intestinal tract, they also play critical roles that extend beyond the gut (i.e., body weight, mental health, metabolism, and immune regulation).[2]

When the gut's microbiome gets disrupted, the term 'dysbiosis' can be adopted.[3] Factors causing such profound imbalance can be attributed to toxic insults from frequent antibiotic use, unwanted dietary changes, poor dental hygiene, and even physical and psychological stress.[4] In the event of deteriorating microbial diversity in persons with diarrhea, there is an excess amount of free amino acids, especially proline, and a lack of inhibitory bile acids.[3] Together, they create the ideal environment for dysbiosis-related pathologies as seen in an initial *Clostridioides difficile* infection (CDI) – the world's leading hospital-acquired illness.[5] Patients with CDI can be diagnosed with a positive PCR result for CDI toxin and a clinical presentation of more than three episodes of diarrhea, abdominal pain (that only resolves with defecation), mild fever, and leukocytosis.[6]

Current guidelines to treat CDI include mono- and combination therapies with vancomycin and fidaxomicin.[1] Of the existing dosage regimens, pulsed dosing of these first-line agents has starkly reduced recurrence rates compared with standard protocols. Unfortunately, even after the recommended treatment, recurrence is still seen in up to 10–20% of patients after the initial visit – with up to 40–65% of previously treated patients experiencing further recurrences after the second visit.[5] In 30% of the cases with severe, refractory CDI, colectomy becomes the last resort for treatment despite many of its feared complications: toxic megacolon, septicemia, and multiorgan failure.[7]

In the last few decades, there has been a surge in interest to revamp and revolutionize an ancient procedure known as fecal microbiota transplant (FMT) to correct the dysbiosis responsible for refractory *Clostridioides difficile* Infection (rCDI).[8] Unfortunately, because FMT meets the legal definition of a drug and biological product, it remains unqualified for regular use until it gets accepted through the investigational new drug (IND) approval.[9] However, this clause's exception emerges under 'enforcement discretion', which allows FMT for patients who are refractory to standard therapy with proper consent in order.[9]

FMT is a procedure that essentially involves a sophisticated administration of fecal matter obtained from a healthy, screened donor to a qualified recipient suffering from rCDI. The procedure's outcome most often results in the recipient altering his or her gut microbiota so that it closely resembles that of the stool donors' profile, which paves the way for its imminent success.[10] The American guidelines suggest a primary endpoint as the resolution of symptoms and the absence of CDI within 8 weeks of FMT as a secondary endpoint.[10] Currently, the cure for rCDI has been seen within hours to 4–5 days in struggling patients post-FMT.[9] This article aims to evaluate and analyze current and reliable sources of evidence

[1] Non-inferior to vancomycin; however, it is not studied in severe/fulminant cases of CDI.[17]

that support FMT as an optimal method to conventional therapy for resolving rCDI.

METHODS

Search Strategy

This literature review was executed according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA). PubMed, Medscape, and Cochrane Review searches consisted of titles of relevance, sorted by publication dates from 2010 to 2020. The PubMed search used the following filters: free full text, clinical trial, meta-analysis, randomized control trial, and systematic review. Search criteria were studies that were representative of the sustainability of FMT in treating rCDI in adults. Articles were retrieved from online databases using a combination of the key phrases: fecal microbiota transplant, donor feces infusion, fecal transplant, FMT, *Clostridium difficile* infection, *Clostridioides difficile* infection, *C. difficile colitis*, and CDI.

Inclusion and Exclusion Criteria

For all selected literature, the study population of interest was moderate to high-risk adults (age ≥ 18 years) of any demographic who had at least one incidence of recurrent *C. difficile* infection. Studies were also included if the following inclusion criteria were met: (1) participants with recurrent CDI supported by a clinical diagnosis and/or laboratory parameters and (2) subjects with recurrent CDI having received FMT through any method of administration. Studies were excluded if there were: (1) scoring <6 on controlled intervention studies and cohort studies; (2) scoring <4 on systematic reviews and meta-analyses; (3) lacking standard treatment of care for primary CDI before FMT; (4) evaluating FMT in the immunocompromised or patients with or without severe comorbid conditions; (5) including pediatric patients; (6) testing small (<15 subjects) and nondiverse sample sizes; (7) duplicated studies; (8) not in English.

Outcomes of Interest

The primary outcome of interest is clinical and bacteriologic resolution of CDI with FMT versus conservative treatment at least 4 weeks after the final FMT treatment – as most treatment failures with FMT occurred before this time point. Secondary outcomes of interest included the following: (1) treatment success and failure after single versus multiple infusions of FMT in the posttreatment phase; (2) long-term implications post-FMT; and (3) efficacy of mono- and/or adjunctive therapy with common antibiotics (vancomycin vs. fidaxomicin) for CDI and rCDI.

Data Extraction

All full texts were independently reviewed by the primary investigator to ascertain that each source contained information on the topic of choice. Following a meticulous search, a total of 106 articles met the selection criteria – out of which only 8 were independently selected based on providing the most valuable insight into the efficacy of FMT over antimicrobial treatments in the management of rCDI (see Fig. 1 and Table 1).

Quality Assessment and Risk of Bias of Individual Studies Assessment

The primary investigator independently evaluated all the included studies with ≥ 4 patients using the National Institute of Health (NIH) Study Quality Assessment Tools.[11] The score range for controlled intervention studies and cohort studies is between 0 and 14, where a score <6 was identified as poor in quality. The score range for systematic reviews and meta-analyses is between 0 and 8, where a score <4 was considered as poor in quality. Studies that were deemed poor in quality were excluded from this literature review. Additionally, with the help of the Risk of Bias in Nonrandomized Studies of Interventions tool (ROBINS-I) and the Risk of Bias tool for randomized control trial, the primary investigator also thoroughly assessed the risk of bias of each study.[12,11] The scores were classified to be either low, moderate, serious, or critical. Studies that were categorized as serious or critical were immediately excluded.

RESULTS

The search strategy identified 106 unique studies, of which 8 met the inclusion criteria. Of these, 2 were systematic reviews and meta-analyses, 4 were randomized controlled trials, and 2 were retrospective cohort studies (see Fig. 1 and Table 1). Table 1 highlights the notable components of each literature source, including the following: (1) name of the first author; (2) research design; (3) year of publication; (4) independent and dependent variables; (5) data collection method; (6) pertinent

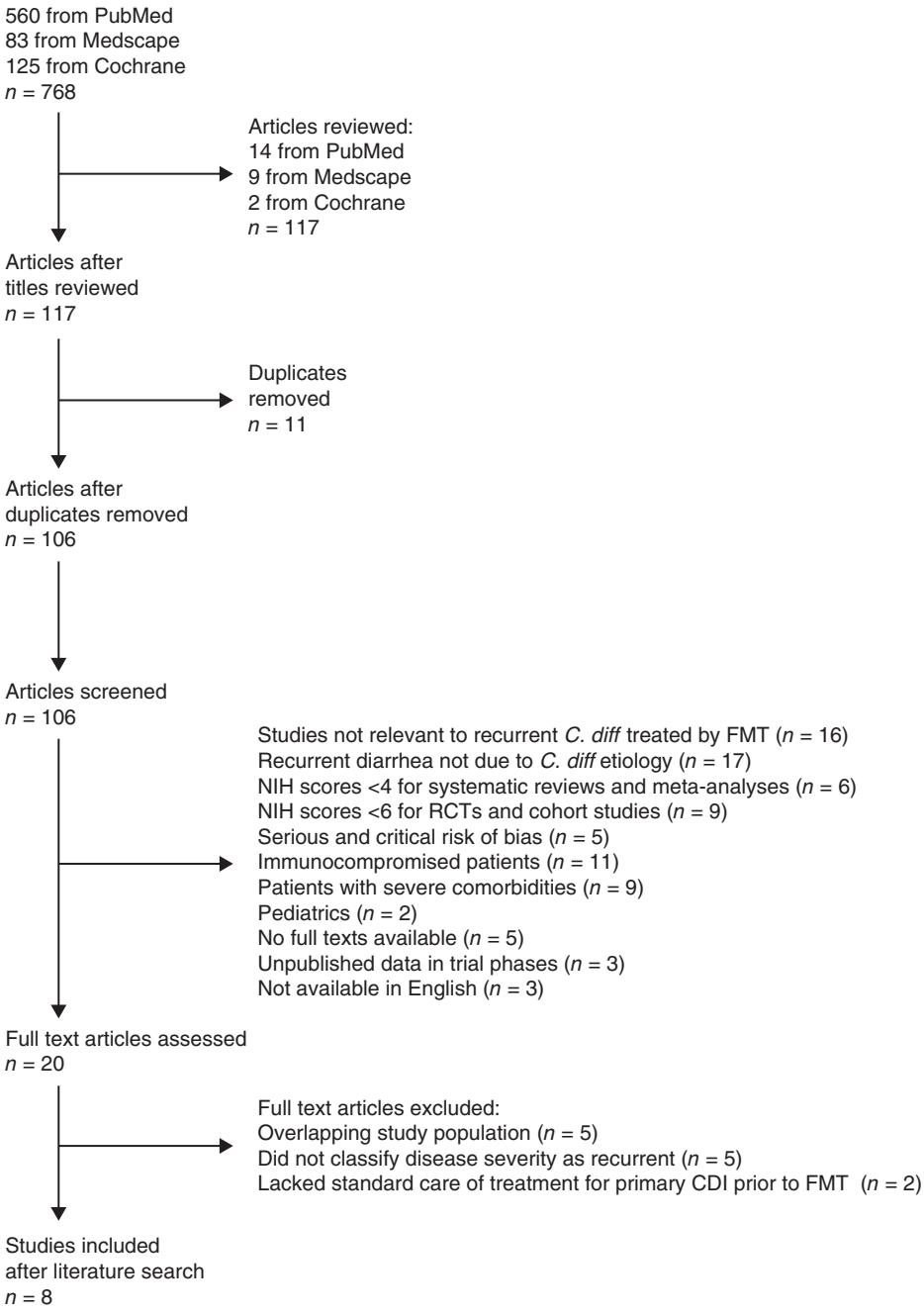


Figure 1. Flowchart outlining the selection strategy during the literature search.

findings; (7) strengths; (8) weaknesses; (9) NIH scores; (10) ROBINS-I scores; (11) level of study based on the Evidence-Based Medicine Pyramid.

M.N. Quraishi and colleagues did a systematic review and meta-analysis on the efficacy of FMT of different delivery methods and preparation in the treatment of rCDI.[13] Of the 37 studies, 34 reported positive responses to FMT with a cure rate of 84%; 25 case series and 7 RCTs demonstrated that the lower gastrointestinal route was superior to the upper gastrointestinal route (95 vs. 88%)

Table 1. Evidence table.

1st Author	M.N. Quaraishi	Wenjia Hui	G. Ianiro	Colleen R. Kelly	Christian Lodberg Hvas	Louie TJ	J. Jalanka	Jae Hyun Shin
Research design	**Systematic review and meta-analysis**	**Systematic review and meta-analysis**	**RCT**	**RCT**	**RCT**	**RCT**	**Retrospective cohort study**	**Retrospective cohort study**
Pub. Yr.	**2017**	**2019**	**2016**	**2018**	**2019**	**2012**	**2018**	**2019**
Ind. V.			1(a). Donor FMT 1(b). Autologous FMT	2(a). FMT-S group 2(b). FMT-M group	1(a). FMTv (n = 24) 2(b). Fidaxomicin b.i.d. (n = 24) 2(c). Vancomycin q.i.d. (n = 16)	1(a). Vancomycin-treated patients (n = 44) 1(b). Fidaxomicin-treated patients (n = 45)	1(a). FMT group 1(b). Antibiotic group (AB)	1(a). Lower GI-FMT delivery 1(b). Upper GI-FMT delivery 2(a). Non-FMT tx
Dep. V.			Clinical cure within 8 weeks after FMT or at the time of early withdrawal	Clinical cure within 8 weeks after FMT or at the time of early withdrawal	Clinical cure in the intention-to-treat population 8 weeks after FMT or at the time of early withdrawal	Spore counts and *C. difficile* cytotoxin B titers at study entry; on days 4,10,14,21,28; on days 38–42	Clinical cure in the intention-to-treat population 8 weeks after FMT or at the time of early withdrawal	CDI recurrence within 3 months of FMT or since initial visit
Data collection method	37 papers: 7 RCTs and 30 case series	Researchers chose 8 studies using electronic database search and compiled data from each	46/179 patients were randomly assigned: (a). Donor (n = 22) (b). Autologous (n = 24)	56 enrolled subjects (a). FMT-S (n = 28) (b). FMT-M (n = 28)	64/120 adults w/rCDI were seen at a gastro clinic in Denmark between 5/5/16 and 6/10/18 and randomly assigned	89/629 patients were randomly assigned to a 10-day course of: (a). Vancomycin 125mg q.i.d. OR (b). Fidaxomicin 20 mg b.i.d.	(a). FMT (n = 45); (b). AB (n = 39)	FMT = 52/113; done at the CDCC from 6/2012 to 3/2015
Findings	Single FMT infusion cure rate = 84% (better than abx tx)	The 8 studies yielded 273 patients, of which 243 had clinical resolution	Donor FMT = 91% cure rate (20/22); Autologous FMT = 63% cure rate (15/24); Crossed over to donor FMT = 9	FMT-S: 21/28 cured; 7 retreated and cured but 1/7 died. FMT-M: 28/28 cured	Clinical resolution: FMT = 92% (n = 24); Fidaxomicin = 42% (n = 24); Vancomycin = 19% (n = 24)	Recurrence was observed in 23% (10/44) in vancomycin-treated patients versus 11% (5/44) in fidaxomicin-treated patients	↑ Bowel fxn: 53.3 versus 25.6% ↑ Mental health 31.1 versus 8.9% Upper GI pain 31.3 versus 51.3% FMT readiness 97.6 versus 60% ~3.8 years observational period post-FMT	Recurrence rate: FMT = 4.5 versus Non-FMT = 16.7%
Strengths	Stringent section criteria	8 high-quality RCTs updated to 9/20/18	Double-blinded, multicenter design	Use of expert endoscopist	Appropriate statistical analysis	Double-blinded; 10 samples from healthy controls were analyzed via qPCR		Use of CDI-focused clinic
Weaknesses	Lacks adverse event data	Not generalizable	Not generalizable	No double-blinding	No double blinding	No quality assessment	Questionnaires	Telephone surveys
NIH score	6	6	9	8	10	9	8	7
ROBINS-I	Low	Low	Low	Moderate	Moderate	Moderate	Moderate	Low
Level of study[1]	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**

[1] Level 1 includes RCT, systematic review of RCTs ± meta-analysis of RCTs; Level 3 includes retrospective cohort studies.

GI, gastrointestinal; qPCR, quantitative polymerase chain reaction.

(*p = 0.02*). Fresh FMT revealed a cure rate of 85% and a lower cure rate of 68% with frozen FMT; however, neither was statistically significant (*p = 0.10*). However, FMT still appeared promising as an effective and safe treatment choice for rCDI, as seen in controlled and uncontrolled studies.

A systematic review and a meta-analysis were executed to confirm the efficacy of fresh FMT in the clinical resolution of rCDI. Two of the researchers, W.J. Hui and Ting Li, independently extracted articles with stringent eligibility criteria that resulted in eight RCT studies.[14] The pooled relative risks were calculated with a 95% confidence interval (CI), and the heterogeneity between studies was assessed using the I2 statistic; 537 patients met the inclusion criteria and were divided into the fresh FMT group (*n* = 273) and control group (*n* = 264). The control groups included antibiotic therapy or placebo, frozen FMT, and capsule groups. The eight studies determined that 243 out of the 273 patients experienced clinical resolution from rCDI through FMT (RR = 0.38, *p = 0.02*) with a high heterogeneity (I2 = 67%) between them. The recurrence rate of clinical diarrhea in the control group was significantly higher compared with the fresh FMT group (24.6% or 65/264 vs. 11.0% or 30/273; $p \leq 0.05$). Like previous findings, multiple infusions showed greater improvement in the remission rate (RR = 0.24; *p = 0.001*). The combination of self-limiting adverse events and high-quality RCTs provides overpowering evidence to endorse FMT as a curative treatment for rCDI.

An open-labeled RCT at the Gemelli University Hospital was carried out by G. Ianiro et al to compare single infusion (FMT-S) with multiple infusions (FMT-M) of FMT in the treatment of rCDI.[15] Using randomization software, a total of 56 subjects were enrolled and randomly assigned to either FMT-S (*n* = 28) or FMT-M (*n* = 28). Outcome data were assessed using the Student's *t*-test and Fisher's exact test, according to the intention-to-treat principle. All statistical tests were 2-sided, and a *p*-value <0.01 was considered statistically significant and analyzed using an online calculator; 21 of the 28 subjects in the FMT-S group had shown clinical resolution. All 7 remaining in the FMT-S group received further infusions and resulted in 100% cure. Ultimately, the cure rate was greater with FMT-M than FMT-S (100 vs. 75%), favoring FMT as an effective alternative for resolving rCDI.

Colleen R. Kelly et al conducted a double-blinded RCT at the University of Minnesota in Minneapolis to compare the clinical outcome of autologous FMT to donor FMT.[16] Patients were enrolled between 11/15/2012 and 03/10/2015 at two academic hospitals in New York (NY) and Rhode Island (RI). Stool specimens of both the donor and the patient were collected 1 h before the scheduled FMT procedure; 46 patients were randomly allocated to either the donor group (*n* = 22) or autologous FMT group (*n* = 24). Baseline demographic and clinical data were described, and groups were assessed using Stata (version 12), SAS (version 9.4), and a 2-sample *t*-test. Clinical resolution was seen in 90.9% (*p = 0.042*) in the donor FMT group and 62.5% in the autologous group. Although the donor FMT group was statistically superior to the autologous FMT group, the interaction between NY and RI was not statistically significant for treatment effects (*p = 0.24*). One of the two treatment failures from the donor FMT group was cured after the second donor stool infusion. Nine patients who had recurrence after autologous FMT switched over to treatment with donor FMT and were cured.

An open-labeled RCT was conducted at a gastroenterology clinic in Denmark by Christian Lodberg Hvas et al. to compare the combined clinical resolution of fresh FMT and non-FMT treatments (vancomycin and fidaxomicin).[17] Between 04/05/2016 and 06/10/2018, 64 of 120 adults with rCDI were randomly assigned to 1 of the 3 predetermined vancomycin courses or fidaxomicin before rescue FMT (*n* = 24); 24 patients were assigned to 4–10 days of vancomycin (125 mg 4 times daily), 24 patients were assigned to 10 days of fidaxomicin (200 mg twice daily), and 16 patients were assigned to 10 days of vancomycin (125 mg 4 times daily). Outcome data were assessed using chi-squared analysis and Kruskal–Wallis analysis of variance, and a *p*-value of 0.05 was decided to be clinically significant. At the eighth-week follow-up, combined clinical resolution and negative PCR test for CD toxin were observed in 17 of the 24 patients with rescue FMT (71%). After week eight, a clinical resolution was found in up to 22 patients (92%). In the case of fidaxomicin, a combined resolution was found in only eight of the 24 patients (33%), with an increase in clinical resolution to 10 patients after the eighth week (42%). Finally, only 3 of the 16 patients (19%) had combined resolution with vancomycin at week eight with no clinical resolution increase afterward. In summary, FMT showed greater efficacy to fidaxomicin (*p = 0.009*) and vancomycin (*p = 0.001*) than either of the antibiotics alone (*p = 0.31*).

Thomas J. Louis et al performed a double-blinded, multicenter RCT at the Foothills Medical Center (Calgary,

Canada) to compare the efficacy of a 10-day course of vancomycin 125 mg q.i.d. versus fidaxomicin PO 200 mg b.i.d. in the treatment of rCDI.[18] Using the randomization software, a total of 89 out of 629 subjects were registered and randomly assigned to either vancomycin ($n = 44$) or fidaxomicin ($n = 45$). The primary outcome was to assess for the reduction of both *C. difficile* toxin reexpression and rCDI during and after treatment through the collection of fecal samples (>10 g/samples) on days 1, 4, 10, 21, 28, 38–42. Quantification of target bacterial DNA in fecal samples was performed using real-time quantitative polymerase chain reaction (qPCR) and was log-transformed. Vancomycin-treated patients experienced more recurrence than fidaxomicin-treated patients (10/44 or 23% vs. 5/44 or 11%, $p = 0.03$). Similarly, vancomycin-treated patients had more toxin reexpression in fecal samples than fidaxomicin-treated patients (29/94 or 28% vs. 13/91 or 11%, $p = 0.03$). Provided the results, it can be presumed that fidaxomicin encompasses microflora-sparing properties that make it more potent against rCDI compared with its competitor, vancomycin.

A retrospective cohort study was instigated by Jae Hyun Shin and colleagues in all patients' medical records that received FMT between June 2012 and March 2015 at the University of Virginia Complicated *C. difficile* Clinic (CCDC).[19] Patient follow-up for recurrence data occurred through telephone contact at 1 week, 1 month, 3 months, 6 months, and 1 year post-FMT. Of the 113 patients who were reviewed, 52 patients who had three or more CDC recurrences were eligible to be treated with FMT. Of the remaining, 25 patients were deferred, and 36 patients who had fewer than two recurrences received non-FMT treatment. Outcome data were assessed using the chi-squared analysis, the Fisher's exact test, or the Student's *t*-test. When treated with standard non-FMT treatment, there was a higher recurrence (16.7 vs. 8.8%, $p = 0.05$) and mortality (12.5 vs. 6%, $p = 0.05$) rates than FMT treatment. In contrast, FMT-treated patients had fewer recurrence (4.5 vs. 8.8%, $p = 0.05$) and mortality (7 vs. 6%, $p = 0.05$) rates – findings suggest that patients with greater than three recurrences benefit from FMT regardless of route of delivery.

DISCUSSION

Donor versus Autologous FMT

Even though modern technologies are still not capable of determining the fecal composition responsible for both the positive and negative responses to FMT, progress still has been made in distinguishing the safety and efficacy of autologous versus heterologous FMT. According to the findings of Colleen R. Kelly et al., 90.1% ($p = 0.042$) of the patients experienced clinical resolution with donor FMT versus only 62.5% seen with autologous FMT.[16]

Normally, during remission periods with rCDI, the patient's stool is 'banked' for FMT use before starting the patient on any antibiotic therapy.[20] Following antimicrobial treatment, when the patient is increasingly vulnerable to recurrences with CDI, the patient's stool could serve as a rapid approach to reinstate the possibly depleted commensal organisms using FMT. Unlike heterologous FMT, autologous FMT is shown to have little to no improvement from prior dietary changes[2] due to the already weakened microbiome of the patient. However, because it is better tolerated with a higher safety profile, it reduces the need for strict screening methodologies, thus increasing the patients' and physicians' willingness to opt for autologous over heterologous FMT in those suffering from rCDI.[21]

Even so, as determined by the findings of Colleen R. Kelly et al., the results with donor FMT have been more promising due to the effectiveness of more protective microbes that are most often scarce from the patients' stool: *Bacteroides* and *Firmicutes*.[16,22] The basis for the higher therapeutic potential seen with heterologous FMT can be attributed to the fact that the donors' feces are better equipped with microbes that are more favorably anti-inflammatory and diverse.[22] For such reasons, donor FMT necessitates only a *partial* rather than complete engraftment of the donor's feces to resolve rCDI.[22] Of course, donor FMT still carries a greater risk of exposing the individual to potentially pathogenic microorganisms that could lead to possible autoimmune complications; however, with more definite screening protocols in place, heterologous FMT's feasibility seems to be of reasonable value over autologous FMT. In both situations, regardless of their distinct favorable and unfavorable features, it can be said that FMT possibly proves advantageous to standard treatments of care, namely, vancomycin and fidaxomicin, as the objective is deemed at restoring the microflora necessary to resolve the recurring infection versus ridding the body of the pathogenic strains in the symptomatic period.

[2] Protein consumption has a positive correlation with overall microbial diversity.[8]

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

Fresh versus Frozen FMT

Similar outcomes were also seen in another systematic meta-analysis by Wenjia Hui et. al.[14] The study has shown that there is a higher recurrence rate of diarrhea within the control group compared with the fresh FMT group (24.6 vs. 11.0%, $p = 0.05$), which leads to the presumption that, despite the difficulty involved with its preparation, fresh FMT is more efficacious in preventing recurrent bouts of diarrhea associated with rCDI. Although frozen FMT has been known to decrease the number and frequency of donor screenings and expenses with application in healthcare settings, the study could not detect a significant clinical difference with frozen FMT compared with its counterparts, including antibiotic treatment ($p = 0.79$) and capsule forms ($p = 0.45$).[23] Although the ideal form of FMT remains unknown, one may still argue that both fresh and frozen FMT serve as beneficial alternatives to antimicrobial therapies in the prevention of recurrent bouts of CDI, especially following the initial clinical resolution of CDI with typical mainstays of treatment.

Multiple versus Single Infusion of FMT

Irrespective of delivery modality, multiple rather than a single infusion of FMT seemed to have assured a better prognosis of rCDI after initial treatment failure with FMT. In the comparison between donor FMT and autologous FMT by Colleen R. Kelly et al., multiple infusions increased the overall cure rate to 93.5%.[16] Similarly, in the study conducted by G. Ianiro et al., there was complete resolution in the FMT-M group compared with the FMT-S group (100 vs. 75%).[15] In both cases, the patient's response to FMT was concentration-dependent, favoring its efficacy in preventing recurrent episodes of CDI. Then again, it is worth mentioning that more adverse events were recorded in the FMT-M group than in the FMT-S group (7 vs. 19) in the investigation led by G. Ianiro and colleagues, which questions the safety profile of the stool specimens utilized.[15] Regardless, while antibiotics attempt to cure the disease course of CDI during the first episode itself, many of the relapsing cases can be attributed to the depleted microbiome profile of the patients. Thus, in cases of critical exhaustion of patients' microflora, more than a single infusion of FMT may be required to acquire the desired effects of the novel procedure.

FMT versus Antibiotics

Additionally, the results of both Christian Lodberg Hvas et al. and Jae Hyun Shin et al. conveyed the increased ineffectiveness of both antibiotics in curing rCDI and how useful FMT is as a rescue treatment following initial failures with traditional approaches.[17,19] For instance, in the open-labeled RCT by Christian Lodberg Hvas et al., FMT showed greater efficacy to fidaxomicin ($p = 0.009$) and vancomycin ($p = 0.001$) than either of the antibiotics alone ($p = 0.31$) after the eighth-week follow-up.[17] Even in the retrospective cohort study executed by Jae Hyun Shin et al., the non-FMT treatment showed higher recurrence (16.7 vs. 8.8%) and mortality (12.5 vs. 6%) rates with rCDI than what was seen with FMT.[19] Given that data were collected from a CDI-focused clinic, there was an intensive evaluation of the patient at the initial admission to determine their FMT qualification. With such strict inclusion and exclusion selection criteria in place, it gives way for increased generalizability of FMT's outcome data to patients suffering from severe cases of rCDI.

In another comparison with antibiotics, FMT contributed to better gastrointestinal health in the long run. With very few studies following patients post-FMT for even a year, the retrospective cohort study by Jalanka et al. had managed to observe patients for almost 3.8 years to determine the worst- and best-case scenarios of FMT's practical use for rCDI.[24] The findings disclose more upper gastrointestinal pain and overall discomfort post-antibiotic treatment than what was seen with FMT (25.6 vs. 11.1%, $p = 0.06$). In fact, better bowel function was reported with FMT than with antibiotics (53.3 vs. 25.6%, $p = 0.016$). There was up to 31.1% of patients who experienced improved mental health than the patients in the antibiotics group (8.9%, $p = 0.06$). For the reasons mentioned, the study also supported the patients' increased readiness to consider FMT as an initial treatment for rCDI over antibiotics for the extraintestinal benefits (FMT = 97.6%, AB = 60%). With further research underway, it can be understood that patients are more likely to fend for its regular use with the emergence of more favorable clinical outcomes irrespective of its unappealing esthetics.

Then again, a reasonable argument should still be made for the efficacy of antibiotics. For example, the RCT study by Louie et al investigates the distinct effectiveness of fidaxomicin and vancomycin during and after the treatment of CDI. In the study, fidaxomicin proved to be more superior to vancomycin, especially in its pursuit to reduce recurrence and toxin reexpression in the intestinal microbiome. Statistically speaking, while reappearance of

toxin in collected fecal samples was observed in 28% of vancomycin-treated patients (29 of 94 patients, $p = 0.03$), only 14% was observed in fidaxomicin-treated patients (13 of 91 patients, $p = 0.03$). Similarly, while 23% of vancomycin-treated patients (10 of 44 patients) experienced rCDI, only 11% of fidaxomicin-treated patients had a recurrence. Collectively, it can be understood that compared with vancomycin, fidaxomicin may serve as a robust choice of treatment during both the pretreatment and posttreatment phases of FMT, making way for a higher treatment prognosis in the event of using FMT as a rescue modality in refractory cases of CDI.

LIMITATIONS

As far as limitations are concerned, this article is flawed by its intent to solely focus on publications where FMT was more successful; hence, minimal consideration was given to those reporting poor treatment outcomes, despite comparing its efficacy to standard antibiotic therapies. For instance, this article failed to assess rCDI patients infected by the CD ribotype 027 strain, which is commonly associated with the poorest outcomes.[11] Thus, FMT results might not be completely representative of patient populations with a high frequency of this strain.

This article also does not focus heavily on the mentioned adverse events caused by FMT nor the efficacies of different delivery modalities of FMT due to the lack of information available; hence, it calls for future studies that can help compensate for these deficits using bigger sample sizes in more controlled testing environments.

Despite the limitations, there is still considerable evidence that supports FMT's role in ridding the patient of rCDI without the need for detrimental rescue treatments involving antimicrobials and elective surgeries. However, before declaring the novel procedure as the best form of medical practice, future studies should have a stronger emphasis on diverse non-FMT treatments outside of vancomycin to allow for a more accurate assessment of FMT's therapeutic role.

Conflict of interest and funding

The authors have no conflict of interest. The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

1. Lawson RD, Coyle WJ. The noncolonic microbiome: does it really matter? Curr Gastroenterol Rep 2010; 12:259–62. doi: 10.1007/s11894-010-0111-6

2. Littman D, Pamer E. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host & Microbe 2011; 10(4): 311–23. doi: 10.1016/j.chom.2011.10.004

3. Battaglioli EJ, Hale VL, Chen J, Jeraldo P, Ruiz-Mojica C, Schmidt BA. Clostridioides difficil amino acids associated with gut microbial dysbiosis in a subset of patients with diarrhea. Sci Transl Med 2018; 10(464): eaam7019. doi: 10.1126/scitranslmed.aam7019

4. Woodworth MH. Challenges in fecal donor selection and screening for fecal microbiota transplantation: a review. Gut Microbes 2017; 8(3): 225–37. doi: 10.1080/19490976.2017.1286006

5. Feuerstadt P, Strong L, Dahdal DN, Sacks N, Lang K, Nelson WW. Healthcare resource utilization and direct medical costs associated with index and recurrent *Clostridioides difficile* infection: a real-world data analysis. J Med Econ 2020; 23(6): 603–9. doi: 10.1080/13696998.2020.1724117

6. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. JAMA 2015; 313(4): 398–408. doi: 10.1001/jama.2014.17103

7. Cheng Y, Fischer M. Clinical management of severe, fulminant, and refractory *Clostridioides difficile* infection. Expert Rev Anti-Infect Ther 2020; 18(4): 323–33. doi: 10.1080/14787210.2020.1730814

8. Taur Y. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. Sci Transl Med 2018; 10(460): 1–8. doi: 10.1126/scitranslmed.aap9489

9. Mullish BH, Quraishi MN, Segal JP, McCune VL, Baxter M, Marsden GL. The use of faecal microbiota transplant as treatment for recurrent or refractory clostridium difficile infection and other potential indications: Joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. J Hosp Infect 2018; 100(Suppl. 1): S1–S31. doi: 10.1016/j.jhin.2018.07.037

10. Pan D, Yu Z. Intestinal microbiome of poultry and its interaction with host and diet. Gut Microbes 2013; 5(1): 108–19. doi: 10.4161/gmic.26945

11. National Intitute of Health. Study quality assessment tools. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [cited 24 October 2021].

12. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ 2019; 366: l4898. doi: 10.1136/bmj.l4898

13. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory clostridium difficile infection. Aliment Pharmacol Therapeut 2017; 46(5): 479–93. doi: 10.1111/apt.14201

14. Hui W, Li T, Liu W, Zhou C, Gao F. Fecal microbiota transplantation for treatment of recurrent *C. difficile* infection: an updated randomized controlled trial meta-analysis. PLoS One 2019: 1–14. doi: 10.1371/journal.pone.0210016

15. Ianiro G, Masucci L, Quaranta G, Simonelli C, Lopetuso R, Sanguinetti M. Faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory clostridium difficile. Alimentary Pharmacol Therapeut 2018; 48(2): 152–9. doi: 10.1111/apt.14816
16. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M. Effect of fecal microbiota transplantation on recurrence in multiply recurrent clostridium difficile infection: a randomized trial. Annals of Internal Medicine 2016; 165(9): 609–16. doi: 10.7326/M16-0271
17. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, Storgaard M, Lemming L, Hansen MM. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent clostridium difficile infection. Gastroenterology 2019; 156(5): 1324–32. doi: 10.1053/j.gastro.2018.12.019
18. Louie TJ, Cannon K, Byrne B, Emery J, Ward L, Eyben M, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clin Infect Dis 2012; 55 (Suppl 2): S132–42. doi: 10.1093/cid/cis338
19. Shin JH, Chaplin AS, Hays RA, Kolling GL, Vance S, Guerrant RL. Outcomes of a multidisciplinary clinic in evaluating recurrent *Clostridioides difficile* infection patients for fecal microbiota transplant: a retrospective cohort analysis. J Clin Med 2019; 8(7): 1–11. doi: 10.3390/jcm8071036
20. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355: i4919.
21. Singh RK, Chang H, Yan D, Lee KM, Ucmak D, Wong K. Influence of diet on the gut microbiome and implications for human health. J Transl Med 2017; 15: 73. doi: 10.1186/s12967-017-1175-y
22. Wilson BC. The super-donor phenomenon in fecal microbiota transplantation. Front Cell Infect Microbiol 2019; 9(2): 1–11. doi: 10.3389/fcimb.2019.00002
23. Paknikar R. Fecal microbiota transplantation for the management of clostridium difficile infection. Surg Infect 2018; 19(8): 785–91. doi: 10.1089/sur.2018.221
24. Jalanka J, Hillamaa A, Satokari R, Mattila E, Anttila VJ, Arkkila P. The long-term effects of faecal microbiota transplantation for gastrointestinal symptoms and general health in patients with recurrent clostridium difficile infection. Aliment Pharmacol Therapeut 2018; 47(3): 371–9. doi: 10.1111/apt.14443

Bypassing the Blood–Brain Barrier to Treat Brain Cancer: A Systematic Review of the Efficacy of Carmustine Wafer Implant Therapy

Mark Sharobim[1]*, Peter A. Tsivis[1,2]

[1]Saba University School of Medicine, The Bottom, Saba, The Caribbean Netherlands;
[2]Rocky Vista University College of Osteopathic Medicine, Ivins, UT, USA

Corresponding Author: Mark Sharobim; m.sharobim@saba.edu

INTRODUCTION

Gliomas are cancers of the central nervous system (CNS) that arise from stem and progenitor cells of neuroglial origin. These cancers may generate from any of the following neuroglia: astrocytes, oligodendrocytes, and ependymal cells.[1] Other glial cells include microglia and radial glial cells, and though these cells often do not constitute tissue forming primary CNS tumors, certain lineages such as radial glial cells may be a source of stem cells that give rise to glioma.[2]

Primary brain tumors are grouped according to histologic features and are graded I–IV. Recently expanded criteria include molecular and genetic characteristics. Astrocytomas are the most commonly diagnosed glioma. According to World Health Organization (WHO) guidelines, astrocytomas are separated into four grades (I-IV) based on histologic features and malignant potential. Grade IV tumors include glioblastoma multiforme (GBM; common in adults), or diffuse midline glioma, the latter which affects children.[3] Over 30 different types of glioma are described in the 2016 WHO Classification of Tumors of the CNS report.[3]

Gliomas make up approximately 30% of primary brain tumors, and 80% of malignant cases.[1] In fact, primary CNS tumours account for the highest annual incidence of any neoplasm in children (≤19 years old) and are the second leading cause of mortality due to primary cancer in this age group. In adults, they are the most common primary malignant brain tumor. In the United States between 2007 and 2011, the incidence of gliomas was 6.6 per 100,000 people. GBM, the most aggressive subtype, accounted for almost 50% of cases.[4] The incidence of other gliomas can be up to 10 times lower than GBM. Like many other malignancies, incidence increases with age, with rates in the elderly being more than double the population average.[5]

In the most aggressive gliomas, treatment warrants a multi-disciplinary approach from a team of healthcare professionals. Despite major advances in understanding of the pathophysiology of glioma, it is still among the deadliest cancers. Standard treatment is surgical excision of the tumor followed by concomitant chemotherapy and radiotherapy. The median overall survival (OS) for those diagnosed with GBM is 12–18 months and 3-year survival remains below 15%. After disease recurrence, the outcome is almost invariably death, as progression free survival is typically 10 weeks and median OS can be anywhere from 25 to 40 weeks.[6] Another reason for poor patient performance is the fact that current standard of care for gliomas such as GBM is clearly defined, but no consensus is available regarding second line treatment options.[7] Thus, there is a need to develop more efficacious approaches to therapy.

The blood–brain barrier (BBB) separates blood perfusing the CNS from the surrounding brain tissue. The BBB is formed by tight junctions between the endothelial cells of vasculature found within the CNS. Furthermore, it is a functional unit composed of neuronal cells, astrocyte foot processes, and pericytes, which reinforce the barrier.[8] It is also a selective barrier that permits the passage of nutrients while excluding the entry of neurotoxins or macromolecules that are damaging to nervous tissue.

The permeability of the BBB can be altered in the natural progression of diseases such as infections, brain cancer, multiple sclerosis, and stroke. In the development of a cancer, the changes in the tumor microenvironment and neovascularization modify this

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

barrier so that it is considered distinct from a normally functioning BBB, leading some to refer to it as the blood–brain tumor barrier (BBTB).[9] Although the BBTB is more porous than the BBB, it remains unclear whether this permeability difference allows for any meaningful accumulation of chemotherapeutic drugs or substances.[10]

Reports from the 1970s by Rapoport and colleagues demonstrated that injection of hypertonic solutions mixed with Evans blue dye into arteries resulted in staining of surrounding brain tissue. The hypothesis was that the osmotic shift of fluid out of the endothelial cell in a hypertonic environment disrupted the tight junctions and integrity of this barrier.[11,12] Similar experiments subsequently confirmed this hypothesis, and this technique was termed blood–brain barrier disruption (BBBD). Among the earliest forms of bypassing the BBB, this technique has been used with intra-arterial injection of chemotherapeutic agents to increase the uptake of drugs in the CNS. Another method to bypass the BBB is to couple drugs to ligands that bind receptors on the surface of the endothelial cells lining the barrier. These ligands are transcytosed across the endothelial cell and taken up into the brain parenchyma.[13,14] Another way to bypass the BBB is via direct deposition of the drug in the brain cavity. This is routinely done, and the drug can be implanted at the surgical resection site of the tumor. Gliadel® wafers are small circular discs of biodegradable wafers containing a chemotherapeutic agent called carmustine. These wafers disintegrate in the presence of water to allow the slow local release of carmustine in a surgical resection cavity.[15] This prevents residual cancer cells from growing. Also, because gliomas such as GBM frequently recur near the primary neoplastic site of origin,[16] they also prevent disease relapse. Many placebo-controlled randomized clinical trials (RCTs) in the past have demonstrated their efficacy in treating different types of primary or recurrent glioma. They have been approved as the treatment for newly diagnosed high-grade gliomas by the FDA since 1996.[17]

Candidate treatments not discussed at length in this report still in the early phases of clinical development include bradykinin-mediated BBB opening (now discontinued)[18] and drug efflux transporter inhibitors,[19] both reviewed elsewhere.[9] In the case of bradykinin-mediated BBB disruption, the authors of the most recent clinical trial have suggested that the negative results are because the already transient nature of the barrier opening by bradykinin requires concomitant and continuous dosing with the desired agent (e.g., chemotherapy) and that these schedules often result in tachyphylaxis to bradykinin, as shown in early animal models. Drug efflux transporters implicated in CNS tumors have not reached clinical trial testing, and while there is more evidence that they cause drug resistance in other cancers such as breast and leukemia, no drugs are available in the clinic today.[20]

To date, the first-line therapy for newly diagnosed GBM is surgical resection followed by concomitant radiotherapy and chemotherapy. This is based on the clinical trial data by Stupp et al., who showed that postoperative chemoradiotherapy with the alkylating agent temozolomide (TMZ) improved median survival and 2-year survival as compared with radiotherapy alone. In some cases where a patient carries a favorable genetic mutation, the survival difference can be five-fold.[21,22] Although the standard of care of this treatment modality has not been updated recently,[23] gliomas remain among the most aggressive cancers. Since in this protocol TMZ is given peripherally, its uptake in the CNS is limited by the BBB. Thus, newer therapies may be designed with the intent of overcoming the limitations of the physiologic barrier to the brain.

The purpose of this report was to review relevant literature to determine if a therapy that bypasses the BBB has resulted in improved treatment outcomes for patients diagnosed with glioma. Although other reports have reviewed the status of treatments that bypass the BBB,[9] none have attempted to make a conclusion as to the efficacy of these treatments relative to standard of care. Our hypothesis is that overall, the treatment that actively circumvents this barrier will lead to better outcomes for patients with glioma as compared with the treatment that does not actively breach the BBB. To date and to our knowledge, the most clinically developed method of BBB diversion is wafer therapy as they are the only treatment modality that has reached phase III clinical testing. Therefore to test our hypothesis, we analyzed whether wafer implant therapy with or without chemoradiation post-surgical resection of brain tumor improved OS in patients with high-grade gliomas when compared with placebo or no wafer therapy.

METHODS

Inclusion and Exclusion Criteria

Initially, all studies gathered were RCTs or studies with a treatment arm and control arm, with treatment arms

including intervention consisting of post-surgical tumor resection wafer therapy with or without chemoradiation; control arms used no wafer or placebo wafer (for specific keywords used, see below). Studies with adult patients of all ages that had a histologically confirmed diagnosis of recurrent or *de novo* glioma were considered. Studies with patients that had prior unrelated malignancy that was present in the patient's medical history were excluded. Therefore, patients with brain metastases were not included as this represents a different primary disease.

For efficacy analysis comparing wafer therapy with published data from trials using current standard of care protocols only, patients with primary gliomas were not compared with those with recurrent glioma (see Results section), since a recurrent tumor is frequently a different disease to manage.[24] Also for efficacy analysis, gliomas in children were not included since pediatric and adult tumors are frequently unrelated.[25] The primary outcome for analysis was the percent change in median survival or OS, and all studies compared included this measure.

Search Methods

Two databases, PubMed and Web of Science, were used to gather data. The keywords ('glioma(s)' OR 'glial cell tumor(s)' OR 'malignant glioma(s)') were used with the terms (carmustine wafers OR BCNU wafers OR chemotherapy wafers OR Gliadel wafers) as described previously.[15] Of note, the keywords carmustine, BCNU, and Gliadel wafer refer to the same drug and were thus linked using the 'OR' Boolean operator.

Study Tabulations and Outcomes Measured

The definitions of clinical outcomes from various studies are summarized in Table 1. Percent increase in survival rates among treatment versus control cohorts using wafer therapy was graphed for studies meeting inclusion and exclusion criteria as shown in Fig. 1. Statistical significance was determined by $P<0.05$, and survival rates were depicted in each study using the Kaplan–Meier survival analysis; differences were determined using the log-rank method unless otherwise stated in the Results section. The evidence table (Table A1) generated in Appendix A describing the types of study was determined using previously published criteria.[29]

RESULTS

Using the search criteria outlined previously in the Methods section, a total of 10 papers were gathered. These encompassed over 500 patients across all studies. The studies gathered included 2 RCTs, 3 prospective cohort studies, and 6 retrospective case control studies, as summarized in Appendix A. The following includes a summary

Table 1. Definitions of patient outcomes measured in cancer clinical trials.[26–28]

Outcome parameter	Definition	Source
Partial response (PR)	≥50% reduction of the initial enhancing tumor, stable or reduced use of steroids, and stable or improved neurological function. Must be sustained for 4 weeks.	1
Complete response (CR)	Resolution of the enhancing tumor as shown on computed tomograms or magnetic resonance (MR) images, no need for steroids, stable or improved neurological function, and negative results on cerebrospinal fluid (CSF) tests.	1
Stable disease (SD)	No CR, PR, or progression. Stability of tumor on imaging (T2 or fluid-attenuated inversion recovery (FLAIR))	1
Progression	≥25% increase in perpendicular diameter of the tumor Significant increase in tumor size on imaging with stable or increasing doses of steroids	1
Overall survival (OS)	Length of time from diagnosis that patient remains alive.	2
Event free survival (EFS)	The time it takes from the end of primary treatment for cancer until there arises a complication the treatment is trying to prevent.	3,4
Time to tumor progression (TTP)	Essentially the same definition as EFS, except the 'event' is the progression of the tumor.	3,4

[1]Gallego[7], Chaichana[36], Valtonen[31], McGirt[35], Westphal[33], Affronti[34], Noel[38], Stupp.[22]
[2]Definition of overall survival – NCI Dictionary of Cancer Terms – National Cancer Institute.[26]
[3]Definition of event-free survival – NCI Dictionary of Cancer Terms – National Cancer Institute.[27]
[4]Saad and Katz.[28]

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

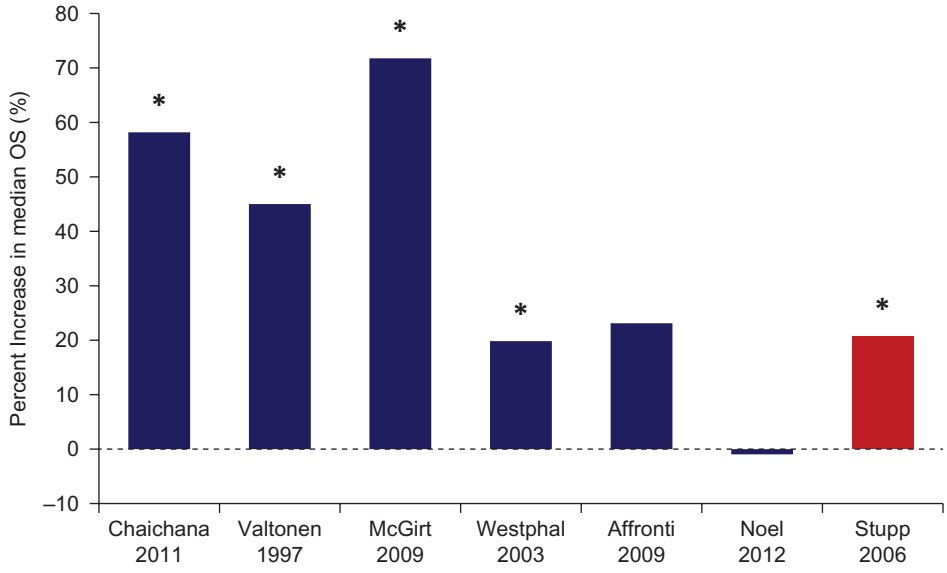


Figure 1. Percent (%) increase in overall survival (OS) in treatment versus control groups from carmustine wafer studies and the Stupp protocol.
Percent increase in OS from all studies in carmustine wafer trials (blue bars). These were compared to the percent increase in OS demonstrated previously in the standard of care for GBM (temozolomide AND radiotherapy vs. radiotherapy alone – red bars) according to the Stupp protocol.[22]
* indicates a study that demonstrated a significant difference in OS as compared to control ($P<0.05$).

of major outcomes from each study. In each study, median survival or OS was depicted using the Kaplan–Meier survival analysis, and differences were determined using the log-rank method unless otherwise stated.

Summary of Drug Wafer Therapy Studies

The earliest study published on this treatment modality is by Brem and colleagues.[30] The trial enrolled 222 patients with recurrent malignant glioma confirmed by CT or MRI. All patients had not taken systemic chemotherapeutic drugs at least 1 month prior to treatment. Patients were randomized into two treatment groups: surgical resection followed by carmustine wafer implant versus resection followed by placebo wafer implant. Most patients (~ 65%) had GBM. The primary outcome reported by the authors was mortality rate after treatment at 6 months. The authors demonstrated that implantation of wafers significantly decreased mortality in patients when stratified according to specific pathology (i.e., GBM or anaplastic astrocytoma) but no difference when combined. In glioblastoma, treatment with wafer implants resulted in a mortality rate at 6 months of 44% as opposed to 64% in the control group (OS of 56% and 37%, respectively; P=0.02). This resulted in a hazard ratio of 0.67 (95% CI: 0.48–0.95, P=0.02). Across all patients, mortality at 6 months was 40% in the treatment group, and 53% in the control group (OS of 60 and 47%, respectively; P=0.061), with a hazard ratio of 0.67 (95% CI: 0.51–0.90, P=0.061).

In a prospective cohort study, Valtonen and colleagues[31] enrolled 32 patients with a histopathological diagnosis of grade III or IV glioma. Other inclusion criteria included unilateral tumor based on CT or MRI, age between 18 and 65 years, and a minimum score of 60/100 on the Karnofsky Performance Scale (KPS). Exclusion criteria were evidence of systemic disease, thrombocytopenia, pregnancy, or hypersensitivity reaction to contrast material. Patients in the treatment group received Gliadel wafers or placebo wafer post-surgical resection of brain tumor. In patients with grade IV tumors (n=27), median survival post-surgical resection in the control group was 39.9 weeks (95% CI: 37.6–45.0) as compared with 53.3 (95% CI: 40.1–77.7) in the wafer group (P=0.008). Treatment was associated with a hazard ratio of 0.28 (95% CI: 0.10–0.71, P=0.008) using the Cox proportional hazards model. No difference was seen with variables such as KPS or age using the same model.

Subach et al[32] reviewed the outcomes of 94 patients with recurrent GBM treated with craniotomy and

surgical resection of the tumor followed by wafer implant. All participants were included if there was histological confirmation of GBM, completion of prior radiotherapy, radiographic evidence of tumor growth, and a KPS score of ≥70. Patients were excluded if they received systemic chemotherapy less than 1 month prior to surgery. The treatment arm consisted of surgical resection with carmustine wafer implantation. A mean of six wafers was implanted in each surgical resection cavity. The control group was made up of patients receiving surgical resection of the tumor only. Median survival from surgery was 14 weeks for the wafer treatment group and 54 weeks for the control group ($P<0.001$).

Westphal et al[33] conducted a clinical trial with 240 patients who had malignant glioma. All patients had a supratentorial tumor, unilateral tumor, and cerebral tumor as evidenced by MRI and KPS score of ≥60. After tumor resection, patients either received implanted carmustine wafer or placebo wafer. Postoperative radiotherapy was administered to both groups. Most patients (~83%) had GBM. Differences in prognostic factors of survival in the multiple-regression analysis were calculated using the Cox proportional hazards model. Median survival time was 13.9 months for the wafer group and 11.6 months for the placebo group ($P=0.03$). This was associated with a hazard ratio of 0.71 (95% CI: 0.52–0.96, $P=0.03$). Stratifying patients by GBM diagnosis only did not reveal a difference in survival.

In the investigation by Affronti et al,[34] retrospective chart reviews from 176 patients with primary GBM were used to determine if wafer implants improved the clinical outcome. All patients must have had a primary GBM diagnosis based on histology, a lack of chemotherapy treatment prior to resection, gross or total resection, and post-surgical adjuvant radiotherapy, and TMZ treatment. No significant difference in overall, 1-year, 2-year, and median survival was observed across both treatment groups. Despite this, median survival was higher in the carmustine wafer group as compared with control (89.4 [95% CI: 65.9–136.4] vs. 72.7 [95% CI: 62.7–84.3] weeks, respectively; no *P* value reported).

McGirt and colleagues[35] combined the use of wafer implants with adjuvant TMZ therapy and radiation. All patients had received a primary resection of malignant GBM. All patients received adjuvant radiotherapy (XRT) and TMZ therapy as described in the Stupp protocol.[22] Thirty-three patients received XRT + TMZ + Gliadel wafer, and 45 patients received XRT + TMZ alone post-resection. Patients receiving the treatment regimen lacking Gliadel wafers had a median survival of 14.7 months as compared with a similar cohort with Gliadel wafers who had a median survival of 20.7 months ($P<0.01$). A difficulty arose in which some patients did not receive Gliadel because the total resection was not achieved in all patients. Thus, more patients (60% vs. 30% in control vs. treatment groups, respectively, $P<0.05$) in the control group had a subtotal resection. In cases where a gross total resection was achieved, the median survival increased in both cohorts but was disproportionately increased in the control group, and therefore, the difference in survival was not significant.

The report by Chaichana and others[36] limited the scope of their study to patients over 65 with primary supratentorial GBM. All patients received either wafer or none post-resection and post-surgical radiotherapy. The median survival for the treatment arm was 8.7 months, while it was 5.5 months for the control group ($P=0.007$). Survival rates were also significantly higher ($P=0.04$) for the treatment group at 3, 6, 9, and 12 months. The same trend was found in patients older than 70 and 75 years.

A total of 165 patients with newly diagnosed or recurrent GBM were treated in the study by De Bonis et al[37] Histological diagnosis of grade IV GBM was performed after craniotomy and resection. Patients received either Gliadel wafers or nothing post-surgical resection. All were treated with TMZ and XRT post-surgery. If TMZ was too toxic, other drugs such as cisplatin and irinotecan were used; 47 patients were in the treatment group and 13 patients were in the control arm. Median survival did not significantly change between treatment or control groups (14 months [95% CI: 8–18] vs. 11 months [95% CI: 8–14], respectively; $P=0.77$). The same was true when patients were stratified for recurrent or *de novo* GBM.

In the study by Noël et al,[38] 28 patients received Gliadel wafers post-surgical resection of histologically confirmed grade III or IV glioma (treatment group) versus 37 patients with similar glioma who did not receive wafer treatment. There was no difference in median OS in either treatment group (20.6 months vs. 20.8 months, $P=0.81$).

In the most recently published study on wafer implant therapy, Samis-Zella et al[39] compared the use of implantable wafers for recurrent grade IV GBM with patients with similar glioma who did not get wafer treatment. All patients were given TMZ as well as prophylactic cefazolin and dexamethasone post-surgically. Sixty-three patients received wafer therapy and thirty-two did not post-resection. Patients were matched for age, KPS

performance, and treatment for the initial primary tumor. The primary outcome reported was PFS. The median PFS from disease recurrence was 6.0 months (95 % CI: 4.2–7.7) in the treatment group and 5.0 months (95% CI: 2.3–7.6) in the control group, and this difference was not significant (P=0.8).

Five of the ten studies determined statistically significant differences in median survival or OS as determined by the Kaplan–Meier survival analysis (indicated by a *, where P<0.05 in Table 2). Their efficacy as compared to the standard of care is further analyzed in the proceeding section. A summary of the results of these studies is found in Table 2. A similar table comparing only study designs and evidence level is found in Appendix A (Table A1).

Overall Efficacy

To determine whether carmustine wafer treatment resulted in improved clinical performance for glioma patients, the percent change in survival seen in wafer studies was compared with previously established guidelines of the first-line treatment. In all 10 studies gathered, 6 trials using therapeutics that bypassed the BBB met the criteria for analysis as determined in the Methods section (e.g., exclusion of patients with disease recurrence). One study did not report OS or median survival and was excluded.[39] All patients had high-grade III or IV glioma. Of the 6 trials, 4 (75%) demonstrated a significant (P≤0.05) percent increase in median survival as compared with control or non-disruptive treatment (Fig. 1). Two studies did not find a significant increase in survival.[34,38] Thus, 75% of eligible trials using wafer treatments showed a significant survival advantage over no wafer treatment.

To determine the usefulness of carmustine wafer therapy compared with the current first-line treatment for GBM, the percent change in survival seen among each study using wafer therapy was plotted against the survival benefit seen in the Stupp study, which was the first trial that described the current treatment protocols.[22] This is depicted in Fig. 1. In the four trials that demonstrated a significantly increased survival benefit with wafer therapy, 3 (75%) showed equal or greater percent increase in survival than the Stupp study.

DISCUSSION

GBM is the most common malignant brain tumor and is associated with poor clinical outcomes. The first-line treatment for gliomas such as GBM consists of surgical resection followed by concomitant radiotherapy and TMZ chemotherapy, referred to as the Stupp protocol.[22] Phase III studies have shown significant survival improvements using this protocol. Since no other treatment regimen is currently comparable, and nothing is effective at treating recurrent GBM, more research is needed to further improve patient outcomes.

An area of interest is in the circumvention of the BBB, since most therapeutics that would otherwise effectively treat cancer cannot accumulate in sufficient concentration in brain parenchyma. One of the most clinically developed modalities that physically bypass the BBB is via direct access through the cranium. With drug wafer treatments, surgically resected cancers can be treated by inserting a polyanhydride drug wafer (made up of the alkylating agent, carmustine) into the resection cavity, allowing for its slow release over time.

Compared with the current first-line treatment for GBM (Stupp protocol), 3 out of 4 (75%) selected studies in this report determined a greater overall percent increase in survival when using wafer implants. This indicates that using wafers may improve existing established treatment guidelines. In general, 9 out of 10 studies showed some benefit to receiving wafer post-surgical resection. Some studies were underpowered (Valtonen et al,[31] n=27) and yet still were able to distinguish a statistically significant difference in survival. It is possible more patients would further separate changes in clinical outcomes. The only study to demonstrate risk, and not benefit, to using wafers was by Subach et al[32] This may be partially because both treatment and control groups were not the same size (n=17 and 45, respectively), and nearly half the patients in the wafer group (47%) had perioperative complications as opposed to only 13% of those who did not receive wafers post-resection. Furthermore, some have suggested that tumor location can be a prognostic factor, and thus, easily accessible tumors (cerebrum vs. brainstem) have better prognosis.[40] Indeed, a greater proportion of tumors were in the frontal and temporal lobes of control group cases (72%) as compared with treatment cases (67%).

A major limiting factor in the results is the heterogeneity of controls between all the studies. There was not one variable that was consistently controlled for across all studies, although age and functional impairment score (KPS) were the most common variables. This is in line with others that show age and Karnofsky performance are both independent factors predicting the

Table 2. Summary of studies demonstrating clinical outcomes after use of carmustine (Gliadel) wafer therapy in patients with glioma.

Authors	Method of BBB disruption	Study methods, population, exposure	Notes/outcomes
1) Brem et al.[30]*	Carmustine Wafers	Patients undergoing surgical excision of glioma received carmustine or placebo wafer.	• Most patients had GBM, but other types of glioma (e.g., anaplastic astrocytoma, oligodendroglioma) were also compared. • 222 patients with recurrent brain tumors were randomized to wafer or no wafer therapy. • A significant overall survival difference at 6 months was seen for patients with GBM or anaplastic astrocytoma.
2) Valtonen et al. [31,]*	Carmustine Wafers	Patients received carmustine or placebo wafers after surgical excision and then radiotherapy	• Patients had either grade III or IV glioma as determined by histopathology • 32 patients, 16 in each treatment group. • OS increased in the wafer treatment group significantly by about 20 weeks as compared to control.
3) Subach et al.[32]	Carmustine Wafers	Patients undergoing secondary excision of recurrent GBM received wafers (study group) or simply a craniotomy (cohort group)	• Patients all had recurrent GBM and all received similar primary treatment with radiotherapy while most had received prior systemic chemotherapy (carmustine/cisplatin). • 62 patients underwent operation, 17 were implanted with wafers, 45 did not. • A survival benefit was seen in the control group as opposed to the wafer group, but this was not significant.
4) Westphal et al.[33]*	Carmustine Wafers	Carmustine wafers + radiotherapy as compared to placebo wafers + radiotherapy	• 120 patients were in the placebo group and 120 were in the Carmustine wafer group. • Most patients had a diagnosis of glioma, 1 and 2 patients in either group with brain metastases were not included in the outcome calculations. • Overall survival of GBM patients (majority of the patients) was significantly higher in the carmustine wafer group at 13.6 and 11.4 months for the placebo wafer group.
5) Affronti et al.[34]	Carmustine Wafers	Surgical resection, temozolomide, radiotherapy with or without wafer implantation	• All patients treated had GBM, majority of patients were Caucasian and above 50 years old • 97 patients did not receive wafers, 85 did. • No significant differences in OS were observed
6) McGirt et al.[35]*	Carmustine Wafers	Patients received resection, radiotherapy, and temozolomide with or without carmustine wafers.	• All patients had GBM • Median survival significantly increased in patients having implanted wafers by 9 months. • 38 patients were treated with wafers, 78 patients were treated without. • Survival at 2 years was also doubled for those receiving wafers (statistically significant). • 6-month PFS was also significantly higher, more than double in wafer treatment group (90% vs. 40%).
7) Chaichana et al.[36]*	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Patients > 65 years of age with a supratentorial GBM were selected. • 45 patients with carmustine wafer implantation were matched with 45 who did not. • Patients receiving resection with wafer implant as opposed to those without were matched for other variables such as age, extent of resection, and post-operative radiation or chemotherapy. • A significant OS difference (P=0.007) was seen in the wafer treatment group as compared to control (8.7 and 5.5 months respectively).

Continued

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

Table 2. Summary of studies demonstrating clinical outcomes after use of carmustine (Gliadel) wafer therapy in patients with glioma.

Authors	Method of BBB disruption	Study methods, population, exposure	Notes/outcomes
8) De Bonis et al.[37]	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Both patients with newly diagnosed (n=77) and recurrent (n=88) GBM were treated. • Use of wafers did not significantly affect overall survival in either group of patients as compared to without wafers.
9) Noël et al.[38]	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Patients were treated for either grade III or IV glioma. • 65 patients underwent surgery, 28 had wafer implants, 37 did not. • Use of Gliadel wafers did not change PFS or OS significantly.
10) Samis Zella et al.[39]	Carmustine Wafers	Patients had surgical resection, radiotherapy, and concomitant temozolomide. Patients then either received wafers or no wafer treatment post excision.	• All patients had supratentorial grade IV glioma (GBM) • 63 patients were given wafers post resection and 32 without implantation. • No significant difference in disease-free interval (DFI) or PFS in both treatment groups.

A * indicates that the study determined a significant difference in overall survival in treatment versus control groups.

outcome of GBM.[41] Only one study (Brem and colleagues[30]) matched patients according to race. Others have shown similar survival outcomes across Caucasian and Afro-Caribbean patients with GBM, but significantly decreased survival in those of Hispanic descent.[42] Therefore. in addition to age and performance, the race is a factor that was not properly controlled that could change patient outcomes. Furthermore, the number of patients was not congruent in all 10 reports, with treatment arm sizes ranging from 17 to 120.

In the future, the development of treatment modalities that actively disrupt the BBB is desired. Not only does survival statistics for high-grade gliomas remain poor, the standard first-line TMZ therapy may not benefit patients with genetic variations in certain DNA repair mechanisms.[43] Thus, TMZ resistance is a problem for patients with GBM as there is no widely accepted second-line treatment for this patient population. Further work in developing treatments that open the BBB may therefore alleviate this problem.

CONCLUSION

The BBB provides a significant hurdle to developing chemotherapeutics that could successfully treat brain tumors such as glioma. One notable hindrance to reducing the dismal clinical outcomes in glioma is that no method to breach the BBB has proved to be successful enough to be used as a primary treatment. The challenge is that the understanding of the pathophysiology of gliomas may develop at a quicker pace than our knowledge of how to circumvent the BBB. Future work must address this disparity to adequately improve patient outcomes.

This report reviewed all the relevant studies regarding wafer therapy, a method of actively bypassing the BBB via the direct implantation of drug-eluting wafers in an intracranial resection cavity to treat brain cancer. Other, newer therapies such as receptor-mediated transport drug conjugates are promising due to their potential for low side effect profile; however, they are less clinically developed. For example, since only two studies[44,45] to date that describe drugs using receptor-mediated transport have failed to reach phase II level of development, more research is needed to develop more clinically suitable targets. At this time, of the candidate therapies that can bypass the BBB, carmustine wafers for patients with glioma have the most utility. In some cases, we have shown that they offer a clear advantage to current treatment regimens, but further investigation may be necessary to determine who may benefit from this therapy the most. This may be inherent to the mechanism of action of carmustine wafer therapy, an alkylating agent, as certain genetic factors may play a role in treatment response.[21] This is in line with our current hypothesis that truly effective

opening of the BBB will improve the clinical performance of patients with glioma.

These minor, yet significant successes have also demonstrated there is clinical value in pursuing the goal of overcoming the BBB. The future will determine if the goal of translating research on the bench to outcomes at the patient bedside is feasible. Past trials have already provided valuable lessons that can be applied to current research paradigms. Development of clinical trials addressing the lessons and questions outlined in this report may lead to the discovery of novel therapies that change the lives of those with malignant brain tumors.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

1. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, et al. Glioma. Nat Rev Dis Prim 2015; 1: 15017. doi: 10.1038/nrdp.2015.17

2. Castillo M. Stem cells, radial glial cells, and a unified origin of brain tumors. AJNR Am J Neuroradiol. 2010; 31(3): 389–90. doi: 10.3174/ajnr.A1674

3. Louis DN, Perry A, Reifenberger G, Von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016; 131(6): 803–20. doi: 10.1007/s00401-016-1545-1

4. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a state of the science review. Neuro Oncol 2014; 16(7): 896–913. doi: 10.1093/neuonc/nou087

5. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y, Dowling J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. Neuro Oncol 2014; 16(Suppl 4): iv1–iv63. doi: 10.1093/neuonc/nou223

6. Heiland DH, Masalha W, Franco P, Machein MR, Weyerbrock A. Progression-free and overall survival in patients with recurrent Glioblastoma multiforme treated with last-line bevacizumab versus bevacizumab/lomustine. J Neurooncol 2016; 126(3): 567–75. doi: 10.1007/s11060-015-2002-z

7. Gallego O. Nonsurgical treatment of recurrent glioblastoma. Curr Oncol 2015; 22(4): e273–81. doi: 10.3747/co.22.2436

8. Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. Pharmacol Rev 2005; 57(2): 173–85. doi: 10.1124/pr.57.2.4

9. Van Tellingen O, Yetkin-arik B, De Gooijer MC, Wesseling P, Wurdinger T, De Vries HE. Overcoming the blood – brain tumor barrier for effective glioblastoma treatment. Drug Resist Updat 2015; 19: 1–12. doi: 10.1016/j.drup.2015.02.002

10. Zhan C, Lu W. The blood-brain/tumor barriers: challenges and chances for malignant gliomas targeted drug delivery. Curr Pharm Biotechnol 2012; 13(12): 2380–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23016643 [cited 6 May 2018].

11. Rapoport S, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. Am J Physiol Content 1972; 223(2): 323–31. doi: 10.1152/ajplegacy.1972.223.2.323

12. Rapoport S. Effect of concentrated solutions on blood-brain barrier. Am J Physiol Content 1970; 219(1): 270–4. doi: 10.1152/ajplegacy.1970.219.1.270

13. Daneman R, Zhou L, Agalliu D, Cahoy JD, Kaushal A, Barres BA. The mouse blood-brain barrier transcriptome: a new resource for understanding the development and function of brain endothelial cells. Ikezu T, ed. PLoS One 2010; 5(10): e13741. doi: 10.1371/journal.pone.0013741

14. Uchida Y, Ohtsuki S, Katsukura Y, Ikeda C, Suzuki T, Kamiie J, et al. Quantitative targeted absolute proteomics of human blood-brain barrier transporters and receptors. J Neurochem 2011; 117(2): 333–45. doi: 10.1111/j.1471-4159.2011.07208.x

15. Xing WK, Shao C, Qi ZY, Yang C, Wang Z. The role of Gliadel wafers in the treatment of newly diagnosed GBM: a meta-analysis. Drug Des Devel Ther 2015; 9: 3341–8. doi: 10.2147/DDDT.S85943

16. Chamberlain MC. Radiographic patterns of relapse in glioblastoma. J Neurooncol 2011; 101(2): 319–23. doi: 10.1007/s11060-010-0251-4

17. Buonerba C, Di Lorenzo G, Marinelli A, Federico P, Palmieri G, Imbimbo M, et al. A comprehensive outlook on intracerebral therapy of malignant gliomas. Crit Rev Oncol Hematol 2011; 80(1): 54–68. doi: 10.1016/j.critrevonc.2010.09.001

18. Prados MD, Schold SC, Fine HA, Jaeckle K, Hochberg F, Mechtler L, et al. A randomized, double-blind, placebo-controlled, phase 2 study of RMP-7 in combination with carboplatin administered intravenously for the treatment of recurrent malignant glioma. Neuro Oncol 2003; 5(2): 96–103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12672281 [cited 6 May 2018].

19. Sane R, Wu S-P, Zhang R, Gallo JM. The effect of ABCG2 and ABCC4 on the pharmacokinetics of methotrexate in the brain. Drug Metab Dispos 2014; 42(4): 537–40. doi: 10.1124/dmd.113.055228

20. Jaramillo AC, Al Saig F, Cloos J, Jansen G, Peters GJ. How to overcome ATP-binding cassette drug efflux transporter-mediated drug resistance? Cancer Drug Resist 2018; 1(1): 6–29. doi: 10.20517/cdr.2018.02

21. Stupp R, Hegi ME, Mason WP, Van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10(5): 459–66. doi: 10.1016/S1470-2045(09)70025-7

22. Stupp R, Mason WP, Van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and

adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352(10):987–96. doi: 10.1056/NEJMoa043330
23. Kazda T, Dziacky A, Burkon P, Pospisil P, Slavik M, Rehak Z, et al. Radiotherapy of glioblastoma 15 years after the landmark Stupp's trial: more controversies than standards? Radiol Oncol 2018; 52(2): 121–8. doi: 10.2478/raon-2018-0023
24. Campos B, Olsen LR, Urup T, Poulsen HS. A comprehensive profile of recurrent glioblastoma. Oncogene 2016; 35(45): 5819–25. doi: 10.1038/onc.2016.85
25. Nishikawa R. Pediatric and adult gliomas: how different are they? Neuro Oncol 2010; 12(12): 1203–4. doi: 10.1093/neuonc/noq175
26. Definition of overall survival – NCI Dictionary of Cancer Terms – National Cancer Institute. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival [cited 5 May 2018].
27. Definition of event-free survival – NCI Dictionary of Cancer Terms – National Cancer Institute. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/event-free-survival [cited 5 May 2018].
28. Saad ED, Katz A. Progression-free survival and time to progression as primary end points in advanced breast cancer: often used, sometimes loosely defined. Ann Oncol 2009; 20(3): 460–4. doi: 10.1093/annonc/mdn670
29. Ackley BJ, Ledwig G, Swan BA, Tucker S. Evidence-based nursing care guidelines: medical-surgical interventions. Mosby/Elsevier; 2008.
30. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. Lancet 1995; 345(8956): 1008–12. doi: 10.1016/S0140-6736(95)90755-6
31. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. Neurosurgery 1997; 41(1): 44–8; discussion 48-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9218294 [cited 3 May 2018].
32. Subach BR, Witham TF, Kondziolka D, Lunsford LD, Bozik M, Schiff D. Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. Neurosurgery 1999; 45(1): 17–22; discussion 22–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10414561 [cited 7 May 2018].
33. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 2003; 5(2): 79–88. doi: 10.1215/S1522-8517-02-00023-6
34. Lou Affronti M, Heery CR, Herndon JE, Rich JN, Reardon DA, Desjardins A, et al. Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. Cancer 2009; 115(15): 3501–11. doi: 10.1002/cncr.24398
35. McGirt MJ, Than KD, Weingart JD, Chaichana KL, Attenello FJ, Olivi A, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. J Neurosurg 2009; 110(3): 583–8. doi: 10.3171/2008.5.17557
36. Chaichana KL, Zaidi H, Pendleton C, McGirt MJ, Grossman R, Weingart JD, et al. The efficacy of carmustine wafers for older patients with glioblastoma multiforme: prolonging survival HHS Public Access. Neurol Res 2011; 33(7): 759–64. doi: 10.1179/1743132811Y.0000000006
37. De Bonis P, Anile C, Pompucci A, Fiorentino A, Balducci M, Chiesa S, et al. Safety and efficacy of gliadel wafers for newly diagnosed and recurrent glioblastoma. Acta Neurochir (Wien) 2012; 154(8): 1371–78. doi: 10.1007/s00701-012-1413-2
38. Noël G, Schott R, Froelich S, Gaub MP, Boyer P, Fischer-Lokou D, et al. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior Gliadel implantation (Carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. Int J Radiat Oncol Biol Phys 2012; 82(2): 749–55. doi: 10.1016/j.ijrobp.2010.11.073
39. Samis Zella MA, Wallocha M, Slotty PJ, Isik G, Hänggi D, Schroeteler J, et al. Evaluation of post-operative complications associated with repeat resection and BCNU wafer implantation in recurrent glioblastoma. Acta Neurochir (Wien) 2014; 156(2): 313–23. doi: 10.1007/s00701-013-1931-6
40. Walid MS. Prognostic factors for long-term survival after glioblastoma. Perm J 2008; 12(4): 45–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21339920 [cited 9 August 2018].
41. Stark AM, Van de Bergh J, Hedderich J, Mehdorn HM, Nabavi A. Glioblastoma: clinical characteristics, prognostic factors and survival in 492 patients. Clin Neurol Neurosurg 2012; 114(7): 840–5. doi: 10.1016/j.clineuro.2012.01.026
42. Shah AH, Barbarite E, Scoma C, Kuchakulla M, Parikh S, Bregy A, et al. Revisiting the relationship between ethnicity and outcome in glioblastoma patients. Cureus 2017; 9(1): e954. doi: 10.7759/cureus.954
43. Kitange GJ, Carlson BL, Schroeder MA, Grogan PT, Lamont JD, Decker PA, et al. Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro Oncol 2009; 11(3): 281–91. doi: 10.1215/15228517-2008-090
44. Drappatz J, Brenner A, Wong ET, Eichler A, Schiff D, Groves MD, et al. Phase I study of GRN1005 in recurrent malignant glioma. Clin Cancer Res 2013; 19(6): 1567–76. doi: 10.1158/1078-0432.CCR-12-2481
45. Gaillard PJ, Kerklaan BM, Aftimos P, Altintas S, Jager A, Gladdines W,et al. Abstract CT216: phase I dose escalating study of 2B3-101, glutathione PEGylated liposomal doxorubicin, in patients with solid tumors and brain metastases or recurrent malignant glioma. Cancer Res 2014; 74(19 Suppl): CT216-CT216. doi: 10.1158/1538-7445.AM2014-CT216

APPENDIX A

Table A1. Summary of study types and evidence level

Authors	Method of BBB disruption	Study type	Evidence level
1) Westphal et al.[33]	Carmustine Wafers	Randomized Clinical Trial (RCT)	1
2) De Bonis et al.[37]	Carmustine Wafers	Prospective Cohort study	2
3) Noël et al.[38]	Carmustine Wafers	Retrospective Case Control Study	3
4) Chaichana et al.[36]	Carmustine Wafers	Retrospective Case Control Study	3
5) Affronti et al.[34]	Carmustine Wafers	Retrospective Case Control Study	3
6) Valtonen et al.[31]	Carmustine Wafers	Prospective Cohort Study	2
7) Subach et al.[32]	Carmustine Wafers	Prospective Cohort Study	2
8) Brem et al.[30]	Carmustine Wafers	Randomized Clinical Trial (RCT)	1
9) McGirt et al.[35]	Carmustine Wafers	Retrospective Case Control Study	3
10) Samis Zella et al.[39]	Carmustine Wafers	Retrospective Case Control Study	3

The criteria used to determine the evidence level for each study design were determined using previously published guidelines.[29]

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

Generational Giving: Japanese High School Students' Motivation to Donate Blood

Luna Kinoshita[1]*, Aya Goto[2], Makoto Kashimura[3], Norihiko Watanabe[4], Kenneth E. Nollet[5]

[1]School of Medicine, Fukushima Medical University, Fukushima, Japan; [2]Center for Integrated Science and Humanities, Fukushima Medical University, Fukushima, Japan; [3]Education Evaluation Division, Fukushima Medical University, Fukushima, Japan; [4]Medical Information and Supply Management Division, Fukushima Red Cross Blood Donor Center, Fukushima, Japan; [5]Department of Blood Transfusion and Transplantation Immunology, Fukushima Medical University, Fukushima, Japan

Corresponding Author: Luna Kinoshita; m171034@fmu.ac.jp; kcluna1997@gmail.com

INTRODUCTION

According to the World Health Organization, most countries recruit blood donors aged between 18 and 65 years for allogeneic transfusion, that is, for transfusion to patients unrelated to the donor. In high-income countries, 75% of blood transfusions are given to people aged 65 years or older.[1] In Japan, the population over 65 years old comprised more than 28%,[2] whereas the working-age (15–64 years old) comprised 59.7% of the population in 2018.[3] The number of young people (under 15 years old) who could be future donors has been decreasing rapidly, comprising just 12% of the 2018 population.[3] The Ministry of Health, Labour and Welfare estimated that the annual blood transfusion demand would increase from about 8,500,000 blood component units in 2020 to 9,000,000 blood component units in 2027, while the donated blood from which those components are derived would decrease from about 6,500,000 units in 2020 to 6,300,000 units. Therefore, the proportion of young people who donate blood and the frequency with which they donate warrant urgent attention. Fukushima is Japan's third largest prefecture by area, but with only 1.5% of the nation's total and working-age population; 29% of Fukushima's population is 65 years old and above.[4] In Japan, a transfused 'unit' of red cells, platelets, or plasma is historically based on a 200 mL whole blood donation; this volume can be collected from healthy volunteers as young as 16 years old. Donations of 400 mL are accepted from 17-year-old men and 18-year-old women, according to policies liberalized in 2011. However, anxiety about COVID-19 infection greatly reduced the number of volunteer donors at various places affected by the spread of SARS-CoV-2.[5] The Japanese Red Cross Society was already concerned about maintaining an adequate pool of blood donors. They have been trying to increase organizational participation and familiarity with blood donation, but putting even more effort into donor recruitment has been required in this context.[6] Transfusion demand in a rapidly aging society is thus complicated by various health crises. The aim of this article is to explore factors influencing young people's motivation to donate blood.

We previously asked university students about motivators and barriers to donating blood and found that the proportion of those 'frightened by blood donation' significantly differed between donors and non-donors.[7] According to Lowe and Ferguson, people who receive positively framed messages (e.g., 'lives saved') tend to be more confident about blood safety than those who receive negatively framed messages (e.g., 'lives lost').[8] A study conducted in Korea showed that altruism among high school students greatly increased blood donation rates and concluded that such correlates are important to develop a blood donation program.[9] Another study also indicated that altruistic feelings were associated with donors' satisfaction with their treatment and blood donor loyalty after giving blood for the first time.[10] Since our previous study focused on students' negative attitudes toward blood donation, we explored their positive attitudes in this study to advance previous work. We focused on a questionnaire item that asked one's perceptions of blood donation as 'doing good for others' and actual donation behaviors among Japanese high school students. Our specific hypothesis was that the perception of blood donation as 'doing good for others' would associate with students' actual donation behavior, and the following analysis plan was to explore factors associated with that perception.

MATERIALS AND METHODS

This was a cross-sectional study implemented by the Fukushima Red Cross Blood Donor Center. The center conducted a questionnaire survey in 2018 at 10 high schools in Fukushima Prefecture. Four students did not respond to the survey. The questionnaire assessed basic characteristics of students and past blood donation experience, along with 10 items as motivators and 8 items as barriers for blood donation. These motivator and barrier items emerged from our previous study,[7] which was also conducted in collaboration with the Fukushima Red Cross Blood Donor Center. The age range of Japanese high schoolers in general is 15 to 18 years.

From that database, we analyzed the following: basic student characteristics (which school, year in school, gender); subjective health; ABO blood group and Rh (almost always Rh-positive among Asians); transfusion experience of close friends, family members, and neighbors; and familiarity with donor eligibility criteria (Table 1). As for the last knowledge item, we asked, 'Do you know any of the criteria under which you are not eligible to donate blood?' and the response options were yes or no.

As the main outcome measurement, the questionnaire asked, 'How important do you think the following reason is when you decide whether or not to donate blood, on a 5-point scale ranging from 1 = very important to 5 = not important at all?' Among the motivators, our focus this time was 'doing good for others'. For statistical analysis, we placed the perception of 'doing good for others' into 2 groups. Included in the 'important' group are those who answered very important or important (1 and 2), and others (3, 4, and 5) were included in the 'not important' group. After confirming this perception associated with students' donation behavior, we investigated its association with other variables.

Survey data were analyzed using SPSS version 25 for Windows. As for factors associated with the perception of 'doing good for others' through blood donation, we first performed chi-square tests. Significant items by univariate analysis ($P<0.05$) were entered into multivariate analysis using binomial regression.

The original survey was conducted by the Fukushima Red Cross Blood Donor Center. It was an anonymous self-administered questionnaire survey conducted in classrooms. Our secondary analysis of the database was approved by the Fukushima Red Cross Blood Donor Center, as guided by Red Cross policy, national law, and the World Medical Association Declaration of Helsinki. Of note, the school names were masked in the database we received.

Table 1. Characteristics of students.

Variables	*N* (%)
	N=4,506
Year in high school	
First	1,433 (31.8)
Second	1,654 (36.7)
Third	1,414 (31.4)
School	
School 1	373 (8.28)
School 2	43 (0.95)
School 3	235 (5.22)
School 4	664 (14.7)
School 5	1,189 (26.4)
School 6	57 (1.26)
School 7	455 (10.1)
School 8	1,267 (28.1)
School 9	166 (3.68)
School 10	53 (1.18)
Gender	
Male	2,489 (55.2)
Female	2,005 (44.5)
Subjective health	
Excellent	1,205 (26.7)
Good	2,696 (60.0)
Not good	409 (9.08)
Poor	94 (2.09)
Knowing ABO blood type	
Yes	4,298 (95.4)
No	202 (4.48)
Knowing Rh blood type	
Yes	516 (11.5)
No	3,985 (88.4)
Close friends, family members, neighbors ever received blood transfusion	
Yes	246 (5.46)
No	4,221 (93.7)
Knowing eligibility criteria of blood donation	
Yes	1,960 (43.5)
No	2,492 (55.3)

RESULTS

Among those in the Red Cross database, 4,506 students from all 10 high schools responded (99.9%). Male students comprised 55.2% overall; first-, second-, and third-year students comprised 31.8, 36.7, and 31.4%, respectively (Table 1).

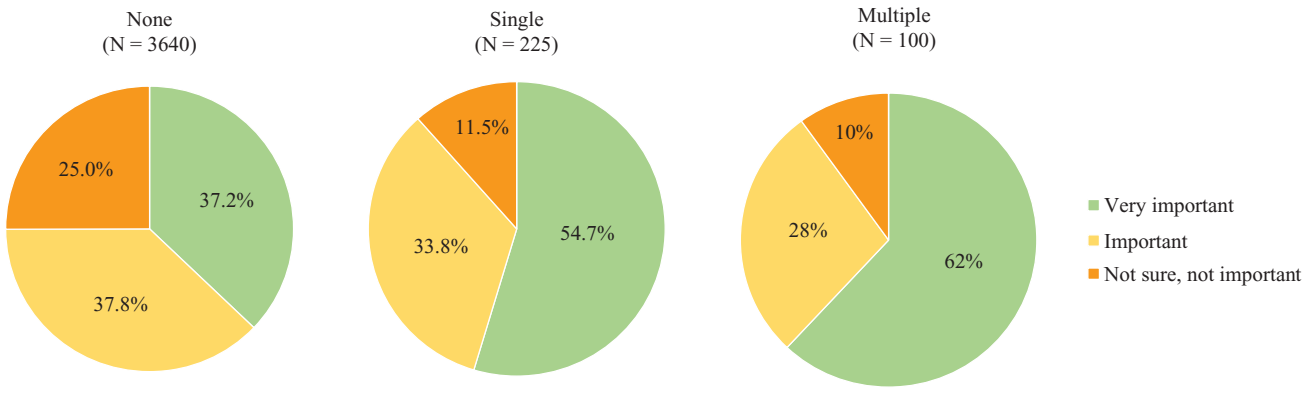


Figure 1. Number of past blood donations correlates with the perception of blood donation as 'doing good for others'.

Figure 1 illustrates how the number of past blood donations relates to the degree that 'doing good for others' is perceived. The 'very important' and 'important' groups correspond to exactly those survey answers, with the remaining answers aggregated in the 'not sure, not important' group. We found that students who donated blood more often tended to cite 'doing good for others' as an important motivator: the percentage of those answering 'very important' was 37.2% in the no donation group, 54.7% in the single donation group, and 62.0% in the multiple donation group.

By multivariate analysis, as shown in Table 2, two high schools had a significantly lower proportion of students answering that 'doing good for others' was important: 67.2% for School 1 and 65.5% for School 5. The probability of answering 'doing good for others' as important was significantly higher among female students [adjusted odds ratio (AOR)=1.853], those with better subjective health (AOR=2.433), those knowing their blood type (AOR=1.694), and those knowing eligibility criteria of blood donation (AOR=1.633).

DISCUSSION

As hypothesized based on previous studies from Korea[9] and Germany,[10] we found that the perception of 'doing good for others' was associated with students' past blood donation experiences. Our further analysis of factors associated with the perception might usefully inform donor recruitment efforts.

Encouraging healthy activities is intrinsically good and has the potential to improve subjective self-assessments of health. Especially for female students, we need to address low hemoglobin while striving to motivate potential donors. In our previous report analyzing data from blood centers in northeastern Japan (Miyagi and Fukushima Prefectures), over 20% of students attempting donation were deferred, mainly for low hemoglobin, with the probability of such a deferral 35 times higher for female students than for male students.[11]

In contrast to low hemoglobin as a donation barrier for female students, low motivation seems to be a barrier for male students. Outreach efforts should address this. Hupfer showed that male undergraduates in Canada responded well to moderately self-referencing and agentic donor recruitment messages.[12] A systematic review of motivating factors, by gender, suggests that it could also motivate male students if marketing campaigns encouraged current donors to recruit their friends.[13]

Our findings that knowledge – of blood type and donor eligibility criteria –associates with the perception of blood donation as 'doing good for others' concurs with Hong and Loke that enhancement of health education programs related to blood and blood donation for young people is important to increase their awareness.[14] However, a primary limitation to the generalization of our results is that this cross-sectional study cannot infer causality from statistical correlations between perceptions and behavior.

Nevertheless, education is widely perceived as an essential element of effective donor recruitment. Gender and other factors warrant further attention. Currently, we are developing blood donation education programs for elementary and junior high school students as a part of a student-initiated Popularization of Medical knowledge (POMk) Project.[15] Mentors in this

Table 2. Comparison of variables between those who think 'doing good for others' is important, or not, when deciding whether or to donate blood.

Variables	Doing good for others *N* (%)		Univariate[a]	Multivariate[b]		
	Important (*N*=3,028)	Not important (*N*=949)	P value	AOR	(95% CI)	P value
Year in high school						
First	981 (75.2)	323 (24.8)	0.014	1.088	(0.896, 1.321)	0.397
Second	1,178 (78.6)	321 (21.4)		1.171	(0.961, 1.427)	0.117
Third	868 (74.0)	305 (26.0)		Reference		
School						
School 1	232 (67.2)	113 (32.8)	<0.01	0.335	(0.136, 0.823)	0.017
School 2	34 (87.2)	5 (12.8)		1.115	(0.286, 4.349)	0.875
School 3	187 (85.8)	31 (14.2)		0.695	(0,268, 1.804)	0.455
School 4	433 (76.5)	133 (23.5)		0.416	(0.171, 1.013)	0.053
School 5	675 (65.5)	356 (34.5)		0.280	(0.116, 0.673)	<0.01
School 6	45 (84.9)	8 (15.1)		0.689	(0.216, 2.196)	0.529
School 7	356 (82.8)	74 (17.2)		0.577	(0.233, 1.427)	0.234
School 8	891 (81.2)	206 (18.8)		0.519	(0.215, 1.253)	0.145
School 9	132 (88.6)	17 (11.4)		1.041	(0.374, 2.892)	0.939
School 10	43 (87.8)	6 (12.2)		Reference		
Gender						
Males	1,553 (70.3)	656 (29.7)	<0.01	Reference		
Females	1,469 (83.4)	292 (16.6)		1.853	(1.566, 2.194)	<0.01
Subjective health						
Excellent	853 (79.1)	225 (20.9)	<0.01	2.433	(1.464, 4.043)	<0.01
Good	1,815 (76.5)	558 (23.5)		1.93	(1.178, 3.163)	<0.01
Fair	241 (67.7)	115 (32.3)		1.288	(0.753, 2.204)	0.355
Poor	46 (59.7)	31 (40.3)		Reference		
Knowing ABO blood type						
Yes	2,912 (76.6)	892 (23.4)	<0.01	1.694	(1.191, 2.410)	<0.01
No	114 (66.7)	57 (33.3)		Reference		
Knowing Rh blood type						
Yes	387 (83.0)	79 (17.0)	<0.01	1.216	(0.927, 1.596)	0.158
No	2,640 (75.2)	870 (24.8)		Reference		
Close friends/family members/neighbors ever received blood transfusion						
Yes	186 (82.7)	39 (17.3)	0.018	1.321	(0.911, 1.917)	0.142
No	2,818 (75.7)	903 (24.3)		Reference		
Knowing eligibility criteria of blood donation						
Yes	1,474 (83.0)	301 (17.0)	<0.01	1.633	(1.381, 1.931)	<0.01
No	1,528 (70.7)	633 (29.3)		Reference		

[a]Chi-square test was used.

[b]Binominal logistic regression was used to calculate odds ratios of answering 'doing good for others' as important by entering variables that were significant in the univariate analysis. AOR=Adjusted odds ratio, 95% CI = 95% Confidence interval.

program are themselves part of a legacy that includes Fukushima Medical University's response to the 2011 Great East Japan Earthquake, when students were among the hospital volunteers ready to donate blood for emergency transfusions if Red Cross inventories were insufficient or unavailable.[16] Education spans generations. Generation-specific health education aiming to ensure the future of blood donation may also improve the overall health of society.

Acknowledgments

This work was funded by a grant from high schools in Fukushima Prefecture. We are also grateful to the Fukushima Red Cross for their cooperation.

Disclosure

The authors declare that they have no conflicts of interest pertinent to the work described in this manuscript.

Conflict of interest and funding

The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

1. Blood safety and availability. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/blood-safety-and-availability [cited 18 August 2021].
2. Japan crosses new aging milestone, with 20% now 70 or older. 2018. Available from: https://asia.nikkei.com/Economy/Japan-crosses-new-aging-milestone-with-20-now-70-or-older [cited 18 August 2021].
3. Demography. Available from: https://data.oecd.org/pop/population.htm#indicator-chart [cited 18 August 2021].
4. Population of three age groups by prefecture. 2015. Available from: https://www.stat.go.jp/english/data/nenkan/66nenkan/1431-02.html [cited 18 August 2021].
5. Xiaohong C, Ming R, Fenghua C, Liliang L, Hang L, Xuefeng W. Blood transfusion during the COVID-19 outbreak. Blood Transfus 2020; 18(2): 79–82. doi: 10.2450/2020.0076-20
6. Japanese Red Cross on alert as blood donations fall amid virus outbreak. 2020. Available from: https://www.japantimes.co.jp/news/2020/03/05/national/red-cross-blood-donations [cited 18 August 2021].
7. Ngoma AM, Goto A, Nollet KE, Machida M, Kanno T, Nollet KE, et al. Barriers and motivators to blood donation among university students in Japan: development of a measurement tool. Vox Sang 2013; 105(3): 219–24. doi: 10.1111/vox.12044
8. Lowe KC, Ferguson E. Benefit and risk perceptions in transfusion medicine: blood and blood substitutes. J Intern Med 2003; 253(5): 498–507. doi: 10.1046/j.1365-2796.2003.01149.x
9. Kim YJ, Shin MH. The effect of knowledge and altruism on the blood donation behavior among high school students [abstract]. Korean Soc Blood Transfus 2010; 21(1): 16–24.
10. Boenigk S, Leipnitz S, Scherhag C. Altruistic values, satisfaction and loyalty among first-time blood donors. Int J Nonprofit Volunt Sect Mark 2011; 16(4): 356–70. doi: 10.1002/nvsm.433
11. Ngoma AM, Goto A, Nollet KE, Sawamura Y, Ohto H, Yasumura S. Blood donor deferral among students in Northern Japan: challenges ahead. Transfus Med Hemother 2014; 41(4): 251–6. doi: 10.1159/000365406
12. Hupfer ME. Helping me, helping you: self-referencing and gender roles in donor advertising. Transfusion 2006; 46(6): 996–1005. doi: 10.1111/j.1537-2995.2006.00834.x
13. Carver A, Chell K, Davison TE, Masser BM. What motivates men to donate blood? A systematic review of the evidence. Vox Sang 2017; 113(3): 205–19. doi: 10.1111/vox.12625
14. Hong J, Loke AY. Hong Kong young people's blood donation behavior. Asian J Transfus Sci 2011; 5(1): 49–52. doi: 10.4103/0973-6247.76000
15. POMk Project. 2021. Available from: http://www.pomk.org [cited 18 August 2021].
16. Nollet KE, Ohto H, Yasuda H, Hasegawa A. The great East Japan earthquake of March 11, 2011, from the vantage point of blood banking and transfusion medicine. Transfus Me Rev 2013; 27(1): 29–35. doi: 10.1016/j.tmrv.2012.07.001

The Crooked Tree: An Essay and Sculpture

Hettiarachchige Diluksha Prasad Jayawardana*

Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

*Corresponding Author: Hettiarachchige Diluksha Prasad Jayawardana; dilukshaprasad@gmail.com

The Crooked Tree.[1]

Some months ago, I participated in an orthopedic surgery workshop as a medical student delegate. There was an eye-catching centerpiece in one stall that serves as the logo for many orthopedic organizations. It was a small tree strapped to a stake by a rope. This tree was an illustration of the idea behind the prevention and correction of bone deformities in children of the 17th century.[2] Each part of this tree served to represent the relationship between orthopedic surgery and nature.

BENT TRUNK WITH A ROPE AROUND IT

The trunk of this crooked tree was strapped to a stake. Simply, it is to make straight the trunk of the young tree. The same strategy is applied in clinical practice to treat fractures, crooked spines, and straighten bowed legs of children. To become an orthopedic surgeon, a physician has to master general orthopedics for 5 years with an additional 1-year training in a chosen orthopedic subspecialty. Therefore, the strapped trunk illustrates an orthopedic trainee mastering general orthopedic skills with the guidance of senior clinicians and curving his career to deliver better orthopedic care. Perhaps the bent trunk rather than the straight trunk denotes the gratefulness, respectfulness, and humbleness of the trainee to his/her teachers, peers, and, of course, the patients.

BRANCHES

The field of orthopedics has two different components. They are orthopedic subspecialties and various scopes of treatment. The subspecialties are Hand and Upper Extremity, Arthroplasty, Pediatric Orthopedics, Foot and Ankle Surgery, Spine Surgery, Orthopedic Oncology, Sports Medicine, and Orthopedic Trauma.[3] The scopes of treatment include management of fractures and dislocations, torn ligaments, sprains, tendon injuries, pulled muscles, bursitis, ruptured disks, sciatica, low back pain, scoliosis, knock knees, bow legs, bunions, hammertoes, arthritis, osteoporosis, bone tumors, muscular dystrophy, cerebral palsy, club foot, unequal leg length, abnormalities of the fingers and toes, and growth abnormalities of bones.[4] Therefore, branches of the crooked tree adequately depict the compilation of pathologies encompassed by orthopedic surgery. On the contrary, the branches could also highlight the subspecialty training of an orthopedic resident in a chosen field after completing the general orthopedic training.

BUDS AND LEAVES

Orthopedic surgery is an advancing medical field. Day-by-day discoveries at the molecular and population levels come to light for the improvement of patient care. The field has evolved in understanding and technology since Nicholas Andry's first description. For example,

the evolution of arthroscopy, a method of visualizing the interior joint, has opened a new era of therapy. It is consistent with the budding and growing of young leaves of the tree. Likewise, an orthopedic trainee gains new clinical experiences and knowledge every day throughout his career similar to the tree budding and leafing daily.

ROOTS

The roots of this tree depict the basics of modern orthopedics and its principles. The modern technology of orthopedics has been evolved from the discoveries of the forefathers of orthopedics over decades. Therefore, orthopedists still look at roots when faced with patient care decisions. Finally, strong roots keep the tree steady, just as our skeleton provides structure to the flesh.

It is my sincerest hope that I have successfully captured the meaning of this tree famous to orthopedists worldwide. From the roots to the new leaves, there are many translations to the field of orthopedic surgery hidden in this small crooked tree that can serve as a discussion between those who wish to ponder the meaning.

Conflict of interest and funding

The authors have no conflict of interest. The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

REFERENCES

1. Wongworawat MD. The living orthopaedic tree. 2007.
2. Ponseti IV. History of orthopaedic surgery. Iowa Orthop J 1991; 11: 59–64.
3. American College of Surgeons. Orthopedic surgery. Chicago, IL: American College of Surgeons; 2020.
4. Orthopedic Doctors. Physical therapy clinics in Council, Idaho. Orthopedic.io; 2020.

Medical School is Killing My Personality

Haleigh Prather*

Oregon Health & Science University, Portland, Oregon

*Corresponding Author: Haleigh Prather; pratherh@ohsu.edu

A peer once described professionalism for medical students on clinical rotations as a strategic 'pageantry'. Like a trapeze artist, I am consistently toeing the line between formal yet relaxed, demure yet approachable, knowledgeable yet teachable, and all the while trying to bring a unique sense of personal style and zest that meets (but doesn't overstep) the subjective expectations of a wide range of preceptors and their patients. This whole song-and-dance act leaves me open to *constant* evaluative critiques that I'm not doing something right and need to change it. And at the end of a long day, I feel like a modern-day Sisyphus, exhausted from pushing my personality up a mountain of professionalism in an effort to keep it alive. A partial explanation for the friction I'm experiencing is the fact that I am very unapologetically myself – extroverted, silly, and dare I say it, loud – and I don't like to be told to be different. But unfortunately, I have chosen a career that is the opposite of those qualities, and I have gotten feedback to 'be myself less' more than once, leaving me feeling disenchanted and disconnected to the career I've decided to dedicate my life to.

From a young age, I have been confident, bold, and brave enough to be remembered with a big personality. And until recently, I believed that my personality could be one of my strongest qualities as a medical student. I envisioned it helping me to connect with and care for patients swiftly and effortlessly, in the same way I have with so many peers and colleagues over the years. However, after completing more than half of my clinical rotations, I have learned that instead of being seen as a refreshing energy and asset to my medical career as I had hoped, it is seen by many of my superiors as one of my most fatal flaws and a problem to be evaluated and corrected.

After completing my pediatric rotation, I received a performance evaluation from an intern which read 'Continue to work on gathering a history and physical from the patient/their family in a respectful manner while using professional language'. I remember feeling my face flush and my blood run cold after reading it. I thought back to the mere 2 days she and I had worked together and searched my memory desperately, wanting to remember if I had done something worth frowning upon. But the only thing I could think of was the fact that our professional styles were very different; she was very stern and serious, whereas I am very casual and laid back. I tried to let it roll off my back, but this testimony's wording felt unfair and unwarranted. I reached out to the pediatric course coordinator over concern that this feedback (which had the potential to end up on residency applications) would be misconstrued as profanity or something else truly inappropriate, and she comforted me that everyone occasionally gets bad feedback and that sometimes professional styles can really clash and that I should keep this in mind moving forward.

What stayed with me after that was the fact that I no longer felt allowed to be myself freely in the clinical setting. I felt like I needed to censor or muffle the shine that makes me *me* and I felt at the absolute mercy of my overworked and under-slept supervisors – once victims of this culture of professionalism themselves – who clearly did not want to connect with me in the way I was looking to connect with them. And more to the point, I felt that this was an indication that a personality is not seen as an asset but as a liability, informed by the power politics that lead so many medical trainees and attending physicians to believe their way of practicing medicine is superior to those subservient to them.

Over time, I forgot about my experience on my pediatric rotation, until this feedback reared its ugly head on my evaluations during my family medicine rotation. This time the feedback was 'change how much energy I bring into a room'. I was once again embarrassed that I had had the audacity to be myself. In my opinion, being bright, enthusiastic, and extroverted is also professional, and it felt demoralizing to me that I once again felt like my personality didn't fit nicely into the preconceived, cookie-cutter qualities dictated by the medical power figures that be.

MSRJ © 2022 VOL: 08. Issue: Spring
epub February 2022; www.msrj.org

This feedback would feel warranted if I were unable to titrate my energy to match that of a patient, but I have never felt this to be the case. I enter the exam room with my best self on display and if a patient is in acute pain, or if the topic of a conversation migrates to more serious topics – for example, mental health or social stressors – I lower my volume and replace enthusiasm with active listening and supportive head nodding, mirroring their energy and leaving space for a patient to feel heard. Therefore, who is this feedback to be 'different' for? Who is it benefitting? It seems like it is less of critique to be a better doctor and more of a subjective personal preference. In other words, it's something *they* wouldn't do, but that does not mean it's wrong.

It's moments like these where I wonder, am I not cut out for medicine? There are already very few people in this field with a background like mine or a body like mine, and now I'm being told I shouldn't have a personality like mine either. What I'm getting at with all this is that maybe it's just *me*. And if I must change so many things about myself just to satisfy these personality criteria I never even wanted to fit into in the first place, then I can't help but feel disillusioned in my career choices. Medicine already asks me to pay six figures in out-of-state tuition and almost never see my family, what else do I have to give up? Is the expectation that I must perform life-long code switching in order to be successful? Being different and being unique is both important and brave, and it is hurtful and disappointing to me to hear my superiors chastise me for it.

Maybe it *is* that I'm letting myself get too comfortable. Or maybe it's that I am trailblazing a new kind of informal and colloquial style of medicine that will benefit a distinct set of patients. Either way, I am urging those in evaluative positions of power to stop insinuating medical students should not feel free to be themselves in the name of toxic professionalism. If a patient were to be harmed by a personality, then of course this should be corrected. But to claim that I need to change simply because I am different or am not you, reader, is both harmful and untrue. To put it plainly, I am not open to feedback on things I am not interested in changing, and my personality is one of my favorite things about myself. So no, I will not 'be myself less' with patients as a student, as a resident, or as an attending. Patients deserve to have a doctor like me 1 day and they deserve the best version of myself and nothing less.