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American Osteopathic Board of Family Physicans Exam Schedule

EXAM	DATES AND EXAM LOCATION	POSTMARK APPLICATION DEADLINE
Sleep Medicine CAQ Certification Cognitive Exam	Lombard, IL August 22, 2015	
Sleep Medicine CAQ - Recertification Cognitive Exam	Lombard, IL August 22, 2015	
Family Medicine/OMT Certification - Cognitive Exam	Electronic Testing; Regional Sites September 26, 2015	April 1, 2015; filing with late fee thru June 1, 2015
Family Medicine/OMT OCC/Recertification - Cognitive Exam	Electronic Testing; Regional Sites September 26, 2015	April 1, 2015; filing with late fee thru June 1, 2015
Family Medicine/OMT Certfication - Performance Evaluation ONLY	AOA OMED Conference October 17-21, 2015; Orlando, FL October 17-18, 2015	April 1, 2015; filing with late fee thru June 1, 2015
Family Medicine/OMT OCC/Recertfication - Performance Evaluation ONLY	AOA OMED Conference October 17-21, 2015; Orlando, FL October 17-18, 2015	April 1, 2015; filing with late fee thru June 1, 2015
Hospice & Palliative Medicine Conjoint CAQ	October 18, 2015; Orlando, FL	July 1, 2014; filing with late fee July 15, 2015

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Osteopathic Family Physician Call for Paper Topics

- Abnormal Loss of Weight
- Dysuria
- Empathy and Quality of Care
- Fibromyalgia
- Hemorrhoids
- Infertility
- Monetary Incentives in Care - Both the Ethics, and How Do I Calculate my RVU Bonus?
- Nausea with Vomiting
- Sprain/Strain Neck (Request OMT component in this paper)

Didactic Images

We are seeking clinical images from the wards that covers essential concepts or subject matter to the primary care physician. Please provide a brief synopsis of how the case presented along with 1-4 questions and approximately 1 page of education with **reference to the image and questions**

Editor's Message

Alphabet Soup

Amy J. Keenum, DO, PharmD, Editor, Osteopathic Family Physician

In my first editorial message I wish to thank the outgoing editor Meridith Norris, DO, FACOFP; managing editor, Belinda Bombei, MS and the chair of the editorial committee, Peter Zajac, DO, FACOFP for their encouragement. Let me introduce Ronald Januchowski, DO, FACOFP who has agreed to serve as the associate editor for the next three years with plans of assuming the editor position after that time. This journal requires reviewers, writers and especially readers to continue, and as a reader we invite you to become a writer.

This edition of the journal offers several articles of interest to the osteopathic family physician as we go about our work as generalists. Each article contains acronyms that are used freely in the specialties of the subjects.

The article about new oral anticoagulants (NOA) reviews these new alternatives to warfarin and heparin. These medications are approved to treat non-valvular atrial fibrillation (NVAF) as well as prevention and treatment of deep vein thrombosis (DVT) and stroke. There is some convenience in avoiding injections to treat DVT at the time of diagnosis and avoiding bridging therapy. These drugs are expensive and we need to make sure the patient can get care if they cannot afford these medicines.

The article on stroke prevention also stresses the same anticoagulants. Elderly patients are at the highest risk for stroke and thus may benefit the most from these medicines for stroke prevention. Many elderly patients in America are poor and they fall. Ask if they can afford the medicine or will they need to go without food to purchase the drug? Ask when they last fell and observe the gait of the patient. If it takes a long time to watch them or you are reaching out to hold the patient it is time to have a longer conversation about the risks vs. benefits of anticoagulants.

The article that researches whether post traumatic stress disorder (PTSD) has a higher association with obstructive sleep apnea (OSA) is full of more abbreviations which I do not need to know to care for my patients. I will leave those to the sleep doctors, you know who you are.

The short article on tetanus reminds us to consider human tetanus immune globulin (HTIG) as well as tetanus vaccine if we think a patient has tetanus. It is not wise to assume that folks are vaccinated these days as many parents are opting out of vaccinating their children (and then they go to Disneyland™.) Folks are living longer and may not have had a tetanus shot in many years.

For those continuing to work in the inpatient setting we have an article on patient blood management (PBM) and blood components. New terms include treatment caused transfusion associated circulatory overload (TACO), especially in the elderly, or less commonly transfusion related acute lung injury (TRALI). In the past we called it acute respiratory distress syndrome (ARDS). Febrile non-hemolytic transfusion reactions (FNHTR) are not common and transfusion associated graft vs. host disease (TA-GVHD) is even less common but may be deadly. The key to patient safety is the right product to the right patient. Double checks and bar codes are used to ensure safety.

As we have an article mentioning TACO let's take a moment for a laugh. I direct you to one of my favorite comedians Trevor Noah. Check out his skit about his first taco on YouTube.com and maybe he will become one of your favorites too.

REVIEW ARTICLE

Review of New Oral Anticoagulants

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KEYWORDS:
Anticoagulation
Atrial Fibrillation
Deep Vein Thrombosis
Pulmonary Embolus
Warfarin

New oral anticoagulants have been developed over the past several years. These include the factor Xa inhibitors and direct thrombin inhibitors. These anticoagulants have been tested for safety and efficacy against standard therapies including subcutaneous enoxaparin or oral warfarin. The following is a review of pertinent trials comparing the new oral anticoagulants to standard therapy.

INTRODUCTION

Disorders of venous thromboembolism (VTE) have plagued physicians for hundreds of years. For the past half century the only oral treatment available for prevention and treatment of these diseases was warfarin. While warfarin is certainly effective, it is cumbersome requiring diet restrictions, close monitoring of international normalized ratio (INR), and avoidance of medications that potentially interact with its metabolism. The beneficial effects of warfarin in preventing VTE are undeniable, however, so are its bleeding risks. Practitioners have had to closely weigh the risk of bleeding with the potential therapeutic effects of anticoagulation with warfarin which can be quite difficult in certain patients.

Over the past decade, pharmaceutical companies have been developing new oral anticoagulants which affect different steps in the coagulation cascade than the traditional vitamin K antagonists. For the first time, there is a choice with regards to oral anticoagulation therapy. This leaves us to wonder, what is desired in the 'perfect oral anticoagulant'? Some desirable characteristics include: once daily oral dosing, predictable pharmacokinetics, low rates of interactions with other medications, no need for routine monitoring, low risk of bleeding, reliable and readily available reversal agents, affordable, low side effect profile, and no need for renal/hepatic dose adjustments. The new oral anticoagulants are more costly than warfarin, however it is difficult to compare the cost/benefit analysis. The need to monitor warfarin and the risks of suboptimal or supratherapeutic anticoagulation with warfarin need to be weighed against the cost and risks of the new agents. Patient characteristics are the strongest predictors of the cost/benefit ratio of each anticoagulant.

Currently there are more oral anticoagulants than before and each has its own unique desirable qualities. There are no head-to-head studies comparing these new medications to each other. Therefore, it is impossible to determine which agent is the best. However, many of the new oral anticoagulants have had promising results when compared to warfarin. The new oral anticoagulants' pharmacokinetic properties include rapid onset/offset of action, few drug interactions, and predictable pharmacokinetics, and eliminate the requirement for regular laboratory monitoring. The following is a summary of the major trials examining each new oral anticoagulant. Individually, each new oral anticoagulant was evaluated for the following indications: stroke prevention in non-valvular atrial fibrillation (AFIB), deep vein thrombosis (DVT) prevention after orthopedic surgery, and treatment of DVT or pulmonary embolism (PE).

DABIGATRAN

Dabigatran etexilate, Pradaxa®, is a direct thrombin inhibitor. The indications studied include anticoagulation for non-valvular atrial fibrillation, prevention of venous thromboembolism and treatment of deep vein thrombosis or pulmonary embolism. The usual dosage is 150 mg by mouth twice daily however, since dabigatran is excreted primarily through the urine, patients with a creatinine clearance of 15-30 mL/min use a lower dose of 75 mg by mouth twice daily. Use with caution in patients greater than 75 years old, have renal issues or have a bleeding risk. The half life of dabigatran is 12–17 hours, and due to its predictable pharmacokinetics does not need to be routinely monitored.

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The trials that demonstrate the efficacy and safety of dabigatran are summarized below.

Stroke Prevention in Non-valvular Atrial Fibrillation

The Randomized Evaluation of Long term anticoagulant therapy, RE-LY, trial was a randomized, partially blinded (warfarin was open, dabigatran was closed) phase III study, non-inferiority trial that compared the efficacy and safety of two different doses of dabigatran, 110 mg and 150mg, to warfarin with a dose adjusted INR of 2-3, in patients with non-valvular atrial fibrillation[1]. 18,113 patients with atrial fibrillation and at increase risk of stroke were enrolled in the study[1]. The primary endpoint, stroke or systemic embolism, occurred in 1.53% of patients given 110 mg of dabigatran twice daily, in 1.11% of patients given dabigatran 150 mg twice daily and in 1.69% of patients given warfarin[1]. The study revealed that both doses of dabigatran were non-inferior to warfarin in reducing rates of stroke or systemic embolism, however dabigatran 150mg twice daily was statistically superior[1]. Both the 110 mg and 150mg dose of dabigatran (0.12%, 0.10% of patients respectively) showed a significantly lower annual rate of hemorrhagic strokes than warfarin (0.38%)[1]. Major bleeding occurred in 2.71% of patients receiving dabigatran 110 mg twice daily, 3.11% in patients receiving 150 mg of dabigatran twice daily and 3.36% in patients receiving warfarin with the lower dose having statistically less major hemorrhage and the higher dose with similar rates[1]. There was a statistically significant increase in dyspepsia and gastrointestinal bleeding in the dabigatran groups compared to the warfarin group[1].

In 2013, RELY-ABLE trial was released. The purpose of this trial was to evaluate the long term safety of dabigatran at the dosages used in the RE-LY trial. It was a randomized, phase II safety study that enrolled 5,851 patients greater than or equal to 18 years old with atrial fibrillation who had participated in the RE-LY trial[2]. The results of the trial showed that during the 2.3 years of continued treatment after the RE-LY trial, there was no significant difference in stroke or mortality comparing dabigatran 150mg twice daily to 110 mg twice daily[2]. Dabigatran 150mg twice daily did have a higher rate of major and minor bleeding.[2] Net clinical benefit was examined between the two doses of dabigatran and was found to be similar: high dose dabigatran demonstrated superior efficacy in preventing embolic stroke while increasing major bleeding, and low dose dabigatran was less effective at preventing embolic stroke with lower bleeding risks[2].

Prevention of Venous Thromboembolism

The RE-MODEL trial was a randomized, double blinded study that compared oral dabigatran to subcutaneous enoxaparin for the prevention of VTE after total knee replacement. 2101 patients were involved in the study[3]. Dabigatran 150 mg or 220 mg by mouth once daily starting 1-4 hours after surgery for 6–10 days was compared to enoxaparin 40 mg subcutaneous daily, starting the evening before surgery for 6 -1 0 days[3]. The primary endpoint (DVT, symptomatic PE, or death) occurred in 40.5% of patients given dabigatran 150 mg daily, 36.4% in patients given dabigatran 220 mg and 37.7% in patients receiving enoxaparin[3]. Both doses of dabigatran were found to be statistically non-inferior to subcutaneous enoxaparin with regards to efficacy[3]. Major bleeding was similar between each group[3].

A similar randomized, double blind trial known as RE-NOVATE, compared dabigatran to enoxaparin for prevention of VTE after total hip replacement with anticoagulation lasting 28–35 days. 3,494 patients were enrolled in this study[4]. VTE or death from any cause occurred in 8.6% of those taking dabigatran 150 mg, 6.0% of those taking dabigatran 220 mg and 6.7% of those given enoxaparin[4]. The similar results among the 3 groups proved once again that dabigatran was not statistically inferior to enoxaparin for the prevention of VTE in the setting of hip replacements. The rates of minor and major bleedings with the dabigatran 150 mg, 220 mg or the enoxaparin 40 mg was comparable in all 3 study groups, 1.3%, 2.0% and 1.6%, respectively[4].

The RE-NOVATE II trial in 2011 was a randomized, double blind study that compared dabigatran 220 mg daily for 28-35 days verses enoxaparin 40 mg subcutaneously for 28-35 days for thromboprophylaxis after total hip arthroplasty. 2,055 patients age 18 years or older scheduled for a total hip arthroplasty were involved in this study[5]. VTE or death from any cause occurred in 7.7% of those given dabigatran and 8.8% of those given enoxaparin which was not statistically different[5]. Risk of bleeding was statistically similar in both groups[5].

The RE-MOBILIZE trial, that consisted of 2,615 patients scheduled for elective total knee replacement, compared dabigatran 150mg or 220 mg daily for 12–15 days versus enoxaparin 30 mg subcutaneous twice daily for 12-15 days for prevention of venous thromboembolism after knee arthroplasty[6]. This randomized, double blind study showed that combined incidence of VTE and death was higher in patients treated with both doses of dabigatran (33.7%, 31.1%) compared to enoxaparin (25.3%)[6]. Although inferior to enoxaparin in VTE events or death, major bleeding events were seen more frequently in those receiving enoxaparin[6].

Treatment of DVT/PE

The RE-COVER trial was a randomized, double blind study involving 2,539 patients, that compared dabigatran 150 mg twice daily to dose-adjusted warfarin with a target INR of

2-3 as treatment in the setting acute VTE[7]. Both groups were initially treated with 5 days ofparenteral anticoagulation with low molecular weight or unfractionated heparin[7]. Symptomatic VTE and VTE related deaths occurred in 2.4% of patients given dabigatran 150 mg twice daily and in 2.1% of patients given dose-adjusted warfarin[7]. Dabigatran was non-inferior to warfarin in the prevention of recurrent or fatal VTE in patients with acute VTE[7]. Patients on dabigatran also had significantly lower rates of major and clinically relevant non-major bleeding events, 5.6%, compared to 8.8% in those taking warfarin[7].

In 2013, the RE-COVER II trial was a randomized, double blind, double dummy, phase III, non-inferiority study with 2,568 patients that was done to confirm the results of RE-COVER I. After 6 months, 2.3% of patients on dabigatran had recurrent fatal or non-fatal VTE compared with 2.2% of patients on warfarin[8]. This proved once again that dabigatran was non-inferior to warfarin for treatment of acute VTE. Rates of bleeding favored dabigatran, 15.6% over warfarin, 22.1%[8].

RIVAROXABAN

Rivaroxaban, Xarelto® is a factor Xa inhibitor which has come onto the market in recent years. It reaches peak plasma concentrations within 2-4 hours with a half life of 5-9 hours. It is about 50% excreted by renal route requiring dose adjusted in patients with renal insufficiency, and should be avoided in patients with severe renal insufficiency. It is currently FDA approved for VTE prophylaxis post orthopedic surgery, treatment of DVT/PE, and stroke prevention in non-valvular afib. Rivaroxaban dosage in prevention of non-valvular afib is 20mg by mouth daily. The usual dose for DVT prophylaxis is 10mg by mouth daily. Treatment dose for DVT/PE includes 15mg by mouth twice daily for the first 21 days followed by 20mg by mouth daily. The 15mg and 20mg doses should be taken with food. There is no need for routine blood monitoring.

The following summarizes the trials analyzing the efficacy and safety of rivaroxaban.

Stroke Prevention in Non-valvular Atrial Fibrillaion

The study which prompted the FDA to consider Rivaroxaban for the prevention of strokes and embolic phenomena in non-valvular atrial fibrillation is the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolization Trial in Atrial Fibrillation (ROCKET-AF). This was a multicentered, randomized, double blind, double dummy, event driven trial which included 1,178 participants in 45 countries[9].

To be included in this study, participants must have atrial fibrillation documented on electrocardiogram and have had a history of stroke, TIA, systemic embolization or a CHADS2 score of at least 2[9]. Trial participants were assigned to either a 20mg once daily oral dose of rivaroxaban or a 15mg once daily oral dose if creatinine clearance of 30-49 ml/min, or warfarin dose adjusted to a target INR 2-3[9]. The mean duration of therapy was 590 days[9].

The primary efficacy endpoint which included stroke (ischemic or hemorrhagic) and systemic embolization occurred in 1.7% per year of rivaroxaban patients and 2.2% per year in warfarin patients which significantly met criteria for non-inferiority[9]. The principal safety outcome of the trial was major and clinically relevant non-major bleeding. The principal safety outcome occurred in 14.9% per year of rivaroxaban patients and 14.5% per year of warfarin patients, which was not a significant difference[9]. Decreases in hemoglobin of more than 2 grams/dL and blood transfusions occurred more frequently in rivaroxaban group[9]. However, rates of intracranial bleeding and fatal bleeding were significantly less frequent in the rivaroxaban arm[9]. Conversely, GI bleeding occurred more frequently in the rivaroxaban group[9].

Prevention of Venous Throboembolism

Rivaroxaban was examined for prevention of VTE in 2008 in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1 (RECORD 1 trial). This was a randomized multinational double blinded trial enrolling 4,591 patients[10]. This study included patients undergoing elective total hip arthroplasty. After surgery, patients were randomized to receive either 10mg oral rivaroxaban daily versus 40mg subcutaneous enoxaparin daily[10]. Primary outcomes included any DVT, non-fatal PE, and death from any cause up to 36 days[10]. Safety outcomes included major and clinically significant non-major bleeding[10]. The primary efficacy outcome occurred in 0.8% of patients in the rivaroxaban group and 3.4% of patients in the enoxaparin group which met the non-inferiority margin[10]. The combined incidence of major and clinically relevant non-major bleeding occurred in 3.2% of rivaroxaban group and 2.5% in the enoxaparin group[10]. Incidence of hemorrhagic wound complications and the number of blood transfusions were similar in both treatment arm[10].

RECORD 2 was another trial analyzing VTE prevention in 2,509 patients undergoing total hip arthroplasty[11]. This trial examined extended duration rivaroxaban (31-39 days) versus short term enoxaparin (10-14 days) in patients post hip arthroplasty[11]. The same doses of each medication were used as in RECORD 1 and primary efficacy outcomes were the same as well. In this trial, extended dose rivaroxaban was found to be significantly more effective at preventing venous thromboembolism than short dose enoxaparin[11].

RECORD 3 and 4 published in 2008 and 2009 respectively analyzed rivaroxaban in prevention of VTE in patients receiving total knee arthroplasty. The RECORD 3 trial enrolled 2,531 patients undergoingtotal knee arthroplasty and randomized them to receive either rivaroxaban 10mg by mouth daily starting 6-8 hours post surgery or enoxaparin 40mg subcutaneously daily starting 12 hours before surgery[12]. Primary outcomes which included DVT, PE, or death from any case 13-17 days after surgery occurred in 9.6% of patients in the rivaroxaban arm and 18.9% of patients in the enoxaparin arm demonstrating non-inferiority of rivaroxaban[12]. The combined incidence of major and clinically relevant non-major bleeding events was similar in the two groups[12].

RECORD 4 trial enrolled 3,148 patients who were randomized to receive once daily 10mg rivaroxaban dose initiated 6-8 hours post knee replacement versus enoxaparin 30mg subcutaneous twice daily dose initiated 12-24 hours after surgery[13]. The primary efficacy outcome which was DVT, PE, or any cause of death within 17 days of surgery occurred in 6.9% of patients in rivaroxaban group, and 10.1% in enoxaparin group demonstrating that rivaroxaban was significantly superior to enoxaparin in preventing venous thromboembolism post knee surgery[13]. Major bleeding was similar between the two treatment groups[13].

Due to the RECORD 1-4 trials, the FDA approved rivaroxaban for administration 6-10 hours post surgery for prevention of venous thromboembolism post hip/knee surgery.

Treatment of DVT/PE

With oral rivaroxaban being shown to prevent DVT in patients after surgery, it was next the aim of investigators to examine rivaroxaban's efficacy in treatment of DVT and PE. The EINSTEIN investigators examined three trials which analyzed the efficacy of rivaroxaban in treatment of DVT and PE.

EINSTEIN DVT was a randomized open label study enrolling 3,449 participants[14]. Patients included had an acute objectively confirmed DVT without signs or symptoms of PE[14]. Patients were treated with Rivaroxaban 15mg by mouth twice daily for three weeks then switched to rivaroxaban 20mg by mouth daily versus standard therapy during which patients were treated with subcutaneous lovenox 1mg/kg body weight with simultaneous warfarin therapy until INR reached 2-3 for at least 2 consecutive days with at least 5 days of treatment with enoxaparin[14].

These groups were analyzed at 3, 6, and 12 months[14]. 3499 patients underwent randomization[14]. During the study, the primary efficacy outcome which included symptomatic recurrent VTE, DVT, or non-fatal PE occurred in 2.1% of rivaroxaban patients and 3.0% in standard therapy patients which met the non-inferiority margin[14]. The principal safety outcome which included major and clinically relevant non-major bleeding occurred in 8.1% of rivaroxaban patients and in 8.1% of standard therapy with no statistical difference[14].

The EINSTEIN PE study was a randomized, open-label, event driven, non-inferiority trial which examined the efficacy and safety of rivaroxaban as compared with vitamin K antagonists in patients who had an acute symptomatic pulmonary embolism with or without DVT[15]. The primary efficacy outcome was symptomatic recurrent VTE. The principal safety outcome was major or clinically relevant non-major bleeding. Patients were randomized to standard therapy of enoxaparin 1mg/kg body weight subcutaneous injection twice daily with simultaneous dose adjusted warfarin until therapeutic INR (2-3) was achieved for 2 consecutive days with at least 5 days treatment with enoxaparin[15]. 4832 patients were enrolled in the study[15]. The primary efficacy outcome occurred in 2.1% of the rivaroxaban group versus 1.8% in the standard- therapy group demonstrating that rivaroxaban is non-inferior to standard therapy in the treatment of PE[15]. The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group which was found to be statistically similar[15].

There was another group that was analyzed called the Extended Treatment group in which 1,197 patients were enrolled. The purpose of this group was to explore the long term benefit to risk ratio of anticoagulation with rivaroxaban in prevention of VTE. These patients were enrolled in either the Acute DVT study or the Acute PE study or were enrolled from outside the study. These patients completed 6-12 months of either rivaroxaban therapy or warfarin therapy for a confirmed DVT[14,15]. They were then randomized to either rivaroxaban 20mg by mouth daily or placebo for a following 6-12 months[14,15]. The primary efficacy outcome in this group was symptomatic recurrent VTE and was seen in 1.3% of the rivaroxaban group and 7.1% in the placebo group[14,15]. Major and non-major bleeding occurred in 0.7% of the rivaroxaban group and none occurred in the placebo group.[14,15]

APIXABAN

Apixaban, also known as Eliquis, is a Factor Xa inhibitor. The indications for use include anticoagulation for non-valvular atrial fibrillation, prevention of venous thromboembolism and treatment of deep vein thrombosis or pulmonary embolism. The usual does for apixaban is 5 mg by mouth twice daily. The dose is decreased to 2.5 mg by mouth twice daily in patient with at least 2 of the following: greater than 80 years old, less than 60 kg, or creatinine of greater than 1.5mg/dL. Apixaban is adjusted for creatinine of greater than 1.5mg/dL, and if the patient has severe hepatic impairment apixaban should be

avoided. The half-life of apixaban is 12 hours. Apixaban does not require routine blood monitoring.

The trials that demonstrate the efficacy and safety of apixaban in these situations are summarized below. Stroke Prevention in Non-valvular Atrial Fibrillation

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was a randomized, double blind study that compared apixaban 5 mg by mouth twice daily for up to 39 months to dose adjusted warfarin with an INR of 2.0-3.0 in preventing stroke and systemic embolism in patients with atrial fibrillation[16]. A lower dose of apixaban, 2.5 mg by mouth daily, was used in patients who have two of the following criteria: 80 years or older, have a body weight of 60 kg or less or a serum creatinine level of 1.5 mg/dL or more[16].

18,201 patients were involved in the study[16]. They had atrial fibrillation and at least one additional risk factor for stroke[16]. 1.60% of patients on warfarin had a stroke or systemic embolism compared to 1.27% of patients on apixaban[16]. This was statistically significant thus, apixaban was superior to warfarin in preventing stroke or systemic embolism[16]. The rate of hemorrhagic stroke was statistically lower in patients on apixaban (0.24% per year) compared to those receiving warfarin (0.47% per year)[16]. The rate of ischemic stokes was similar within the two groups, 0.97% for those assigned to apixaban and 1.05% for those assigned to warfarin[16]. Death occurred less frequently in patients on apixaban (3.52% per year) compared to warfarin (3.94% per year)[16]. There was less major bleeding in the apixaban group (2.13% per year) than in the warfarin group (3.09% per year)[16].

The AVERROES trial was a randomized, double blind study that compared apixaban to acetylsalicylic acid (ASA). The data and safety monitoring board recommended early termination of the study because apixaban was clearly superior to ASA in preventing stroke or systemic embolism exceeding 4 standard deviations[17]. Apixaban 5 mg by mouth twice daily for up to 36 months or the end of the study was compared to ASA 81-324 mg by mouth once daily for 36 months or the end of the study for prevention of ischemic or hemorrhagic stroke in patients with atrial fibrillation[17]. 5,599 patients 50 years or older with atrial fibrillation and increased risk for stroke who are not suitable for vitamin K antagonist therapy were included in this study[17]. Events occurred 1.6% per year in patients taking apixaban versus 3.7% taking ASA[17]. There was no significant difference between major bleeding events when comparing the two groups, 1.4% per year with those taking apixaban and 1.2% with those taking ASA[17].

Prevention of Venous Thromboembolism

The ADVANCE-1 trial, was a randomized, double blind study of 3,195 patients scheduled for elective total knee replacement[18]. This trial compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after surgery for 10–14 days compared to enoxaparin 30 mg subcutaneous every 12 hours, 12-24 hours after surgery for 10–14 days in patient who had elective total knee replacements[18]. VTE and death from any cause occurred in 9.0% of patients given apixaban compared to 8.8% of patients given enoxaparin[18]. Although the rate of events was similar, the statistical criteria for non-inferiority was not met by apixaban however, apixaban was superior to enoxaparin in major bleeding[18].

The ADVANCE – 2 trial was a randomized, double blind study preformed to try to prove non- inferiority of apixaban compared to enoxaparin in prevention of VTE after total knee replacement[19]. 3,057 patients that were scheduled for elective total knee replacement were involved in this trial[19]. This trial compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after surgery for 10–14 days to enoxaparin 40 mg subcutaneously 12 hours preoperatively and then once daily starting 12–24 hours after surgery and continued for 10–14 days[19]. 15.1% of patients given apixaban and 24.4% of patients given enoxaparin had a venous thromboemoblic event proving that apixaban 2.5 mg by mouth twice daily was superior to enoxaparin 40 mg subcutaneous daily for prevention of VTE(19). Major bleeding events were similar in both groups occurring in 0.6% of patients in the apixaban group and 0.9% in the enoxaparin group[19].

The ADVANCE – 3 trial was a randomized, double blind study that compared apixaban 2.5 mg by mouth twice daily, 12-24 hours after wound closure for 35 days to enoxaparin 40 mg subcutaneously 12 hours preoperatively and then once daily starting 12–24 hours after wound closure and continued for 35 days for prophylaxis for VTE after hip replacement surgery[20].

5407 patients scheduled for total hip replacement was involved in this trial[20]. 1.4% of the apixaban group and 3.9% of the enoxaparin group had asymptomatic or symptomatic DVT, non-fatal PE, or death[20]. Major VTE was seen in 0.5% of those treated with the apixaban group and 1.1% of those treated with enoxaparin[20]. Symptomatic VTE or death related to VTE during the 60 day follow up never occurred in the apixaban group and occurred in 0.2% of patients treated with enoxaparin[20]. It was found that apixaban 2.5 mg by mouth twice daily was superior to enoxaparin 40 mg subcutaneous daily for all VTE and major VTE in patients after total hip replacement[20]. Major bleeding was similar between the two groups and occurred in 0.8% of those in the apixaban group and 0.7% in the enoxaparin group[20].

Treatment of DVT/PE

The AMPLIFY trial, was a randomized, double blind study with 5,395 participants, 5,244 patients were included in the primary efficacy analysis and 5,365 patient were included in the safety analysis[21]. This trial compared apixaban 10 mg by mouth twice daily for one week and then 5 mg by mouth twice daily for 6 months thereafter to standard therapy with enoxaparin 1 mg/kg subcutaneously twice daily, for at least 5 days, with dose adjusted warfarin until INR is 2.0 or greater and then dose adjusted warfarin to an INR of 2.0 – 3.0 for 6 months for the treatment of acute DVT/PE(21). The primary efficacy endpoint of recurrent VTE or death related to VTE occurred in 2.3% of patients taking apixaban and 2.7% of those taking standard therapy[21].

Apixaban therefore proved to be non-inferior to standard therapy of enoxaparin and warfarin treatment[21]. Major bleeding occurred in 0.6% of patients on apixaban and 1.8% of patients on conventional therapy with enoxaparin and warfarin therefore, treatment with apixaban was associated with significantly less major bleeding events compared to treatment with enoxaparin and warfarin[21].

The AMPLIFY-EXT trial was an extension of the AMPLIFY trial looking at long term VTE prophylaxis after treatment of an acute DVT/ PE[21]. This was a randomized, double blind study with 2,486 patients[21]. This trial compared two different doses of apixaban, 5 mg by mouth twice daily or 2.5 mg by mouth twice daily for up to 12 months versus a placebo twice daily for up to 12 months[21]. Patients had to be 18 years or older and had an acute DVT or PE and completed 6-12 months of prior anticoagulation treatment with no symptomatic recurrence[21].

Symptomatic recurrent VTE or VTE related deaths occurred in 1.7% of patients treated with apixaban 2.5 mg by mouth twice daily and 1.7% in patients receiving 5mg by mouth twice daily[21]. In the placebo group, 8.8% of patients encountered a symptomatic recurrent VTE or death from a venous thromboembolic event[21]. Therefore, it was determined that extended anticoagulation with either apixaban 2.5 mg by mouth twice daily or apixaban 5mg by mouth twice daily significantly reduced the risk of recurrent symptomatic VTE and fatal VTE[21]. The rates of major bleeding was low in all groups, 0.2% of patients taking apixaban 2.5 mg by mouth twice daily, 0.1% of patients taking apixaban 5 mg by mouth twice daily and 0.5% of patients taking the placebo pill[21].

EDOXABAN

Edoxaban is a factor Xa inhibitor which is the newest of the new oral anticoagulants to be studied. It is a once daily medication which has been studied in 30 mg and 60 mg doses. It was recently approved by the FDA in January 2015, and is the newest oral anticoagulant on the market. Edoxaban reaches peak plasma levels in 1-2 hours. Edoxaban is mainly excreted renally. Patients with low body weight, moderate-to-severe renal dysfunction, or concomitant use of a potent P-glycoprotein inhibitor should have the edoxaban dose reduced by 50%. So far it has be studied in stroke prevention in atrial fibrillation, VTE prophylaxis, and in treatment of DVT/PE.

Stroke Prevention in Non-Valvular Atrial Fibrillation

The trial which evaluated stroke prevention in non-valvular afib for Edoxaban was called the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). It was a multinational three group, randomized, double blind, double-dummy trial comparing two dose regimens of edoxaban with warfarin[22].

Patients enrolled had non-valvular atrial fibrillation at moderate to high risk of stroke with a CHADS2 score (Congestive heart failure, hypertension, age greater than or equal to 75 years old, diabetes, previous stroke/TIA) of 2 or higher[22]. 21,105 patients were enrolled and were randomized in a 1:1:1 ratio to receive either warfarin dose adjusted to achieve and INR 2-3, high dose edoxaban of 60mg by mouth daily, or low dose edoxaban 30mg by mouth daily with a median follow up of 2.8 years[22]. In either edoxaban group this dose was cut in half if creatinine clearance 30-50 ml/min, body weight of 60kg or less, or if patient was taking potent P-glycoprotein inhibitors[22].

The primary efficacy end point included time to first stroke (ischemic or hemorrhagic) or systemic embolic event which occurred in 1.5% per year in warfarin group and 1.18% per year in the high dose edoxaban group and 1.61% per year in low dose edoxaban group[22]. The high dose edoxaban met superiority margins compared to warfarin whereas low dose edoxaban was found to be non-inferior[22]. The rate of ischemic stroke was 1.25% with warfarin as compared with 1.25% with high-dose edoxaban and 1.77% with low-dose edoxaban which was significantly higher[22].

Primary safety outcome which was annualized rate of major bleeding occurred in 3.43% patients in warfarin group, 2.75% of patients in high-dose edoxaban group and 1.61% patients in low dose edoxaban group with both doses of edoxaban having significantly lower bleeding rates[22]. The annualized rate of hemorrhagic stroke was 0.47% with warfarin, 0.26% with high- dose edoxaban and 0.16% with low-dose edoxaban which was statistically significant[22]. The annualized rate of life-threatening bleeding, intracranial bleeding, and major

bleeding plus clinically relevant non-major bleeding were also analyzed and each found to be significantly lower in both high dose and low dose edoxaban group compared to warfarin[22]. The annualized rate of GI bleeding was found to be statistically higher in high dose edoxaban compared to warfarin, but lowest rates of GI bleed occurred in low dose edoxaban[22].

In summary, this trial demonstrated that high dose edoxaban was superior to warfarin in preventing stroke (ischemic plus hemorrhagic) but carried a higher risk of GI bleed. Low dose edoxaban had the lowest rates of GI bleed, and while being non-inferior to warfarin in combined hemorrhagic and ischemic stroke, tended to be less effective in preventing only ischemic strokes compared to warfarin.

Prevention Venous Thromboembolism

There were three phase III trials which were conducted in Japan which investigated the effect of edoxaban on the prevention of DVT/PE. These were the STARS (Studying Thrombosis After Surgery) trials. The STARS e-3 trial assessed a once daily dose of 30mg Edoxaban versus enoxaparin 20mg subcutaneous injection twice daily after knee replacement in 716 patients[23].

The STARS trial which evaluated patients undergoing hip replacement was called STARS j-5, which studied 610 Japanese patients using the same protocol as STARS e-3[23]. Patients in both studies were initiated on therapy after surgery and were continued on therapy for 11-14 days[23]. The primary endpoint which included symptomatic and asymptomatic DVT and PE occurred in 5.1% of patients taking edoxaban and in 10.7% of patients taking enoxaparin which was found to be statistically significant[23]. The primary safety endpoint which was major and clinically relevant bleeding occurred in 4.6% of patients taking edoxaban vs 3.7% of patients taking enoxaparin which was similar[23].

The STARS trials were limited to a Japanese population, so it is impossible to determine from these studies if the efficacy of edoxaban in preventing DVT/PE can be expanded to a more general population. Also, the dose of enoxaparin of 20mg subcutaneous injection twice daily is not a common dose used outside Japan for the prevention of DVT/PE post orthopedic surgery. The future may bring further trials examining edoxaban for this indication.

Treatment DVT/PE

A recent trial which evaluated edoxaban in the treatment of DVT/PE is called the Hokusai VTE trial. This trial was published October 2013. This trial enrolled 8292 patients in 37 countries[24].

Patients with objectively diagnosed acute DVT or PE were randomized to receive edoxaban 60mg by mouth daily (or 30mg by mouth daily if CrCl 30-50ml per min, or body weight

TABLE 1

	Renal dosing for Non-valvular Afib	Treatment of DVT/PE	Pharmicokinetics
Dabigatran etexilate, Pradaxa® ***COST $356-385 per mth***	·CrCl>30 ml/min: 150mg BID ·CrCl 15-30 mL/min: 75mg BID ·CrCl<15 mL/min: not recommended	·For patients who received parenteral anticoagulant for 5-10 days: 150mg BID	·Direct thrombin Inhibitor
Rivaroxaban, Xarelto® ***COST $297-320 per mth***	CrCl >50mL/min 20mg QD with evening meal CrCl 30-50mL/min 15mg QD with evening meal CrCl 15-30mL/min 15mg QD with evening meal CrCl<15 not recommended	15mg BID for 21 days then 20mg QD	Factor Xa Inhibitor
Apixaban, Eliquis® ***COST $302-326 per mth***	Normal kidney function: 5mg BID Serum Creatinine ≥ 1.5 PLUS either Age ≥ 80 or weight ≤ 60 Kg: 2.5mg BID ESRD: 5mg BID Decrease dose to 2.5mg BID if ESRD and either ≥80 years old or weight ≤ 60kg	10mg BID x 7days then 5mg BID	Factor Xa Inhibitor

below 60kg) or warfarin dose adjusted to achieve INR 2-3[24]. Prior to randomization, patients were treated with heparin then switched to either edoxaban or warfarin. Treatment was continued for 3-6 months[24]. The primary efficacy outcome which was recurrent symptomatic VTE, occurred in 3.2% of patients in the edoxaban arm, and occurred in 3.5% of patients in the warfarin arm which met statistical significance for non-inferiority[24]. The safety outcome which was major and clinically relevant bleeding occurred in 8.5% of edoxaban patients and 10.3% of warfarin patients which met statistically significant superiority criteria in favor of edoxaban[24]. (*Table 1)*

CONCLUSION

Rivaroxaban, Dabigatran, Apixaban, and Edoxaban are some of the new oral anticoagulants that have been studied in patients with venous thromboembolic diseases including stroke prevention in patients with non-valvular atrial fibrillation, DVT/PE prophylaxis after orthopedic surgery, and treatment of DVT/PE. Antithrombotic agents should be chosen based upon the absolute and relative risk and benefit for a given patient. While warfarin remains standard in patients with valvular atrial fibrillation and patients with end stage renal disease, the new oral anticoagulants are being accepted by several agencies including the American College of Cardiology, the American Heart Association, and Heart Rhythm Society as a viable alternative for other conditions. Bleeding with any anticoagulant remains a concern. Currently, there are trials underway analyzing efficacy and safety of factor Xa inhibitor antidotes including andexanet alpha. Development of agents to help stop or reverse bleeding with new oral anticoagulants may aid in weighing risk/benefit analysis in patients. The only way to adequately risk stratify patients is to understand how these drugs were studied in the various trials until studies emerge comparing the new oral anticoagulants or until we find the 'perfect anticoagulant'.

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REVIEW ARTICLE

Stroke Prevention in Atrial Fibrillation

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KEYWORDS:
Stroke and Systolic Embolism
Primary Care Physician
Novel Oral Anticoagulants

Background: Management of anticoagulation for atrial fibrillation is often the responsibility of the primary care physician. Knowledge of current literature and recent important clinical trials is essential to choose and monitor the best anticoagulation medication for your patient.

Methods: This paper reviews mechanisms of atrial fibrillation and patient characteristics which determine stroke risk, including use of the $CHADS_2$ and $CHADS_2$-VASc scores. We discuss recent large double blinded trials of new novel oral anticoagulants, and 2014 ACC/AHA Guidelines for Atrial Fibrillation.

Conclusion: With a better understanding of stroke risk and knowledge of evidenced based trials the primary care physician can manage anticoagulation for stroke prevention.

INTRODUCTION

Stroke as a complication of atrial fibrillation (AF) has long been acknowledged. Patients with AF have 4-5 fold increase in stroke than the patient without AF.[1] It is associated with approximately 75,000 strokes per year[1] and 16% of all ischemic strokes[2]. In a large outpatient cohort, the overall risk of stroke in the AF patient without prior stroke or transient ischemic attack, not on anticoagulation was found to be 2.5%[3]. The incidence is much higher in patients with a previous stroke or risk factors for a stroke such as Diabetes Mellitus.

Consequently, stroke prevention has become the standard of care. Warfarin, a vitamin K antagonist, has been used for the prevention and treatment of thromboembolic events associated with AF for more than 60 years. Four oral anticoagulants are now available for nonvalvular AF; dabigatran, rivaroxaban, apixaban, and edoxaban. They are similar in efficacy to warfarin for stroke prevention, have a reduced incidence of intracranial hemorrhage, and do not have dietary restrictions or require serial blood testing[4]. Anticoagulation for AF is often the responsibility of the primary care physician. Stroke prevention is considered conventional therapy and can be managed with knowledge of current recommendations.

AF has been evaluated by numerous studies. A review of AF and prevention of stroke is crucial for optimal patient care and safety. Additionally, updated AF guidelines were released by the AHA/ACC in March 2014. They highlight the new agents, recommend less use of aspirin for the low risk patient, and the use of AF catheter ablation for the symptomatic AF patient[5].

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BACKGROUND

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting approximately 2.2 million Americans in 2010 and may exceed 12 million by 2050 according to the American Heart Association.[5] AF prevalence is 5.5% in patients age 55 to 59, and 17.8% in patients over the age of 85.[5] More than one third of all AF patients are over the age of 80.[5] AF is more common in individuals of European descent, and less common in African Americans.[6]

Intrinsic cardiac rhythm is controlled by the SA node. In AF, electrical impulses are initiated in other zones of the atria, most notably in the area of the pulmonary vein. Rapid firing and re-entry of these impulses prevents the SA node from gaining control. This chaotic firing prevents efficient filling and contraction of the heart. Stagnant blood, particularly in the left atrial appendage (a sock-like structure attached to the left atrium) contributes to thrombus formation and emboli, creating the risk for stroke. Some cardiologists believe that AF is also an independent risk of hypercoagulopathy.[7]

The risk of stroke varies with associated morbidities. Patient risk stratification is essential to choose the best stroke prevention for each patient.[8] The $CHADS_2$ and the newer $CHADS_2$-VASc scores have been used to predict stroke risk. The $CHADS_2$, (one point each for history of CHF, hypertension, age greater than 75, or diabetes, and 2 points for a previous stroke or TIA ***(Table 1))***

Table 1: $CHADS_2$ score for risk of stroke in patients with Atrial Fibrillation.

		Score
C	History of CHF	1
H	Hypertension (Treated or untreated)	1
A	Age >75	1
D	Diabetes Mellitus (controlled or uncontrolled)	1
S2	Prior Stroke or TIA	2
		6 maximum total

Table 2. Risk of stroke using $CHADS_2$ score

CHADS2 score	Number of patients N= 1733	Number of strokes N=94	NRAF Crude Stroke Rate per 100 patient years	NRAF Adjusted stroke rate (95% CI)*
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	3.8	2.8 (2.0-3.8)
2	523	33	6.6	4.0 (3.1-5.1)
3	337	25	8.4	5.9 (4.5-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

* The adjusted stroke rate is the expected stroke rate per 100 patient years from the exponential survival model assuming aspirin was not taken.

has traditionally been used to predict stroke. ***(Table 2)*** 2014 AHA/ACC Guidelines recommend the updated $CHADS_2$-VASc score.[6] This score uses the traditional CHADS2 score and adds one additional point each for a history of coronary or vascular disease (V), age in the range of 65-74, or two for age 75 or greater (A), and female gender (Sc). ***(Tables 3)*** The $CHADS_2$-VASC may be more reliable in predicting those who are at very low risk for stroke and do not need anticoagulation, and more

Table 3: The $CHADS_2$-VASc score for stroke risk stratification of patients with Atrial Fibrillation and stroke rate.

	Risk Factor	Score
C	CHF/ LV dysfunction	1
H	Hypertension	1
A2	Age ≥ 75	2
D	Diabetes Mellitus	1
S2	Stroke/TIA/ Thromboembolism	2
V	Vascular Disease	1
A	Age 65 to 74	1
Sc	Female sex	1
Total		9

accurately defines risk for older female patients who were likely underscored with the original $CHADS_2$ tool. ***(Table 4)***[9,10,11] For a $CHADS_2$-VASc score of 2 or greater, anticoagulation with warfarin or one of the newer oral anticoagulants is indicated, with a Class I indication.[6] For a patient with a CHADS2-VASc of 1, no anticoagulation therapy, aspirin or oral anticoagulation may be considered, with a Class IIb indication. For patients with AF and a CHA2DS2-VASc of 0, it is reasonable to omit anticoagulation.[6]

Table 4: Adjusted stroke risk according to the $CHA2DS_2$-VASc score.

CHADS2-VASc score	Patients (n = 7329)	Adjusted stroke rate (percent/year)
0	1	0
1	422	1.3%
2	1230	2.2 %
3	1730	3.2%
4	1718	4.0%
5	1359	6.7%
6	679	9.8%
7	264	9.6%
8	82	6.7%
9	14	15.2%

Therapy can be divided into two categories: antiplatelet therapy and anticoagulation therapy.

ANTIPLATELET AGENTS

Aspirin is an antiplatelet agent which interferes with prostaglandin synthesis. Specifically, aspirin irreversibly inhibits the enzymes cyclooxygenase 1 and 2 thus preventing the production of thromboxane A_2.[12] Thromboxane A2 induces platelet aggregation and vasoconstriction. It has been used for patients with a low risk of stroke. Older studies have supported the use of aspirin in patients with AF. In 1991, the Stroke Prevention in Atrial Fibrillation (SPAF) trial found that 325mg of aspirin used in patient with AF reduced the risk of primary ischemic stroke event by 42% when compared to the control group[13]. Some benefits of aspirin therapy as an early treatment for patients with AF have been confirmed; however, concerns of bleeding remain.[14] In a 2014 study published by the American Journal of Medicine, the authors suggest that practitioners may be overprescribing aspirin for stroke prevention when alternative therapies are more efficacious with fewer side effects.[15] The 2014 AHA/ACC AF Guidelines only recommend the use of aspirin in patients with a CHADS2-VA2Sc score of 1, and with the less robust IIb indication.[6]

Clopidogrel is also an antiplatelet agent. Clopidogrel is administered as a prodrug that is metabolized by the cytochrome P450 enzyme.[16] The active metabolite irreversibly prevents adenosine 5'-diphosphate from binding to the P2Y12 platelet receptor.[16] Activation of the cytochrome P450 system may affect the metabolism or clearance of other medications. It has been shown to be beneficial in stroke prevention in patients with Arteriosclerosis.[17]

Dipyridamole inhibits platelet adhesion by causing an accumulation of adenosine, adenine nucleotides and cyclic AMP through the inhibition of adenosine deaminase and phosphodiesterase.[18] Dipyridamole has been found to be efficacious as a monotherapy and in combination with aspirin for preventing secondary stroke in select cases.[19] Nonetheless, the literature does not support use in AF.

ANTICOAGULATION AGENTS

Warfarin works by binding to vitamin K epoxide reductase to inhibit vitamin K–dependent coagulation factors II, VII, IX, and X to prevent thrombus formation in AF.[20] It has been shown to significantly reduce the risk of stroke if the INR is maintained in the range of 2.0 to 3.0.[21] In case of emergency procedures or toxicity, Vitamin K (phytonadione) may be used to reverse the effects of warfarin.

Negative aspects of this drug include lifestyle modification to include monitoring to maintain an INR in the narrow therapeutic range between 2 and 3. Patients must avoid many foods and other drugs to minimize interactions. Such foods and drugs that are contraindicated with warfarin use include: kale, collards, spinach, broccoli, and many herbs and spices.[22] To achieve the proper therapeutic range to reduce stroke risk, regular blood tests are essential, and the dose of warfarin often

needs to be adjusted. Some studies have reported that only 15% of patients on warfarin for anticoagulation were in the therapeutic range.[23] In the recent Rocket AF trial of more than 14,000 patients, time in therapeutic range was 55%.[24] In the recent ARISTOTLE trial of more than 18,000 patients, time in therapeutic range was 66%.[25]

NOVEL ORAL ANTICOAGULATION DRUGS (NOAC)

New anticoagulants were approved by the FDA and recommended for use in stroke prevention in atrial fibrillation by the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for antithrombotic therapy and prevention of thrombosis.[26] They are now included in the ACC/AHA Guidelines for AF. Novel Oral Anticoagulants (NOAC) do not have the same dietary restrictions, drug interactions and laboratory monitoring. The NOAC are now considered first line therapy (with a level of evidence B) for AF, alongside warfarin (with a level of evidence A).[6]

The first NOAC to be released was dabigatran, which is a direct thrombin inhibitor. It inhibits thrombus formation by preventing the conversion of fibrinogen to fibrin.[27] The next two NOAC to be released were apixaban and rivaroxaban. They are factor Xa inhibitors, which inhibit the conversion of prothrombin to thrombin, thus preventing the conversion of fibrinogen to fibrin. These medications offer the advantage of fixed dosing either once or twice daily. Currently there is no reversal treatment in the event of an emergent procedure. Hemodialysis reduces the plasma concentration of dabigatran, while rivaroxaban and apixaban cannot be eliminated by dialysis.[28] Many hospitals have developed reversal guidelines for the management of bleeding, using activated prothrombin complexes and coagulation factors.

Dabigatran was the first NOAC to be approved by the FDA for stroke prevention with patients with AF. The Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) studied patients over 65 with atrial fibrillation. Dabigatran given at a dose of 110mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, with lower rates of major hemorrhage.[29] Dabigatran administered at a dose of 150 mg twice daily, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. The 110mg dosing is not available in the US. There is a 75mg twice daily dose available for patients with renal impairment and a creatinine clearance of 30 mL/min. Economic analysis reveals that dabigatran is cost effective when considering the cost of INR monitoring.[30]

Rivaroxaban was the first factor Xa inhibitor on the market and has been FDA approved for stroke prevention in patients with AF. The ROCKET AF trial compared rivaroxaban (20mg/day; 15mg/day in patients with creatinine clearance 30-49ml/min) with dose-adjusted warfarin (international normalized ratio 2-3) in 14,264 patients with AF and a prior history of stroke or at least two other additional risk factors for stroke. The ROCKET AF trial demonstrated the noninferiority of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism, with a similar rate of major bleeding and a reduction in intracranial hemorrhage.[31] There is a dose adjustment for patient with renal impairment but it is not recommended in liver impairment (a Child–Pugh class of B or C). Economic analysis has stated that it is cost effective for use over warfarin.[32]

Apixaban is the second factor Xa inhibitor that has been FDA approved. The recommended dosage is 5mg twice daily. A reduced dose of 2.5mg twice daily is recommended in patients with two or more of the following: age 80 years or older, body weight 60kg or less, and a serum Cr level of 1.5mg/dL or higher.[33] In the ARISTOTLE trial, apixaban was compared to warfarin in 18,201 patients with AF and ≥ 1 additional risk factor for stroke. Apixaban reduced the risk of stroke or systemic embolism by 21% compared with warfarin (1.27% vs 1.60% per year; hazard ratio, 0.79; 95% confidence interval, 0.66-0.95). Apixaban also reduced major bleeding by 31% ($P < 0.001$) compared with warfarin. Additionally in the AVERROES trial, apixaban was more effective than aspirin for stroke prevention and had a similar rate of major bleeding.[34]

Edoxaban is the newest direct oral factor Xa inhibitor which has now been approved for stroke preventions in non-vascular AF. In the Engage AF-TIMI[48] trial Edoxaban was found to be "non-inferior" to warfarin in stroke prevention in atrial fibrillation. It was also associated with a lower risk of bleed and death from cardiovascular events.[35]

CONCLUSION

By the year 2050 5.6 million patients will have AF.[36] Many of these patients will be treated by the primary care physician. Consequently, knowledge of stroke prevention is paramount in their care. Warfarin is beneficial for stroke prevention and the NOAC should be considered first line for stroke prevention according to some authors.[37] These newer agents have a rapid onset of action, predictable pharmacokinetics, and no need for routine monitoring.[36] The NOAC have higher acquisition costs; however, the benefit of cost savings may be derived from the potential for decreasing the incidence of hemorrhagic stroke, intracranial bleeding and reducing the need for anticoagulation monitoring.[36] A recent systematic review of 27 studies demonstrated that these agents are cost effective in stroke prevention. It is difficult to recommend one NOAC over the other, as the studies were not similar in design, including patient characteristics and end points. A pubmed search revealed only

studies comparing each agent to warfarin and not each other. A meta-analysis showed shows that the overall net clinical benefit of the NOA versus warfarin is favorable.[39] Additional studies with head to head comparison of NOAC, using the CHADS2-VASC score, may be helpful. Both physicians and industry look forward to a reliable antidote for the NOAV. An understanding of these agents and trials will help the primary care physician manage anticoagulation.

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REVIEW ARTICLE

Blood Component Therapy

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KEYWORDS:
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Given the frequency of inpatient transfusion and the possibility that delayed reactions may be noted during outpatient follow up, an update in blood component therapy is worthwhile. Noninfectious complications are far more frequent than infectious complications and require heightened clinician awareness to ensure recognition and provision of appropriate supportive care. Transfusion Associated Circulatory Overload, a preventable consequence of transfusion, is particularly common and may be preemptively managed in selected patients. Risks associated with transfusion therapy can be reduced through application of patient blood management strategies. In this context, a working understanding of the modern literature surrounding the primary blood components is valuable. Evidence-based transfusion guidelines for RBCs, platelets, plasma and cryoprecipitate optimize patient care and improve patient outcome. This review focuses on utilization of blood components and selected alternatives as well as pretransfusion testing.

INTRODUCTION

Transfusions are a frequent occurrence among hospitalized patients. Roubinian and colleagues, in a retrospective cohort study of hospitalized, non-obstetric adult patients, found that among 444,969 hospitalizations involving 275,874 patients, RBC transfusions occurred in 32,493 (11.8%) patients and during 61,988 (13.9%) of hospitalizations[1]. Compared to the non-transfused group, those receiving transfusions had lower admission hemoglobin values (9.9 g/dLvs 12.9 g/dL) and were more commonly admitted for gastrointestinal bleeding and orthopedic surgery.

New developments in the literature and establishment of the patient blood management movement have consistently driven transfusion thresholds for stable patients to lower and more restrictive levels. Anemic patients may benefit from perioperative anemia management to reduce the risk of intraoperative transfusion. Alternatives to transfusion, particularly as plasma alternatives, are gaining attention. Transfusion laboratory tests may be confusing to choose from, and will be addressed in this review. Complications of transfusion may be delayed and detected only during an outpatient hospital follow-up visit. This article will review recent developments in the literature, touch upon utilization of the transfusion services laboratory, and discuss utilization of blood components and selected alternatives.

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DONOR SCREENING

Transmission of blood-borne pathogens is prevented through application of a multi-layered process of donor screening. Unless labeled otherwise[2] blood components are collected from non-remunerated, volunteer donors. At the time of donation, prospective donors are asked to read an established set of donor education materials[3] that review the signs and symptoms of HIV, risk factors for acquiring blood-borne pathogens, definitions of what constitutes sexual contact, and medications and vaccines that constitute deferral criteria. This material educates donors as to risk factors they will be questioned about on the required, 48-item Donor History Questionnaire (DHQ)[4]. This questionnaire screens for high-risk behaviors and other factors that heighten risk, collects donor demographic and contact information, and provides an informed consent area that must be read and signed. Donors qualifying by DHQ, vital signs, minimal weight (50 kg) and hemoglobin (12.5 g/dL) requirements then proceed to donation.

Phlebotomists visually inspect the arms for evidence of track marks or lesions suspicious for Kaposi's Sarcoma and the skin is meticulously prepared prior to phlebotomy using either Povidone-Iodine or Chlorhexidine solutions.

Additional prevention is obtained through the use of modern collection kits incorporating a diversion pouch that prevents the first few mL of blood collected from entering the primary collection bag. This reduces the risk of bacterial contamination resulting from entrainment of residual skin bacteria. Specimens for testing are drawn from this diversion pouch and sent for routine testing ***(Table 1)***. Platelets, owing to the requirement for room-temperature storage, are additionally

tested for evidence of bacterial contamination.

COMPLICATIONS OF TRANSFUSION THERAPY

Risks associated with selected infectious and noninfectious complications of transfusion are enumerated in Table 2 [5-20]. Note

Table 1: Current Testing performed with each donation (AABB Standard 5.8). For selected donations, anti-CMV and Red Cell phenotype testing may also be performed.

Determination of ABO Group
Determination of Rh Type
Detection of Unexpected Antibodies to Red Cell Antigens
Testing for Infectious Disease Markers
• HBV DNA
• Hepatitis B Surface Antigen
• Anti-HBc (Hepatitis B core antigen)
• Anti-HCV
• HCV RNA
• Anti-HIV 1/2
• HIV 1 RNA
• Anti-HTLV I/II
• WNV (West Nile Virus) RNA
• Syphilis
• Antibodies to TrypanosomaCruzi*
• Antibodies to CMV (Cytomegalovirus)**

* Tested at least once. ** Tested but results do not exclude donation.

that in most instances, complications are more immediately problematic for non-infectious as opposed to infectious reactions. The exception is bacterial sepsis; a complication far more common than viral transmission.

TRANSFUSION ASSOCIATED CIRCULATORY OVERLOAD

The most common serious reaction is Transfusion Associated Circulatory Overload (TACO), an event that in one retrospective review[6] led to ICU transfer, major complications, or death in 18%, 8%, and 2% of patients, respectively. Risk factors include congestive heart failure, renal dysfunction, and age >70 years. The assessment of net volume status, including volume of preceding intravenous fluid administration (including suspension media for intravenous medications), clinical risk factors for volume overload, and post-transfusion B-type Natriuretic Peptides (Pro-NT-BNP or BNP)[21,22] are helpful in diagnosing TACO.

TRANSFUSION RELATED ACUTE LUNG INJURY

As opposed to TACO, which results from cardiogenic pulmonary edema, Transfusion Related Acute Lung Injury (TRALI) reflects a non-cardiogenic pulmonary edema state with a clinical picture similar to Acute Respiratory Distress Syndrome (ARDS). Suspected TRALI may be diagnosed using the following criteria[23]:

- Dyspnea:onset within 6 hours after transfusion,
- Hypoxia: PaO2/FiO2 ratio of < 300 mmHg,
- Infiltrates (new, bilateral):noted on the post-transfusion chest film,
- Noncardiogenic: pulmonary capillary wedge pressure < 18 mmHg or central venous pressure ≤15 mmHg)
- Competing causes – ruled out: no other risk factors present for acute lung injury

The most severe cases of TRALI are associated with activation of recipient leukocytes by preformed antibodies contained within donor products. The implicated antibodies, typically the result of sensitization during pregnancy or prior transfusion, are primarily directed against Human Leukocyte Antigens (HLA). If, by chance the recipient expresses the cognate antigen, then TRALI may result.

The prevalence of detectable HLA antibodies among women enrolled in the Leukocyte Antibody Prevalence Study (LAPS) [24] correlated with the number of full-term pregnancies: among those with zero, one, two, three, or ≥4 pregnancies expression of HLA antibodies was found in 1.7% (same as previously transfused and non-transfused males), 11.2%, 22.3%, 27.5%, and 32.2%, respectively. Donor deferral policies based upon deferral of female (particularly multiparous) donors have resulted in significant reductions in the incidence of TRALI ***(Table 2)***[13,14].

ALLERGIC TRANSFUSION REACTIONS

A less common cause of dyspnea during transfusion is allergic reaction, although most are limited to cutaneous symptoms. In one study[25], cutaneous manifestations of pruritis and urticaria occurred in 86% and 84%, respectively, of 143 allergic reactions to platelets whereas dyspnea occurred in only 10.5%, wheezing in 3.6%, and nausea/vomiting in 2.1% to 4.2%. The authors found that recipient atopy – particularly hay fever – was a risk factor for allergic transfusion reaction to platelets. In addition, the rate of allergic transfusion reaction rates decrease with subsequent transfusions, suggesting the occurrence of desensitization. This phenomenon was also noted in a recent review[26] of severe urticarial reactions occurring in the Trial to Reduce Alloimmunization to Platelets[8].

PLATELET REFRACTORINESS

Alloimmunization to HLA (and other platelet-surface) antigens, can in some cases result in immunologic platelet

refractoriness. Platelet refractoriness, defined as a Corrected Count Increment (CCI– see Equation 1) of < 5x 103/mcL [8,9] following two sequential, ABO compatible platelet transfusions, represents a complex management issue. With modern, leukoreduced platelet products, this outcome may occur in 4% to 14% of subjects[8].

In the Trial to Reduce Alloimmunization to Platelets [8], patients with newly diagnosed Acute Myelogenous Leukemia were randomized to control, unmanipulated platelet concentrates or any of several leukocyte reduced (either by filtration or UV-B irradiation) products. At the end of the eight week study period 13% of control subjects developed both HLA alloimmunization and platelet refractoriness, whereas this combined outcome occurred in only 3-5% of the experimental arm subjects. Transfusion-related immunization to HLA occurred more commonly than did clinical refractoriness – 45% of control subjects and 17% to 21% of experimental arm subjects developed detectable antibodies. The take-away message is that laboratory evaluation for immunologic refractoriness (ie, testing for HLA or other antibodies with provision of HLA-matched/compatible platelet products) should follow, rather than precede, demonstration of clinical refractoriness. Once diagnosed, platelet refractoriness due to HLA alloimmunization may respond to transfusion from donors HLA compatible either with the recipient or their antibodies – a process known as 'HLA matching'.

Other instances where platelet refractoriness may be noted include coagulopathy of liver failure and Immune Thrombocytopenia (ITP). In the cirrhotic patient, an expanded blood volume and increased pooling in the enlarged spleen lead to reduced post-transfusion increments whereas enhanced immunologic removal effects on megakaryocytes via platelet glycoprotein-directed autoantibodies are a major etiology in ITP. In these instances, refractoriness is typically unresponsive to HLA matching.

FEBRILE NONHEMOLYTIC TRANSFUSION REACTIONS

Febrile, Non-Hemolytic Transfusion Reactions (FNHTR) occur among 0.5% to 6.8% of transfusions and may arise within 6 hours of transfusion. These reactions may consist of temperature rise (≥ 1°C) or other signs of a systemic inflammatory reaction syndrome (SIRS) such as tachycardia, blood pressure changes, tachypnea, chills, or rigors. Fever is not an absolute requirement to diagnose FNHTR provided other causes for the symptoms are ruled out and a clear temporal relationship between onset and transfusion exists. This complication is felt to be mediated, in large part, through infusion of biologic response mediators and other cellular antigens that accumulate during product storage[27]. Evaluation of these transfusion reactions also entails a careful search for competing clinical factors, including hemolytic and septic transfusion reactions or fever and chills due to underlying illness (i.e., sepsis).

Prestorage leukoreduction reduces the number of residual leukocytes contained in a transfusion product, thereby reducing the risk of FNHTR while also reducing the risk of CMV infection[28] and HLA alloimmunization[8]. In-line filters effect for 3-4 log reduction of leukocytes – equivalent to removal of more than 99.9% of leukocytes[29] - from the original unit. Alternatively, leukoreduction may be accomplished by virtue of an exclusion effect related to the high degree of specificity for platelets allowed with modern plateletpheresis instruments – referred to as 'in-process' leukoreduction. To qualify as leukoreduced, RBCs and apheresis platelets must contain fewer than 5 x 106 WBC/unit[30] (plasma and Cryoprecipitated Antihemophilic Factor (CRYO) are considered 'acellular' products and therefore not subject to minimum WBC criteria). Data demonstrating reduced FNHTR rates[10,31] as well as reduction in transmission of leukotropic viruses and HLA alloimmunization has resulted in a change to predominantly leukoreduced inventories at many blood centers.

TRANSFUSION ASSOCIATED GRAFT VERSUS HOST DISEASE

An uncommon but fatal leukocyte-associated complication is Transfusion Associated Graft Versus Host Disease (TA-GVHD), a circumstance that may occur when recipient leukocytes fail to eliminate viable donor leukocytes. During a TA-GVHD event, viable donor leukocytes recognize recipient tissue as foreign, become activated, and launch an immunologic attack against recipient tissues. The skin, marrow, and gastrointestinal tract are particularly at risk and patients may develop rash, pancytopenia, diarrhea and liver dysfunction. Other organs may also be affected.

Circumstances predisposing to TA-GVHD include unidirectional homozygosity for Human Leukocyte Antigens (HLA) – arising when the donor is either a 1st degree relative to the recipient (ie, 'directed donation') or when HLA-matched products are selected for a refractory recipient – and scenarios associated with severe degrees of recipient immunoincompetence or immunosuppression[32]. The only widely available means of prevention involves irradiation of cellular (i.e., red blood cells, platelets, granulocytes) blood components; leukoreduction alone does not prevent this complication. Indications for irradiation are listed in ***Table 3***.

HEMOLYTIC TRANSFUSION REACTIONS

Hemolytic reactions may be characterized as acute or delayed. Acute hemolytic reactions occur due to interaction between

pre-formed antibodies in the recipient or transfusion product with red cells bearing the target antigen. Most acute hemolytic transfusion reactions are due to ABO incompatibility and typically result from medical error leading to transfusion of an ABO-incompatible component.

Acute hemolytic transfusion reactions are not universally symptomatic, but associated intravascular hemolysis, resulting from rampant complement activation from binding of ABO-directed IgM and IgG against recipient (or donor) red cells, may lead to dramatic clinical deterioration. Signs and symptoms may include hypotension, shock, disseminated intravascular coagulation, hemoglobinuria (as opposed to hematuria), and a rise in hemolytic markers (such as lactate dehydrogenase, total and unconjugated bilirubin) with concomitant decline (or lack of expected hemoglobin increment) in hemoglobin. Haptoglobin may become reduced to undetectable levels.

In one study[15] the frequency of ABO incompatible mistransfusion events was 1:38,000 transfusions, but nearly half (47%) of recipients experienced no untoward clinical or laboratory consequences. Fifty percent experienced either clinical (43%) or laboratory-only (7%) findings leading to an estimated frequency of symptomatic acute hemolytic transfusion reaction in the range of 1:76,000. As there were only 5 deaths, the risk of fatal hemolytic transfusion reaction was 1:1,800,000. These estimates are in agreement with those reported by the United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance program that estimates a risk of ABO incompatible transfusion at 1:100,000 units and risk of fatality due to 'incorrect blood component transfused' at 1:1,500,000 units[33].

Safeguards to prevent Acute Hemolytic Transfusion Reactions include regular staff training, positive patient identification systems, labeling of specimens at the bedside, rejection by the blood bank of mislabeled specimens, and two-person verification of component and recipient prior to transfusion. Positive patient identification systems utilize handheld barcode readers or Radio Frequency Identification (RFID) chips embedded in the patient's hospital wristband and blood containers[34,35] as well as point-of-care label printing to significantly reduce the risk of wrong-blood-in tube.

Wrong-blood-in-tube (WBIT) errors are estimated to occur at a rate of 1:1111 to 1:3333 specimens among patients[36,37]and 1:50,000 among volunteer blood donors[38]. WBIT errors can initiate a chain of events leading to mistransfusion. Blood banks frequently have 'second specimen' policies in place that mandate confirmatory testing of a second specimen in new patients prior to issuing type-specific (ie, non-Group O) red cells. Requests from the blood bank for a second specimen should therefore be respected as they represent normal operation of a quality system aimed at enhancing patient safety.

Delayed hemolytic reactions occur when recipients develop antibodies against non-ABO antigens expressed on transfused red cells. Delayed hemolysis ensues when the immune system is either challenged (primary sensitization) or rechallenged (leading to an anamnestic antibody response) with foreign antigens (most commonly those within the Rh,Kell, Duffy,and Kidd[39,40] red cell antigen systems).

In delayed hemolytic reactions, hemolysis is most often extravascular with clearance of sensitized red cells in the spleen and reticuloendothelial system. Patients may experience fatigue, malaise, and mild elevations in bilirubin. In a nonbleeding patient, the hemoglobin will typically decline toward pretransfusion levels, the absolute nadir being related to the rate of clearance, endogenous erythropoietic response, and number of antigen-positive units the patient received.

Hemolytic reactions become apparent on post-transfusion testing. In addition to other clinical supportive evidence, the Direct Antiglobulin Test (DAT) turns positive, and a causative antibody can usually be eluted from the surface of DAT-positive red cells. Segments (lengths of tubing containing donor red cells from the original unit) may still be retained by blood bank for testing purposes. Donor cells from these segments can be typed for the implicated antigen to determine the number of antigen positive units transfused to the patient. Future transfusions should be antigen-negative for any historical or currently active alloantibodies and crossmatch compatible (at anti-human globulin phase) with the patient's serum.

SEPTIC TRANSFUSION REACTIONS

Septic transfusion reactions occur most commonly with platelets ***(Table 2)*** owing to the necessity for room temperature storage, a requirement for preservation of platelet function. Septic transfusion reactions to red cells are estimated at 1:250,000 transfusions respectively[12]. Standard treatment of septic reactions – including administration of broad spectrum antibiotics, and fluid and vasopressor resuscitation as indicated should ensue. Immediate cessation of the transfusion is required with delivery of the residual unit to the blood bank for gram stain, culture, and testing of the post-transfusion specimen via DAT (since acute hemolytic transfusion reaction would be within the differential). Blood cultures in the patient should be drawn from a peripheral site and from the catheter used to infuse the implicated blood component. If fevers previously occurred in relation to utilization of the implicated catheter then catheter colonization or infection should be suspected.

Table 2: Current transfusion risks for blood products collected and manufactured in the United States (except HTLV I/II, UK estimate used).

Complication	Estimated Risk	Notes
Transfusion Associated Circulatory Overload (TACO)	1:12.5 [5-7] to 1:68 [5]	Rate [5] determined via a 1 month prospective observation period when recipients were evaluated within 24 hours of (non-ED, non-OR) receipt of plasma transfusion using a set of clinical, laboratory, and radiologic variables associated with volume overload. Historic rate (clinician reported) of TACO was 1:1566 suggesting under-recognition. After TACO, 18% of patients required ICU transfer, 0% suffered a major complication, 2% died [6].
Fever*	1:15 [7]	Among participants within the Platelet Dosing Study [8], a multicenter, randomized controlled trial that examined the effects of prophylactic platelet transfusion among bleeding outcomes among hematology-oncology patients with hypo-proliferative thrombocytopenia. Estimates among other populations and for different blood product types may differ (ie, fever likely higher for RBC than platelets). As opposed to reference [8] that used prospective evaluation for reactions (and, hence, greater reliability of detection), reference [10] relied upon clinician recognition and reporting (hence under-recognition/under-reporting a factor); the higher estimate was derived during pre-universal leukoreduction; the lower estimate during post-universal leukoreduction. Alloimmunization to HLA antigens with subsequent platelet refractoriness (defined as a CCI of < 5000 after two sequential transfusions of ABO compatible platelets) during the 8 week Trial to Reduce Alloimmunization to Platelets [8] was 5% in the filtered, apheresis platelet group – a product that best approximates modern platelet inventory.
HLA Alloimmunization with Refractoriness*	1:20 [8]	
Allergic/Hyper-sensitivity*	1:52 [7]	
Sinus Tachycardia*	1:55 [7]	
Rigors or Chills*	1:90 [7]	
Febrile Nonhemolytic Transfusion Reactions	1:222[‡] to 1:909[§] [10] 1:303[‡] to 1:526[‡] [10]	
Septic Transfusion Reactions*	1:41,173 to 1:193,305 [11]	For 2004-2006; apheresis platelet collections – lower estimate of septic transfusion reactions is for collections utilizing single-needle collections. Most septic reactions (16/20 due to *Staphylococcus sp* and occurred on Day 5 (13/20) after collection). Septic transfusion reactions occurring with RBC transfusion is much less frequent, about 1:250,000 units [12].
Transfusion Related Acute Lung Injury† (TRALI)	1:38,022 to 1:238,095 [13]† 1:434,782 [14]ε	†For 2008-2011; higher risk estimate is specific for AB plasma; lower risk estimate is for non-AB plasma. Study evaluates reduced risk of non-AB plasma for TRALI following conversion to predominantly male-only plasma donor population. Owing to its rarity among donors and demand as universal donor plasma for trauma resuscitation, restriction of AB plasma donors to male-only restriction was not feasible. ε For 2008; RBC risk estimate not statistically different from Platelet estimate (1:500,000) [13].
Acute Hemolytic Transfusion Reactions	Symptomatic, 1:76,000; Fatal, 1:1,800,000[16]	Analysis of transfusion errors reported by over 250 transfusion services to the New York State Department of Health between 1990 through 1998 comprising approximately 9,000,000 transfusions.
Septic Transfusion Reactions[‡]	1:250,000 [15]	Estimated based upon multiple sources.
HBV	1:282,000 to 1:357,000 [16]	For 2006-2008; window period 44 days; Current estimate is reflective of a reduction from 1997 to 1999 risk of 1:86,000 to 1:110,000
Fatal Septic Transfusion Reaction*	1:498,711 [11]	For 2004-2006; American Red Cross data.
Variant Creutzfeldt-Jakob Disease	1:480,000 to 1:134,000,000 [17]	Risk model provided both high (1:480,000) and low (1:134,000,000) per RBC transfusion risk estimates based upon UK prevalence estimates.
HCV	1:1,149,000 [18]	For 2007-2008; HIV window period 9.1 days; HCV window period 7.6 days.
HIV	1:1,467,000 [18]	
HTLV I/II	1:9,090,909 [19]	For 2002-2006 among UK blood donors; window period 46 days. Tested using similar EIA platforms used in the United States. In a US study [20]; the confirmed-positive rate for HTLV I/II in repeat donors was found to be 1:737,000 donations, or 1 donor requiring lookback investigation per 921,000 tested allogeneic (both first-time and repeat) donations.

* Apheresis Platelets. ‡ Platelet Concentrates. § Red Blood Cells. †Plasma.

The implication of the catheter in suspected septic reactions was recently studied by Ricci and colleagues[41] who evaluated 999 transfusion reactions among 489,000 transfusion (a rate of 2:1000 transfusions) events over a 5 year study period). Of the reactions, 738 occurred in association with transfusion via an indwelling central venous catheter (CVC), 217 via peripheral access, 44 via unspecified access. Although 10% of these reactions were associated with a positive blood culture, none of the organisms cultured were concordant with organisms cultured from residual blood components. The authors concluded that investigation of febrile reactions occurring during transfusion should take into account the route of administration and the possibility of catheter-related infection.

PATIENT BLOOD MANAGEMENT

Patient Blood Management (PBM) describes a transfusion culture aimed at identification and reduction of unnecessary transfusions through patient-centered modalities that include preoperative anemia diagnosis and management, adherence to restrictive transfusion thresholds, application of intraoperative techniques (such as minimally invasive surgery and intraoperative cell-salvage), and use of transfusion alternatives where possible[42]. Within the PBM paradigm, clinicians are encouraged to move away from specific hemoglobin triggers and arbitrary (ie, 2 unit) transfusion orders and instead take into account patient symptoms and comorbidities and a strategy aimed at transfusing the least number of units to accomplish resolution of those symptoms.

RED BLOOD CELLS (RBCS) – PATIENT BLOOD MANAGEMENT CONSIDERATIONS

A key function of RBCs is to carry oxygen. Equipoise between too few RBC transfusions versus over-transfusion should be considered. Carson, et al, studied postoperative outcomes in 300 patients who refused red cell transfusion for religious reasons. A progressive increase in mortality was observed as their hemoglobin progressively fell below 7.0 g/dL. No deaths occurred in patients with postoperative hemoglobin levels between 7.1 and 8.0 g/dL[43]. Randomized controlled trials[45-48] ***(Table 4)*** and a recent evidence-based guideline statement[48] support both the application of clinical criteria ***(Table 5)*** and restrictive hemoglobin thresholds (ie, 7 to 8 g/dL in non-ACS patients) to transfusion decision-making.

Table 3: Clinical Indications for Irradiated Components

Intrauterine transfusions
Pre-mature, low birthweight infants
Newborns born with severe hemolytic disease of the fetus and newborn (HDFN)
Inherited immunodeficiency disorders
Hematologic malignances or solid tumors
Candidates and recipients of peripheral blood stem cell and marrow transplant
Components that are HLA matched or directed donation units from family members or relatives
Patients undergoing immunosuppressive chemotherapeuticagents that alter lymphocyte function

The higher the transfusion burden, the higher the risk of infection. In a meta-analysis of randomized, controlled trials evaluating restrictive (≤8 g/dL) compared to liberal (≥ 9 g/dL) hemoglobin transfusion thresholds, Rohde, et al[49] found the pooled risk of all serious infections to be higher in liberal transfusion groups 16.9% [95% CI, 8.9% to 25.4%] compared

Table 4: Recent Studies Comparing Restrictive to Liberal Transfusion Thresholds in Various Patient Populations

Study	Patient Population	Arms	Primary Outcome
TRICC Hebert, et al, NEJM 1999 [44]	838 Critical Care patients [RCT]	7 g/dL (n=418) vs 9 g/dL (n=420)	30 Day ACM: [18.7% vs 23.3%, p = 0.11]
TRACS Hajjar, et al, JAMA 2010 [45]	502 Cardiac Surgery with Cardiopulmonary Bypass [RCT, noninferiority study]	8 g/dL (n=249) vs 10 g/dL (n=253)	NI margin for 30 day ACM predefined at -4%. Observed between group difference 1% [95% CL -6% to 4%], p = 0.85.
FOCUS Carson, et al, NEJM 2011 [46]	2016 Patients with CAD/Risk of CAD after Hip Fracture Surgery	< 8 g/dL (n=1009) vs 10 g/dL (n=1007)	Death or inability to walk across room unassisted at 60 days: Abs Risk Difference 0.5 percentage points [95% CL, -3.7 to 4.7]
Acute UGI Bleed Villanueva, et al, NEJM 2013 [47]	921 Patients with severe Upper GI bleeding	< 7 g/dL (n=461) vs < 9 g/dL (n=460)	45 Day ACM: 91% restrictive vs 95% liberal; HR for death with Restrictive Strategy 0.55 [95% CL: 0.33 to 0.92], p = 0.02.

Table 5: Clinical Criteria for Red Cell Transfusion (Adapted from Carson, et al[46]).

Clinical Criteria*
Chest Pain deemed Cardiac in Origin
Congestive Heart Failure
Unexplained Tachycardia or Hypotension Unresponsive to fluid Replacement

*In patients with dementia, FOCUS investigators used hemoglobin trigger of < 8 g/dL.

to restrictive groups 11.8% [95% CI, 7.0% to 16.7%] with a risk ratio of 0.82 [95% CI, 0.72 to 0.95] supporting a reduced serious infection risk when restrictive transfusion thresholds are in place.

Of interest, the use of Intravenous Iron formulations to reduce reliance upon red cell transfusions found that while transfusions could indeed be reduced – risk ratio 0.74 [95% CI, 0.62 to 0.88]) – this reduction came at the cost of slightly higher infection risk – relative risk of 1.33 [95% CI, 1.10 to 1.64][50]. The authors note, however, that their findings could also represent a false positive finding since infection was not a predefined endpoint of the studies encompassed by their review leading to introduction of bias due to missing data. A common thread linking infectious risk of red cells and intravenous iron may be infusion of free iron, an essential nutrient for microbes. Patients enrolled in the trials summarized in ***Table 4*** resemble patients encountered in clinical practice. Of note, there was no major difference in mortality or serious cardiovascular outcomes between the two arms of these studies. Subjects enrolled in the Transfusion Trigger Trial for Function Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) study[46] were ≥ 50 with Coronary Artery Disease (CAD) or CAD risk factors (the mean age was 81.5 ± 9.0). Those enrolled in the Transfusion Requirements in Critical Care (TRICC) trial[44] were critically ill adults with a mean age of 57.1 ± 18.1 years. The Transfusion Requirements after Cardiac Surgery (TRACS) study[45] enrolled patients undergoing elective Coronary Artery Bypass Graft or Valvular surgery employing cardiopulmonary bypass; subjects had a mean age of 58.6 ±12.5 and more than 30% had prior histories of diabetes mellitus, unstable angina, and myocardial infarction.

Patients in the restrictive arms were far less likely to receive any blood and, when transfused, received far fewer total red blood cell units than did subjects randomized to liberal strategies. In the FOCUS study[46] for example, nearly 60% of subjects in the restrictive arm (compared to only 3.3% in the liberal arm) were able to completely avoid receipt of red cells following randomization. The total number of units transfused to subjects in the restrictive arm was 652 units, compared to 1866 units to subjects in the liberal arm.

In the Transfusion Strategies for Acute Upper Gastrointestinal Bleeding trial[47], only 49% of patients randomized to the restrictive arms received red cells compared to 86% of subjects in the liberal arm. The mean number of units transfused per patient was also lower in the restrictive arm (1.5±2.3 compared to 2.9±2.2 in the liberal arm). Of particular interest was the finding that patients with cirrhosis were at greater risk of further bleeding when randomized to the liberal strategy arm (22% compared to 12% in the restrictive arm). There were also small, but statistically significant increases in cardiac complications (acute coronary syndrome and pulmonary edema) and transfusion reactions among patients in the liberal arm (16% vs 11% for cardiac complications and 9% vs 3% for transfusion reactions).

The transfusion decision tool utilized in the FOCUS study[46] is presented in ***Table 5***. This allowed investigators to temper their decision making by including clinical features alongside prevailing hemoglobin levels. It also explains the increase in these clinical findings among patients randomized to the restrictive arm, since these very features were incorporated into the decision to transfuse.

In the setting of perioperative anemia, a recent systematic review[51] concluded that patients with preoperative iron deficiency anemia demonstrate earlier and more robust responses to intravenous iron compared to oral iron. Additionally, a short preoperative regimen of erythropoietin (EPO) or EPO plus IV Iron appears to significantly reduce red cell transfusion rates in selected patients.

Red cell substitutes (none are currently FDA approved) are not as safe as standard red cell products or asanguinous resuscitation fluids. A meta-analysis of sixteen trials involving five different hemoglobin based blood substitutes in 3711 patients concluded that excess occurrences of death and myocardial infarction occurred with the use of these products compared to control groups (Relative Risk: 1.30, 95% CI:1.05, 1.61; and 2.71, 95% CI:1.67, 4.40, respectively)[52].

PLATELETS

Platelets are critical in primary hemostasis; severe degrees of impairment or thrombocytopenia are associated with 'platelet-type' bleeding characterized by petechiae, ecchymoses, epistaxis, and other mucocutaneous (i.e., gingival bleeding, menorrhagia) bleeding. Wet purpura is an ominous sign that may portend subsequent, more severe hemorrhagic sequelae.

Platelets are available as either Platelet Concentrates or Apheresis Platelets. Providers may confirm with their Transfusion Medicine Service/Blood Bank the products locally available. To achieve a typical adult platelet dose, 4 to 6 platelet concentrates are pooled at time of issue (i.e., a 'six-pack' of platelets) into a single bag. Alternatively, a single Platelets Pheresis unit constitutes an adult platelet dose.

In the Optimal Platelet Dose Strategy for Management of Thrombocytopenia (PLADO) study[9], patients with hematologic or oncologic malignancies and hypoproliferative thrombocytopenia were randomized to three different (prophylactic) platelet-dosing strategies when the morning platelet count was ≤ 10 K/mcL. The primary outcome of World Health Organization (WHO) Grade 2 or greater bleeding was reached in approximately 70% of all groups regardless of platelet transfusion dose (1/2, 1, or 2 apheresis units per episode in nonbleeding patients). The median (IQR) post-transfusion (measured within 4 hours) platelet increment following 1 apheresis platelet unit transfusion among subjects with a median Body Surface Area of 1.9 m2 was $19^{11\text{-}30}$ K/mcL.

For patients undergoing treatment for Acute Myelogenous Leukemia or Autologous Hematopoietic Stem Cell Transplantation (HSCT)[53], prophylactic platelet transfusion (ie, when the platelet count was < 10K/mcL) was compared to therapeutic platelet transfusion (platelet transfusion only when a thrombocytopenic patient is bleeding). The therapeutic arm in the study received a third fewer platelet transfusions however, a difference in bleeding risk emerged based upon diagnosis. Increased risk of (mostly central nervous system) bleeds was observed among AML patients randomized to the therapeutic arm, while those undergoing autologous HSCT had no difference in risk of major hemorrhage between strategies.

In a subsequent randomized study by Stanworth and colleagues [54], 600 patients 16 or older receiving chemotherapy or undergoing stem cell transplantation were randomized to therapeutic or prophylactic platelet transfusion strategies. The primary outcome of this noninferiority study (WHO Grade 2 bleeding or higher up to 30 days after randomization) occurred more frequently in the therapeutic (50%) than in the prophylactic group (43%; adjusted difference in proportions, 8.4 percentage points, 95% CI: 1.7 to 15.2; p=0.06 for noninferiority – therefore, the study did not establish noninferiority for the therapeutic strategy). Patients in the therapeutic group developed their first bleed sooner than-, had a higher proportion of higher severity bleeds than, and had a higher number of days with bleeding- than did the prophylactic group.

These studies continue to support the practice of prophylactic platelet transfusions in severely thrombocytopenic, non-bleeding patients receiving chemotherapy and stem cell transplantation when platelet counts fall to below 10 K/mcL or less[55]. In other circumstances, platelets are typically transfused prior at counts < 50 K/mcL prior to non-neuraxial surgery or diagnostic lumbar puncture and at platelet counts < 100 K/mcL prior to central nervous system or intraocular bleeding[56].

PLASMA

Plasma is a source of all coagulation factors and may be used in the setting of bleeding when either multiple coagulation factors are reduced (such as dilutional coagulopathy or warfarin anticoagulation) or for bleeding disorders where the deficient factor lacks an approved or readily available specific factor concentrate ***(Table 6)***. The use of plasma in a bleeding patient with coagulation test derangements (ie, INR elevation) is justifiable, whereas prophylactic transfusion prior to procedures in a non-bleeding patient is controversial. Two authoritative meta-analyses[57,58] encompassing 80 randomized, controlled trials of plasma transfusions across multiple patient populations and clinical applications conclude"no consistent evidence of significant benefit for prophylactic and therapeutic [plasma] use across the range of indications evaluated".

Table 6: Selected Factor Concentrates and Recombinant Factors. This list is not exhaustive and other formulations exist for FIX, FVIII, and VWF/FVIII concentrates.

Blood Product	Coagulation Factor	Concentrate/ Recombinant Form	Manufacturer	FDA Labeled Indications	Typical Dosing
Plasma (Contains all endogenous coagulation factors)	FVII	rVIIa NovoSeven [76]	NovoSeven – Novo-Nordisk, Denmark	Bleeding or peri-operative management in patients with hemophilia A or B with inhibitors, acquired hemophilia, congenital factor VII deficiency, Glanzmann's thrombasthenia with refractoriness to platelet transfusion	15 -30 mcg/kg for congenital factor VII deficiency 70 -90 mcg/kg for all other indications listed.
	FII, FVII, FIX, FX	Prothrombin Complex Concentrate (Human), KCENTRA [67]	CSL Behring, Germany	Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist therapy with major bleeding, the need for urgent surgery or invasive procedure.	25 – 50 units factor IX/body weightdepending upon INR values. Maximum dose not to exceed 2500 – 5000.
	FII, FIX, FX (reduced VII)	Factor IX Complex Profilnine [77]	Grifols Biologicals, USA	Prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B	Body weight (kg) x 1.0IU/kg x desired increase in Factor IX= Number of Factor IX IU required
	FIX	Coagulation Factor IX (Recombinant) BeneFIX [78]	Wyeth Biopharma, USA	Prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B	Body weight (kg) x 1.0IU/kg x desired increase in Factor IX (IU/dL) = Number of Factor IX IU required
	Antithrombin III	ATryn [Recombinant ATIII] [79]	GTC Biotherapeutics	Prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients	Bolus (IU): Body weight (kg) x [(100-baseline ATIII)/x]; Maint: (IU/hr): Body weight (kg) x [(100-baseline ATIII)/y]
		Thrombate III [pooled plasma derived) [80]	Grifols Therapeutics	Treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism	Dose (IU): Body weight (kg) x [(Desired ATIII% – Baseline ATIII%)/(1.4%/IU)] (2)
Cryoprecipitate (enriched for Fibrinogen VWF, FVIII, FXIII)	FI (Fibrinogen)	Fibrinogen Concentrate (Human) RiaSTAP [81]	CSL Behring, Germany	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogerenia and hypofibrinogenemia	Single use vial containing 900 mg to 1300 mg lyophilized fibrinogen concentrate. Target level (mg/dL– measured level (mg/dL) / 1.7 mg/dL per mg/kg body weight
	FXIII	Factor XIII Concentrate (Human) Corifact [82]	CSL Behring, Germany	Prophylactic and peri-operative management of patients with congenital Factor XIII	40 IU per kg body weightrate not to exceed 4mL per min. Adjust dose ±5 IU to maintain trough level of Factor XIII activity
	vWF/FVIII	vWF Concentrate/ Coagulation Factor VIII Complex (Human) Wilate [83]	Octapharma, Austria	Treatment of spontaneous and trauma-induced bleeding episodes in patient with severe vWD as well as moderate vWD with ineffective or contraindicated desmopressin	Minor hemorrhage: 20 -40 IU/kg (loading dose) 20-30 IU/kg q12-24 hr (maintenance dose) Major hemorrhage: 40 -60 IU/kg (loading dose) 20 -240 IU/kg q 12 -14 hrs (maintenance dose)
	FVIII	Antihemophilic Factor (Recombinant) Advate [84]	Baxter Healthcare, USA	Control and prevention of bleeding episodes and perioperative management in patients with hemophilia A Routine prohylaxis to reduce bleeding episodes in patients with hemophilia A	Total dose (IU)/kg x ? IU/dl Or Body weight (kg) x desired factor VIII Rise (IU/dL) x 0.5 IU/g per IU/dL

Surgical Setting: x=2.3, y=10.2; Pregnancy: x=1.3; y=5.4; adjust ATryn infusion rates as described in package insert or according to institutional protocols to monitor ATIII activity levels at least every 12 hours and prior to next dose to maintain ATIII levels at >80% or according to institutional protocols. ATIII enhances heparin effect, so heparin dosing should be adjusted accordingly.

The trigger for plasma transfusion is often a prolonged Prothrombin Time (PT) or International Normalized Ratio (INR). Segal, et al[59] reviewed the literature to determine whether prolongations of the PT or INR predict excessive bleeding during invasive procedures. Among the 14 of 25 reviewed studies that included a comparison group, no significant risk difference could be demonstrated for the outcome of bleeding between those with normal versus abnormal preprocedural coagulation test results. The firmness of this conclusion was tempered by the wide confidence intervals about the event rates and risk differences as well as limitations of the studies themselves. Not all studies reported the degree of coagulation test prolongation, either.

Abdel-Wahab and colleagues[60] reviewed INR responses following plasma infusion in patients with mild coagulopathy (INR 1 to 1.85) and a wide range of medical and surgical conditions. No dose-response effect could be demonstrated, and the delta INR following plasma transfusion was negligible. Likewise, Holland and colleagues[61] confirmed the findings of Abdel-Wahab and further concluded that in patients with high normal to mildly elevated INRs (1.3 to 1.6), supportive care and treatment of the underlying condition alone were sufficient for natural correction of prolonged coagulation tests.

Also, recall that Heparin effect – suggested by isolated prolongation of the activated Partial Thromboplastin Time (PTT) in a patient receiving heparin – is reversed by protamine sulfate, not plasma. The effects of Low Molecular Weight Heparin and Fondaparinux are not reflected by routine tests of coagulation. With these latter two agents, routine coagulation test results (ie, PT/INR and PTT) are usually normal even in the face of therapeutic anticoagulation. An isolated prolongation of the PTT could also reflect presence of a Lupus Anticoagulant – which typically portends thrombotic, rather than hemorrhagic risk.

Coagulation test results therefore, should be interpreted in the proper context. Mild, stable elevations in test parameters in nonbleeding patients with no history of major bleeding would not be as impactful as the same parameters in a patient with ongoing stigmata of coagulopathy.

Certainly if a patient demonstrates signs of active bleeding on physical examination – new spontaneous ecchymoses or petechiae, large hematomas at procedural or intramuscular injection sites, oozing or bleeding from catheterization or intravenous access sites, labile or actively decompensating coagulation status (progressive prolongations of routine tests

of coagulation or significant changes from previous baseline – particularly if accompanied by a declining hemoglobin level), has acute organ failure, is receiving ongoing anticoagulation, or particularly if there has been a previous history of major bleeding – then abnormal coagulation and platelet count values would better justify preemptive or prophylactic transfusions prior to surgery. Appropriate reversal agents (rather than plasma), or an appropriate anticoagulant-free window, should be considered in the setting of anticoagulant therapy depending upon the clinical situation.

Thrombotic Thrombocytopenic Purpura (TTP) is caused by emergence of an autoantibody directed against ADAMTS-13 (A Disintegrin and Metalloprotease with Thrombospondin-type 1 repeats -13), an endothelial cell luminal-side protease that cleaves emerging strands of vWF at the A-2 Domain. The autoantibody depletes ADAMTS-13 leading to accumulation of attached ultra-large molecular weight multimers of vWF which promote microvascular thrombosis through platelet activation[62].

Plasma exchange is the primary treatment for TTP and both reduces the titer of autoantibodies directed against ADAMTS-13 and replaces deficient ADAMTS-13 with donor derived ADAMTS-13 through the use of donor plasma as the replacement medium.

Plasma, as opposed to albumin, saline or cryoprecipitate-poor plasma, is the replacement medium of choice during plasma exchange treatment of TTP and any delay in initiation of therapeutic plasma exchange should be addressed with infusion of plasma and initiation of steroids[63]. A randomized controlled trial comparing standard plasma against cryoprecipitate poor plasma (ie, the supernatant plasma from CRYO production – see below) plasma[64] demonstrated no difference in response rates by day +6 or +13 of treatment.

The rationale for cryoprecipitate poor plasma revolves around its reduced concentration of larger multimers of von Willebrand Factor. However, this reduction in vWF that occurs during cryoprecipitation is also accompanied by a reduction in ADAMTS-13 rendering cryoprecipitate poor plasma a less effective ADAMTS-13 replacement medium[65]. Standard, Fresh Frozen Plasma (FFP), therefore, remains the authors' replacement medium of choice for therapeutic plasma exchange in the setting of TTP.

Figure 1: Calculation of the Corrected Count Increment (CCI)

$$CCI = \frac{(1\text{-hour Post-Count} - \text{Pre-Count}) \times BSA}{\text{Platelet Dose } (\times 10^{11})}$$

Pre- and Post-counts are expressed as K/mcL, BSA is m^2, the average number of platelets (i.e., platelet dose) in a single apheresis platelet unit = 4×10^{11}.

Sample Calculation: A patient with hypoproliferative thrombocytopenia and BSA 1.4 m^2 presented with epistaxis and a platelet count of 8 K/mcL. After receiving a single apheresis unit of platelets, the epistaxis resolved and a post-transfusion platelet count measured within 1 hour transfusion was 32 K/mcL.

CCI = [(32,000 – 8,000) x 1.4] / 4 = 8400/mcL representing an adequate (>5000/mcL) increment.

Figure 1: Calculation of the Corrected Count Increment (CCI)

In the treatment of dilutional coagulopathy or warfarin reversal in a bleeding patient, it is reasonable to include plasma as a therapeutic option. Varying doses are reported in the literature, but a dose of 15 to 20 mL/kg is reasonable. For whole-blood derived plasma units, the volume per unit is typically in the range of 270 to 300 mL. However, plasma alone incompletely reverses the INR and has a limited duration of effect (no more than 8 hours) upon the degree of resultant correction achieved among warfarin-treated patients[66]. Given the prolonged duration of effect of warfarin, rebound elevations in the INR may occur if concomitant Vitamin K is omitted.

For the treatment of bleeding in a warfarin treated patient, a four-factor Prothrombin Complex Concentrate (KCENTRA, CSL Behring, Marburg Germany) was recently approved by the Food and Drug Administration (FDA). It is dosed according to the degree of INR elevation and administered as 25, 35, and 50 Factor IX units/kg body weight when the INR is 2 to <4, 4 to 6, and >6, respectively. Dosing should not exceed 2500, 3500, or 5000 Factor IX units, respectively[67].

In a randomized, plasma-controlled noninferiority trial of KCENTRA[68] (also known as Beriplex in other countries), warfarin-treated adults with acute bleeding events were randomized to plasma or KCENTRA with co-primary endpoints of hemostatic efficacy and rapid INR reduction (to ≤ 1.3 at 0.5 hours after end of infusion. Notably, subjects with history of thrombosis or Antiphospholipid Antibody Syndrome were excluded. KCENTRA dosing was carried out as described above, and plasma was dosed at 10, 12, and 15 mL/kg, respectively based upon the above-stated INR categories.

Effective hemostasis was achieved in 72.4% of KCENTRA treated and 65.4% of plasma treated subjects. Rapid INR correction was achieved 62% of KCENTRA patients compared to 9.6% of plasma treated patients. Thromboembolic complications and deaths were evenly distributed between groups.

A recent systematic review[69] concluded that: 1) prospective studies in cardiac surgery support a reduction in allogeneic red cell transfusion and reduction in chest tube drainage with the use of Prothrombin Complex Concentrates (PCCs) in the setting of warfarin reversal and, 2) that although PCCs

more rapidly correct the INR in warfarin treated patients than does plasma, functional outcomes in intracranial hemorrhage remain poor regardless of reversal strategy.

PCCs allow administration of significant amounts of clotting factors in a small volume whereas adequate plasma doses may exceed 1.2 to 1.4 liters and require additional delay for ABO typing, thawing, and labeling. Therefore, PCCs remain a reasonable alternative to plasma for warfarin reversal particularly when volume overload is a significant concern and the bleeding is critical.

CRYOPRECIPITATED ANTIHEMOPHILIC FACTOR (CRYO)

CRYO is the cold-insoluble portion of plasma that is enriched for Fibrinogen, von Willebrand Factor, and Factors VIII and XIII[70]. Many of the primary constituents of CRYO have gradually been recapitulated in either Factor Concentrate or Recombinant Single Factor form ***(Table 6)***. Currently, the major remaining indication for CRYO is acquired hypofibrinogenemia. A recently approved Fibrinogen Concentrate (RiaStap, CSL Behring, Marburg, Germany) is now available, however, the FDA-approved indications for RiaStap are limited to bleeding in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia (but not dysfibrinogenemia)[71].

Indications for CRYO include the development of dilutional coagulopathy during massive transfusion in bleeding patients or prophylactically in severely hypofibrinogenemic patients prior to major invasive procedures. In such patients, transfusion of CRYO can be considered when the fibrinogen level is below or declining toward 100 mg/dL[72]. During massive transfusion or active bleeding, it is reasonable to maintain fibrinogen levels in the 150 mg/dL range[73]. A single unit of CRYO contains approximately 250 mg/dL of fibrinogen; and dosing can either be estimated as 1 unit per 5 kg/body weight (each unit estimated to raise the fibrinogen by 5 to 10 mg/dL) or through calculation ***(See Figure 2)***.

Acquired hypofibrinogenemia also occurs in Disseminated Intravascular Coagulation (DIC). In this circumstance, transfusion of CRYO becomes indicated when bleeding develops in the setting of prolonged coagulation test results and hypofibrinogenemia. Because of its position in the common pathway of hemostasis, very low levels of fibrinogen can contribute to additional prolongation of PT/INR and PTT. Additional blood components, such as platelets and plasma may also be required, but definitive treatment requires correction of the underlying driver (ie, sepsis).

In the appropriate settings, patients with Factor Deficiencies, such as von Willebrand Disease, Hemophilia A, Congenital Antithrombin III Deficiency should preferentially receive the appropriate Factor Concentrate (some options recombinant) whenever available rather than Plasma or CRYO ***(Table 6)***[67,76-84].

Figure 2: Calculation of Cryoprecipitate Dose (Desired Delta Fibrinogen = Desired Fibrinogen (mg/dL) – Current Fibrinogen (mg/dL). A typical target fibrinogen in a bleeding patient might be 150 to 200 mg/dL.

Total Blood Volume (TBV mL) = 70 mL/kg x Kg body weight

Total Plasma Volume (TPV mL) = TBV x (1-Hct)

Conversion of TPV mL to TPV dL = TPV in mL x 1 dL/100 mL

Fibrinogen deficit (mg) = Desired Delta Fibrinogen (mg/dL) x TPV (dL)

CRYO dose (number of units) = Fibrinogen Deficit (mg)/250 mg Fibrinogen per unit of CRYO

Following completion of massive transfusion in a 70 kg trauma patient, postoperative oozing from all catheter sites, surgical drains persists. The PT, INR, PTT are prolonged, the Hematocrit is 70%, and a measured fibrinogen level is determined to be 40 mg/dL. The decision is made to transfuse CRYO first, then recheck all coagulation parameters.

TBV = 70 mL/kg x 70kg = 4900 mL

TPV = 4900 mL x (1-0.30) = 3430 mL; 3430 mL x 1 dL/100 mL = 34.3 dL

Fibrinogen Deficit (in mg) = (200 mg/dL- 40 mg/dL) x 34.3 dL = 5488 mg Fibrinogen

CRYO Dose (*number of units*) = 5488 mg Fibrinogen/250 mg Fibrinogen per unit

= 22 units*

*At many centers, a conversion to pre-pooled units of CRYO is occurring. Rather than individual unit dosing, the dose is rounded to the minimum number of pooled CRYO supplied by the vendor – in most cases, 5 Units.

For the calculation above, therefore, the patient was administered 20 Units of CRYO (issued from the blood bank as 4 bags of pre-pooled CRYO (each bag containing 5 units).

Because Fibrinogen resides in the common pathway, severe deficiencies result in prolongation of both PT and PTT. Following transfusion, the expected increment in Fibrinogen level was realized along with normalization of the PT, INR, and PTT.

PRETRANSFUSION TESTING

When red blood cell transfusion becomes a strong consideration, pretransfusion testing becomes necessary. This testing consists of an ABO Rh (Type) Antibody Screen (Screen) and Crossmatch (Cross). For patients whose final transfusion decision is unclear, a Type & Screen may be sufficient. For patients in whom transfusions are very likely, a Type & Cross (this test includes the antibody screen) is ordered. The Type & Cross requires designation of the number of units to be cross-matched for the patient. In clinical circumstances, such as rapidly exsanguinating bleeds, there may be not be sufficient time for standard pretransfusion testing. For these scenarios, Group O (or type specific, if known), uncrossmatched blood may be issued as an emergency measure.

Patients with red cell antibodies may require extended laboratory workup to further define the specificity of the antibody or antibodies present. If multiple antibodies are present, the investigation could become quite protracted. In such cases, the procurement of antigen-negative red cells may also be delayed. Fortunately, this circumstance is rare among most patient populations.

It is instructive, however, from the standpoint that if a patient is known to be alloimmunized against red cell antigens then

preoperative planning should incorporate additional time needed for laboratory investigation and procurement of antigen negative, cross-match compatible units.

Pretransfusion specimens for Type & Screen or Type & Cross(match) will be rejected if improperly labeled (bearing full name and medical record number of patient, name of phlebotomist and time and date of draw). Acceptable specimens remain active for 72 hours, after this point a new specimen must be drawn. This interval seeks to strike a balance between reduced recipient testing and ensured detection of emerging antibodies. In certain circumstances (clinician attestation to absence of pregnancy, transplant or transfusion in the patient for the past 3 months) the pretransfusion specimen may be extended to 10 to 14 days depending upon local blood bank policies.

PREMEDICATION PRIOR TO TRANSFUSION

A randomized, placebo-controlled trial of acetaminophen and diphenhydramine premedication among subjects admitted for leukemia or hemotopoietic stem cell transplant demonstrated no significant difference in the risk of overall transfusion reactions using leukoreduced products[74]. A similar lack of overall benefit was noted in a prior trial[75]. The routine use of premedication in unselected transfusion recipients does not, therefore, represent evidence-based practice. Premedication should therefore be reserved for patients with an established pattern of transfusion reactions or for those whose clinical circumstance would poorly tolerate a transfusion reaction.

CONCLUSION

Blood centers and hospital transfusion services employ a multi-layered screening process to reduce donor and recipient risk. While these deferral and testing practices effectively reduce infectious risks, noninfectious complications of blood transfusion – which are typically more common and immediately problematic – remain a concern. Transfusion Associated Circulatory Overload is especially common and potentially preventable through risk factor assessment and possibly administration of diuretic therapy in selected patients. Selected patients may benefit from receipt of irradiated blood components - irradiation being the only widely available modality known to effectively prevent TA-GVHD.

Recognition of transfusion-related risks has driven institutions to re-evaluate transfusion practices and bring them in line with evidence-based guidelines. The safety of restrictive transfusion thresholds for red blood cell and platelet transfusions in otherwise nonbleeding patients have been verified by large clinical trials. Recent studies argue against a conversion to a no-prophylaxis platelet transfusion strategy among hematology oncology patients. Prophylactic plasma transfusion has been studied in two, large meta-analyses comprising over 80 studies that call into question its therapeutic benefit. Therapeutic plasma transfusion in bleeding patients with documented coagulopathy continues to remain a reasonable modality. In patients with bleeding in the setting of warfarin anticoagulation, a recently approved four-factor prothrombin complex concentrate is now available for use as a plasma alternative. Cryoprecipitate may be administered in bleeding patients with hypofibrinogenemia. While the factors contained within CRYO are also available as factor concentrates and recombinant forms, the use of these agents is generally restricted to those with congenital bleeding disorders (in the case of Hemophilia A, B, congenital afibrinogenemia, and von Willebrand Disease) or off-label circumstances when alternatives are either unavailable or based upon institutional experience.

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REVIEW ARTICLE

Screening for Sleep Apnea in Posttraumatic Stress Disorder

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KEYWORDS:
PTSD
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Sleep problems are one of the most enduring complaints from individuals with post-traumatic stress disorder. In this study, the investigators explored the relationships between a commonly administered post-traumatic stress disorder screening instrument, the Posttraumatic Stress Disorder Checklist – Military Version (PCLm) and results obtained from home sleep studies obtained from active duty service members. This retrospective study was conducted among active duty service members receiving care on the Psychiatry Continuity Service (PCS) at Walter Reed National Military Medical Center. The investigators examined 135 records of subjects referred for an enhanced sleep assessment from October 1, 2010 through November 30, 2013. There were significant direct correlations between the PCLm score and the sleep assessment values: wake percent (n=121, p=.022).onset of first deep sleep (n=106, p=.024) the apnea/hypopnea index (n=110, p=.028) and the oxygen desaturation index (n=110, p=.025).

INTRODUCTION

The diagnostic criteria for posttraumatic stress disorder (PTSD) involve a pathologic constellation following a traumatic event that involves intrusive recollections, avoidance of triggering stimuli, negative thinking, and hyperarousal.[1] Some of the more troubling complaints cluster around the person's sleep, such as intrusive nightmares, problems falling asleep due to hyper vigilance, and even futile efforts to avoid sleep. The inextricable link between PTSD and sleep problems has led some researchers to speculate that PTSD is fundamentally a sleep disorder.[2] As researchers continue to probe the relationship between PTSD and sleep, other evidence is emerging suggesting that abnormalities in the sleep cycle, specifically rapid eye movement (REM) sleep may be associated with the persistence of troubling dreams and disruptive behaviors while abnormalities in non-rapid eye movement (NREM) are more likely related to insomnia.[3,4]

One of the frustrations for clinicians treating PTSD is the intractability of the disorder. Since sleep is such a central component of PTSD it would seem reasonable to include a detailed sleep assessment in each case to ensure treatment planning incorporated this element. Doing so may help improve one of the most common complaints of PTSD patients. The value of such an approach is increasingly suggested, by emphasizing for example, initial medication management that includes trazodone and prazosin that more selectively target sleep fragmentation and nightmares. [5,6] Sleep problems such as insomnia and nightmares also independently contribute to a heightened risk of suicide, which when added to PTSD, offers an even more potent argument for addressing this issue.[7]

A more obscure association with PTSD that is getting more research attention is the apparent increased incidence of obstructive sleep apnea (OSA). This relationship has come to the attention of researchers studying service members with combat related PTSD suggesting that the incidence and severity of their PTSD may be related to OSA.[8-10] Taking a deep dive into the specific parameters affected through this relationship reveals changes in the sleep cycle of combat veterans, such as a significant reduction in both REM and NREM and more severe breathing problems than seen in non combat related PTSD cases.

In another study, the authors investigated sleep complaints among service members with combat related PTSD and through the use of polysomnography determined that two-thirds of the subjects met the diagnostic criteria for OSA.[11] Interestingly, the same study reported that OSA was significantly higher among service members without accompanying physical injuries, leading to speculation that an undiagnosed, pre-existing breathing problem might be a risk factor for the subsequent development of PTSD.

Similar findings have been reported among individuals with PTSD from other traumas such as crime, natural disasters, and terrorism.[12-15] In these cases, the OSA-PTSD dyad differs from non trauma related breathing problems with PTSD patients more commonly complaining of nightmares, difficulty initiating sleep, and an overall less satisfying night's sleep.

Despite newer studies increasingly pointing to a higher rate of OSA among individuals with PTSD, the exact etiology possibly uniting the pair in not yet well understood. Even so, it seems clear that recognizing and simultaneously treating

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both conditions will improve combat related PTSD[16,17] More specifically, one of the most distressing symptoms arising from PTSD involves the endless repetition of nightmares, a condition that may improve when the OSA is appropriately managed.[17-20]

In this study, the investigators explored the relationships between a commonly administered PTSD screening instrument and results obtained from home sleep studies obtained from active duty service members.

METHODS

This retrospective study was conducted among active duty service members receiving care on the Psychiatry Continuity Service (PCS) at Walter Reed National Military Medical (WRNMMC) Center. The PCS is a partial hospital program providing eight hours of clinical activities five days a week with an average length of stay of approximately one month, adjusted as necessary by the treatment plan. As a tertiary care facility WRNMMC tends to receive more complicated cases, a trend mirrored on the PCS. The most common diagnoses include all depressive disorders, PTSD, and substance use disorders. Sleep problems are one of the most common concerns, leading to the implementation of an enhanced sleep assessment that includes a home sleep study.

Home sleep devices allow patients to do sleep studies at home. These portable home sleep devices are sophisticated instruments capable of measuring several physiologic parameters that produce objective information about a person's sleep. The commercially available devices vary in their capacity to report different factors such as accurate respiratory data, the sleep-wake cycle, and the actual sleep time. The better home sleep monitors rely in part on the well-established relationship between fluctuations in the blood pressure and changes in the sleep cycle.[21] The sleep cycle is characterized by predictable changes in blood pressure, most dramatically represented by the rise in blood pressure that accompanies REM sleep.[22] Cardiac activity changes through the phases of the sleep cycle.[23] For example, during REM sleep the heart rate and blood pressure all increase. The connection between autonomic activity and the phases of the sleep-wake cycle awaited technological innovations that could reliably measure these subtle physiologic changes. One important advance was the development of a finger mounted plethysmographic sensor to measure peripheral arterial tone (PAT). The PAT sensor is constructed to monitor the decrease venous engorgement while simultaneously unloading arterial wall tension, thereby promoting the dynamic range of the device.[24]

Study investigators used the WatchPAT™, a commercially available FDA approved medical device (Itamar Medical, Caesarea, Israel) for the home sleep studies. This medical device is a wrist-worn device that captures information from the PAT sensor, an actigraph, and a finger mounted pulse oximeter; and then stores the data on a secure digital card through the duration of the sleep study.

In a study comparing the WatchPat™ with concurrently administered polysomnography (PSG), the authors' reported a significant correlation (r=0.87, P<0.001) between the two procedures in detecting arousals.[25] The same device was the subject of another study examining the accuracy of the WatchPAT™ in diagnosing obstructive sleep apnea (OSA). The researchers reported a significant agreement (r=0.87, P<0.001) between the results obtained through PSG and the WatchPAT™.[26] In another study, researchers assessing the accuracy of respiratory parameters produced by this device reported that it was, "accurate, robust, and reliable ambulatory method for the detection of…" obstructive sleep apnea.[27]

Researchers have tested the actigraph portion of the WatchPAT™ and reported reasonable accuracy, versus PSG, in measuring wakefulness and sleep.[28] The device was capable of identifying respiratory values used by Medicare for diagnosing OSA.[29] In a study comparing the apnea-hypopnea index (AHI) as reported from a PSG versus a simultaneous recording from the WatchPat, the authors reported a significant (r=.90, P< .0001) agreement.[30] Another study comparing PSG with the WatchPAT™ also reported significant (r=.93, P< .0001) agreement on the AHI.[31]

Reasonable clinical guidelines for the use of portable home sleep monitors emphasize the need for a comprehensive clinical assessment, particularly for the common co-occurring problems in the study group. In cases where the monitors are used exclusively to diagnose OSA, the guidelines recommend close collaboration with sleep medicine experts.[32]

In this study, the investigators used the WatchPAT 200™ to conduct the home sleep studies. This FDA approved medical device calculates the severity of sleep apnea through three measurements, the apnea/hypopnea index (AHI), oxygen desaturation index (ODI), and the respiratory disturbance index (RDI). The AHI represents the total number of complete cessations (apneas) and partial obstructions (hypopneas) of breathing per hour of sleep. An AHI score from 5-14 indicates mild OSA, 15-30 moderate and severe is greater than 30.[33] The ODI measures changes in blood oxygenation from baseline. The RDI assesses the severity of sleep apnea by measuring respiratory efforts, or RERAs (Respiratory Effort Related Arousals). A RERA is an arousal from sleep that follows 10 seconds or more of increased respiratory effort

that does not meet the criteria for apnea or hypopnea.[34]

The investigators compared the home sleep study results with the Posttraumatic Stress Disorder Checklist – Military Version, (PCLm).[35] The PCLm is a 17-item self-report instrument from which subjects choose among 5 descriptions:

1= Not at all

2= A little bit

3= Moderately

4 - Quite a bit

5 = Extremely

A typical question from the PCLm asks the service member if they are "Having physical reactions when something reminded you of a stressful military experience from the past." For purposes of this study, scores above 49 suggest that the symptoms are consistent with the clinical diagnosis PTSD.

PCS patients were scheduled for an enhanced sleep assessment based on the results of the Pittsburg Insomnia Rating Scale (PIRS). The PIRS is a 20-item self-report instrument assessing sleep over the preceding 7-day period.[36] The range of scores on the PIRS is from 0-60 with scores above 20 suggesting insomnia. Typical questions on the PIRS include: "From the time you tried to go to sleep, how long did it take to fall asleep on most nights?" and "If you woke up during the night, how long did it take to fall back to sleep on most nights?"

In addition to the PIRS, all patients referred for a more detailed sleep assessment had their basal metabolic index (BMI) calculated and completed the Alcohol Use Disorders Identification Test (AUDIT)[37] The AUDIT consists of ten questions and five responses per item. Typical questions include, "How often do you have a drink containing alcohol?" and "How often do you have six or more drinks on one occasion?" In responding to these questions, subjects could choose from "never "which scored 0 for that scale item, "monthly or less (1)", "2-4 times a month (2)", "2-3 times a week (3) ", and "4 or more times a week (4)" which earned the maximum score for that scale question of four. Scores exceeding seven are associated with harmful drinking.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.

RESULTS

The investigators examined 135 records of subjects referred for an enhanced sleep assessment from October 1, 2010 through November 30, 2013. Almost two-thirds of the participants

Table 1 - Sleep Results for Total Study Group

Test Name	n*	Mean	SD
PIRS	135	41.10	10.52
AUDIT	111	4.68	7.66
PCLm	122	51.36	18.13
BMI	133	27.10	4.28
REM%	119	20.63	8.35
Deep Sleep%	119	20.81	6.09
Light Sleep%	119	58.56	11.14
Wake%	134	21.25	12.69
Time to Sleep(minutes)	118	25.28	15.60
Time First Deep Sleep(minutes)	118	65.27	48.63
Time First REM Sleep(minutes)	117	150.99	77.38
Sleep Time(minutes)	134	366.68	93.61
Apnea/Hypopnea Index	123	3.78	4.60
Oxygen desaturation index	123	1.66	2.69

*n varies due to missing data

Table 2 - Relationships between PCLm and Sleep Factors

Test		PCLm
AUDIT	Pearson Correlation	.101
	Sig. (2-tailed)	.295
	n*	110
PIRS	Pearson Correlation	.350
	Sig. (2-tailed)	.000***
	n	122
BMI	Pearson Correlation	.053
	Sig. (2-tailed)	.565
	n	120
Time to Sleep	Pearson Correlation	-.006
	Sig. (2-tailed)	.950
	n	106
Sleep Time	Pearson Correlation	-.279
	Sig. (2-tailed)	.002***
	n	121
Wake %	Pearson Correlation	.208
	Sig. (2-tailed)	.022**
	n	121
First Deep	Pearson Correlation	.219
	Sig. (2-tailed)	.024**
	n	106
First REM	Pearson Correlation	.168
	Sig. (2-tailed)	.087
	n	105
Light Sleep %	Pearson Correlation	.116
	Sig. (2-tailed)	.234
	n	107
REM %	Pearson Correlation	-.203
	Sig. (2-tailed)	.036**
	n	107
Deep Sleep%	Pearson Correlation	.068
	Sig. (2-tailed)	.487
	n	107
AHI	Pearson Correlation	209
	Sig. (2-tailed)	.028**
	n	110
ODI	Pearson Correlation	.214
	Sig. (2-tailed)	.025**
	n	110

* n varies based on missing data

**Correlation is significant at the 0.05 level

were male (n=87/135, 64%) and roughly the same percentage of subjects' (n=90/129, 69.8%) age range was between 21-35.

All subjects referred for an enhanced sleep study had evidence of insomnia based on the average PIRS score (n=135, Mean 41.10, SD 10.52), as well as trauma symptoms based on the PCLm (n=122, Mean 51.36, SD 18.13), and a slightly elevated BMI (n=133, Mean 27.10, SD 4.28). Subjects needed almost a half an hour to fall asleep (n=118, Mean 25.28, SD 15.60), had about six hours total time asleep, (n=118, Mean 6.12, SD 1.57) and based on the average AHI (n=123, Mean 3.78, SD 4.60) did not manifest breathing problems while asleep ***(See Table 1)***.

Correlations between the PCLm and various sleep factors revealed several significant findings. Not surprisingly the higher the PCLm score the higher was the PIRS. (n=122, p=.002). Other results included an inverse relationship between total time slept (n=121, p=.002) and the percent of REM sleep (n=107, p=.036). There were significant direct correlations between the PCLm score and the wake percent (n=121, p=.022).onset of first deep sleep (n=106, p=.024). AHI (n=110, p=.028) and the ODI (n=110, p=.025). There were no significant correlations between the PCLm and the AUDIT score or the BMI. ***(See Table 2)***

DISCUSSION

This study confirms what patients bitterly complain about, that sleep problems are inextricably intertwined with PTSD. The main casualties are seen in the inverse relationship between PTSD and total sleep time, as the former goes up the latter goes down. In a similar fashion, the amount of REM sleep also decreases as the symptoms of PTSD increase. The first episode of deep sleep is delayed and in a nearly significant trend the first episode of REM sleep is also pushed later into the sleep cycle as the PCLm scores increase.

Perhaps one of the more interesting correlations is the relationship between PTSD and breathing problems while asleep. Two common parameters of OSA, the AHI and the ODI both increased along with the intensity of PTSD. Undiagnosed OSA could be an important factor complicating PTSD improvement.

Another interesting finding showed no significant relationship between the PClm and the person's BMI or alcohol use as screened by the AUDIT. Both of these findings would benefit from further study since alcohol use and obesity can independently and adversely affect sleep but in this study when compared with the PCLm there were no significant correlations.

Based on the findings in this study clinicians should routinely incorporate screening tests to assess trauma symptoms and sleep. Not every patient with PTSD will need a PSG or a home sleep study but as revealed in this study the higher the PCLm score the more likely is the possibility that a significant problem, such as OSA is present.

There are limitations in this study. The investigators used the PCLm that is tailored for military trauma. Other versions of the instrument are available, and while the investigators believe they would result in similar findings, this opinion would benefit from research. Also, the subjects in this study had combat-related PTSD, a stressor that may be specific enough to affect the results. Other research might address different trauma types.

CONCLUSION

For the typical patient with PTSD, sleep problems often lead the list of enduring complaints. A poor night's sleep dominated by frequent awakenings, troubling dreams, and short duration may suggest more significant underlying pathology such as OSA. A simple screening tool used in this study, the WatchPat™ could help clinicians more accurately predict the problems, tailor therapy, or seek referral as needed.

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense. The authors are not endorsing any commercial product.

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REVIEW ARTICLE

Wound Tetanus

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KEYWORDS:
Tetanus
Antibiotic Therapy
HTIG

We report a case of wound tetanus in a previously immunized patient. The patient developed generalized tetanus requiring IV antibiotic therapy & human tetanus immune globulin (HTIG) therapy. This is only the 15th case reported this year in the United States.

INTRODUCTION

Tetanus occurs worldwide. It is a common problem in areas of the world that are densely populated, and in hot climates in which the soil is rich in organic matter. Reported cases occur more frequently in underdeveloped, overcrowded and economically disadvantaged countries. The disease has been described in the Bible and ancient writings of Greek and Egyptian physicians. It is the only vaccine preventable disease that is infectious but not contagious.

Approximately seventy-five percent of cases occur between April and October. There are between 800,000 and one million cases worldwide yearly. Worldwide deaths have been reported between 210,000 to one million yearly. Greater than fifty percent of these deaths are from neonatal tetanus. Many cases go unreported each year.[1,2,3,9]

In 1903 there were 406 deaths reported from tetanus due to infections obtained from 3983 hand injuries on the fourth of July from fireworks. This led the American Medical Association to recommend banning hand held fireworks. Prophylaxis against tetanus began in World War I. Immunization programs for the military were in place by 1924 and were routine by 1946. All United States military dog tags from 1940 bore the date of the soldier's tetanus immunization. There were no reported military cases of tetanus during the Vietnam War.

Since 2000 there has been an average of approximately thirty cases per year in the United States. The mortality rate has decreased from ninety-one percent in 1947 to 13-42% today. In the early-to-mid 1940's nationwide immunization programs were instituted in the United States. Tetanus became a reportable disease in 1947. The 560 cases reported yearly have dramatically decreased directly due to the institution of immunization protocols. Only 14 cases were reported in 2014. There have been zero deaths in those patients who have completed a primary immunization series.[4,7]

Risk factors for the development of tetanus include: age > 60, short incubation period, inadequate tetanus toxoid vaccination, tetanus prone wounds, intravenous drug use (IVDU), diabetes mellitus, chronic venous stasis ulcers. Currently most cases if tetanus in the United States occur in patients with a history of under immunization. At greater risk are heroin IVDU and older adults because of their higher rate of being unvaccinated or under vaccinated.

PATHOGENESIS

Tetanus is caused by a gram-positive obligate anaerobic spore forming bacillus, Clostridium tetani. Spores of C. tetani are ubiquitous in nature. They have been found in the gastrointestinal tract of humans and domesticated animals, soil, house dust, fresh and salt water. The spores are highly resistant to temperature extremes and humidity and can survive indefinitely. The spores will not germinate unless adequate anaerobic conditions are present. When favorable tissue conditions exist the spores germinate to form mature bacilli which produce exotoxins tetanolysin and tetanospasmin.

Tetanolysin has an undefined role in the development of clinical tetanus. It is thought to contribute to the development of localized anaerobic tissue conditions by direct damaging effects on traumatized tissue. However, the exact mechanism by which this process takes place is still undetermined.[5,6]

Tetanospasmin is second only to botulinum toxin in potency and is responsible for the clinical manifestation(s) of the disease. Tetanus toxoid is an inactivated form of tetanospasmin. The majority of toxin production occurs at the end of the germination phase which only occurs under strict anaerobic conditions. This exotoxin enters peripheral nerves and via the axonal retrograde transport system is transported

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to the central nervous system (CNS). The exotoxin enters presynaptic neurons and interrupts neurotransmitter release. The inhibitory neurotransmitters gamma-aminobutyuric acid (GABA) and glycine are primarily affected. Once inside inhibitory nerve terminals this exotoxin inhibits the release of GABA and glycine. Lack of GABA prevents inhibition of sustained excitatory nerve impulses. This results in a cumulative disinhibition of end-organ neurons such as motor neurons and those of the autonomic nervous system. This entire process accounts for the characteristic muscle spasms and autonomic instability seen in severe tetanus. Tetanospasmin binding is irreversible and symptoms last for the lifetime of the neuron.[8]

SYMPTOMATOLOGY

Tetanus toxin causes hyperactivity of voluntary muscles, i.e. rigidity and spasm. Tetanus is categorized into four clinical forms: generalized, local, cephalic, neonatal. Excluding the neonatal form, the generalized form accounts for approximately 80% of reported cases.

Tetanus usually follows a recognized injury excluding the neonatal form. The incubation period can range from one day to several months. Most commonly the incubation period is from 3-21 days. The length of time between an injury and the onset of symptoms is a predictor of severity of the disease. Symptoms occurring within one week of injury are frequently more severe.

Localized tetanus involves muscular rigidity generally on the side of inoculation and may persist for weeks or months. Symptoms generally resolve without sequelae. Mortality rate of the localized form is less than one percent.

Generalized tetanus presents with trismus (lockjaw) 75% of the time. The clinical triad of muscular rigidity, spasms and autonomic dysfunction characterize generalized tetanus. The development of "risus sardonicus", the "ironical smile of tetanus" occurs in 50-75% of cases. As the disease progresses camptocormia and opisthotonus may develop. This is a poor prognostic finding. Acute, paroxysmal, uncoordinated generalized muscle spasms are characteristic of generalized tetanus . Muscular spasms last from seconds to minutes and are extremely painful. Periods of relaxation occur in between these episodes. Spasms may be precipitated by a variety of external stimuli such as cold air, noise, lights, drinking, voiding or simple movement of the patient. The peripheral muscles of the hands and feet are relatively spared from any involvement. Sensory nerves may become impaired causing altered sensation and allodynia. Impairment of cognition and mood alterations is generally not reported.

Autonomic instability occurs several days after the onset of generalized symptoms occur. This is a major cause of death of these patients. Approximately one-third of patients with generalized tetanus will develop autonomic instability during the course of their disease. "Autonomic storms" occur with marked cardiovascular instability. Severe fluctuation between hypotension, hypertension, brady-tachy arrhythmias and rapid alterations in systemic vascular resistance predispose the patient to malignant arrhythmias and death. Severity and long term recovery can be based on a severity scale, the Ablett Classification ***(Table 1)***.[10]

TABLE 1

Modified Ablett Classification
Grade 1 (mild) muscle rigidity affecting one or more groups of muscles sparing the muscles of deglutition
Grade 2 (moderate) muscle rigidity involving the muscles of deglutition (trismus, risus sardonicus)
Grade 3a (severe) generalized muscle rigidity/spasms (opisthotonus)
Grade 3b (very severe) autonomic nervous system involvement

DIAGNOSIS

The diagnosis of tetanus is generally clinically based. The causative microorganism is recovered in less than 30% of cases. Bacteriologic studies have confirmed the presence of C. tetani in only approximately one-third of cases. The presence of C. tetani does not mean that the patient has tetanus. There are no laboratory tests that conclusively diagnose tetanus. The measurement of a serum antitoxin level greater than 0.15 units/ml makes the diagnosis of tetanus very unlikely but not impossible.

A bedside diagnostic tool, the "spatula test" may be useful as an adjunct to aid the diagnosis of clinical tetanus. If a spatula (tongue blade) inserted in the posterior pharynx elicits a gag response the test is negative. If the patient has an involuntary biting reflex, the test is positive and suggestive of early tetanus.

Because the diagnosis of tetanus is primarily a clinical determination certain other conditions may mimic the symptoms of tetanus. A useful diagnostic list would include: seizure disorder, serotonin syndrome, black widow spider envenomation, strychnine poisoning, botulism, hypocalcemic tetany, antipsychotic medication toxicity and rabies.

TREATMENT

The medical management of acute tetanus revolves around the prevention of further toxin release, neutralization of unbound toxin and minimizing the effects of bound toxin. Wound management including debridement is an important part of the treatment protocol.

Penicillin and metronidazole are the antibiotics of choice to eliminate viable C. tetani bacteria as a source of infection. Erythromycin and clindamycin are acceptable alternative antibiotics. Some studies have shown the use of metronidazole may decrease both recovery time and mortality.

Minimization of external stimuli is required. Most patients do better symptomatically is a quiet, secluded, lowly lighted room. Maintenance of an adequate airway and control pf muscle spasms are of paramount importance. Early intubation must be undertaken if there is any evidence of airway compromise.

An active case of tetanus itself does not impart immunity. Nonimmunized survivors of tetanus have been victims a second time. Tetanus toxoid vaccination should be given as a part of the treatment regime. It takes 4-7 days for clinically detectable antibody levels to be achieved. This immune response is frequently delayed for weeks in the elderly.

Fifty percent of leukemia/lymphoma patients who undergo chemotherapy lose immunity to tetanus. Bone marrow transplant patients need revaccination 12-24 months post-transplant.

Neutralization of unbound tetanus toxin is achieved by the use of human tetanus immunoglobulin (HTIG). This should be administered within 24 hours of the clinical suspicion of acute tetanus. HTIG has a half-life of 25-30 days. It neutralizes circulating tetanospasmin but has no effect of neuron-bound toxin. A single dose is sufficient. However, there is great controversy surrounding optimal dose therapy. Most authorities consider 500 IU administered intramuscularly as the optimal dose for both pediatric and adult patients.

The use of botulinum toxin in the treatment of generalized tetanus has been attempted in several cases with varying results.[11]

CASE HISTORY

A 43-year-old Caucasian male presented to a rural hospital emergency department following a skill saw accident resulting in a 3.8 cm laceration to the palmar aspect of his left thumb. There was no tendon or bone involvement and minimal contamination with wood fragments. He underwent a simple laceration repair with the placement of 5 interrupted sutures, received a diphtheria-pertussis-tetanus injection and placed on double strength sulfamethoxazole-trimethoprim twice daily for ten days. Seventeen days later he followed up in the emergency department for a wound recheck. His laceration had healed with only a small escar remaining. There was no discharge or drainage from the sutured wound. He did have a small amount of erythema to the palmar surface of the left thumb. A decision was made to continue antibiotics and he was placed on minocycline 100mg P.O. BID and clindamycin 300mg P.O. QID. Three days later (20 days post injury) the patient presented again to the emergency department for complaints of left jaw pain, muscle spasms of his abdomen and right upper extremity. He complained of being awakened from sleep with left jaw pain followed by the development of abdominal wall fasciculation's. These symptoms progressed to painful muscle spasms of the right and left upper extremity. He had no complaints of difficulty breathing or swallowing. A tentative diagnosis of tetanus was made. The patient received 2.5 mg diazepam IV, 2mg morphine sulfate IV and 250 IU HTIG IM. He was transferred to a tertiary medical center where he received supportive care in ICU. He received an additional 3000 IU HTIG IM and was placed on metronidazole 500mg IV every eight hours after transfer. He remained hospitalized for 72 hours and was discharged home with minimal residual spasms of the right lower extremity. He remained asymptomatic sixty days post discharge.

CONCLUSION

Tetanus is an uncommon disease in the United States. It is a very rare disease in children because of laws mandating pediatric immunization. The patient population in the US most likely to present with acute tetanus are older adult males and intravenous drug users (IVDU).

Lack of routine medical care and failure to maintain updated tetanus vaccination status contribute to low levels of tetanus immunity. This translates into a population at risk for the development of tetanus. The diagnosis of tetanus is generally clinically based. The presentation of this disease is so characteristic that a presumptive diagnosis can be made in most circumstances. Treatment includes preservation of an adequate airway, controlling muscle spasms, administration of HTIG and appropriate antibiotic therapy. Mortality rates are generally low and no tetanus deaths have occurred in individuals who received primary tetanus immunization. The best treatment is prevention of injury and maintenance of tetanus immunity.

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2015 Calendar of Events

May 6-10, 2015

Maine AOMA 93rd Annual Convention
Arizona Grand Resort & Spa
Phoenix, AZ
www.az-osteo.org

June 5-7, 2015

Maine ACOFP
Samoset Resort
Rockport, ME
www.mainedo.org

June 5-7, 2015

Indiana Osteopathic Association 118th Annual Spring Update
Crowne Plaza Union Station
Indianapolis, IN
www.inosteo.org

July 10-12, 2015

Direct Primary Care Summit
InterContinental Kansas City at the Plaza
Kansas City, MO
www.dpcsummit.org

July 22-26, 2015

ALOMA 25th Annual Emerald Coast Conference
Hilton Sandestin
Destin, FL

July 29 - August 2, 2015

Florida Society ACOFP 35th Annual Convention and Family Medicine Update
Hilton Bonnet Creek
Orlando, FL

July 30 – August 2, 2015

MAOFP Summer Family Medicine Update Conference
Grand Traverse Resort
Acme, MI
www.maofp.org/cme

August 4-9, 2015

TOMA-Texas ACOFP 2015 Joint Annual Convention
Omni Bay Front, Corpus Christi, TX

August 6-9, 2015

CA-ACOFP 39th Annual Scientific Medical Seminar
Disneyland Hotel
Anaheim, CA
www.acofpca.org

August 7-9, 2015

POFPS 40th Annual CME Symposium
Hershey Lodge, Hershey, PA
www.poma.org

August 12-16, 2015

AOMA 30th Annual State Convention
Chateau on the Lake
Branson, MO
www.arosteopathic.org

August 13-16, 2015

CSOM Summer CME & Membership Program
Vail, CO
coloradodo.org

August 14-16, 2015

NC Society of the ACOFP Annual CME Meeting
Pinehurst Resort
Pinehurst, NC
www.nc-acofp.org

August 21-23, 2015

ACOFP Intensive Update & Board Review
Loews Chicago O'Hare
Rosemont, IL
www.acofp.org

August 28-31, 2015

KMA Annual Meeting
Hyatt Regency Louisville
Louisville, KY
www.kyma.org

September 18-20, 2015

OPSO Annual Primary Care CME
Downtown Portland Embassy Suites
Portland, OR
www.opso.org

October 17-21, 2015

OMED 2015: ACOFP/AOA's 121st Annual Osteopathic Medical Conference & Exhibition
Hyatt Hilton and Convention Center
Orlando, FL
www.acofp.org

November 5-8, 2015

WVOMA 113th Annual Fall CME Conference
The Greenbrier Resort
White Sulphur Springs, WV
www.wvoma.org

April 6-10, 2016

ACOFP Annual Convention & Scientific Seminars
Puerto Rico Convention Center
San Juan, Puerto Rico
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MARCH/APRIL 2015 ANSWERS: **1.** C **2.** B **3.** D **4.** A **5.** A **6.** B **7.** C **8.** B **9.** A **10.** A

TETANUS

Peter Zajac, D.O., FACOFP, AUTHOR
Ronald Januchowski, D.O., Health Literacy Editor

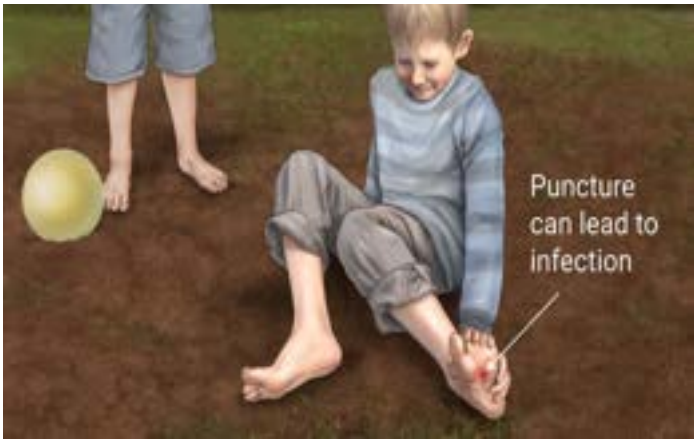
Tetanus, also known as lockjaw, is an infection caused by bacteria that live in the soil and usually enter the body through a break in the skin as a result of a cut, puncture wound, deep scrape or burn. The bacteria produce a poison that causes seizures. It also will cause severe muscle spasms making it hard to open the mouth and difficult to swallow and breathe. Tetanus can be very dangerous and lead to death. Symptoms of tetanus start 7-8 days after tetanus bacteria enter the body and may also include: stiff muscles in the neck, shoulder and back, muscle spasms in the chest, abdomen, arms and legs, fever, sweating, high blood pressure, and an irregular heartbeat. Tetanus is diagnosed based on these symptoms and a good history and physical exam. Individuals who have tetanus usually need to be treated in a hospital. Recovery can take up to several months. Immunization can prevent almost all cases of tetanus.

PREVENTING TETANUS INFECTIONS:

A Primary Vaccination Series (DTaP):

- First shot: age 2 months
- Second shot: age 4 months
- Third shot: age 6 months
- Fourth shot: age 15 to 18 months
- Fifth shot: age 4 to 6 years

After the above is complete, a child should receive a tetanus booster between the ages of 11 and 12 years. After the age of 12, a tetanus booster shot usually is recommended every 10 years.



- All women of childbearing age should be immunized against tetanus. Newborns rely on their mother's tetanus immunity to protect themselves from tetanus until their own shots begin.

- Any wound should be cleaned thoroughly as soon as possible, especially if it is contaminated with dirt to reduce the risk of infection with the bacteria that cause tetanus.

MEDICAL CARE AND TREATMENT OPTIONS:

Call your family doctor immediately for any deep cut, puncture in the skin or any wound contaminated by dirt, manure, sewage, or flood water. If you are an adult, please check your shot records for the date of your last tetanus shot. If you are a parent, be sure your child's shots are all up-to-date. If you have any questions about tetanus immunization(s) please contact your Osteopathic Family Doctor.

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Source(s): Tetanus.gov, Up-To-Date, and Web MD.

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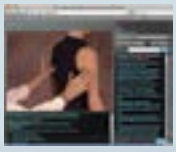

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