

STATE OF INDIANA)	IN THE PULASKI CIRCUIT COURT
)	
COUNTY OF PULASKI)	
State of Indiana)	
v.)	Cause No. 66C01-0704-FB-00004
Lynnette Finnegan)	
State of Indiana)	
v.)	Cause No. 66C01-0704-FB-00002
Roman Finnegan)	
In the Matter of)	
Tabitha Abair)	Cause No. 66C01-0611-JC-0121
In the Matter of)	
Katelynn Salyer)	Cause No. 66C01-0611-JC-0122

Declaration of Edith Nutescu

1. My name is Edith Nutescu. I am the Director of the Antithrombosis Center, a member of the Affiliate Faculty at the Center for Pharmacoeconomic Research, and a Clinical Associate Professor in the Department of Pharmacy Practice at the College of Pharmacy, University of Illinois at Chicago. My publications include several textbook chapters, 48 articles in refereed journals, and numerous invited presentations, primarily on anticoagulants, including warfarin. My curriculum vita is attached.

2. I have been asked to comment on the pharmacy records of Jessica Salyer and to provide background information on anticoagulation, particularly warfarin, to the Court.

3. I have reviewed the pharmacy printout from Fagen Pharmacy, Francesville IN, covering prescriptions filled at the pharmacy from June 18 to December 14, 2005, as well as prescriptions written by Dr. Bartush on October 12, 2005. I have also reviewed a printout showing an INR of 1.18 on September 14, a letter from Dr. Roger Hurwitz to Dr. Joseph Bartush dated September 16, 2005, a printout showing an INR of 1.7 on October 4, and lab results showing a post-mortem warfarin level of 3.07 mcg/mL. It is my understanding that the September and October INRs were the only INRs taken between June and December 2005.

4. Dr. Hurwitz' September 16, 2005 letter to Dr. Bartush indicates that Jessica was a 14 year old post-Fontan patient who was known to have seizures and whose medications included Coumadin (generic warfarin), Dilantin (generic phenytoin) and digoxin (brand name Digitek). His evaluation indicates that she was doing "quite well" with perhaps very mild mitral regurgitation and small VSD. Since her INR was only 1.2, he increased her Coumadin dose to 3 mg daily, with a target INR of approximately 2. He asked for

INR testing in about 2-3 weeks but did not request or recommend that additional INRs be taken.

5. The pharmacy records indicate that the following prescriptions were filled for Jessica at the Fagan Pharmacy between June 18 and December 14, 2005:

- 0.125 mg Digitek (for heart), 100 mg phenytoin (for seizures) and 2.5 mg warfarin (for anticoagulation) on June 18, July 20 and Sept. 2 (Drs. Wetzel and Bartush);
- 3 mg warfarin on September 16 (Dr. Hurwitz);
- mupirocin ointment on Oct. 3 (Dr. Travers);
- 0.125 mg Digitek and 2 mg and 5 mg warfarin on Oct. 13 and Nov. 18 (Dr. Bartush), with no prescriptions noted for phenytoin;
- nystatin oral suspension on Dec. 14 (Dr. Bartush).

6. It is my further understanding that Jessica received vaccinations on December 5, 2005; became ill with flu-like symptoms on December 6; was treated for flu, vomiting and possible thrush by Dr. Bartush on December 13; began her first period and had cramping, backache, nausea and some lip/tongue bleeding from December 13-19; and had a headache on the night of December 19, for which she took a children's pain reliever. She was found dead by the side of her bed on December 20.

7. It is my understanding that the autopsy revealed no external bruising other than a large bruise on the right knee and a possible light bruise or contusion on the left forehead; a small skull fracture; and internal bleeding in many parts of the body, including the brain and abdomen.

8. The increase in warfarin dose from 3mg to 7 mg daily shown in Fagen Pharmacy records is outside the bounds of acceptable medical practice and would have placed Jessica at a high risk of potentially fatal internal bleeding. The internal bleeding in many parts of the body found at autopsy is characteristic of death from over-anticoagulation.

Warfarin guidelines

9. Warfarin (also sold under the brand name Coumadin) is an anticoagulant that slows blood clotting and thus helps prevent strokes and other adverse cardiovascular events. The major side effect of warfarin is internal bleeding, which may occur in any body organ or tissue. Because anticoagulants carry significant risks as well as benefits, they are subject to professional guidelines and recommendations.

10. The professional guidelines and recommendations for anticoagulant therapy are published in CHEST, The Cardiopulmonary and Critical Care Journal of the American College of Chest Physicians. The most recent guidelines are entitled The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines and were published in September 2004 ("*Chest*"). A new edition will be published in 2008.

11. I have attached two chapters from the *Chest* guidelines that are most relevant to warfarin therapy. These are: The Pharmacology and Management of the Vitamin K Antagonists, Ansell *et al* (*Chest* at 204-233) and Hemorrhagic Complications of Anticoagulant Treatment, Levine *et al* (*Id.* at 287-310).

Risk of bleeding

12. The relationship between warfarin therapy and major or fatal internal hemorrhage is well-established. *Chest* at 209 (bleeding is the most feared and major complication of oral anticoagulant therapy). A major risk of warfarin therapy is intracranial hemorrhage, *i.e.*, bleeding in the brain, which is always viewed as major and is often fatal. *Id.* at 216 (intracranial bleeds generally fatal or life-threatening).

13. Because of the risk of bleeding, warfarin has carried a “black box” warning, the highest alert from the Food and Drug Administration, since October 2006. This warning states:

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR > 4.0), age \geq 65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**), and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS: Information for Patients**).

14. While the risk of major or fatal hemorrhage increases with the dosage and/or the intensity of the anticoagulation, major or fatal bleeding may occur even at relatively low warfarin doses. In addition to dosage and intensity of anticoagulant effect, the risk of fatal bleeding in warfarin patients may be increased by illness, drug interactions, dietary changes, and underlying medical conditions. In Jessica’s case, these factors would have increased the risk of internal bleeding, with a fatal outcome, in the days prior to death.

Warfarin doses and interactions

15. Warfarin is difficult to prescribe because it has a very narrow therapeutic window and individual patients react very differently to particular doses and/or levels of warfarin in the blood. Thus, a dose that may be therapeutic or produce relatively little change in blood clotting for one person may be fatal for another. Genetic differences alone may

account for a 5 to 20-fold variation in the doses required to achieve a desired anticoagulant effect. *Chest* at 205.

16. The bleeding risks of a person on warfarin may vary significantly even if the warfarin dose is unchanged and the patient has been stable for an extended period of time. These variations are due to environmental factors, such as drugs, diet and various disease states. *Chest* at 206.

17. Warfarin has more known interactions with other drugs than any other drug on the market. For example, even low doses of aspirin combined with low or moderate intensity anticoagulation therapy are associated with increased rates of bleeding. *Chest* at 207, 289. Fungicides also increase the impact of warfarin, while Dilantin may either increase or decrease the impact. Because of these interactions, any changes in medications must be carefully monitored and their impact on anticoagulant control (INR level) frequently evaluated. *Id.* at 206-207.

18. Dietary changes and illness have also been well documented to interact with and affect the anticoagulant effect of warfarin. For example, increased Vitamin K consumption (e.g., broccoli, spinach, etc.) decreases the anticoagulant effect of warfarin, while acute illness (e.g. fever, vomiting, diarrhea) increases the anticoagulant effect. *Id.* at 207-208 (healthy and sick patients on long-term warfarin therapy sensitive to fluctuating levels of dietary Vitamin K; fever increases warfarin responsiveness).

INR testing.

19. Because warfarin is a dangerous medication and the anticoagulant effect to specific doses vary widely from patient to patient, it is critical to monitor its anticoagulant effect in all patients taking the drug. The recommended international standardized laboratory test used to measure the anticoagulant effect of warfarin is the INR, or international normalized ratio. This standardized measurement was created to eliminate the impact of variances between labs found in the more traditional clotting tests (specifically, prothrombin time or PT measurements). While the INR is a better test, it has some potential problems and is not always dispositive. *Chest* at 208-209.

20. The INR is determined by dividing the patient's prothrombin time by the mean *normal* prothrombin time (i.e., the mean prothrombin times of healthy control subjects using the same methodology). By definition, a normal INR is 1. For therapeutic purposes, prescribing physicians often aim for an INR of 2 to 4, depending on the condition that is being treated. Targeted INRs of 2.5 (range 2.0 to 3.0) are associated with lower risk of bleeding than therapy targeted at an INR > 3 (*Chest* at 287), with several studies showing a steep increase in hemorrhagic events as the INR increases above 5. *Id.* at 216.

21. It is important to take frequent (often daily) INRs when warfarin is first prescribed because of its unpredictable impact (dose-response) and the possibility that it may unmask or trigger underlying conditions, such as ulcers. While the risk of internal

bleeding is highest in the first month, warfarin can cause internal bleeding at any time, particularly if there are changes in diet, health, other medications or dose causing excessive anticoagulant effect. This risk increases with time. *Chest* at 216.

22. A major obstacle to the safety and effectiveness of warfarin therapy is poor quality dose management. *Chest* at 222. The accuracy of physicians' estimates of risk for anticoagulant-related bleeding is particularly inaccurate in long-term outpatient therapy. *Id.* at 291.

23. To maintain patients in a therapeutic range, the health care provider must have a solid understanding of the influence of physiologic and pharmacologic factors affecting the impact of warfarin, including interacting drugs or illnesses; dietary or GI factors that affect the availability of Vitamin K1; and physiologic factors that affect the vitamin K-dependent coagulation factors. To make appropriate dosage and follow-up decisions, the health-care provider must also have an organized system of follow-up with reliable PT/INR monitoring and good patient communication and education. *Chest* at 210.

24. Once the INR is stable and a maintenance warfarin dose has been determined, the professional guidelines recommend that physicians take monthly INRs. *Chest* at 212, 224. When doses are adjusted, more frequent monitoring should be done until a stable response is achieved. *Id.* at 212. More frequent long-term monitoring may be needed for particular patients, including those with variable INRs.

25. The professional guidelines strongly recommend that physicians who manage anticoagulation therapy do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions. *Id.* at 225. This recommendation is a Grade I recommendation, *i.e.*, the strongest level of recommendation based on available evidence. *Id.* at 204.

Fontan procedure

31. Given the dangers of warfarin, there is presently considerable controversy over whether it is preferable to prescribe warfarin or aspirin following the Fontan procedure. The data on this issue is very limited and at best controversial. Most pediatric cardiologists prescribe warfarin since its anticoagulation effects are well-established for other indications, but others prefer aspirin since warfarin presents a higher risk of internal bleeding.

32. Given the limited data on the risks and benefits of warfarin in post-Fontan patients, there is no clear-cut target INR documented in professional guidelines for Fontan patients. However, many pediatric cardiologists aim for a target INR of 2, with a desired range of approximately 1.8 to 2.2. Since the use of warfarin for Fontan patients is purely precautionary, a lower target range may also be acceptable.

33. Dr. Hurwitz' September 15, 2005 letter suggests that he was prescribing warfarin for Jessica as a precautionary (prophylactic) measure rather than to address specific clotting problems. He was therefore prescribing a relatively low dose (2.5 mg, increased to 3 mg daily), aiming for an INR of 2. This is a fairly standard dosage and target for post-Fontan patients on warfarin

Bleeding risks and mortality

26. While warfarin saves lives by preventing blood clots and strokes, it carries the risk of internal bleeding even at therapeutic doses. INRs in the range of 2-3 are associated with a lower risk of bleeding than therapy targeted at an INR >3.0. *Chest* at 209, 287. The addition of aspirin is associated with a higher frequency of bleeding even with relatively low INRs (e.g., mean INRs of 1.5). *Id.* at 289. The risk of fatal bleeding is higher in patients with underlying heart conditions or predisposition to stroke. *See Chest* at 294-295, Tables 3-5.

27. The guidelines summarize some of the major studies on major and/or fatal hemorrhage in patients managed under an anticoagulation management service (AMS) and by family physicians ("UC," or "usual care"). *Chest* at 220-221, Tables 10-12. These tables confirm that there is a significant risk of major or fatal bleeding even with careful monitoring by an anticoagulation clinic. *Id.* at 220, Table 11 (1.4-7.3% risk of major bleeding per patient-year and .14-.77% risk of fatal bleeding per patient-year when managed by anticoagulation management service).

28. The risk of major and/or fatal bleeding increases when the monitoring is done by a family physician, with four large retrospective studies finding a rate of major hemorrhage of approximately 6% per patient-year of therapy. *Chest* at 219, 221, Table 10 (5-7.4% risk of major bleeding of patient-year and .45-1.1% of fatal bleeding per patient-year when managed under "usual care" standards).

29. Fatal bleeding may be spontaneous, or may follow falls that would not normally present a significant health risk but that cause disproportionate bleeding in warfarin patients. Internal bleeding may also trigger underlying conditions, such as heart abnormalities, in which case the internal bleeding may be a trigger rather than the direct cause of death.

30. Internal bleeding from warfarin is particularly dangerous when it causes bleeding in the brain. *Any* bleeding in the brain is viewed as major and may be potentially fatal. The risk of intracerebral hemorrhage is directly correlated with the INR. *Chest* at 287 (intensity of anticoagulant effect probably most important risk factor for intracranial hemorrhage, with risk increasing with INRs of 4-5; in one study, risk of intracerebral hemorrhage doubled for each increase of approximately 1 in the INR).

Increases in dosage

34. Due to an unpredictable and non-linear dose-response of warfarin, dosage adjustments can be difficult. Even in stable patients, a very small increase in dose may trigger a large increase in the INR, greatly increasing the risk of internal bleeding. As a result, increases in dose must be monitored very closely. To lessen the risk of large INR changes and the risk of bleeding, warfarin doses should not be increased by more than 20% of the weekly dose. *Chest* at 213 (weekly cumulative dose usually increased by 10 – 20%, with more frequent monitoring until the INR is stable); Dose increases in excess of 20% of the weekly dose can lead to large and excessive INR increases, thus significantly increasing the patient’s risk of bleeding. *Chest* at 212 (patients whose INR is just outside the therapeutic range can be managed by adjusting the dose up or down in increments of 5-20% or by more frequent monitoring, with the expectation that the INR will return to therapeutic levels without a dosage change). Because warfarin is affected by so many interactions, some fluctuations in the INR are to be expected.

35. According to his September 16, 2005 letter, Dr. Hurwitz increased Jessica’s warfarin dose from 2.5 mg to 3 mg daily based on a relatively low (1.18) INR measurement. This was an increase of 20% of the weekly dose. On October 4, Jessica’s INR was 1.7, which was very close to her desired INR range.

36. Given this increase in Jessica’s INR, it is unclear whether any further adjustment would have been desirable, at least without further testing. Even if the dose were to be further increased, the *maximum* permissible increase would be to 3.6 mg a day, possibly with alternating doses of 3 and 4 mg daily. However, such an increase would require very careful monitoring since it might result in INRs well above the target range of 2.

37. The pharmacy records indicate that Jessica’s warfarin prescription was increased in mid-October from 3 mg to 5mg and 2 mg, for a total of 7 mg daily. (The fact that both tablet strengths were refilled one month later, indicates that she was compliant and likely taking both the 2mg and 5mg tablets) This would have increased her weekly dose from 21 mg to 49 mg, an increase of 133%. Since any increase in dose of more than 10-20% can lead to very large INR increases, greatly increasing the risk of bleeding, this would have been a very large overdose under current medical standards and would have greatly increased the likelihood of internal bleeding.

38. I am told that the State has indicated that the prescribing physician may have intended to increase the warfarin dose to 5 mg rather than 7 mg. An increase from 3 to 5 mg would have resulted in an increase of 66%, which is also in excess of the maximum increase recommended by current medical guidelines. This increase would require careful monitoring as it would greatly increase the risk of internal bleeding.

39. I do not know of any medical justification for an increase of this magnitude, especially in light of her INR of 1.7 on October 4th. Since this increase is not acceptable under the current anticoagulation practice guidelines, this increase appears to have resulted from prescription error.

INR monitoring

40. As indicated, to reduce the risks of bleeding, patients on warfarin should generally be monitored once a month, with more frequent monitoring when doses are adjusted (increased or decreased) or when there are changes in medical condition, medications or diet. *Chest* at 206 (more frequent monitoring recommended when virtually any drug is added or withdrawn). It is the responsibility of the prescribing physician to ensure that this monitoring is done and that the patient or, in the case of a child, the patient's parents are educated *and re-educated* on the risks and dangers of warfarin.

41. In our clinic, we schedule regular INR blood tests for warfarin patients and follow current practice guidelines for frequency of testing. In cases of missed appointments, patients receive a reminder call on the day of the missed appointment in an attempt to reschedule as soon as possible. If a patient misses three consecutive appointments, the prescription for warfarin is not renewed (until the patient comes in to be seen and INR tested) as the risk of complications to therapy (such as over-anticoagulation) outweigh the benefits of warfarin.

42. It is my understanding that the State is alleging that it was the responsibility of Jessica's parents to obtain INR tests. However, parents are not legally authorized to order blood tests, and it is unusual for them to have the medical training needed to determine the frequency of testing or interpret the results. For this reason, the physician who writes the prescriptions is responsible for monitoring and determining the appropriate frequency of the required blood tests. It is the patient's responsibility to fill the prescriptions and obtain the tests, including blood tests, ordered by his or her physicians, but it is the physician's responsibility to write appropriate prescriptions, order the appropriate tests, communicate with the patient on the necessity and timing of blood tests, and to follow up with the patients on the results and any necessary changes or adjustments to therapy.

Impact of increased warfarin dose on INR

43. Because patients respond very differently to increases in warfarin doses, it is not possible to determine Jessica's INR in the days or weeks before her death. Since, however, Jessica's INR increased from 1.18 on September 14 to 1.7 on October 4, 2005, following an increase from 2.5 to 3 mg of warfarin daily, we can say with some confidence that her INR would have been considerably in excess of 1.7 after the prescription increase and would likely have placed her at a high risk of major bleeding. Since warfarin does not follow a linear response to increases in dose and even a minute increase in dose may cause a very large increase in the INR, it is possible that Jessica's INR could have increased exponentially to 20, or even have been so high as to be unreadable, solely as a result of the prescription increase.

44. Jessica's INR and bleeding risk were likely further increased by other factors in the days and weeks before death. The removal of Dilantin may have increased or decreased the INR, depending on a variety of factors, while increasing the risk of seizure. Illness and the institution of a liquid diet (with elimination of high Vitamin K foods)

would have likely increased the INR. To determine the likely impact of the fungicide, I would need to know whether this medication was to be swallowed or swished and spit out. The use of a pain reliever the night before death would depend on whether the pain reliever was aspirin, acetaminophen or ibuprofen. Aspirin increases the risk of bleeding without affecting the INR. Acetaminophen has been associated with increased INR bleeding but the relationship is not yet established through randomized controlled studies. Ibuprofen is not generally linked with increased INRs, however concurrent use with warfarin can increase bleeding risk as it is a non-steroidal antiinflammatory agent that has an effect on platelet function. *Chest* at 206-207 (drug and food interactions); 290-291 (well-established increased risk of bleeding with aspirin; no randomized studies on acetaminophen or ibuprofen).

45. It also appears that Jessica was taking more than the recommended dose of warfarin for nearly two months before her death. Since the risk of bleeding increases with the anticoagulant effect, underlying patient characteristics and length of therapy (*Chest* at 303), the risk of major or fatal bleeding would have been increasing steadily during this period. When the INR increases to around 4, any trigger can cause a drastic and logarithmic increase in the INR. In Jessica's case, it is very likely that her INR was well above 4 as a result of the prescription increase and other factors.

46. I have been asked whether it is possible to determine Jessica's INR from the post-mortem warfarin level of 3.07 mcg/mL. This post-mortem test presumably reflected Jessica's last warfarin dose, which according to her mother was approximately 27-30 hours prior to death. Warfarin plasma concentrations have limited applicability to the optimization of warfarin therapy because there is no direct relationship between drug concentration and therapeutic effect. Warfarin plasma concentrations associated with therapeutic response and toxicity are poorly defined, these levels have limited clinical applicability to optimization of warfarin therapy and can only serve as a rough guide but can not be used a mandate to determine exact therapeutic effect. As the concentration of warfarin in the blood is poorly correlated with the INR and the half-life of warfarin is variable, with maximum concentration reportedly occurring 90 minutes after dosage and with a typical half-life of 36 to 42 hours. *Chest* at 205. Given these factors, it is likely that Jessica's warfarin level could have been considerably higher than 3.07 mcg/mL in the day before death. Since this is a relatively high level of warfarin, this suggests that Jessica's INR was likely well above her target INR and into a range that would have produced a high risk of major or fatal bleeding on the day before death.

47. I have also been told that Jessica's family noticed that she had a cut or sore on her lip and/or tongue that she bit repeatedly and that bled on and off for the week before her death. Continued bleeding from a relatively small cut or sore suggests a clotting abnormality and suggests that Jessica's INR was likely outside the therapeutic range in the week before death.

Bone density

48. I have been asked whether warfarin decreases bone density. It is well understood that warfarin interferes with the carboxylation of the proteins that are synthesized in bone, and some studies report decreased bone density in newborns whose mothers have taken warfarin during pregnancy. *Chest* at 205. There is also a body of literature suggesting that long-term warfarin use is correlated with osteoporosis in adults.

49. Since warfarin is not commonly used in children, there is very little data on the relationship between warfarin and bone density in children. Two relatively recent studies suggest that there may be a correlation between long-term warfarin use and reduced bone density in children. However, these relationships are not well-established.

Symptoms of over-anticoagulation

50. Because it is not possible to detect internal bleeding, warfarin deaths are often characterized by sudden collapse following an illness. Patients who are over-anticoagulated may be asymptomatic or have flu-like symptoms, *i.e.*, they may feel sick, dizzy or tired, and may have a headache or stomachache. These symptoms may be followed by death or cardiac arrest without further warning.

53. As this suggests, it is extremely difficult to detect the signs of over-anticoagulation or internal bleeding. When Jessica's prescription increased from 3 to 5 or 7 mg, one would not necessarily see any symptoms even though she would be at increased risk of internal bleeding. Triggering factors such as illness, other medications and dietary changes would then push the INR higher, causing noticeable illness. Since internal bleeding is not apparent, such illness may be attributed to the flu or, in Jessica's case, a first menstrual period. This is very characteristic of warfarin and is the primary reason that warfarin is such a dangerous drug.

54. Because what appears to be a minor illness is often the only sign of over-anticoagulation and internal bleeding, it is important for physicians to take INRs whenever a patient presents with generalized flu symptoms. In my opinion, an INR should have been taken on December 6th, when Jessica presented to the Pulaski County Health Department with flu-like symptoms following vaccination, and on December 13th, when Jessica went to the family doctor for flu-like symptoms and what was diagnosed as dermal erosions on the tongue.

55. As indicated, it is very likely that INR testing on December 6th or 13th would have revealed an INR well over the recommended range. A CT scan may also have revealed internal bleeding. Recommended treatment of elevated INRs without significant bleeding includes omission of doses and oral administration of vitamin K1. Elevated INRs with serious bleeding are treated with vitamin K1 by IV infusion supplemented with fresh plasma, prothrombin complex concentrate or recombinant factor VIIa, depending on the urgency of the situation. *Chest* at 213-214, 224.

Bruising

56. Since warfarin causes increased bruising as well as bleeding, it is common for warfarin patients to have multiple bruises from everyday events. In an over-anticoagulated patient, even small bumps are likely to cause significant bruising.

57. I have briefly reviewed a set of post-mortem photographs of Jessica. These photographs show a bruise on the right knee, typical of bruising from a fall or surface-contact in a warfarin patient, and possibly a light bruise on the left forehead. I did not see any other bruises.

58. In my opinion, the absence of bruising precludes the possibility that Jessica's internal bleeding was caused by a beating or other external forces. In a warfarin patient, it would be extremely difficult, if not impossible, to cause internal bleeding without obvious external bruising.

Coordination of care

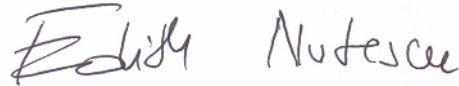
59. Since warfarin carries the risk of fatal bleeding and interacts with many other drugs and medical conditions, it is very important to coordinate the care of a warfarin patient. This responsibility rests on the prescribing physicians, who are responsible for monitoring the INRs and guarding against interactions with other drugs or conditions that might increase the INR. Clinical care should include patient education, systematic INR testing, tracking and follow-up, and good communication with patients on results and dosing decisions. *Chest* at 204, 225.

60. When patients have been stable for long periods, there is a tendency to develop a higher comfort level with warfarin use. Since, however, the risk of internal bleeding may change dramatically even when warfarin doses are unchanged, it is critical to take INRs whenever a patient presents with illness, fever, diarrhea, vomiting, changes in medication, or dietary changes.

61. Even if a warfarin patient has been stable for an extended period, it is also critical to have a very clear follow-up plan, with clear directions to the patient or the patient's parents. Jessica's medical records suggest a lack of coordination between her physicians, resulting in an almost complete system failure. Several failures are obvious. First, the prescribing physicians are responsible for ordering monthly INRs and ensuring that they are taken. Such orders should be written in prescription form and recorded in the patient's chart. If the patient or the patient's parents do not comply with these orders, the physician should not refill the prescription as the risk of therapy may outweigh the benefit. Second, the treating physicians are responsible for taking INRs when the patient presents with illness or other conditions that might increase the effect of warfarin. Third, it is the physician's responsibility to educate *and re-educate* patients or the patient's parents on the dangers of warfarin. Fourth, when care is shared between physicians, the physicians are responsible for coordinating the patient's care, including the scheduling of INRs. In this case, it appears that none of these steps were taken.

I hereby affirm under penalties of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Signed this 29 day of May 2007 .

A handwritten signature in black ink that reads "Edith Nutescu". The signature is written in a cursive style with a horizontal line above the first name.

Edith Nutescu, Director
Antithrombosis Center
University of Illinois at Chicago Medical Center