

status are also unfavorable for NMSCT.^{8,15,20} It remains open whether better results would be achievable in younger patients with earlier stage of disease. We, therefore, support the final statement by Martino *et al.* that, at present, NMSCT should only be offered in patients with a high risk of TRM and within the context of clinical trials. It is still no alternative to conventional SCT in younger patients with ALL.

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Economy-class syndrome: media hype or real risk?

Venous thromboembolism (VTE) is a multifactorial disease resulting from the interaction between genetic and environmental risk factors. The former include abnormalities causing inherited thrombophilia, such as deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, protein S, and the gain-of-function mutations in genes encoding coagulation factor V (factor V Leiden) and prothrombin. The environmental, transient risk factors associated with an increased risk of VTE are cancer, recent surgery, pregnancy and puerperium, use of oral contraceptives and prolonged immobilization. For many decades, flights have been considered a risk factor for VTE. Recently, the interest in this topic increased both in the lay and medical press because of the death from pulmonary embolism of a 27-year old woman at the arrival hall in Heathrow airport (London) after a 20-hour flight from Australia.¹

In 1946, Homans first referred to flights as a possible risk factor for VTE reporting an episode of venous thrombosis in a doctor after a 14-hour flight.² The most important pathogenic mechanism for VTE during air travel is stasis in the lower limbs. During the London Blitz in the Second World War it was observed that the incidence of fatal pulmonary

embolism was increased 6-fold. The main reason for this was that the mechanical impairment of venous circulation, due to squatting for a prolonged period in air raid shelters, promoted formation of venous thrombosis in the lower limbs and therefore pulmonary embolism.³ In 1977, Symington and Stack used, for the first time, the term *economy-class syndrome*, underlying the pathogenic role of stasis during long flights in restricted seats, such as those of the economy class.⁴ In 1986, Sarvesvaran observed that 18% of 61 cases of sudden death occurring in the arrival hall were attributable to pulmonary embolism, compared to 3.5% of 28 cases of sudden death which occurred in the departure hall of Heathrow airport in London during a three-year period.⁵ Although various case reports⁶ and some retrospective observations^{7,8} became available following Homans' observation of a patient with deep-vein thrombosis after an airflight, we had to wait until 1999 for studies estimating the risk of VTE related to air travel. Three case-control studies on this topic appeared in the literature, giving conflicting results. Two French studies found a positive association between VTE and long-haul flights.^{9,10} In particular, Ferrari *et al.*,⁹ in 160 consecutive patients with deep-vein thrombosis and 160 healthy controls, estimated a relative risk of 4 for any travel (car, train or flight). In contrast, a Dutch study¹¹ failed to confirm such findings; only 17 out of 788 (2%) individuals with VTE had taken a flight before the event. However, these studies had some limitations that need to be discussed. The two French, positive studies^{9,10} analyzed the different types of transport together without dividing air travel from travel by car or train. Moreover, both of them suffered from referral bias and in one study⁹ the control group was inappropriately selected. In contrast, the referral bias was limited in the Dutch study,¹¹ since cases and controls were individuals consecutively referred to a hospital for a suspected deep-vein thrombosis and in whom objective techniques had confirmed (cases) or did not confirm (controls) the presence of the disease. Despite the large sample size, the study did not show an association between air travel and deep-vein thrombosis. Unfortunately, one problem of this study was that only 4 cases (2%) and 13 controls (2%) had been exposed to the factor of interest (air travel) in the month preceding symptoms.

Recently, an observational study, carried out over a ten-year period at the arrival hall of the Charles de Gaulle airport in Paris, showed a strong association between flights, in particular long-haul flights of more than 8 hours, and symptomatic, non-fatal pulmonary embolism.¹² Following this observation, several companies advised people to follow simple measures during flight, such as to drink water, avoid alcohol consumption, sedative drugs and crossing legs, use comfortable clothes, and move leg muscles by walking the aisle or doing mild exercise. In fact,

besides stasis, hemoconcentration due to a low intake of water, to the diuretic effect of alcohol, and perspiration in the dry atmosphere in the cabin, and lower limb muscle areflexia due to sedative drugs are possible pathogenic factors for VTE. It has been recently observed that the relative hypoxia and low pressure in a flight cabin can also contribute to the occurrence of VTE through activation of the coagulation cascade.¹³

To date, few and inconclusive data are available on the interaction between air travel and thrombophilia. A small, uncontrolled retrospective study¹⁴ on 20 patients with VTE after air travel showed the presence of thrombophilia in 6 of them (30%), previous thrombotic events in 4 (20%), other risk factors such as oral contraceptives, cancer or plaster casts on a leg in 10 (50%), whereas in the remaining 5 (25%) no risk factors were identified. Another study,¹⁵ on 16 patients with a deep- or superficial-vein thrombosis after long-haul flights, showed the presence of factor V Leiden or the prothrombin mutation in 3 cases. However, all the patients with deep-vein thrombosis had thrombosis in the veins of the calf diagnosed with ultrasonography, which is an inaccurate technique for diagnosing distal thrombosis.¹⁶ Therefore, the possibility of misdiagnosis in this study cannot be ruled out.

In order to establish whether or not air travel is a risk factor for VTE and to investigate the interaction between air travel and thrombophilia or the use of oral contraceptives, we carried out a case-control study on 210 patients with proximal, objectively documented deep-vein thrombosis of the lower limbs with or without pulmonary embolism, and 210 healthy controls.¹⁷ Thirty-one patients (15%) and 16 controls (8%) had flown in the month preceding the event (cases) or the visit (controls), for an odds ratio of 2.1 (95% CI 1.1-4.0). Three-quarters of the cases and controls had made short flights (less than 8 hours) and in the economy class. The odds ratio for VTE was slightly higher (3-fold) for long-haul flights (more than 8 hours). Thrombophilia was found in 49% of patients and 12% of the controls, and oral contraceptives were used by 61% of women in fertile age in patients and in 27% of the corresponding controls. After stratification for the presence of air travel and thrombophilia, considering as the referral group individuals who did not fly and did not have thrombophilia, the risk for VTE was 6 times higher in the presence of thrombophilia, 2 times higher in the presence of air travel, and 16 times higher in the presence of both risk factors. Similarly, when stratification was done according to the presence of air travel and oral contraceptive use, considering as the referral group women who did not fly and were not taking oral contraceptives, the risk for VTE was 4 times higher in oral contraceptive users, 2 times higher in those who flew and 14 times higher in the presence of both risk factors. This study

demonstrates that air travel is a minor risk factor for VTE, being associated with a 2-fold increase of thrombotic risk. The risk for VTE is greatly increased in the presence of thrombophilia or oral contraceptive use, indicating a multiplicative interaction between these risk factors and air travel.

Whether or not simple measures such as walking in the aisle, drinking water, avoiding alcohol, might be sufficient to prevent VTE, even during short flights, in high risk subgroups of individuals, such as those with known thrombophilia or oral contraceptive users, remains to be established. Only one randomized trial is available on the efficacy of prophylaxis with drugs in high risk individuals. This trial showed that a single dose of low-molecular weight heparin before a flight was more effective than aspirin in preventing venous thrombosis.¹⁸ The use of elastic stockings was also effective in reducing the risk of VTE in high risk individuals.¹⁹ Thus, specifically tailored studies are needed to establish which type of prophylaxis (heparin, elastic stockings or other) should be suggested before taking a flight to individuals with thrombophilia or to women who use oral contraceptives.

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