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Committee to Advise on Travel and Tropical Medicine (CATMAT)*

TRAVEL MEDICINE RECOMMENDATION: DENGUE FEVER AND INTERNATIONAL TRAVEL

The incidence of dengue fever, a mosquito-transmitted disease, is rising in areas frequented by Canadian tourists. A marked increase in cases has been observed over the past decade, especially in tropical and subtropical areas of Central and South America. This increased activity has recently been associated with the re-emergence of one type of the virus that has not been observed in Central America for some time[1].

Dengue fever is an acute febrile illness, associated with myalgias, arthralgias, headache, and skin rash. It is caused by one of four serotypes of the dengue virus. The disease is distributed throughout the tropical and subtropical areas of the globe and has been reported in over 100 countries[1] (see Table 1); worldwide, there may be up to 2 billion people at risk[2]. All four of the dengue virus serotypes are circulating in Asia, Africa, and the Americas. The incidence of dengue has increased markedly in Central and South America and areas of the Caribbean since 1980[2].

Dengue fever is commonly spread by urban mosquitoes of the *Aedes* genus, and one of the most common vectors, *Aedes aegypti*, lives in close proximity to man. Increases in prevalence are believed to be related to increasing urbanization and other social factors that favour increased mosquito reproduction[3].

* **Members**: Dr. W. Bowie; Dr. L. S. Gagnon; Dr. S. Houston; Dr. K. Kain; Dr. D. MacPherson (Chairman); Dr. V. Marchessault; Dr. H. Onyett; Dr. R. Saginur; Dr. D. Scheifele (NACI): Dr . F. Stratton; Mrs. R. Wilson (CUSO).

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While the disease is often mild and self-limiting, it may present in a severe form associated with hemorrhagic complications, shock, and, in some cases, death. This severe form, called dengue hemorrhagic fever (DHF), may be associated with certain strains of the virus or may be related to the age or immune status of the individual infected. DHF is more common in people less than 15 years of age and in people having their second infection[4].

Although dengue fever has been reported in some international travellers, in general there is a low risk of DHF in tourists returning to the developed world[5,6].

Prevention is key, because there is no specific therapy for dengue fever. International travellers to areas endemic for dengue fever should use personal measures to avoid the day-biting *Aedes* mosquitoes. These precautions should be added to their efforts to avoid the night-biting *Anopheles* mosquito responsible for malaria.

Personal Measures to Avoid Mosquitoes

All travellers to areas endemic for dengue fever are advised to use personal insect protective measures to reduce the risk of day-biting mosquitoes.

Any measure that reduces exposure to the daytime-feeding female *Aedes* mosquito will also reduce the risk of acquiring dengue fever: remaining in well-screened or completely enclosed air-conditioned areas, and wearing clothing that reduces the amount of exposed skin.

In addition, the use of insect repellent on exposed skin is recommended. Insect repellents containing N,N diethyl-methyltoluamide (DEET) are the most effective. The concentration

Table 1
Global Distribution of Dengue Fever

Risk of Epidemic Dengue		
AMERICAS		
Anguilla	French Guiana	St. Lucia
Antigua & Barbuda	Grenada	St. Martin
Argentina	Guadeloupe	St. Vincent
Aruba	Jamaica*	Suriname
Bahamas	Martinique	Trinidad & Tobago
Barbados	Montserrat	United States
British Virgin Islands	Netherlands Antilles	Virgin Islands
Dominica	St. Kitts & Nevis	
AFRICA		
Benin	Ghana	Seychelles
Botswana	Guinea	Sierra Leone
Burundi	Guinea-Bissau	Somalia
Cameroon	Kenya	Sudan
Central African Republic	Liberia	Tanzania
Congo	Madagascar	Togo
Ethiopia	Malawi	Uganda
Equatorial Guinea	Mauritius	Zambia
Gabon	Rwanda	Zimbabwe
Gambia	Senegal	
ASIA		
China*	Papua New Guinea	
OCEANIA		
Solomon Islands		

Recent Dengue Activity		
AMERICAS		
Belize	Dominican Republic	Nicaragua
Bolivia	Ecuador*	Panama*
Brazil*	Guatemala*	Paraguay
Colombia*	Guyana	Puerto Rico
Costa Rica*	Haiti*	Venezuela*
Cuba*	Mexico*	
AFRICA		
Angola	Ivory Coast	Nigeria
Burkina Faso	Mozambique	
ASIA		
Bangladesh	Laos*	Singapore*
Brunei	Malaysia*	Sri Lanka*
India*	Maldives*	Taiwan
Indonesia*	Myanmar	Thailand*
Kampuchea*	Philippines*	Vietnam*
MIDDLE EAST		
Saudi Arabia		
OCEANIA		
Australia*	New Caledonia	Tahiti
Cook Islands	Palau	Tonga
Fiji	Samoa	Vanuata
Kiribati*		

* indicates countries that have experienced DHF outbreaks

Sources

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3. Wilson ME. *A world guide to infections.* New York: Oxford University Press, 1991.
4. PAHO. Press releases. 1995.

of DEET varies from product to product, and the higher concentrations protect for longer periods of time. In rare instances, application of insect repellents with high concentrations (> 35%) of DEET has been associated with seizures in young children; therefore, DEET should be applied sparingly to exposed surfaces only and washed off after the person comes indoors. Thirty-five per cent DEET protects for 4 to 6 hours, whereas 95% DEET protects for 10 to 12 hours. New formulations of DEET are available containing a lower concentration but protecting for longer periods.

There are currently no vaccines for preventing the acquisition of dengue fever.

Medical Intervention

Fever that develops within 2 weeks of leaving a dengue-endemic area should be reported to a physician and the returned traveller should advise the physician of recent travel to tropical regions.

Any fever that is associated with skin rash, bleeding, easy bruising, or other hemorrhagic phenomena, particularly in children, should be immediately brought to the attention of a physician.

In Canada, laboratory investigation of suspected dengue fever may be undertaken at ***Zoonotic Diseases, National Laboratory for Special Pathogens, Bureau of Microbiology, LCDC, Tunney's Pasture, Ottawa, Ontario, K1A 0L2 [Tel: 613-954-0757, Fax: 613-954-0207]*** and the ***Vector-Borne and Special Pathogens Unit,***

Laboratory Services Branch, Ontario Ministry of Health, 81 Resources Road, Etobicoke, Ontario, M9P 3R1 [Tel: 416-235-5766 (5734), Fax: 416-235-5867].

Given current patterns of dengue transmission, there are no indications to suggest that routine travel to areas where dengue is reported should be avoided, providing that travellers adhere to the insect barrier precautions noted above.

More information on specific countries reporting cases of dengue fever can be obtained from the Laboratory Centre for Disease Control's FAX*link* service by dialing 613-941-3900 from a fax phone.

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International Notes

DENGUE IN THE AMERICAS

The number of cases of dengue and dengue hemorrhagic fever continues to rise, and the epidemic is extending to new areas in the Americas. As of 15 November, 1995, over 200,000 cases of dengue and more than 5,500 cases of dengue hemorrhagic fever had been reported to the WHO Regional Office for the Americas/Pan American Health Organization (AMRO/PAHO).

Source: *WHO Weekly Epidemiological Record, Vol 70, No 47, 1995.*

Infection Control

PRELIMINARY REPORT: BIOSAFETY ANALYSIS OF ONE-WAY BACKFLOW VALVES FOR MULTIPLE PATIENT USE OF LOW OSMOLAR INTRAVENOUS CONTRAST SOLUTION

Low osmolar intravenous contrast solutions are widely used in hospitals for radiologic diagnostic studies, such as computed tomography scanning of the head, neck, thorax, and abdomen as well as angiography and venography. Owing to the relatively large volume and high cost of the intravenous solutions, multiple patient infusion of contrast from a single infusion bag has been proposed. Faced with budgetary restraints and increasing demand for radiologic and angiographic studies, many institutions have implemented this practice in their radiology departments.

A potential problem associated with multiple patient dosing from a single infusion bag is the risk of transmission of blood and bloodborne pathogens, such as hepatitis B, hepatitis C, human immunodeficiency virus, and other viral agents from one patient to the next during the diagnostic studies[1,2]. To prevent backflow of blood and avoid the potential transmission of bloodborne pathogens, some institutions have implemented the use of one-way backflow valves for multiple patient dosing. However, there are few published studies to support the integrity of a one-way backflow valve in preventing the contamination of the contrast solution. An advisory notice issued in August, 1994, by the National Steering Committee on Infection Control Guidelines Development, Laboratory Centre for Disease Control, Health Canada, advised against the use of intravenous contrast solution with more than one patient[3].

Given this background, we designed a three-pronged, multidisciplinary study to assess the integrity of one-way valves in the prevention of backflow of potentially blood-contaminated or body fluid-contaminated solution into sterile multi-use intravenous contrast solution used during radiologic and angiographic studies.

Methods

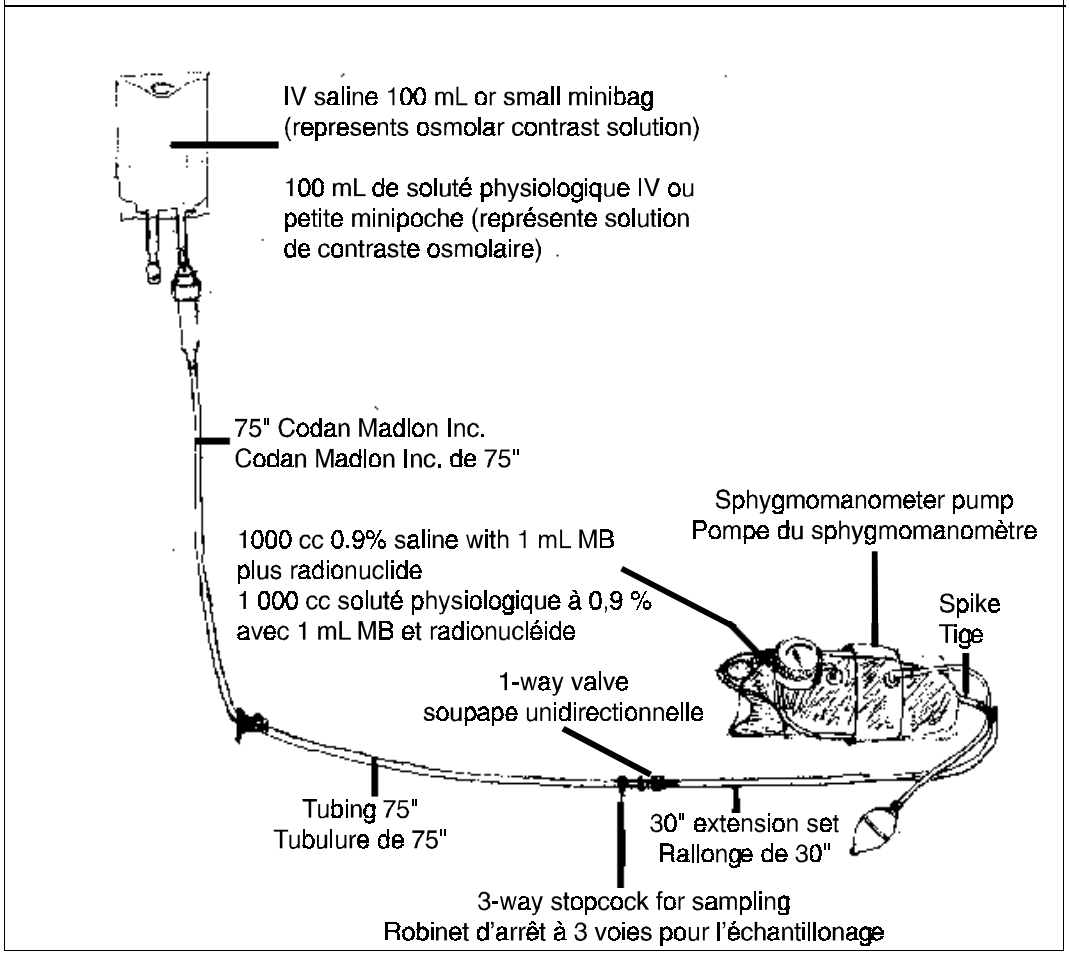
Several one-way valves designed to protect the integrity of an infusion delivery system are available in Canada. In general, these one-way valves are check valves, which provide flow in a forward direction with no backflow leakage. Backflow valves from Medex Inc. (Hilliard, Ohio, USA), Merit Medical System (Salt Lake City, Utah, USA), and Namic (Namic Contrast Saving Delivery System, Glenn Falls, New York, USA) were obtained for the testing procedures. Valves from different lots were used in an effort to assess lot-to-lot production variability.

A series of test procedures were performed to assess the structural, functional, and biologic characteristics of the check valves. A three-part test protocol was developed by the Department of Medical Engineering at The Toronto Hospital and included a valve characteristics test, a static back pressure test, and a clinical simulation test (see Figure 1). Briefly, the valve characteristics test consisted of the determination of the forward operation of the valve. Pressure data for this and subsequent procedures were recorded using Biotek (Winooski, Vermont, USA) DPM III gauges with analog output sent to a personal computer for storage and subsequent analysis. The static back pressure test assessed the performance characteristics of the valve with various amounts of pressure applied against it. A syringe pump was used to supply a short-term pressure for 15 seconds simulating actual duration in clinical settings and a long-term test of 60 minutes to assess durability. A supraphysiologic pressure of 60 pounds per square inch (psi), equivalent to approximately 3,000 mm Hg, was chosen for this test. Each side of the valve was monitored for pressure profile changes during the period of application of the pressure. The clinical simulation test was conducted using the standard

injection delivery system (Liebel-Flarsheim Company, Cincinnati, Ohio, USA) used in our Department of Radiology pressure tests to validate the presence of an active radionuclide during the entire period of the experiments.

Biologic testing of the check valves was performed using a staphylococcal bacteriophage (Group II, phage 55) as a human viral surrogate marker. This bacteriophage and the strain of *Staphylococcus aureus* (phage-propagating strain 3C) were obtained from the Reference Bacteriology Laboratory, Laboratory Services Branch, Ontario Ministry of Health, Toronto, Ontario (courtesy of A. Borczyk). This bacteriophage represents a medium-size virus particle that serves as a surrogate to such human pathogenic viruses as members of the herpes virus family or the human immunodeficiency virus type 1 (HIV-1), which might potentially be transmitted through blood or body fluids in a multiple-patient intravenous delivery system. The bacteriophage was prepared using a broth method according to a procedure obtained from the Laboratory Services Branch of the Ontario Ministry of Health (A. Borczyk: personal communication, 1995). A final working titre of the bacteriophage of 8.0×10^{10} plaque- forming units/mL was subsequently injected into a one-litre bag of normal saline to be used in the one-way valve experiments.

Figure 1
Study Apparatus to Assess the Integrity of One-Way Valves



The same experimental design as described for the radionuclide experiments was employed for the bacteriophage. Aliquots of 1 mL were obtained from the three-way stopcock just proximal to the one-way valve after each of three 1-minute pressure tests, as described previously. Positive control samples were obtained before and after all the pressure challenge experiments to ensure viability of the bacteriophage throughout the entire period of the testing. Twenty µL aliquots of the 1 mL fluid samples were dropped onto a propagating lawn of the fresh *S. aureus* strain (tryptic soy agar), and the plates were then read for lysis after an overnight incubation at 36° C.

Results

Three Medex valves from each of 10 separate lot numbers and three Merit valves from 2 separate lot numbers were used for the complete series of structural, functional, and biologic tests. One Namic valve was obtained and was used only for the structural test.

Structural Testing

The valve characteristics test indicated that the Medex valves required a significant (3.4 ± 0.9 psi; mean ± standard deviation) pressure to open them in the positive direction of flow and were thus considered a "sprung" type of valve. The Merit valves and the Namic valve were considered "unsprung", since the pressure needed to open them was less than 0.1 psi. The sprung nature of the valve represents a resting static pressure that must be overcome to open the valve membrane in the direction of flow. One of the 10 Medex valves exhibited pressure profile changes during the short-term back pressure valve test at a pressure of 15 psi (750 mm Hg). None of the Medex valves exhibited any pressure profile changes during the long-term back pressure valve test (60 psi for 1 h). In contrast, the Merit valves exhibited pressure profile changes of a significant nature in both the short-term and long-term tests. One of the two valves tested had a catastrophic failure during short-term testing. The other valve that passed the short-term back pressure testing failed the long-term testing. The Namic valve exhibited no pressure changes during short-term testing but exhibited pressure changes and leakage when subjected to the long-term back pressure testing. The clinical simulation valve tests demonstrated that the valves performed as expected with no flow

across them when there was back pressure and no flow when the positive pressure exceeded the resting static pressure of the valve.

Functional Testing

Fifty samples were obtained, including pre-study and post-study samples. A 5.0 mL aliquot of each sample was counted for 1 minute (cpm) immediately following the procedure. Counts obtained were corrected for background radioactivity. There was no significant difference in the cpm of the pre-study (1.86×10^6) and post-study (1.88×10^6) samples, indicating no decay in the activity of the radionuclide during the time the experiments were per- formed. The first sample was collected with no pressure on the valve. Radioactivity was detected in none of the samples when the Medex valves were used. In one of two Merit valves tested, all three samples contained a mean of 1.8×10^6 cpm, indicating catastrophic failure of the valve from the pressure challenges. The methylene blue provided a visual aid to the failure of this valve.

Biologic Testing

Lysis was detected on control samples obtained before and after the experimental studies, indicating preservation of bacte- riophage activity throughout the time course of the experiments. Over 50 samples were obtained with one sample taken with no pressure and three others collected after a 1-minute pressure of 300 mm Hg (6 psi) against the valve. Lysis was detected in none of the samples obtained when the Medex valves were used. In one of the two Merit valves tested, all three samples contained significant amounts of bacteriophage with significant lysis of the *S. aureus* strain used as a marker for the bacteriophage. The valve that failed was from the same lot number as the valve that had failed the functional test procedure above.

Discussion

Our experiments tested two different types of valves: sprung and unsprung. None of the sprung valves exhibited failure at pressures that might normally be encountered in actual clinical settings, using multiple test procedures with very sensitive surrogate markers, including pressure measurements, a radionuclide molecule, and a bacteriophage. To further enhance the sensitivity of the experiment design, high concentrations of the radionuclide and the bacteriophage were used. In over 50 experiments performed with these sprung valves, only one gave suboptimal results. This valve exhibited a significant pressure-time profile change 3 seconds after beginning the short-term high back pressure test (15 seconds at 60 psi). It failed at a pressure of approximately 15 psi (equivalent to approximately 750 mm Hg), which greatly exceeds any back pressures that might be encountered in a clinical setting. All of the other sprung valves tested survived pressures of 60 psi without exhibiting failure, suggesting that intralot variability in the manufacturing process may account for this observation.

Although fewer unsprung valves were tested (two separate lots of the Merit valves for each of the test procedures and one Namic valve for the structural test procedure), the consistent failure of one of these unsprung valves (Merit) in the test procedures conducted at pressures that could easily be encountered in the clinical setting suggests that their utility as a safeguard for the prevention of backflow of blood or body fluids in a multi-dosing setting may be compromised. The limited number of experiments conducted on the other type of unsprung valve (Namic) limits the comments that may be made. The connection point on this valve leaked following the short-term high back pressure test, thus limiting further testing. From basic physical principles, plotting the flow rate against the opening area for different spring constant values demonstrates that with a sprung valve there is flow immediately upon opening it, which effectively prevents backflow. This principle in the design of backflow valves would make them desirable for the intended application of the prevention of any cross-contamination of bloodborne pathogens.

The results of these specimens, incorporating the basic physical principles discussed above, suggest that sprung one-way check valves may be safely used to prevent the backflow of potentially blood-contaminated or body fluid-contaminated fluids in a multi-dosing setting of intravenous contrast agents. It may be desirable to use a second valve as a backup to the first valve in the event of an unexpected catastrophic failure of the initial primary valve. Further studies are warranted by other investigators, but our findings suggest that the incorporation of sprung backflow valves should allow a high margin of safety in the use of multiple patient dosing of expensive low osmolar dyes, thus achieving significant cost reductions by reducing wastage.

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Source: *M Garcia, BScN, RN, S Woodward, MRT(N), R Reilly, MSc, PhM, K Anderson, RN, D Gretzinger, BEng, J Cafazzo, MHSc, PEng, J Ratner, PhD, A Easty, PhD, PEng, H Dedier, RT, J Yao, MD, W Wobeser, MD, J Conly, MD, Departments of Microbiology, Nuclear Medicine, Radiology and Medical Engineering, The Toronto Hospital, University of Toronto, Toronto, Ontario.*

UPDATED ADVISORY NOTICE: LOW OSMOLAR DYE INTRAVENOUS DELIVERY SYSTEMS

On 30 August, 1995, the National Steering Committee on Infection Control Guidelines Development published an advisory notice on the practice of using **single use**, low osmolar dye intravenous delivery systems (e.g., for cardiac catheterization, CAT scans) on more than one patient[(1)].

The following is an update related to this advisory. The Steering Committee states that the practice of using **single use**, low osmolar dye intravenous delivery systems on more than one patient will always present a risk of cross contamination of blood and body fluids between patients. However, the previous article has suggested that placement of a “sprung” type, backflow valve (i.e., significant pressure is required to open the valve in the positive direction of flow) in the delivery system distal to the syringe ports and proximal to the dye container may substantially reduce the risk of blood backflow and subsequent contamination of the fluid reservoir. Short administration times and increasing the length of the tubing are not acceptable alternatives because these

manoeuvres have not had rigorous scientific evaluation and may offer little in the prevention of blood backflow.

Health care facilities that use sprung type, backflow valves should institute ongoing surveillance procedures to monitor the efficacy of the practice in their institutions. As suggested in the previous article, it may also be desirable to use a second valve, acting as a backup to the first one, in the event of an unexpected catastrophic failure. In addition, facilities should continue to work towards finding other methods of reducing the waste of costly dye products for radiologic studies.

This Advisory Notice has been endorsed by The National Steering Committee on Infection Control Guidelines Development, Laboratory Centre for Disease Control, Health Canada.

Reference

1. Paton S, Nicolle L. *Advisory notice: Low osmolar dye intravenous delivery systems*. CCDR 1994;20:144.

Source: *S Paton, RN, MN, Chief, Nosocomial and Occupational Infections, Bureau of Infectious Diseases, LCDC, Ottawa; J Conly, MD, Hospital Epidemiologist, The Toronto Hospital, Toronto, Ontario.*

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Scientific Advisors	Dr. John Spika	(613) 957-4243
	Dr. Fraser Ashton	(613) 957-1329
Editor-in-Chief	Eleanor Paulson	(613) 957-1788
Assistant Editor	Nicole Beaudoin	(613) 957-0841
Desktop Publishing	Joanne Regnier	

Submissions to the CCDR should be sent to the Editor-in-Chief at the following address: Laboratory Centre for Disease Control, Tunney's Pasture, Ottawa, Ontario K1A 0L2.

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