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Case Report

A Methanol Intoxication Outbreak From Recreational Ingestion of Fracking Fluid

David Collister, MD,[1,2,3] Graham Duff, MD,[1] Wesley Palatnick, MD,[2,4] Paul Komenda, MD, MHA,[1,3] Navdeep Tangri, MD, PhD,[1,3] and Jay Hingwala, MD, MSc[1,2]

Single-patient methanol intoxications are a common clinical presentation, but outbreaks are rare and usually occur in settings in which there is limited access to ethanol and methanol is consumed as a substitute. In this case report, we describe an outbreak of methanol intoxications that was challenging from a public health perspective and discuss strategies for managing such an outbreak.
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INDEX WORDS: Methanol; intoxication; toxic alcohol ingestion; poisoning; outbreak; fomepizole; folinic acid; hemodialysis; alcohol dehydrogenase inhibition; case reports; remote medicine; contact tracing; public health.

Single-patient methanol intoxications are common,[1-3] but outbreaks are rare, especially in developed countries.[4-12] They usually occur in settings in which there is limited access to ethanol due to its cost or ethanol is not available due to cultural, religious, or social reasons, and so methanol is consumed as an ethanol substitute.

Oxidation of methanol by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase to formate causes an anion gap metabolic acidosis and may lead to end-organ damage, including retinal injury, central nervous system dysfunction, and death.[13] Rapid identification of methanol intoxication and inhibition of ADH with fomepizole[14] or ethanol is critical to preventing morbidity and mortality; hemodialysis (HD) therapy[15] might also be necessary.

Providing optimal effective therapy may be challenging during outbreaks of methanol intoxication when patient volume and acuity may exceed the availability of resources. In this report, we describe a series of methanol intoxications that was challenging from a public health perspective and suggest strategies that centers may apply to prepare and appropriately manage potential future outbreaks.

From the [1]Section of Nephrology, Department of Medicine, University of Manitoba; [2]Health Sciences Center; [3]Seven Oaks General Hospital, Chronic Disease Innovation Centre; and [4]Department of Emergency Medicine, University of Manitoba, Winnipeg, Canada.

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Address correspondence to David Collister, MD, Seven Oaks General Hospital, Chronic Disease Innovation Centre, 2300 McPhillips Street, 2PD13, Winnipeg, MB, Canada R2V 3M3. E-mail: dtcollister@gmail.com

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CASE REPORTS

We report a series of 10 intentional methanol intoxications from the ingestion of a fluid used in the mining industry for fracking.[16] The 3 index cases included a 28-year-old First Nations man who presented to a nursing station in remote Northern Manitoba, Canada, with nausea and vomiting. He did not report any other symptoms. Approximately 24 hours prior to presentation, the man had recreationally consumed an undisclosed amount of "frosted white" with friends. The substance was later confirmed to be a fracking mining fluid consisting of 85% ethanol, 13.7% methanol, and 0.85% acetate. A toxic alcohol ingestion was suspected, and after consultation with a toxicologist, the patient was transferred by air ambulance to a tertiary-care facility with HD facilities in Winnipeg. No ethanol or fomepizole was given at the nursing station because they were not available.

Upon arrival to the tertiary-care facility, the patient's arterial pH was 7.19; anion gap, 28; osmolal gap, 41 mOsm/L; and methanol level, 30.1 mmol/L (96.4 mg/dL). Intravenous fomepizole (15 mg/kg) and intravenous folinic acid (50 mg) were administered to the patient, along with 5% dextrose mixed with 3 ampules of sodium bicarbonate per liter at a rate of 250 mL/h. A right femoral vascular catheter was inserted and HD was performed in the intensive care unit for 6 hours, the session time predicted by the Halifax formula (estimated dialysis time in hours $= [-V \times \ln(5/A)]/0.06k$, where V is the Watson estimate of total-body water in liters, A is the initial toxin concentration in millimoles per liter, and k is 80% of the manufacturer-specified dialyzer urea clearance in milliliters per minute at the initial observed blood flow rate[17,18]). The Halifax formula targets a serum concentration ≤ 5 mmol/L for methanol and ethylene glycol.[17,18] The patient recovered clinically and was discharged without adverse sequelae.

Given the history of group intoxication, we engaged the public health infrastructure and with contact tracing, identified 10 individuals who had ingested the fracking solution. Public health officials then contacted these individuals by telephone, or if this method was not possible, law enforcement officials conducted home visits. We ensured adequate staffing at the nursing station, aviation resources, and paramedic services to prevent delays in patient transportation to our tertiary center. The clinical summary of each patient is presented in Tables 1 and 2, and a timeline of events is displayed in Fig S1 (available as online supplementary material). Two of the 10 patients required fomepizole therapy with HD, and an additional patient required fomepizole therapy without HD.

Table 1. Demographics, Anthrometry, Medical History, Symptoms, and Timing of Medical Care

Pt No.	Age, y/Sex	Height, cm	Weight, kg	Medical History[a]	Symptoms	Time Since Ingestion to: Initial Contact With Health Care System	Time Since Ingestion to: Flight Dispatch	Time Since Ingestion to: Presentation to ED Triage in Tertiary Hospital
1	45/M	162	73.2	Rheumatoid arthritis	Nausea, vomiting	24 h 45 min	26 h 55 min	32 h 5 min
2	28/M	176	114	Smoker, marijuana use, LTBI	Nausea, vomiting, "hungover"	24 h 50 min	26 h 55 min	32 h 4 min
3	28/M	170	88.4	Healthy	"Hungover"	25 h	28 h 22 min	32 h 26 min
4	21/M	—	—	Healthy	"Hungover"	26 h 30 min	28 h 22 min	32 h 25 min
5	27/M	179	74.9	Asthma, HCV	NA	28 h 15 min	28 h 15 min	33 h 34 min
6	39/M	165	75.6	Chronic back pain	Nausea, vomiting	30 h 45 min	33 h 25 min	42 h 26 min
7	31/M	—	—	Migraines	NA	32 h	33 h 15 min	37 h 1 min
8	22/M	176	92	Idiopathic immune complex MPGN, HTN, eczema	NA	32 h	33 h 15 min	37 h 2 min
9	35/M	180	114	Peritonsillar abscess	NA	33 h 15 min	37 h 30 min	42 h 25 min
10	38/M	168	73	HTN, smoker, appendectomy, I+D, iron deficiency anemia	NA	34 h	37 h	40 h 42 min

Abbreviations: ED, emergency department; HCV, hepatitis C virus; HTN, hypertension; I+D = incision plus drainage; LTBI, latent tuberculosis infection; MPGN, membranoproliferative glomerulonephritis; NA, not applicable; Pt, patient.

[a]None of the patients were taking any medications at the time of presentation.

DISCUSSION

This methanol intoxication outbreak involved a variety of settings (nursing station, emergency department, and intensive care unit) and was managed by a multidisciplinary team composed of nurses, public health officials, paramedics, pharmacists, physicians, and a toxicologist. Fortunately, most patients presented without evidence of methanol toxicity and did not require interventions. We suspect that this was due to limited ingestion or inhibition of ADH by the 85% ethanol content of the fluid, resulting in delayed but controlled methanol clearance.

For these 10 cases, outcomes for all patients were favorable. However, if faced with a similar scenario of greater patient acuity or volume,[5,7,8] we would have found it challenging due to resource limitations. Our experience prompted a formal review of the processes at our center and resulted in the development of a regional framework for a methanol intoxication outbreak (Fig 1).

Rapid case finding and diligent contact tracing are critical to identify individuals at risk for harm, as well as to quantify the potential burden of an outbreak. Engaging all relevant stakeholders from the multidisciplinary team is important to mobilize resources to fit patient needs. If possible, determining a patient's pH, acid-base status, anion gap, osmolal gap, and neurologic status at initial presentation provides valuable information for predicting health resource use, such as the need for fomepizole, dialysis, and intensive care.[19,20] If the anticipated resources are thought to exceed an individual center's operating capacity, patients can be distributed upstream to other facilities with available resources. We suggest that while actively case finding, centers simultaneously account for their available fomepizole stock and dialysis capacity and verify these resources at nearby hospitals. Centers should create a contingency plan for ethanol treatment in cases in which fomepizole treatment is not possible. To avoid medication errors, we have established protocols for the dosing and monitoring of ethanol in case of fomepizole shortages.

Measuring methanol levels in patients identified in an outbreak is favored over using osmolal gap in toxic alcohol ingestions.[21-23] However, if methanol levels are not readily available, osmolal gap is a suitable surrogate for toxic alcohol burden and can help facilitate triage.[24] If laboratory investigations are not available during the patient's initial interaction with a health system and he or she is symptomatic or delayed transfer to a tertiary center is anticipated, empirical ADH inhibition with ethanol or fomepizole therapy should be considered.[25]

Individual therapy needs to be considered in the context of an outbreak and potential resource limitations. Although fomepizole may not carry a mortality benefit over ethanol for ADH inhibition,[26,27] we prefer it to ethanol because it is associated with fewer dosing errors, more reliable pharmacokinetics, and fewer adverse drug events and is well tolerated in most patients.[27,28] In addition, a single dose of fomepizole adequately inhibits ADH for several hours, allowing time for transport to a tertiary health care center.[14]

We chose to treat 2 patients with HD due to their methanol levels (30.1 mmol/L [96.4 mg/dL]

Table 2. Blood Chemistries, ADH Inhibition, and Dialysis Conditions

Pt No.	pH	HCO_3, mmol/L	Pco_2, mm Hg	AG, mmol/L	OG, mOsm/L	Methanol[a]	EtOH, mmol/L	Scr, μmol/L	ADH Inhibition	Dialysis Conditions
1	7.30	16	33	22	13	Pre: 5.1 mmol/L (16.3 mg/dL) Post: NA	<2.2	64	Folinic acid 50 mg IV	NA
2	7.27	13	29	24	18	Pre: 7.8 mmol/L (25 mg/dL) Post: NA	<2.2	76	Fomepizole 15 mg/kg IV, folinic acid 50 mg IV	NA
3	7.19	10	25	28	42	Pre: 30.1 mmol/L (96.4 mg/dL) Post: 3.4 mmol/L (10.9 mg/dL)	<2.2	75	Fomepizole 15 mg/kg IV, 10 mg/kg IV every 4 h, folinic acid 50 mg IV	R FVC; 6 h; Qb, 400 mL/min; Qd, 500 mL/min; OF250 membrane; KoA, 1,662 mL/min
4	7.37	23	39	16	18	<1 mmol/L	<2.2	65	NA	NA
5	7.31	17	33	22	30	Pre: 19.4 mmol/L (62.2 mg/dL) Post: 3.0 mmol/L (9.6 mg/dL)	<2.2	82	Fomepizole 15 mg/kg IV, 10 mg/kg IV every 4 h, folinic acid 50 mg IV	L CVC; 5 h; Qb, 400 mL/min; Qd, 500 mL/min; OF250 membrane; KoA, 1,662 mL/min
6	7.39	25	41	13	NA	<1 mmol/L	<2.2	73	NA	NA
7	7.34	25	31	14	NA	<1 mmol/L	<2.2	76	NA	NA
8	7.33	29	55	13	4	<1 mmol/L	<2.2	73	NA	NA
9	7.4	23	37	13	NA	<1 mmol/L	<2.2	64	NA	NA
10	NA	NA	NA	11	NA	<1 mmol/L	<2.2	100	NA	NA

Note: Osmolality was determined by the method of freezing point osmometry using a Fiske 2400 Osmometer, and calculated osmolality was equal to 2 times sodium concentration plus glucose concentration plus serum urea nitrogen. Plasma alcohol analysis was done by aqueous dilution and direct injection gas chromatography with flame ionization detection (Trace 1 Ultra GC Chromatography; Thermo-Fisher Scientific) with 1-propanol used as the internal standard for quantification of alcohol, which was by single-point calibration. Plasma glycols were analyzed by direct injection gas chromatography with flame ionization detection (Trace 1 Ultra GC Chromatography). Briefly, plasma samples were mixed with zinc sulfate and acetonitrile to precipitate proteins. The mixture was then derivatized with phenylboronic acid prior to direct injection; 2,3-butanediol was used as the internal standard for quantification, which was by single point calibration.

Abbreviations: ADH, alcohol dehydrogenase; AG, anion gap; CVC, central venous catheter; EtOH, ethanol; FVC, femoral vascular catheter; KoA, dialyzer efficiency; L, left; NA, not applicable; OF250, Optiflux 250; OG, osmolal gap; Pt, patient; Qb, blood flow; Qd, dialysate flow; IV, intravenous; R, right; Scr, serum creatinine.

[a]Pre/post refers to before/after treatment.

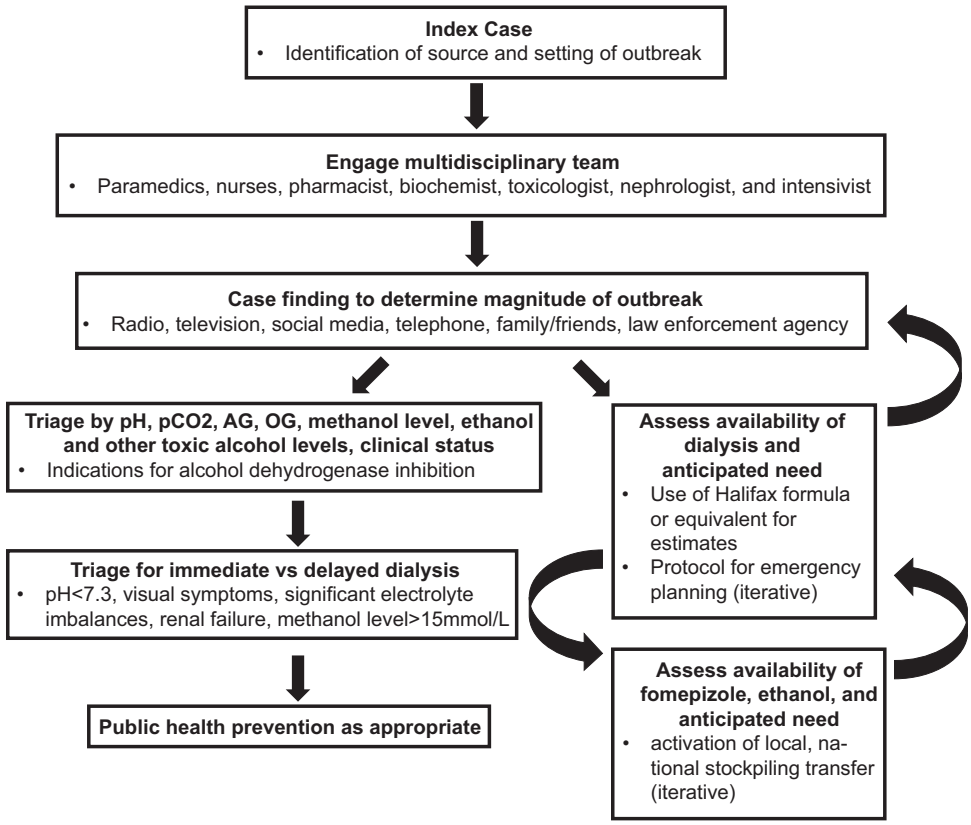

Figure 1. Proposed steps in methanol intoxication outbreaks. Abbreviations: ADH, alcohol dehydrogenase; AG, anion gap; OG, osmolar gap.

and 19.4 mmol/L [62.2 mg/dL]) because the therapy was readily available. However, in the setting of an outbreak, HD should be prioritized for patients with clinical indications (respiratory, neurologic, or visual symptoms or reduced kidney function) rather than absolute methanol levels[19,20] if dialysis resources are limited.[29,30] It is possible to offer prolonged ADH inhibition until dialysis can be performed,[31] if necessary; this approach should be balanced against the longer (52-hour) methanol half-life with fomepizole and need for an extended hospitalization.[5,7,29,31] In patients without significant acidosis or eye symptoms and with methanol levels $<$ 15.6 mmol/L, treatment with ADH inhibition alone has been shown to be safe[14,29] and therefore is a viable option if dialysis is not possible or methanol levels are not significantly elevated. From a cost perspective, HD is generally considered to be more effective compared to prolonged fomepizole therapy. When dialysis is indicated, use of HD with a high-flux dialyzer should be preferred over continuous renal replacement therapy because the former is more efficient. We propose the use of the Halifax formula in all patients to guide adequate dialysis duration and facilitate patient flow.[32] Regardless of the therapeutic plan chosen for an individual patient, methanol levels and acid-base status should be followed up serially in the rare case of delayed absorption or a prolonged half-life from impaired endogenous clearance pathways.[33,34]

Ultimately, prevention is critical from a public health perspective and involves public education regarding the risks of methanol intoxication, limiting the public purchase of methanol-containing substances, and requiring secure storage of these products. Ensuring that a plan is in place in the rare event of an outbreak is key to decreasing morbidity and mortality, and we hope that our experience, although not extreme as in previous reports, assists others in optimizing care in the future.

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SUPPLEMENTARY MATERIAL

Figure S1: Timeline of events.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.10.029) is available at www.ajkd.org

REFERENCES

1. Mowry JB, Spyker DA, Cantilena LR Jr, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st annual report. *Clin Toxicol (Phila)*. 2014;52(10):1032-1283.
2. Thanacoody RH, Gilfillan C, Bradberry SM, et al. Management of poisoning with ethylene glycol and methanol in the UK: a prospective study conducted by the National Poisons Information Service (NPIS). *Clin Toxicol (Phila)*. 2015;23:1-7.
3. Ghannoum M, Hoffman RS, Mowry JB, Lavergne V. Trends in toxic alcohol exposures in the United States from 2000 to 2013: a focus on the use of antidotes and extracorporeal treatments. *Semin Dial*. 2014;27(4):395-401.
4. Levy P, Hexdall A, Gordon P, Boeriu C, Heller M, Nelson L. Methanol contamination of Romanian home-distilled alcohol. *J Toxicol Clin Toxicol*. 2003;41(1):23-28.
5. Hovda KE, Hunderi OH, Tafjord AB, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002-2004: epidemiology, clinical features and prognostic signs. *J Intern Med*. 2005;258(2):181-190.
6. Brahmi N, Blel Y, Abidi N, et al. Methanol poisoning in Tunisia: report of 16 cases. *Clin Toxicol (Phila)*. 2007;45(6):717-720.
7. Paasma R, Hovda KE, Tikkerberi A, Jacobsen D. Methanol mass poisoning in Estonia: outbreak in 154 patients. *Clin Toxicol (Phila)*. 2007;45(2):152-157.
8. Zakharov S, Pelclova D, Urban P, et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. *Clin Toxicol (Phila)*. 2014;52(10):1013-1024.
9. Hassanian-Moghaddam H, Nikfarjam A, Mirafzal A, et al. Methanol mass poisoning in Iran: role of case finding in outbreak management. *J Public Health (Oxf)*. 2015;37(2):354-359.
10. D'Silva J. India's problem with toxic alcohol. *BMJ*. 2015;351:h4536.
11. Bennett IL Jr, Cary FH, Mitchell GL Jr, Cooper MN. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. *Medicine (Baltimore)*. 1953;32(4):431-463.
12. Swartz RD, Millman RP, Billi JE, et al. Epidemic methanol poisoning: clinical and biochemical analysis of a recent episode. *Medicine (Baltimore)*. 1981;60(5):373-382.
13. Liesivuori J, Savolainen H. Methanol and formic acid toxicity: biochemical mechanisms. *Pharmacol Toxicol*. 1991;69(3):157-163.
14. Brent J, McMartin K, Phillips S, Aaron C, Kulig K; Methylpyrazole for Toxic Alcohols Study Group. Fomepizole for the treatment of methanol poisoning. *N Engl J Med*. 2001;344(6):424-429.
15. Austin WH, Lape CP, Burnham HN. Treatment of methanol intoxication by hemodialysis. *N Engl J Med*. 1961;265:334.
16. Lavergne V, Ouellet G, Bouchard J, et al. Guidelines for reporting case studies on extracorporeal treatments in poisonings: methodology. *Semin Dial*. 2014;27(4):407-414.
17. Hirsch DJ, Jindal KK, Wong P, Fraser AD. A simple method to estimate the required dialysis time for cases of alcohol poisoning. *Kidney Int*. 2001;60(5):2021-2024.
18. Youssef GM, Hirsch DJ. Validation of a method to predict required dialysis time for cases of methanol and ethylene glycol poisoning. *Am J Kidney Dis*. 2005;46(3):509-511.
19. Barceloux DG, Bond GR, Krenzelok EP, Cooper H, Vale JA; American Academy of Clinical Toxicology Ad Hoc Committee on the Treatment Guidelines for Methanol Poisoning. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40(4):415-446.
20. Roberts DM, Yates C, Megarbane B, et al; EXTRIP Work Group. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. *Crit Care Med*. 2015;43(2):461-472.
21. Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmol gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol*. 1993;31(1):81-93.
22. Hovda KE, Hunderi OH, Rudberg N, Froyshov S, Jacobsen D. Anion and osmolal gaps in the diagnosis of methanol poisoning: clinical study in 28 patients. *Intensive Care Med*. 2004;30(9):1842-1846.
23. Kraut JA. Diagnosis of toxic alcohols: limitations of present methods. *Clin Toxicol (Phila)*. 2015;53(7):589-595.
24. Khajuria A, Krahn J. Osmolality revisited–deriving and validating the best formula for calculated osmolality. *Clin Biochem*. 2005;38(6):514-519.
25. Zakharov S, Pelclova D, Urban P, et al. Use of out-of-hospital ethanol administration to improve outcome in mass methanol outbreaks. *Ann Emerg Med*. 2016;68(1):52-61.
26. Zakharov S, Pelclova D, Navratil T, et al. Intermittent hemodialysis is superior to continuous veno-venous hemodialysis/hemodiafiltration to eliminate methanol and formate during treatment for methanol poisoning. *Kidney Int*. 2014;86(1):199-207.
27. Lepik KJ, Sobolev BG, Levy AR, et al. Medication errors associated with the use of ethanol and fomepizole as antidotes for methanol and ethylene glycol poisoning. *Clin Toxicol (Phila)*. 2011;49(5):391-401.
28. Lepik KJ, Levy AR, Sobolev BG, et al. Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: a comparison of ethanol and fomepizole. *Ann Emerg Med*. 2009;53(4):439. 450.e10.
29. Hovda KE, Froyshov S, Gudmundsdottir H, Rudberg N, Jacobsen D. Fomepizole may change indication for hemodialysis in methanol poisoning: prospective study in seven cases. *Clin Nephrol*. 2005;64(3):190-197.
30. Kostic MA, Dart RC. Rethinking the toxic methanol level. *J Toxicol Clin Toxicol*. 2003;41(6):793-800.
31. Hovda KE, Andersson KS, Urdal P, Jacobsen D. Methanol and formate kinetics during treatment with fomepizole. *Clin Toxicol (Phila)*. 2005;43(4):221-227.
32. Lachance P, Mac-Way F, Desmeules S, et al. Prediction and validation of hemodialysis duration in acute methanol poisoning. *Kidney Int*. 2015;88(5):1170-1177.
33. Elwell RJ, Darouian P, Bailie GR, Eisele G, McGoldrick MD. Delayed absorption and postdialysis rebound in a case of acute methanol poisoning. *Am J Emerg Med*. 2004;22(2):126-127.
34. Hovda KE, Mundal H, Urdal P, McMartin K, Jacobsen D. Extremely slow formate elimination in severe methanol poisoning: a fatal case report. *Clin Toxicol (Phila)*. 2007;45(5):516-521.