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World Journal of Gastrointestinal Pharmacology and Therapeutics (*World J Gastrointest Pharmacol Ther*; *WJGPT*, online ISSN 2150-5349, DOI: 10.4292), is a bimonthly, open-access, peer-reviewed journal supported by an editorial board of 188 experts in gastrointestinal surgery from 36 countries.

The major task of *WJGPT* is to rapidly report the most recent results in basic and clinical research on gastrointestinal pharmacology and therapeutics, including the effects of drugs on the gastrointestinal, pancreatic and hepatobiliary systems, particularly with relevance to clinical practice. *WJGPT* accepts papers on the following aspects related to gastroenterology or hepatology: (1) Clinical pharmacological research articles on specific drugs, concerning with pharmacodynamics, pharmacokinetics, toxicology, clinical trial, drug reactions, drug metabolism and adverse reaction monitoring, *etc*; (2) Research progress of clinical pharmacology; (3) Introduction and evaluation of new drugs; (4) Experiences and problems in applied therapeutics; (5) Research and introductions of methodology in clinical pharmacology; and (6) Guidelines of clinical trial. Specifically, this journal welcome research and review articles associated with both Western medicine and Chinese herbs as well as their combinations in basic and clinical application.

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Lactose malabsorption and intolerance: What should be the best clinical management?

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therapies are effective. Further double-blind studies are needed to demonstrate treatment effectiveness in lactose intolerance.

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Abstract

Lactose malabsorption (LM) is the incomplete hydrolysis of lactose due to lactase deficiency, which may occur as a primary disorder or secondary to other intestinal diseases. Primary adult-type hypolactasia is an autosomal recessive condition resulting from the physiological decline of lactase activity. Different methods have been used to diagnose LM. Lactose breath test represents the most reliable technique. A recent consensus conference has proposed the more physiological dosage of 25 g of lactose and a standardized procedure for breath testing. Recently a new genetic test, based on C/T13910 polymorphism, has been proposed for the diagnosis of adult-type hypolactasia, complementing the role of breath testing. LM represents a well-known cause of abdominal symptoms although only some lactose malabsorbers are also intolerants. Diagnosing lactose intolerance is not straightforward. Many non-malabsorber subjects diagnose themselves as being lactose intolerant. Blind lactose challenge studies should be recommended to obtain objective results. Besides several studies indicate that subjects with lactose intolerance can ingest up to 15 g of lactose with no or minor symptoms. Therefore a therapeutic strategy consists of a lactose restricted diet avoiding the nutritional disadvantages of reduced calcium and vitamin intake. Various pharmacological options are also available. Unfortunately there is insufficient evidence that these

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INTRODUCTION

Lactose is the disaccharide found in milk and dairy products. Absorption of lactose requires lactase activity in the small intestinal brush border. Hypolactasia, or lactose malabsorption (LM), exists in three distinct forms: congenital, primary and secondary. Congenital lactase deficiency is associated with the least lactase activity. It is a lifelong disorder characterized by failure to thrive and infantile diarrhea from the first exposure to breast milk. Congenital hypolactasia, a single autosomal recessive disorder^[1], is extremely rare, with only around 40 cases having been reported.

Primary adult-type hypolactasia, an autosomal recessive condition resulting from the physiological decline of lactase enzyme activity in the intestinal cells, occurs in a large proportion of individuals. A single nucleotide polymorphism, C/T-13910, 14 kb upstream the lactase gene, has recently been correlated with lactase persistence/non persistence in several populations^[2,3]. Secondary causes

of hypolactasia, such as celiac disease, gastroenteritis and Crohn's disease, may lead to transient lactase deficiency and appearance of abdominal symptoms similar to those of primary LM.

The onset of adult-type hypolactasia is correlated to age: lactase activity is highest at birth and declines after weaning^[4,5]. The frequency of this condition varies according to ethnicity^[6], with reported lower prevalence in Northern Europe (< 5%), compared to Southern Europe (70%-80%) and Southeast Asia (almost 100%). LM represents a well-known cause of abdominal disorders, like diarrhoea, bloating, excessive flatus and abdominal pain. However, sugar malabsorption does not necessarily result in the development of intolerance symptoms; in fact, only about one-third to half of lactose maldigesters are also intolerants.

DIAGNOSIS OF LACTOSE MALABSORPTION

Different methods have been used for the diagnosis of LM. Lactose activity assay by jejunal biopsy has been proposed as the "gold standard"^[7,8]. However, it seems too invasive for the diagnosis of such a mild condition and its results may be influenced by the irregular dissemination of lactase activity throughout the small intestine mucosa. Lactose breath test (BT) represents an indirect test for LM, and it is commonly considered the most reliable, non-invasive and inexpensive technique^[9]. However, it is possible to find false negative BTs, due to the inability of colonic flora to produce H₂ after ingestion of non-absorbable carbohydrates, or after a recent administration of antibiotics. False positive BTs are less frequent and are mainly produced because of small bowel bacterial overgrowth^[4]. Reviewing methodological studies^[3,7,8,10], lactose BT shows good sensitivity (mean value of 77.5%) and excellent specificity (mean value of 97.6%).

A recent consensus conference on BTs^[10], has examined the methodological aspects of BTs, based on a systematic review of the literature. The following recommendations were suggested on how to perform lactose BT: test duration of 4 h (3 h for pediatric use), sample intervals of 30 min and a cut-off value of 20 ppm above the baseline. Finally a more physiological dosage of 25 g of lactose was recommended to be used for BT. In fact many studies of BT validation^[7,8] have utilized the dosage of 50 g lactose (approximately corresponding to one liter of milk) which has been criticized because it represents an amount far higher than that usually ingested at any one time. Besides, patients with lactose intolerance (LI) may experience considerable discomfort with this dosage.

Recently, the C/T-13910 polymorphism roughly 14 Kb upstream of the lactase gene locus on chromosome 2q21, has been found to be completely associated with lactase activity^[2] and proposed as a new diagnostic tool in adult-type hypolactasia^[5,11]. Genomic DNA from patients may be obtained from peripheral blood samples, and DNA isolated using standard techniques^[2,3,11]. Several

recent studies on adult subjects have demonstrated an excellent correlation between BT and the genetic test (GT) based on C/T-13910 polymorphism^[3,11]. The absence of information on symptoms of intolerance represents the only diagnostic limit of GT.

A new LM diagnostic algorithm based on this information (Figure 1) has been proposed^[11,12]: (1) The GT may complement in several aspects the BT, improving the diagnosis of adult-type hypolactasia. In all subjects with negative lactose BT, the GT provides an unambiguous result permitting the exclusion of false negative results (such as low hydrogen producers) and avoiding the need for further tests (lactulose or methane BTs); (2) Secondary causes of hypolactasia may be suspected in subjects with a positive BT and a C/T-13910 variant associated with lactase persistence; and (3) Finally, according to various studies^[4,5], the decline of lactase activity and the onset of adult-type hypolactasia should be evident from 8-12 years onwards. In younger subjects, the GT is not recommended, while the lactose BT remains of paramount utility in diagnosing secondary hypolactasia.

DEFINITION AND DIAGNOSIS OF LACTOSE INTOLERANCE

It is important to distinguish between hypolactasia, a low level of lactase, and clinical LI. The likelihood that a lactose malabsorber will perceive symptoms after ingestion of lactose is a function of many variables, including the dosage of lactose, lactase activity of the mucosa, foods co-ingested with lactose, the lactose fermentation pathways of the colonic flora, and the visceral sensitivity of an individual's colon to LM. Many subjects diagnose themselves as being lactose intolerant. However, these self-identified lactose intolerant individuals may actually be lactase persistent. Some of those lactase persistent (and even lactase non-persistent) may mistakenly ascribe the symptoms of undiagnosed irritable bowel syndrome (IBS) or other intestinal disorders to LI^[13-15]. Since the avoidance of milk and milk-containing products can result in a dietary calcium intake that is below recommended levels of 1 g per day for men and women and 1.3 g for adolescents, osteoporosis and associated fractures secondary to inadequate dietary calcium is the perceived major health risk associated with real or assumed LI^[16,17]. Therefore we think that it is not sufficient to ask patients about the correlation between symptoms and lactose ingestion while an objective diagnostic test remains of paramount utility.

LI should be considered when ingestion of a single dose by a lactose malabsorber subject induces gastrointestinal symptoms not observed when the subject ingests an indistinguishable placebo. Although blind lactose challenge should be the recommended method, other methodological approaches have been considered to evaluate LI: non-blind lactose challenge and self-reported symptoms without lactose challenge^[18].

In fact, no studies of symptoms following blind lactose challenge are available, while only a few studies of

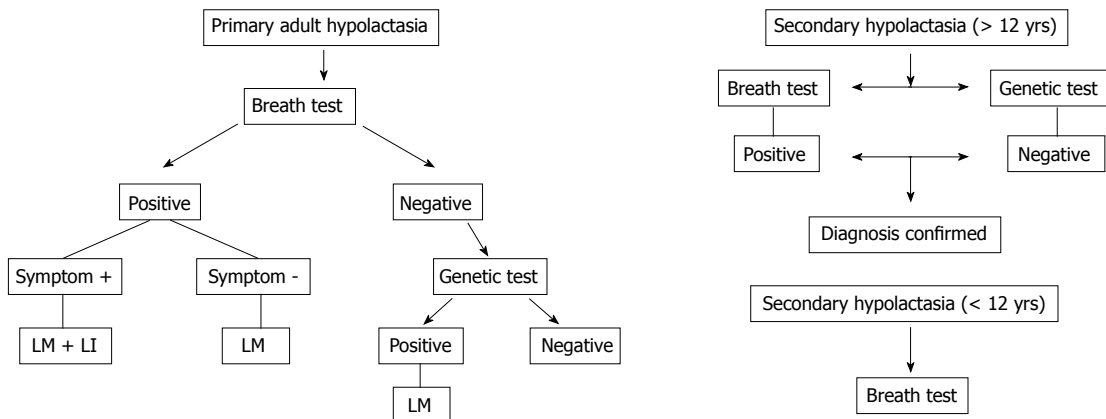


Figure 1 Diagnostic algorithm for suspected lactose malabsorption and intolerance. LM: lactose malabsorption; LI: Lactose intolerance.

Table 1 Treatment of lactose intolerance

Non pharmacological options
Milk with prehydrolyzed lactose
Consumption of fermented and matured dairy products
Ingestion of milk together with other foods
Distribution in little meals of daily milk amount in snacks
Colonic adaptation by increasing lactose load
Pharmacological options
Enzyme replacement with lactase supplements
Probiotics
Antibiotics

Note: Calcium and vitamins support if daily intake is inadequate.

non-blind lactose challenge have been published with conflicting results. For African American, Hispanic, Asian, and American Indian populations LI rates may be 50%, higher in late childhood and adulthood^[18,19].

Seven studies of self-reported symptoms without lactose challenge can be identified^[18,19]. US estimated prevalence of self-reported LI was 12%, with estimates of 8% in European Americans, 10% in Hispanic Americans, and 20% in African Americans. Overall, the prevalence of self-reported symptoms was typically lower than the prevalence of symptoms following a lactose challenge^[18,19]. On the other hand the recording of symptoms, by hydrogen BT following lactose challenge, is commonly considered the most reliable diagnostic method in clinical practice^[7-10]. Variability among scores of the severity and duration of symptoms can be found in the literature as well as a poor agreement on the quality and quantity of symptoms to be considered^[3,10,15]. The recent Rome consensus conference proposed the recording and scoring of the following four symptoms during the test and 8 h after: abdominal pain, bloating, flatulence and diarrhea^[10]. About 33%-97% of the patients, with a positive BT result, reported symptoms after lactose ingestion (lactose intolerants). On the other hand, 0-71% of the lactose absorbers also appeared to report symptoms^[20]. Several studies indicated that subjects with LI can ingest up to 10-15 g of lactose (comparable to approximately one cup of milk), particularly if taken with food, with no or mi-

nor symptoms^[18,19]. Thus, as recently suggested^[21], in the diagnosis of LI a 10-12 g lactose test should probably be substituted for the classic 25 g lactose BT. Moreover this dosage is more physiological and similar to that usually ingested at any one time.

THERAPEUTIC MANAGEMENT

In patients with hypolactasia, treatment is considered exclusively in the presence of intolerance symptoms. The common therapeutic approach tends to exclude milk and milk products from the diet. However, this strategy may have serious nutritional disadvantages in reduced intake of substances such as calcium and vitamins. Therefore since there are no known adverse effects of LM other than gastrointestinal symptoms not all subjects with lactase deficit have to be treated, only symptomatic ones. Moreover it is necessary to distinguish between primary and secondary lactase deficiency. In the secondary form a temporary lactose-free diet is necessary only until a complete recovery of the causative pathological condition is obtained^[22]. In primary hypolactasia, a temporary (2-4 wk) avoidance of milk and dairy products from the diet should be indicated to obtain symptom remission. Subsequently, a gradual re-introduction of low-lactose dairy products can be suggested, considering the individual threshold dose. In fact there may be sizable individual differences in the dose of lactose that can be tolerated by subjects with LI. In order to raise the threshold dose, both non-pharmacological and pharmacological strategies may be considered (Table 1).

Non-pharmacological approach

Treatment to reduce lactose exposure, while maintaining calcium intake from dairy products, consists of a lactose restricted diet or the use of milk in which the lactose has been pre-hydrolyzed via treatment with lactase supplements^[18,22,23]. Ingestion of milk together with other foods, consumption of fermented and matured dairy products, distribution in milky snacks, are other known methods. Another attractive approach in the management of LI is to increase the lactose load giving the colon time to

adapt^[18,22,24,25]. This is supported by the observation that introduction of lactose to the diet causes temporary and transient symptoms in individuals. Since lactase from intestinal brush border is not an inducible enzyme, the reduction in symptoms may be explained by colonic adaptation.

Pharmacological approach

Enzyme replacement therapy with lactase from nonhuman sources to hydrolyze lactose is another important approach to preventing LI. There are multiple commercially available lactase supplements containing variable amounts of beta-galactosidase from a variety of sources^[18,22,26].

Probiotics are live microorganisms that are nonpathogenic and have beta-galactosidase or lactase intracellularly and may aid in the digestion of lactose ingested by the host. These microorganisms can be added to food products, such as milk and yogurt, or used as supplements. Examples of commonly used probiotics include lactobacillus, bifidobacterium, and saccharomyces^[18,22,27].

Other strategies for management of LI include gut decontaminating agents and anti-microbials, such as rifaximin^[18,28].

However, a recent systematic review^[19] has examined the management strategies for LI. There was not sufficient evidence that lactose-reduced solution or milk with a lactose content of 0 to 2 g, compared with greater than 12 g, is effective in reducing symptoms of LI. Evidence for lactase supplements, probiotics, colonic adaptation, and other agents was also insufficient.

CONCLUSION

LM is the most common type of carbohydrate malabsorption and is caused by low lactase levels. Several diagnostic methods are available for the diagnosis of LM. Recently, the Rome Consensus Conference confirmed the diagnostic validity of lactose BT and proposed a more physiological lactose dose in standardized conditions. Besides the recent introduction of a new GT, correlated with lactase persistence /non-persistence and based on C/T13910 polymorphism, may improve the diagnosis of adult-type hypolactasia, complementing the role of BT. When lactose malabsorption gives rise to symptoms, this is called LI. Diagnosing LI is not straightforward. Many subjects diagnose themselves as being lactose intolerant. However, these individuals may actually be lactase persisters and mistakenly ascribe the symptoms of IBS to LI. Blind lactose challenge should be the recommended method to evaluate LI, but there is no data available either in the literature or in clinical practice regarding its adoption.

Most individuals with presumed LI can tolerate up to 15 g of lactose. As the dose is increased above 15 g, several therapeutic options may be proposed.

Treatment to reduce lactose exposure consists of a lactose restricted diet or the use of lactase supplements. Other strategies include probiotics, colonic adaptation

and antibiotics. Unfortunately there is insufficient evidence that these therapies are effective for LI. A major number of double-blind, placebo-controlled studies should be conducted to evaluate treatment effectiveness in individuals with well-documented LI.

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Prolonged fever after Infliximab infusion

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Abstract

Pharmacologic management for ulcerative colitis (UC) has recently been expanded to include anti-tumor necrosis factor (TNF) therapy for severe disease. Infliximab, a chimeric monoclonal antibody directed against TNF α was first tested in patients with Crohn's disease. In addition to serious infections, malignancy, drug induced lupus and other autoimmune diseases, serum sickness-like reactions, neurological disease, and infusion reactions further complicate the use of Infliximab. We report a case of prolonged fever after Infliximab infusion to treat steroid refractory UC.

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Key words: Infliximab; Fever; Ulcerative colitis; Crohn's disease

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INTRODUCTION

Approximately 15 percent of patients with ulcerative colitis (UC) have a severe attack requiring hospitalization for intravenous corticosteroid therapy during the course of their illness^[1]. Remission rates with intravenous corticosteroid therapy, however, are only 60 percent, and patients who fail therapy often require colectomy^[2]. The probability of colectomy within the first five years after diagnosis ranges from 9 percent in patients with distal colitis to 35 percent in patients with total colitis, most commonly because of failed medical therapy^[3]. Patients with steroid refractory UC who wish to preserve their colon can try Infliximab or cyclosporine.

Traditionally the treatment for UC was a step-up approach that began with 5-aminosalicylates in mild to moderate UC. For patients with more severe disease, corticosteroids were used as a bridge to either a higher dose of 5-aminosalicylates or to immunomodulators, namely 6-mercaptopurine or azathioprine. Finally, when medical therapy was failing or if side effects became intolerable, surgery was also considered. Infliximab is proven to be an effective therapy to induce remission in patients with severe UC whose disease is refractory to high dose corticosteroids. In patients who were hospitalized for intravenous steroids to treat a flare of UC, therapy with Infliximab at a dose of 4-5 mg/kg resulted in colectomy avoidance in 71% of patients at 90 d^[4]. Infliximab, however, is associated with multiple toxicities, namely serious infections, malignancy, drug induced lupus and other autoimmune diseases, serum sickness like reactions, neurological disease, and infusion reactions. We report on a case of prolonged fever after Infliximab.

CASE REPORT

A 61-year old woman with a 15-year history of UC who failed oral prednisone was hospitalized for parenteral steroid treatment. After no clinical response was observed, Infliximab was initiated with dramatic improvement which allowed cessation of steroids. A second

Infliximab infusion was administered after 2 wk with no observed reactions. Nine days after the second dose, the patient reported a fever to 101 degrees Fahrenheit. She complained of drenching night sweats with rigors. Her appetite remained normal, weight was stable and she had no diarrhea or abdominal pain. She denied cough, dysuria, headache, neck stiffness, joint pains or rash. A complete physical examination was unremarkable and results of laboratory testing, including complete blood count, chemistry and liver function tests, were within normal limits. The patient's C-reactive protein was elevated at 41.1 mg/L as was her erythrocyte sedimentation rate at 130 mm/h, white count was 3500 mcL, without left shift. Blood cultures, urine culture, stool culture, including clostridium difficile polymerase chain reaction assay and stool for ova and parasite were all negative for pathogens. A urinary cytomegalovirus test was negative. Computed tomography scans of the chest, abdomen and pelvis were negative except for thickening of the left colon. A repeat colonoscopy showed extensive ulceration and pseudopolyps formation in the left colon with an abrupt cut off in the splenic flexure and the proximal colon was not involved. Biopsies showed moderate inflammatory disease with no pathogens. A brain magnetic resonance imaging showed no active inflammation. Her anti-double stranded DNA and anti-histone antibody were negative. After all infectious causes were excluded, a medication-induced side effect was determined to be the most likely explanation of her persistent fevers. After 25 d the patient became afebrile. Infliximab was discontinued after her second dose and she was referred for an elective colectomy.

DISCUSSION

Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor (TNF)- α . In patients with moderate to severe UC, an induction regimen, followed by maintenance infusions proved to be superior to placebo in achieving clinical response, remission and mucosal healing at 30 and 54 wk of therapy^[5]. Nonetheless, there is a high incidence of infection with anti-TNF- α agents because TNF plays a central role in the initial host response to infection. Cases of tuberculosis, serious bacterial infections, listeriosis, atypical mycobacterial infections, histoplasmosis, coccidiomycosis and pneumonia have been reported. These agents also can effect existing viral infections like hepatitis B or C infection or human immunodeficiency virus. Anti-TNF- α therapy has also been found to cause an increased risk of malignancy, most notably lymphoma. Other potential neurological effects of anti-TNF α medication include demyelinating syndromes, like exacerbation of or new onset of multiple sclerosis and seizures. Several studies have demonstrated that the monoclonal antibody can cause autoimmune dis-

ease, for example, drug induced lupus, vasculitis, uveitis or psoriatic skin lesions or serum sickness-like reactions manifest by myalgias, arthralgias, fever and rash. Injection and infusion reactions are the most common adverse events and limited cases of hepatotoxicity, hematological dyscrasias and even death have been reported^[6,7]. Concomitant immunosuppressant therapy has been shown to decrease formation of antibodies to Infliximab and reduce the likelihood of an infusion reaction, although it has also shown to increase the chance of opportunistic infections and neoplasia^[8].

In our literature search, only one case of long-lasting high fever associated with Infliximab was found in a letter to the editor^[9]. The authors reported a case of a 65-year old woman with rheumatoid arthritis who had ceased corticosteroid and methotrexate treatment secondary to serious side effects and was treated with Infliximab. Three weeks after a second infusion, the patient developed a high fever with rigors that persisted for 13 d. A delayed hypersensitivity reaction was thought to be the cause of the febrile reaction. We have reported a patient with inflammatory bowel disease who developed 25 d of spiking fevers, starting 9 d after a second infusion of Infliximab.

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January 20-21, 2012

American Gastroenterological
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Miami Beach, FL, United States

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World Journal of Gastrointestinal Pharmacology and Therapeutics

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.00000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wicczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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