Brunei Darussalam Journal of Health
is published under the sponsorship of
The Yayasan Sultan Haji Hassanal Bolkiah

BRUNEI DARUSSALAM JOURNAL OF HEALTH

The Brunei Darussalam Journal of Health is published annually by the Institute of Medicine, Universiti Brunei Darussalam. Past issues are available on the website of the university at www.ubd.edu.bn. The BJH publishes peer-reviewed articles pertaining to health in the form of original research findings, review articles, novel case reports of general interest, and original commentaries. Review articles are normally submitted after consulting the editorial board of the BJH.

Manuscripts submitted for publication should meet the following criteria: the material should be original; for research articles, the methods used should be appropriate; results should be unambiguous and supported with data, appropriate use of statistics, and illustrations; conclusions should be reasonable and based on the findings; the topic should be of general health interest. Research involving human subjects or animals should have been approved by the relevant ethical committees.

Manuscripts should be prepared in accordance with the Guidelines set by the International Committee of Medical Journal Editors (ICMJE) as uniform requirements for manuscripts submitted to biomedical journals. Details are available on the website www.icmje.org. A current issue of the journal may also be consulted for formatting articles. Manuscripts should be submitted in Microsoft Word™ format on a CD-ROM or via email (bjh@im.ubd.edu.bn). All correspondence regarding submission of manuscripts should be addressed to: The Editor, The Brunei Darussalam Journal of Health, Institute of Medicine, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE 1410, Brunei Darussalam. Telephone +673-2463001 ext 1965, email: bjh@im.ubd.edu.bn.

The Brunei Darussalam Journal of Health can be purchased as individual copies or regularly subscribed from the library of the Universiti Brunei Darussalam.

Editorial Board of the Brunei Darussalam Journal of Health

Universiti Brunei Darussalam

BRUNEI DARUSSALAM JOURNAL OF HEALTH

BASIC SCIENCES

CLINICAL MEDICINE

A genetic database for DNA-based forensic analysis in Brunei Darussalam

Poh Yee Cheong [1], Paul V.O. Liew [1], Hamydon Ibrahim [1], Bruce Budowle [2]

[1] *Forensic Biology/DNA Laboratory, Department of Scientific Services, Ministry of Health Complex, Commonwealth Drive, Jalan Menteri Besar, Bandar Seri Begawan, Brunei Darussalam BB3910*
[2] *Federal Bureau of Investigation, Laboratory Division, Quantico, VA 22135, USA*

Abstract

Allele frequency data for the 9 short tandem repeat (STR) loci, D3S1358, vWA, FGA, D8S1179, D21S11, D18S51, D5S818, D13S317, D7S820 were determined in the Malay and the Chinese populations in Brunei Darussalam. The combined power of discrimination using these loci was determined to be >0.99999999 for both the Malay and Chinese populations. The combined power of exclusion was determined to be >0.9998 for the Malays and > 0.9999 for the Chinese. The Brunei Darussalam Malay and Chinese database for the 9 STR loci is therefore useful for forensic human identification and parentage testing.

Keywords: Brunei Darussalam population data, Chinese, forensic DNA typing, Malay, polymerase chain reaction, short tandem repeats

Introduction

The Department of Scientific Services, Ministry of Health is in the process of establishing forensic DNA testing for the first time in Brunei Darussalam. If the DNA profile determined from samples at a crime scene matches that of the suspect, they may have come from the same person, or they might be a coincidental match between two persons in the population who happen to share the profile. The purpose of a DNA population frequency database is to permit statistical interpretation of DNA profiling results to assess the probability of a coincidental match. This information determines the strength of the DNA-based forensic evidence in a court of law.

Short tandem repeats (STR) markers are polymorphic DNA loci that contain a repeated nucleotide sequence with 2 – 6 bp in length and they are the most informative PCR-based genetic markers for attempting to individualise biological material. Different allelic forms at each loci are composed of different numbers of repeats. In 1998, the Federal Bureau of Investigation of the United States (FBI) selected 13 such STR loci as the basis for a national database to identify criminals termed the Combined DNA Index System (CODIS). A commercial kit that used multiplex PCR of nine of these STR markers (D3S1358, vWA, FGA, D8S1179, D21S11, D18S51, D5S818, D13S317, D7S820) in one reaction, together with size analysis of the PCR products by capillary electrophoresis for determining the different allelic forms, was selected for establishing a Bruneian DNA-type frequency database.

Correspondence:
Poh-Yee Cheong, M.Sc., Acting Director, Department of Scientific Services, Ministry of Health Complex, Commonwealth Drive, Jalan Menteri Besar, Bandar Seri Begawan, Brunei Darussalam BB3910
Tel: +673 2381899
Fax: +673 2381946
Email address: pohyee6@hotmail.com

Materials and Methods

Blood samples from unrelated and healthy individuals in Brunei Darussalam were collected from blood bank donors and volunteers in the Brunei-Muara and Tutong Districts. The sample population consisted of 167 Malays and 125 Chinese. The blood samples were collected as anonymous samples. Clearance of the study was obtained from the director of the department since there was no research ethical review board available at the time of study. Individuals who provided blood samples were asked to respond to a questionnaire about detailed ethnic information indicating racial pedigree over a period of 4 generations. The criterion to include individual DNA data into the nominated racial group was the selection only of Bruneian individuals who indicated greater than three-quarter heritage of that racial group.

DNA was extracted from blood samples stained on FTA Cards (Whatman Bioscience, MA, USA) according to the manufacturer's protocol (Applied Biosystems AmpFlSTR® Profiler Plus™ User's Manual). Some of the DNA was also obtained from standardized 1mm punch out blood samples stained on Ultrastain Cards (Whatman Bioscience, MA, USA) using the Chelex (Bio-Rad, CA, USA) extraction protocol [1]. The extracted DNA was amplified directly using the AmpFlSTR® Profiler Plus™ Amplification Kits (Applied Biosystems, Foster City, USA) on a GeneAmp 9700 PCR system (Applied Biosystems, Foster City, USA) as described by the manufacturer's instruction. The analysis of the amplified PCR product was performed on the ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, USA). The identification of the alleles was analyzed using the GeneScan (Version 3.1.2) and Genotyper (Version 2.5) software (Applied Biosystems, Foster City USA).

Allele designations were determined by comparison of the sample fragments with those of the allelic ladders. The frequency of each allele for each locus was calculated from the numbers of each genotype in the sample set. In other words, allele frequency determination was made by the gene count method [2], which does not require any assumption regarding population substructure. Unbiased estimates of expected heterozygosity were computed [3]. Possible divergence from Hardy-Weinberg Equilibrium was tested by calculating the unbiased estimate of the expected homozygote/heterozygote frequencies [3-5] and the exact test [6], based on 2000 shuffling experiments. An inter-class correlation criterion for two-locus associations was used for detecting disequilibrium between the STR loci [7]. The power of discrimination and power of exclusion were performed as described by Fisher [8]. The computer programme to perform these tests was developed by R. Chakraborty (Department of Environmental Health, University of Cincinnati, Ohio, USA, http://cgi.uc.edu/).

Results and Discussion

The frequency distributions of the observed allele for the 9 short tandem repeat (STR) loci and other forensic related statistics for the Malay and Chinese populations in Brunei Darussalam are shown in Tables 1 and 2 respectively.

Table 1. Observed STR allele frequencies for the 9 STR loci for Brunei Darussalam Malay population (N=167)

Allele	D3S1358	vWA	FGA	D8S1179	D21S11	D18S51	D5S818	D13S317	D7S820
7	-	-	-	-	-	-	0.0060	0.0030	0.0060
8	-	-	-	-	-	-	0.0090	0.2515	0.2066
9	-	-	-	0.0030	-	0.0030	0.0509	0.0958	0.0509
10	-	-	-	0.0659	-	0.0030	0.3024	0.1467	0.2275
11	-	-	-	0.1617	-	0.0060	0.2275	0.3024	0.3533
12	-	-	-	0.0808	-	0.0659	0.2844	0.1796	0.1347
13	-	-	-	0.2395	-	0.0689	0.1078	0.0150	0.0150
14	0.0180	0.1677	-	0.1856	-	0.1976	0.0090	0.0060	0.0060
15	0.2665	0.1018	-	0.1677	-	0.3174	0.0030	-	-
16	0.3323	0.1317	-	0.0928	-	0.1258	-	-	-
17	0.3054	0.2335	-	0.0030	-	0.0659	-	-	-
<18	-	-	-	-	-	-	-	-	-
18	0.0719	0.2784	0.0180	-	-	0.0449	-	-	-
19	0.0060	0.0778	0.0629	-	-	0.0539	-	-	-

19.2	-	-	0.0030	-	-	-	-	-	-
20	-	0.0090	0.0299	-	-	0.0150	-	-	-
20.2	-	-	0.0030	-	-	-	-	-	-
21	-	-	0.1946	-	-	0.0180	-	-	-
21.2	-	-	0.0030	-	-	-	-	-	-
22	-	-	0.1767	-	-	-	-	-	-
22.2	-	-	0.0180	-	-	-	-	-	-
23	-	-	0.1737	-	-	0.0030	-	-	-
23.2	-	-	0.0060	-	-	-	-	-	-
24	-	-	0.1228	-	-	0.0060	-	-	-
24.2	-	-	0.0030	-	-	-	-	-	-
25	-	-	0.0838	-	0.0030	0.0060	-	-	-
25.2	-	-	0.0090	-	-	-	-	-	-
26	-	-	0.0569	-	-	-	-	-	-
26.2	-	-	0.0030	-	-	-	-	-	-
27	-	-	0.0240	-	-	-	-	-	-
28	-	-	0.0090	-	0.0450	-	-	-	-
28.2	-	-	-	-	0.0030	-	-	-	-
29	-	-	-	-	0.2275	-	-	-	-
30	-	-	-	-	0.2305	-	-	-	-
30.2	-	-	-	-	0.0270	-	-	-	-
31	-	-	-	-	0.1856	-	-	-	-
31.2	-	-	-	-	0.0569	-	-	-	-
32	-	-	-	-	0.0419	-	-	-	-
32.2	-	-	-	-	0.1198	-	-	-	-
33	-	-	-	-	0.0030	-	-	-	-
33.2	-	-	-	-	0.0449	-	-	-	-
34	-	-	-	-	0.0030	-	-	-	-
34.2	-	-	-	-	0.0060	-	-	-	-
35.2	-	-	-	-	0.0030	-	-	-	-
H (obs)	0.234	0.192	0.156	0.210	0.144	0.144	0.198	0.257	0.257
H (exp)	0.278	0.192	0.128	0.163	0.161	0.172	0.236	0.216	0.238
P	0.746	0.360	0.734	0.489	0.479	0.963	0.701	0.435	0.479
PD	0.856	0.929	0.968	0.950	0.950	0.949	0.894	0.919	0.905
PE	0.466	0.617	0.739	0.668	0.677	0.668	0.539	0.574	0.541

H (obs): observed homozygosity ;

H (exp): expected homozygosity ;

P: P-value of the exact tests for Hardy-Weinberg equilibrium ;

PD: power of discrimination ;

PE: probability of excluding paternity.

Table 2. Observed STR allele frequencies for the 9 STR loci for Brunei Darussalam Chinese population (N=125)

Allele	D3S1358	vWA	FGA	D8S1179	D21S11	D18S51	D5S818	D13S317	D7S820
7	-	-	-	-	-	-	0.0320	-	0.0080
8	-	-	-	-	-	-	0.0160	0.2800	0.1320
9	-	-	-	-	-	-	0.0680	0.1280	0.0800
10	-	-	-	0.1320	-	0.0040	0.2040	0.1520	0.1400
11	-	-	-	0.0960	-	0.0040	0.3120	0.2640	0.3800
12	-	-	-	0.1640	-	0.0520	0.2120	0.1120	0.2160
13	-	-	-	0.2280	-	0.1720	0.1560	0.0520	0.0360
14	0.0320	0.2680	-	0.1720	-	0.1800	-	0.0120	0.0080
15	0.3560	0.0320	-	0.1480	-	0.1800	-	-	-
16	0.2800	0.1240	-	0.0440	-	0.1480	-	-	-
17	0.2640	0.2800	-	0.0160	-	0.0800	-	-	-
<18	-	-	0.0040	-	-	-	-	-	-
18	0.0640	0.1880	0.0560	-	-	0.0480	-	-	-
19	0.0040	0.0880	0.0400	-	-	0.0640	-	-	-
19.2	-	-	-	-	-	-	-	-	-
20	-	0.0200	0.0840	-	-	0.0200	-	-	-
20.2	-	-	-	-	-	-	-	-	-
21	-	-	0.1240	-	-	0.0160	-	-	-
21.2	-	-	0.0040	-	-	-	-	-	-
22	-	-	0.1560	-	-	0.0280	-	-	-
22.2	-	-	0.0040	-	-	-	-	-	-
23	-	-	0.2160	-	-	0.0040	-	-	-
23.2	-	-	-	-	-	-	-	-	-
24	-	-	0.1400	-	-	-	-	-	-
24.2	-	-	0.0080	-	-	-	-	-	-
25	-	-	0.0920	-	-	-	-	-	-
25.2	-	-	-	-	-	-	-	-	-
26	-	-	0.0520	-	-	-	-	-	-
26.2	-	-	0.0160	-	-	-	-	-	-
27	-	-	0.0040	-	-	-	-	-	-
28	-	-	-	-	0.0680	-	-	-	-
28.2	-	-	-	-	0.0040	-	-	-	-
29	-	-	-	-	0.2360	-	-	-	-
30	-	-	-	-	0.2640	-	-	-	-
30.2	-	-	-	-	-	-	-	-	-
31	-	-	-	-	0.0960	-	-	-	-
31.2	-	-	-	-	0.0760	-	-	-	-
32	-	-	-	-	0.0160	-	-	-	-
32.2	-	-	-	-	0.1560	-	-	-	-
33	-	-	-	-	0.0080	-	-	-	-
33.2	-	-	-	-	0.0560	-	-	-	-
34	-	-	-	-	-	-	-	-	-

34.2	-	-	-	-	0.0200	-	-	-	-
35.2	-	-	-	-	-	-	-	-	-
H (obs)	0.232	0.216	0.112	0.216	0.128	0.168	0.200	0.200	0.240
H (exp)	0.277	0.207	0.126	0.156	0.170	0.130	0.211	0.200	0.233
P	0.282	0.961	0.508	0.510	0.362	0.598	0.706	0.764	0.181
PD	0.860	0.920	0.962	0.952	0.931	0.964	0.918	0.927	0.908
PE	0.469	0.589	0.741	0.679	0.661	0.733	0.582	0.603	0.559

H (obs): observed homozygosity ;
H (exp): expected homozygosity ;
P: P-value of the exact tests for Hardy-Weinberg equilibrium ;
PD: power of discrimination ;
PE: probability of excluding paternity.

None of the 9 loci were found to deviate significantly from Hardy-Weinberg expectations. The overall results of the statistical analysis suggest that the allele frequency data in the Malay and Chinese populations are reasonable and valid for estimating the rarity of a multiple loci profile.

The inter-class correlation test analysis [7, 8] performed to detect any correlations between alleles used 9 loci for pair-wise comparisons in both the Malay and the Chinese population database. For each sample population, there were a total of 36 pair-wise comparisons performed. For the Malay database, the number of significant departures was one observation (2.8%), which is D18S51/D5S818 ($p = 0.033$). The number of observed departures for the Malay dataset is no more than would be expected by chance. For the Chinese database, there were four significant departures (11.1%), namely vWA/813S317 ($p = 0.48$), vWA/D7S820 ($p = 0.019$), FGA/D8S1179 ($p = 0.027$) and D8S1179/D13S317 ($p = 0.020$). The number observed in the Chinese dataset is higher than expected. However, after Bonferroni correction (9), these departures were no longer significant. The combined power of discrimination was > 0.99999999 for both the Malay and Chinese populations. The combined power of exclusion was > 0.9998 for the Malay population and > 0.9999 for the Chinese population.

To further assess the reliability of the Malay and Chinese population data in Brunei Darussalam, the allele frequencies were compared using an RXC test [10, 11] with other similar populations [12, 13]. The commonly occurring alleles are the same in the respective population comparisons. There were no significant differences.

In conclusion the results suggest that the database based on the 9 STR loci established for the Malay and Chinese populations in Brunei Darussalam has the requisite discriminative ability for use in forensic human identification and for establishing parentage. The complete data set is available to any interested researcher upon request from the corresponding author.

Acknowledgements

The authors thank the mobile staff of the Blood Bank, RIPAS Hospital, and the staff of the Department of Scientific Services in Bandar Seri Begawan, Brunei Darussalam for their assistance in the collection of the blood samples.

References

1. Walsh PS, Meztger DA, Higuchi R 1991. Chelex-100 as a medium for simple extraction of DNA for PCR-based typing from forensic material. BioTechniques 10: 506-513.

2. Li CC 1976. First Course in Population Genetics, Boxwood Press, Pacific Grove, CA, First Edition.

3. Chakraborty R, Smouse PE, Neel JV 1988. Population amalgamation and genetic variation: observations on artificially agglomerated tribal populations of Central and South America. Amer J Hum Genet 43: 709-725.

4. Nei M, Roychoudhury AK 1974. Sampling variances of heterozygosity and genetic distance. Genetics 76: 379-390.

5. Nei M 1978. Estimation of average heterozygosity and genetic distance from a small number of individuals. Genetics 89: 583-590.

6. Guo SW, Thompson EA 1992. Performing the exact test of Hardy-Weinberg proportion for multiple alleles. Biometrics 48: 361-372.

7. Karlin S, Cameron EC, Williams PT 1981. Sibling and parent-offspring correlation estimation with variable family size. Proc Natl Acad Sci USA 78: 2664-2668.

8. Fisher, RA 1951. Standard calculations for evaluating a blood group system. Heredity 5: 95-102.

9. Weir BS 1990. "Multiple tests," in Genetic Data Analysis, Sinauer Associates, Inc., Sunderland, Massachusetts pp 109-110.

10. Lewontin RC, Felsenstein J 1965. The robustness of homogeneity tests in 2 X N Tables. Biometrics 21: 19–33.

11. Roff DA, Bentzen P 1989. The statistical analysis of mitochondrial DNA polymorphisms: and the problem of small samples. Mol Biol Evol 6: 539–545.

12. Ang HC, Sornarajah R, Lim SES, Syn CKC, Tan-Siew WF, Chow ST, et al. 2005. STR data for the 13 CODIS loci in Singapore Malays. Forensic Sc Int. 148: 243-245.

13. Syn CKC, Chuah SY, Ang HC, Lim SES, Tan-Siew WF, Chow ST, et al. 2005. Genetic data for the 13 CODIS STR loci in Singapore Chinese. Forensic Sc. Int 152: 285-288.

Recombinant viruses as vectors for vaccines against human diseases – an overview of a rapidly developing field

Ranjan Ramasamy

Institute of Medicine,
Universiti Brunei Darussalam, Brunei Darussalam

Abstract

Traditional vaccines for human use are based on live attenuated or avirulent organisms, killed organisms or inactivated toxoids. Advances in molecular biology and immunology within the past 30 years have led to the development of a new generation of vaccines such as the hepatitis B vaccine and polysaccharide – protein conjugate vaccine against encapsulating bacteria. An exciting prospect that promises to extend the scope of vaccines from infectious diseases to include cancer, is the use of recombinant viruses as vectors to deliver foreign proteins for immunisation. This article provides an overview, and a perspective, of the state–of- art in the field of viral vector vaccines in relation to human diseases.

Keywords: cancer, immunotherapy, infectious diseases, prophylaxis, vaccines, viral vectors, zoonotic diseases

1. Introduction

The discovery of antibiotics and vaccination are perhaps two of the most important medical advances that have led to increased human longevity in recent times. The successful global vaccination campaign against smallpox has eradicated this ancient scourge of mankind, and is a good example of vaccination saving millions of lives [1]. A related procedure, known as variolation, which is the deliberate inoculation with material from the dried scabs or pus from smallpox survivors, had been practiced for more than 1000 years as a means of inducing immunity to smallpox in China, Egypt and India. Variolation had a high incidence of failure in the sense that many recipients succumbed to a smallpox infection caused by the inoculate. However, it was Edward Jenner (1749-1823) who ushered in the modern era of vaccines when he showed that inoculation with cowpox virus (*Vaccinia*) did not cause fatalities, and successfully prevented a subsequent infection with the closely-related smallpox virus (*Variola*). Louis Pasteur (1822-1895) coined the term vaccination to honour Jenner's finding. Pasteur himself worked on the development of several vaccines, including those for anthrax, cholera and rabies. Since that time, vaccines have been used widely to prevent many other human diseases, including diphtheria, tetanus, whooping cough, polio and tuberculosis. Until recently, the so-called traditional vaccines for these bacterial and viral diseases have relied on the use of killed pathogens, avirulent or attenuated strains of pathogens, or chemically inactivated toxoids to induce protective immunity against the disease-causing organisms. The protection is mediated through vaccination inducing the formation of memory B and T lymphocytes that specifically recognise relevant antigens of the pathogen.

Advances in molecular biology over the past 30 years however have opened the possibility that pure proteins derived from pathogenic organisms, that are produced by recombinant DNA technology in bacteria and yeasts, can be used for vaccination. The first application of this approach was the development in 1986 of a vaccine against hepatitis B based on the expression of the viral surface protein in the common yeast, *Saccharomyces cervisiae* [2]. The hepatitis B virus (HBV) surface protein, which assembles as virus-like particles [2], is purified from yeast cultures, treated with formaldehyde, co-precipitated with potassium aluminum hydroxide adjuvant, and delivered intra-muscularly for vaccination. The hepatitis B vaccine has proved to be safe and highly effective, and is now routinely used in most countries. Recombinant coat proteins from human

Correspondence:
R. Ramasamy MA, PhD,
Institute of Medicine,
Universiti Brunei Darussalam,
Jalan Tungku Link, Gadong BE 1410
Brunei Darussalam
Email: ramasamy@ im.ubd.edu.bn

papilloma viruses (HPV) that similarly form virus-like particles in yeast are the basis for two recently licensed HPV vaccines for the prevention of cervical cancer and genetic warts [3].

Advances in fundamental immunology have also given rise to some novel improvements on traditional vaccines. An example is the development of vaccines based on conjugating bacterial polysaccharides to protein carriers that provide T helper cell epitopes, to stimulate IgG antibody formation and memory antibody responses against carbohydrate antigens. This approach has been effective against encapsulated bacteria such as *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* (pneumococci) and *Neisseria meningitidis* (meningococci) [reviewed in 4].

Even more recently, the use of recombinant non-pathogenic viruses carrying heterologous proteins derived from pathogens for vaccination has been considered to offer great potential. Such vaccines are termed viral vector vaccines and have become the subject of intense investigation in many laboratories. The perceived strength of this approach lies in the use of a live viral infection to engage pathogen-pattern recognizing receptors of the innate immune system and concurrently elicit an adaptive immune response to specific pathogen proteins. Because they mimic natural pathogen infections, viral vector vaccines do not require adjuvants, such as aluminium hydroxide, for eliciting a strong immune response. This article provides a perspective and an overview of current trends in the field of viral vector vaccines, and their potential use in preventing human diseases.

2. Types of viral vectors for vaccines

Many different viruses are being developed as vectors for vaccines. They are either harmless viruses causing self-limiting, mild infections or viruses that have been attenuated through genetic modifications to ensure that they are not virulent to the host. Adenoviruses and the modified *Vaccinia* Ankara virus (MVA) are two popular vectors for experimental vaccine development. Indeed a seminal discovery in this field was the demonstration that foreign genes could be cloned and expressed in the *Vaccinia* virus without interfering with its replication [5, 6]. Lentiviruses (*Retroviridae*), adeno-associated viruses, vesicular stomatitis virus, herpes viruses, reovirus, cytomegalovirus, and measles virus are additional examples of the many types of viruses that are in the advanced stages of laboratory evaluation or actually in clinical trials for use as viral vector vaccines. In the veterinary field, vectors such as the viruses causing fowlpox, Newcastle disease, canine distemper and Venezuelan equine encephalitis, are also being developed for use in vaccines.

Specific tropism for tissues and cell types are important properties of the viral vectors that are used for targeting specific tissue sites for generating protective immunity. For example, reovirus can target microfold or M cells in mucosal epithelia to generate mucosal immunity [7], and specific adenoviral strains also locate to the gut [8]. Lentiviral vectors have the advantage that they can infect non-dividing cells [9]. Some other properties of the viral vectors also provide important considerations for developing vaccines. These include the sites of integration into chromosomal DNA (in the case of lentiviruses and adeno-associated viruses), the robustness of the anti-viral immune response, pre-existing immunity to the virus in the human populations, and the relative ability to elicit the different arms of an effector immune response (e.g. antibodies vs helper T cells vs cytotoxic T cells). Too strong an immune response to viral vector antigens during a primary immunisation, or pre-existing immunity to the virus in a population, can diminish the efficacy of immunisation by the reducing viral replication.

3. Overcoming the problem of immunity to viral vector antigens limiting viral replication

Generation of immunity to viral antigens, that limit the use of boosting immunisations, can be overcome in a number of ways. One approach is to use bacterial plasmid DNA expressing the immunizing protein to prime the immune response before boosting with the recombinant viral vector. This approach, termed the prime-boost method, has been widely used in developing experimental malaria vaccines [10]. Another way is to use different viral vectors for the primary immunisation and subsequent boosting immunisations, and is also being trialed in experimental malaria vaccines [10]. The availability of a platform of differ-

ent adenoviruses that do not show strong immunological cross-reactions is an advantage in this regard. Adenoviral isolates from chimpanzees, which do not normally infect humans, are also available for use as viral vectors for human immunisation where pre-existing immunity to human adenoviruses in the target population is a problem.

4. Vaccination against cancer

The recombinant HBV and HPV vaccines, by preventing the corresponding viral infections, are able to reduce the incidence of liver and cervical cancer respectively. In this sense such vaccines may be considered to fall into the common category of prophylactic vaccines. However viral vector vaccines offer the potential for the therapy of a range of already established cancers i.e. they can constitute therapeutic vaccines. Advances in the field of therapeutic cancer vaccines are closely linked to the development of successful protocols for gene therapy, e.g. for severe combined immunodeficiency caused by adenosine deaminase deficiency [11]. Lentiviruses are particularly advantageous in this respect as they are able to transfect non-dividing cells, are relatively non-oncogenic and are able to stably express a large number of heterologous gene inserts [9]. Genes for T cell receptors that react with the melanoma-specific protein MART-1, and from patients who show good immune-control of melanoma, have been isolated and then transfected via lentiviruses for subsequent expression in CD4+ T cells. The transfected T cells show cytolytic and cytokine producing effector functions that are potentially useful in clinical immunotherapy of melanoma [12, 13]. The immunotherapy procedure can be enhanced by technical variations such as using the lentiviral vector to express additional immune-enhancing molecules, e.g. cytokines like interleukin-15 to expand memory T cell populations.

Advanced tumours have undergone many genetic changes that subvert the host immune system [14, 15] and therefore for immunotherapy to be most effective, it has to be performed after resection of the tumour and radio/chemo-therapy to reduce the tumour burden.

Removal of autologous antigen presenting cells (APC) from the patient, their transfection *ex vivo* with viral vectors expressing tumour specific antigens (or tumour-specific epitopes) and expansion of autologous tumour-specific T cells *ex vivo* before introduction back into the patients, are other approaches that are being investigated in the field of cancer immunotherapy. Recombinant MVA or fowlpox viruses are being used to deliver tumour-specific antigens to APC, together with molecules that increase the efficacy of antigen presentation to T cells such as CD80 and CD54. Advances in this approach to treat cancer have recently been reviewed [16]. The United States Food and Drug Administration have not yet licensed a therapeutic cancer vaccine based on viral vector delivery. However, at least two viral vector products are believed to be in phase III licensure trials for renal and cervical cancers, supported by major pharmaceutical companies.

5. Vaccination against infectious diseases

There is considerable interest in using viral vectors to vaccinate against biological warfare agents such *Bacillus anthracis* and a variety of common infectious diseases. As described below, clinical trials have been performed against human immunodeficiency virus (HIV), *Plasmodium falciparum* (Pf) malaria, *Mycobacterium tuberculosis* and Japanese encephalitis virus among other pathogens.

5.1 Vaccination against zoonotic diseases

Viral vector vaccines are already on the market for animal use in preventing zoonotic and veterinary diseases. For example, an avian influenza-fowlpox recombinant is widely used in Asia to prevent H5N1 in chickens [17] and a MVA-based influenza vaccine aiming at cross-strain protection in humans and fowl is entering clinical trials.

Inactivated whole virus vaccine is effective against foot and mouth disease (FMD) but does not permit distinction between infected and immunised animals, which is necessary in countries where the disease is not endemic but occasional imported outbreaks are possible. Similar considerations apply to bovine tuberculosis in the UK. Therefore attempts are being made to develop viral vector vaccines against these diseases that do not suffer from such a disadvantage. Viral vector vaccines based on adenovirus 5 for FMD [18] and MVA against bovine tuberculosis [19] are being developed for use in the UK and the USA.

An MVA-based recombinant vaccine against rabies, used in bait, has proved superior to attenuated rabies viral vaccines, and has been used in many countries to eliminate rabies from wild foxes that form the principal rabies reservoir among land animals [20].

5.2 HIV

Lentivirus has been used to transfect the genes for a broadly neutralising anti-HIV monoclonal antibody into haemopoietic stems cells that are then matured into B cells and plasma cells producing that antibody [21]. This is an approach that helps overcome the difficulty of generating cross-reactive and neutralizing anti-HIV antibodies through immunisation. A prime–boost approach has been used with naked plasmid DNA (engineered to express the relevant HIV proteins) followed by recombinant MVA in a number of laboratories in the USA and Europe with good safety profile, cytokine producing CD4+ and CD8+ T cell responses and antibodies that bind to the native envelope protein of the virus. Replication competent but attenuated strains of other viruses, including adenovirus are being used in the HIV field [reviewed in 22].

A major drawback in this field was the recent, highly publicized failure of Merck's Phase 2 HIV vaccine trial which was based on adenovirus strain 5 and was funded partly by the National Institutes of Health of the USA [23]. The vaccine was meant to elicit broadly-protective cell mediated immune responses in the vaccinees. Adenovirus strain 5 (Ad5) is a human virus and there is significant pre-existing immunity in human populations. Prior studies in monkey models had shown that the vaccine generated good protective immunity. However the trial went ahead despite the knowledge of pre-existing immunity in human populations because it was felt that the vaccine would overcome this and still elicit significant protective immune responses against HIV antigens. Furthermore, in sub-Saharan Africa, where an HIV vaccine is most needed, >80% of persons are estimated to have been exposed to Ad5 [23]. The trial was halted when no protection was observed and when vaccinated volunteers with high levels of Ad5 immunity were shown to have a greater propensity to become infected with HIV than unvaccinated controls. A tendency for the vaccine to protect was however seen in those vaccinated persons with low levels of immunity to adenovirus. The cause for possibly enhanced HIV infectivity in persons with higher levels of pre-existing antibodies to Ad5 is not clear but recent *in vitro* studies with dendritic cell and T cell co-cultures show that Ad5-antibody immune complexes activate the dendritic cells and increase HIV infection of the cells [24].

Recently it was demonstrated that colorectal immunisation with a recombinant adenovirus carrying herpes simplex virus-2 (HSV-2) glycoprotein B was able to protect mice against a lethal rectal or vaginal challenge with HSV-2 [25]. This finding suggests that a similar approach may be successful against HIV.

5.3 Malaria

The most advanced vaccine against malaria, that is currently undergoing Phase 3 trials, is based on the recombinant *Plasmodium falciparum* circumsporozoite protein produced in yeast in fusion with the hepatitis B virus surface antigen as virus like particles. This vaccine is termed RTS, S. When this vaccine is administered with the best available adjuvant licensed for human use, protection against severe falciparum malaria approaches about 50% [26]. There are also several other malaria vaccines under pre-clinical development [reviewed recently in 27]. My own laboratory has investigated the use of the food grade bacteria, *Lactococcus lactis*, *Lactobacillus reuteri* and *Lb. salivarius*, as vectors for experimental mucosal immunisation of laboratory animals using a *P. falciparum* merozoite surface antigen with promising results [28, 29]. We have also examined the use of a recombinant plant virus, cowpea mosaic virus, to immunise animals with peptide epitopes based on a different *P. falciparum* merozoite surface antigen, but the results showed that the immune response to the virus-specific antigens was too highly dominant for the method to be useful for human vaccination against malaria [30].

However viral vector vaccines based on MVA and adenovirus either used alone or in combined prime-boost strategies with plasmid DNA, are also in clinical trials. These vaccines are based on proteins located on

the surfaces of sporozoites and merozoites, and are designed to elicit effector T cells as well as antibodies [10, 31].

5.4 Tuberculosis

While BCG protects against disseminated tuberculosis (TB) in young children living in non-endemic countries, its efficacy in TB-endemic areas and in adults is in doubt. Based on successful tests in mice and guinea pigs as well as cattle, and encouraging early clinical trials [19], clinical Phase 3 trials using MVA or adenovirus expressing the protective bacterial antigen mycolyl transferase, to enhance BCG -induced immunity in Africa, are being planned.

5.5 Japanese encephalitis

The live attenuated yellow fever virus (YFV) vaccine has a long record of efficacy and safe use in human populations with several hundred millions already vaccinated with it [32]. Efforts are therefore underway to insert genes from other flaviviruses into the YFV to generate chimaeric viruses that can be used for vaccination. An effective vaccine against Japanese encephalitis (JE) using this approach is of particular value due to shortcomings of the existing inactivated and attenuated JE virus vaccines. Based on encouraging pre-clinical trial results [33], it is expected that a chimaeric YF-JE vaccine will be licensed soon for human use.

6. Licensing and safety issues with viral vector vaccines

The production and use of viral vector vaccines entail manufacturing challenges, especially to ensure low cost supply for less affluent countries and livestock markets, safety issues relating to the use of live viruses on a large scale, and environmental issues related to their release or shedding in urine and faeces. The genetic stability of attenuated viruses used for vaccination has to be carefully monitored. The production of recombinant, replication defective, viruses for immunisation involves packaging reactions where helper plasmids coding for critical viral proteins that are missing from the attenuated viral vector are utilised. Recombination between these to generate replication competent virus is possible and requires appropriate safeguards. There is also the possibility that the attenuated or replication defective viral vector can recombine with naturally circulating virus strains to yield virulent viruses. Insertion of the virus sequence into host DNA, however rare, can cause insertional mutagenesis leading to cancer. These potential hazards depend on the nature of the vector virus and can be mitigated in a number of ways.

Additionally, the use of the same viral vector, say adenovirus 5, for delivering vaccines against TB, HIV and malaria in countries where all three diseases are co-endemic, will raise issues regarding anti-vector immunity interfering with vaccine efficacy. The use of different viral vectors or vector strains is expected to avoid this problem. Some of the safety issues with viral vector vaccines have been highlighted recently by the preliminary stoppage of a Phase IIb efficacy trial of Merck's adenovirus 5-based vaccine for HIV [23]. The failure of this vaccine is attributed to the high levels of natural immunity in the vaccinees to the adenovirus 5 vector. This drawback may be overcome by using an adenovirus strain for which there is little human immunity, e.g. a chimpanzee adenovirus.

7. Conclusions

The development of effective and safe vaccines for human use is always a lengthy process, inevitably accompanied by pitfalls. With further advances in the relevant molecular biosciences and technology, it can however be safely predicted that viral vector vaccines will eventually become useful components of our prophylactic armoury against a variety of serious infectious diseases of humans and animals. Virally delivered therapeutic vaccines against cancer are also likely to contribute in a major way to the successful remediation of many forms of human cancers where the traditional treatment methods of surgical excision, chemotherapy and radiotherapy are only partially successful.

References

1. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID 1988. Smallpox and its eradiaction. World Health Organisation, Geneve.

2. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD 1982. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 298: 347-350.

3. Jones T 2006. Vaccines against human papilloma viruses. Curr Opin Investig Drugs 7:699-701.

4. Kaufmann SHE 2007. The contribution of immunology to the rational design of novel antibacterial vaccines. Nature Revs Microbiol 5: 491-504.

5. Mackett M, Smith GL, Moss B 1982. Vaccinia virus: a selectable eukaryotic cloning and expression vector. Proc Natl Acad Sci USA 79: 7415–7419.

6. Panicali D, Paoletti E 1982. Construction of pox virus cloning vectors: insertion of the thymidine kinase gene from herpes simplex virus into the DNA of infectious Vaccinia virus. Proc Natl Acad Sci USA 79: 4927–4931.

7. Rynda A, Maddaloni M, Mierzejewska D, Ochoa-Repáraz J, Maslanka T, Crist K et al. 2008. Low-dose tolerance is mediated by the microfold cell ligand, reovirus protein sigma1. J Immunol 180: 5187-5200.

8. Favier AL, Burmeister WP, Chroboczek J 2004. Unique physicochemical properties of human enteric Ad41 responsible for its survival and replication in the gastrointestinal tract. Virology 322: 93-104.

9. Schambach A, Baum C 2008. Clinical application of lentiviral vectors - concepts and practice. Curr Gene Ther 8:474-482.

10. Moorthy VS, Imoukhuede EB, Keating S, Pinder M, Webster D, Skinner MA et al. 2004. Phase 1 evaluation of 3 highly immunogenic prime-boost regimens, including a 12-month reboosting vaccination, for malaria vaccination in Gambian men. J Infec Dis 189:2213–2219.

11. Aiuti A, Cattaeno F, Galimberti S, Benninghoff U, Cassani B, Callegaro L et al 2009. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N Engl J Med 360:447-458

12. Chhabra A, Yang L, Wang P, Comin-Anduix B, Das R, Chakraborty NG, et al 2008. CD4+CD25- T cells transduced to express MHC class I-restricted epitope-specific TCR synthesize Th1 cytokines and exhibit MHC class I-restricted cytolytic effector function in a human melanoma model. J Immunol 181:1063-70.

13. Yang S, Cohen CJ, Peng PD, Zhao Y, Cassard L, Yu Z et al. 2008. Development of optimal bicistronic lentiviral vectors facilitates high-level TCR gene expression and robust tumour recognition. Gene Ther 15: 1411-1423.

14. Zitvogel L, Tesniere A, Kroemer G 2006. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nature Revs Immunol 6: 715-727.

15. Dunn GP, Koebel GM, Schreiber RD 2006. Interferons, immunity and cancer immunoediting. Nature Revs Immunol 6: 836-848.

16. Loisel-Meyer S, Foley R, Medin JA 2008. Immunogene therapy approaches for cancer: from in vitro studies to clinical trials. Front Biosci 13:3202-3214.

17. Qiao C, Jiang Y, Tian G, Wang X, Li C, Xin X et al. 2009. Recombinant fowlpox virus vector-based vaccine completely protects chickens from H5N1 avian influenza virus. Antiviral Res 81:234-238.

18. Pacheco JM, Brum MC, Moraes MP, Golde WT, Grubman MJ 2005. Rapid protection of cattle from direct challenge with foot-and-mouth disease virus (FMDV) by a single inoculation with an adenovirus-vectored FMDV subunit vaccine. Virology 337: 205-9.

19. Williams A, Goonetilleke NP, McShane H, Clark SO, Hatch G, Gilbert SC et al. 2005. Boosting with poxviruses enhances mycobacterium bovis BCG efficacy against tuberculosis in guinea pigs. Infect Immun 73: 3814–3816

20. Brochier B, Aubert MF, Pastoret PP, Masson E, Schon J, Lombard M, Chappuis G et al. 1996. Field use of a vaccinia-rabies recombinant vaccine for the control of sylvatic rabies in Europe and North America. Rev Sci Tech 15:947-70.

21. Luo XM, Maarschalk E, O'Connell RM, Wang P, Yang L, Baltimore D 2009. Engineering human hematopoietic stem/progenitor cells to produce a broadly neutralizing anti-HIV antibody after in vitro maturation to human B lymphocytes. Blood 113:1422-1431.

22. Nabel GJ 2007. Mapping the future of HIV vaccines. Nature 5:482-484.

23. Ledford H 2008. Merck's HIV vaccine flop brings vectors under closer scrutiny. Nature Biotechnology 26: 3-4.

24. Perreau M, Pantaleo G, Kremer EJ 2008. Activation of a dendritic cell-T cell axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells. J Exp Med 205:2717-25

25. Zhu Q, Thomson CW, Rosenthal KL, McDermott MR, Collins SM, Gauldie J 2008. Immunization with adenovirus at the large intestinal mucosa as an effective vaccination strategy against sexually transmitted viral infection. Mucosal Immunol 1: 78-88.

26. Bejon P, Lusingu J, Olotu A, Leach A, Lievens M, Vekemans J, et al. 2008. Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age. N Engl J Med 359:2521-2532.

27. Targett GA, Geeenwood BM 2008. Malaria vaccines and their potential role in the elimination of malaria. Malaria J 7: 1-9.

28. Ramasamy R, Yasawardena S, Zomer A, Venema G, Kok J, Leenhouts K 2006. Immunogenicity in oral immunisations of rabbits of a malaria parasite antigen displayed by recombinant and non-recombinant Lactococcus lactis. Vaccine 24: 3900-3908.

29. Moorthy G, Ramasamy R 2007. Mucosal immunisation of mice with malaria protein on lactic acid bacterial cell walls. Vaccine 25: 3636-3645.

30. Yasawardena S, Lomonosoff G, Ramasamy R 2003. Expression and immunogenicity of a malaria merozoite surface protein displayed on the small coat protein of cowpea mosaic virus. Ind J Med Res 118:115-124.

31. Draper SJ, Moore AC, Goodman AL, Long CA, Holder AA, Gilbert SC 2008. Effective induction of high-titre antibodies by viral vector vaccines. Nat Med 14:819-821.

32. Querec T, Bennouna S, Alkan SK, Laouar Y, Gorden K, Flavell R, et al. 2006. Yellow fever vaccine YF-17D activates multiple dendritic cell subsets via TLR2, 7, 8, and 9 to stimulate polyvalent immunity. J Exp Med 203: 413-424.

33. Dean CH, Alarcon JB, Waterston AM, Draper K, Early R, Guirakhoo F 2005. Cutaneous delivery of a live, attenuated chimeric flavivirus vaccine against Japanese encephalitis (ChimeriVax)-JE) in non-human primates. Hum Vaccin 1:106-111 .

Uninvestigated dyspepsia in Brunei Darussalam

Vui Heng Chong,

Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Bandar Seri Begawan BA 1710

Abstract

Dyspepsia is a common gastrointestinal complaint both in the primary care and hospital settings. It is defined as an abdominal discomfort that is centered in the upper abdomen. This can be attributed to disorders such as peptic ulcer disease, reflux disease, dysmotility disorders, pancreatic disorders, biliary disorders and malignant processes. Functional or non-ulcer dyspepsia accounts for the majority of the cases. Dyspepsia can be categorized into uninvestigated and investigated dyspepsia depending on whether previous evaluations, particularly endoscopy had been carried out. In theory, the management of dyspepsia is straight forward with exclusion of precipitants, use of anti-secretory agents, pro-kinetics or antacids. However, this can be quite difficult for some cases requiring further evaluations and referral to tertiary referral centre. Warning symptoms and family history are important features in deciding when to initiate investigations. Use of over the counter non-steroid anti-inflammatory drugs or salicylate based medications for minor ailments are increasing and should be enquired into, as they are becoming one of the major causes of non-*Helicobacter pylori (H. pylori)* related ulcer disease. This article highlights the management of uninvestigated dyspepsia in the setting outside of the hospital environments and proposed a simple management algorithm.

Keywords: endoscopy, functional dyspepsia, uninvestigated dyspepsia, management

1. Introduction

Dyspepsia is a commonly encountered gastrointestinal complaint both in the primary care and hospital settings. It utilizes a significant proportion of the health care resources. Dyspepsia is defined as an abdominal discomfort that is centered in the upper abdomen [1-3]. Definitions of dyspepsia vary between different guidelines. In the guidelines published by the British Gastroenterology Society and the Canadian Dyspepsia Working Group, dyspepsia included 'ulcer-like', 'reflux-like' and 'dysmotility-like' dyspeptic symptoms [4, 5]. The American Gastroenterology Association guideline and the Rome II Consensus exclude 'reflux-like' dyspeptic symptoms as part of dyspepsia and categorized it under gastro-oesopageal reflux disorders [3, 6].

Correspondence:
Vui Heng Chong, MRCP, FAMS,
Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA 1710
E-mail: chongvuih@yahoo.co.uk

Generally, symptoms arising from the stomach, lower oesophagus, biliary tract, liver and pancreas may be described as dyspepsia. Functional or non-ulcer dyspepsia is a chronic relapsing condition, accounting for upto 60% of patients with dyspepsia [6], and is a major cause of absenteeism [7]. Management begins with a thorough history to localize the possible causes. Warning symptoms and family history of malignancies are important in deciding when to initiate investigations. Use of anti-secretory, antacids, pro-kinetics, eradication of *Helicobacter pylori* infection and avoidance of precipitating agents such as non steroidal anti-inflammatory drugs (NSAIDs) is currently the standard practice [4-5, 8].

2. Prevalence of dysypesia

2.1 World perspectives

Dyspepsia is a common complaint for consultation, representing 5% of all primary care physician visits [9]. The estimated prevalence rate of uninvestigated dyspepsia ranges from 10-40% with less than half seeking medical care [10]. A phone interview study done in Hong Kong,

showed that the prevalence of uninvestigated dyspepsia was 18.4% [11]. In the Southeast Asian region, a study done in Singapore showed that uninvestigated dyspepsia was much lower, with an overall prevalence rate of 7.9% [12]. Chinese to have a slightly higher prevalence of 8.1% compared to the Malays (7.3%) and the Indians (7.5%). This difference may represent a real difference in prevalence, as it is widely recognised that the cultural background may influence presentation and health seeking behavior.

2.2 Negara Brunei Darussalam perspective

Dyspepsia has been referred to as 'oorri', 'dugal', 'indigestion' or 'gastric' in the local setting. The prevalence of uninvestigated dyspepsia among the general public based on a questionnaire study done locally was 16.8%, being higher among females than males. It is also higher in patients with underlying chronic disorders such as end-stage renal failure patients undergoing regular hemodialysis (34.9%) and rheumatology patients (48%) [13,14]. The overall prevalence of gastrointestinal symptoms in the general populations is shown in Table 1. Dyspepsia represents the leading indications for upper gastrointestinal endoscopy at 59.6 % in our institution, in agreement with published data [5, 15].

Table 1. Prevalence of gastrointestinal symptoms among the public in Brunei Darussalam

Symptoms	***Prevalence***
Nausea	10.6%
Vomiting	1.5%
Dysphagia	0.3%
Odynophagia	1.2%
Heartburn	8.7%
Early satiety	13.5%
Dyspepsia	16.8%
Abdominal bloating	11.4%

Questionnaire study (n=506)

3. Causes of dyspepsia

The causes of dyspepsia can be divided into organic (structural) and non-organic. For majority of the patients (60%), the underlying cause is often not found despite extensive investigations and such patients are often labeled as suffering from non-ulcer dyspepsia or functional dyspepsia [5]. This is best defined by the Rome II Consensus for functional gastrointestinal disorders, Table 2 [3]. The organic causes include peptic ulcer diseases (*H. pylori or non-H. pylori* related), malignant processes of the upper digestive tracts and disorders of the lower oesophagus, biliary tract, pancreas and liver. The pathophysiology of non-ulcer dyspepsia remains poorly defined, however sensory and motor disorders of the stomach and duodenum appear to be a have a major role in at least a subset of patients [16, 17]. It is important to consider and assess for the presence additional gastrointestinal symptoms as overlapping and clustering are reported to be common, particularly in those with functional dyspepsia [18-21].

Table 2. Rome II Criteria for non-ulcer or functional dypepsia (1999)

At least 12 weeks, this need not be consecutive, within the preceding 12 months of:

- Persistent or recurrent dyspepsia (pain or discomfort centered in the upper abdomen); and
- No evidence of organic disease (including at upper endoscopy) that is likely to explain symptoms; and
- No evidence that dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not irritable bowel syndrome).

In Brunei Darussalam, patients who were evaluated for dyspepsia in the year 2003, 71.3% had normal findings or gastritis/duodenitis on endoscopy, representing the subset that probably had functional or non-ulcer dyspepsia. Reflux disease was seen in 19.3% and peptic ulcer disease in 12.8%. Not surprisingly, the underlying causes of dyspepsia are often the main drive to the current management strategies [5, 22].

4. Management of dyspesia

4.1 Uninvestigated Dyspepsia

The current management strategies include prompt endoscopy, the 'test and treat' strategy for *H. pylori* and trial of empiric anti-secretory therapy [23]. Due to the complex interplay of the numerous causes, there is currently no single treatment approach that provides a constant and consistent relief of the dyspeptic symptoms.

Patients with alarming symptoms should undergo prompt endoscopy in addition to initiating empiric therapy. A list of such danger symptoms is shown in Table 3. Endoscopy is usually performed without sedation and this is well accepted in our local setting [24]. The issue regarding when to refer for endoscopy has been a matter of debate. Lowering the age of consideration will increase the referral rate and health care cost, making this very unattractive and not cost-effective. This is particularly true in countries where cost of investigations represent major issues. The age consideration needs to be taken into account especially in countries with high gastric cancer rate. Hence, certain cases need to be evaluated on a case by case basis depending on the clinical presentations, risk factors such as strong family history of bowel cancers and warning symptoms.

Table 3. Danger symptoms that should prompt immediate evaluation

• symptoms onset at age > 45 years old *,
• weight loss,
• recurrent vomiting,
• dysphagia,
• gastrointestinal bleeding,
• anaemia,
• family history of gastric cancer,
• abnormal findings on clinical examinations, and
• persistence of symptoms despite appropriate therapies

*Variable depending on other risk factors and history of malignancy

The presence of additional overlapping or clustering of symptoms should be managed accordingly depending on the nature of these symptoms. Additional investigations such as colonoscopy and radiological imaging of the pancreatico-hepatobiliary system may need to be carried out.

4.2 General measures and advice

Often dyspepsia is associated with irregular meals and consumptions of food that may predispose to onset of symptoms (such as heartburn with sour food). Types of food or lifestyle habits that may predispose to or lead to a worsening of dyspepsia are listed in Table 4. Modifications of eating habits and avoidance of certain food or medications may help relieve symptoms without ever needing any medications. Often these symptoms resolve spontaneously when the precipitants are avoided. Use of over the counter medications such as NSAIDs, salicylate based medications, traditional medications or even medications prescribed from other clinics, should always be enquired. A questionnaire study showed that the local prevalence rate of complementary and alternative medication (CAM) usage among the public was 21.1%. Therefore, it is important to inquire into CAM use as these may account for some of the symptoms [25]. Although many medications can lead to gastrointestinal disturbances, some are more common inducers than others. A list of commonly used medications that may cause dyspepsia is shown in Table 5.

Table 4. Lifestyles and dietary habits that predispose or worsen dyspepsia

• Irregular dietary habit and unhealthy dietary habit (i.e. over indulgence)
• Consumption of food that cause intolerance; spicy, oily, lactose, curry, fatty, etc.
• Smoking
• Alcohol
• Coffee
• Sedentary lifestyle

Importantly, thorough explanation and reassurances need to be given, particularly for those with non ulcer dyspepsia. This will also avoid any further unnecessary investigations.

4.3 Complementary and alternative medicine

Use of CAM is widely practiced by patients and it is important to enquire what have been taken as they may be the cause of patients' complaints [26]. This similarly true in our local setting where CAM is used for all kind of ailments either on their own or supplementary to prescribed medications [25]. Complementary medications can also be taken to treat dyspepsia, however data on their efficacy is lacking. A systematic review of available studies on alternative medicines has shown that peppermint and caraway have some effects on dyspepsia [27]. No comments can be made regarding the available CAM use for the management of gastrointestinal disorders in our local settings as there is no study to date that has scientifically assessed their use.

Table 5. Medications that are associated with dypepsia

Over the counter (OTC) medications	
• OTC analgesia	NSAIDs
• Salicylate based medicine	Kaki Tiga (Medicinal Powder), Kaki Tiga (Headache Powder), Tooprin, Three Rifles Medicated Powder, Kangda 800.
Prescribed medications	
• Anti-platelets	Aspirin
• Cardiac medications	Digoxin
• Respiratory medications	Theophylline
• Antibiotics	Tetracycline, Doxycycline, Erythromycin
• Analgesics	
• NSAIDs	Naproxen (Naproxyn), Naproxen Sodium (Synflex), Ibuprofen, Diclofenac (Voltaren), Indomethacin, Ketoprofen (Oruvail), Sulindac
• Others	Bisphosphonate, Potassium supplement, Iron tablets
Traditional medications	
• Traditional medications particularly those taken for musculoskeletal aches	
• Jamu	
• Traditional Chinese medications	

4. 4 Pharmacotherapy

4.4.1 Antacids

Use of antacids such as magnesium hydroxide, aluminum hydroxide, and calcium carbonate are widely practiced either prescribed or self-medicated. Clinical trials have generally not shown significant benefits from antacids [28, 29]. However, due to their availability, low cost and relatively few side effects, use of antacids will remain as part of the first line of dyspepsia management.

4.4.2 Pro-kinetics

Studies on the use of pro-kinetics have produced mixed results. Pro-kinetics agents have been shown to be more effective than placebo in the management of dyspepsia and comparable to histamine-2-receptors antagonists (H2RA) [29]. However, others have shown no benefit of cisapride over placebo [30, 31]. Pro-kinetics may be useful for the management of 'dysmotility-like' dyspepsia, which manifest with symptoms of nausea, vomiting, bloating and early satiety. Currently the options of pro-kinetics (Domperidone and Metaclopramide) are limited with the withdrawal of cisapride from the market due to the association with fatal arrhythmias.

4.4.3 Anti-secretory medications

Histamine-2-receptor antagonists

H2RA medications are widely used for treatment of dyspepsia and have been shown to be superior to placebo and comparable to pro-kinetics for the treatment of dyspepsia [29, 32]. These agents are effective in the treatment of reflux disease and peptic ulcer diseases [33, 34]. Studies comparing H2RA to proton pump inhibitors have shown mixed results but evidences favour the later particularly, in those with 'ulcer-like' or 'reflux-like' dyspepsia [29, 32, 35-37].

Proton pump inhibitors

Potent acid suppression medications particularly the proton pump inhibitors have been shown to be useful in the management of dyspepsia regardless of the sub division of symptoms. Proton pump inhibitors although costing slightly more, have been shown to be superior to placebo, pro-kinetics (Cisapride) and H2RA (Ranitidine) [32]. The response rates of complete relief of symptoms after four weeks of therapies were 24%, 4%, 8% and 11% for omeprazole, placebo, cisapride and ranitidine respectively. Similarly, another randomized multi-centre study of patients with 'ulcer-like' and 'reflux-like' dyspepsia showed superior symptoms-relief after four weeks with lansoprazole compared to ranitidine (69% vs. 44%, $p = 0.001$) [38].

4.4.4 Miscellaneous

Use of sensory modulators such as tricyclic antidepressant and the newer selective serotonin reuptake inhibitor (SSRI) have been shown to help in some of these symptoms, particularly the subset with non-ulcer or functional dyspepsia. However, before considering starting such treatment, exclusion of organic causes need to be done and therefore such group of patients needs to be referred to specialized unit. This group of patients represent one that can be quite challenging to manage and may require referral for psychological assessments, counseling and therapy in additional to their usual therapy for dyspepsia.

5. Overview

For many persons, the symptoms of dyspepsia are of short duration and mild and are therefore self-managed without ever consulting a doctor [39]. In the management of dyspepsia, differentiating symptoms subsets as described seem a good and reasonable approach, enabling physician to prescribe the 'appropriate' therapy (anti-secretory alone or with a pro-kinetic agents). However, the presence of multiple terminologies for dyspepsia may lead to confusion and misdiagnosis. Similarly, there is a considerable overlap of symptoms presenting among the patients and the difference subgroups; making this approach unhelpful in a subset of patients [40].

An empiric trial of antacid, anti-secretory (H2RA or proton pump inhibitors) or pro-kinetics is recommended before initiating any investigations particularly in those without warning symptoms. Patients started on a trial of empiric therapy should always be followed up to assess symptoms response, usually 4 to 8 weeks later. Follow-

up within this time period is recommended because it is unlikely that an early (and hence curable) gastric cancer would progress to advanced cancer within one to two months of presentation [5]. Patients who symptoms persist or improve only slightly should be evaluated further with routine blood tests (full blood count, erythrocyte sedimentation rate and liver function tests), faecal occult blood, ultrasound of the abdomen and upper gastrointestinal study (endoscopy or barium study).

Often, the question of how long to maintain patients on their medications is debated. Currently, there is no recommendation as to duration of treatment. Although, use of anti-secretory therapies with H2RA and proton pump inhibitors have been shown to be safe up to ten years of consumption, it is advisable to stop the medications if symptoms have already settled. Taking acid suppression medications on an as required basis has been recommended to reduce unnecessary consumption and reduce health care cost. However, patients need to be followed up and educated on their condition and treatment regime. Patients who require regular analgesics should try alternatives such as non-NSAIDs analgesics (distalgesics) if possible and the duration of treatment kept to a minimal. Co-prescription of anti-secretory medications is an alternative strategy.

In Brunei Darussalam, the endoscopy unit provides an open access referral for endoscopy in patients who require this investigation. Rapid urease tests for *H. pylori* are routinely done for patients regardless of the indications for endoscopy. *H. pylori* is the main cause of peptic ulcer diseases and is a recognised cause of malignancies such as gastric cancer and mucosa-associated lymphoid tissue l (MALT) lymphoma [41, 42]. Eradication of this infection has been shown to reduce peptic ulcer recurrence. Our local prevalence is currently around 25% [15]. The rates are higher among the expatriates and the indigenous groups. Among Bruneian expatriates; the Nepalese have the highest prevalence [15, 43].

Association with non-ulcer or functional dyspepsia is not well established and studies looking at treatment responses of non-ulcer or functional dyspepsia with *H. pylori* eradications have shown mixed results. Generally due to the association of *H. pylori* with significant diseases, it is our policy to give eradication therapy if *H. pylori* is positive. As the only mean available to detect *H. pylori* in the local setting is with gastric biopsies for rapid urease test or histology, patients need to be referred. Serology for *H. pylori* can be done but require special arrangements. Some private clinics can do these tests (serology and urea breath test) as part of the investigations that are available to them. Positive serology indicates exposure to the organism but not necessary active infections whereas, a positive urea breath-test would indicate active infection. Another alternative method for evaluating the upper gastrointestinal tract is by barium contrast study. However this is only recommended if patients refuse endoscopic evaluations.

Table 6. List of available medications in Brunei Darussalam

Antacids

- Evilene Forte Suspension *, Mucaine Gel, Gaviscon Tablet/Liquid, Hydrogel Tablet *, *Bismag, Gelusil Plus, Wiselin, Wiselin Plus, Alucid Suspension Antacid Gel Plus, Cenvite, Actal, Actal plus,* Victor Antacid, Wiselin Victor, Fullcon's Antacid,Velat-u Stomach tablet, Sure-lin Stomach tablet

Pro-kinetics

- Domperidone (Motilium)*, Metaclopramide (Maxolon)*

Acid Suppression Medications

Histamine -2- receptors antagonist

- Ranitidine *

Proton pump inhibitor

- Omeprazole, Esomeprazole (Nexium)**

* Medications available in peripheral clinics

** Available on name patient basis in government hospital/ also available in JPMC medical centre

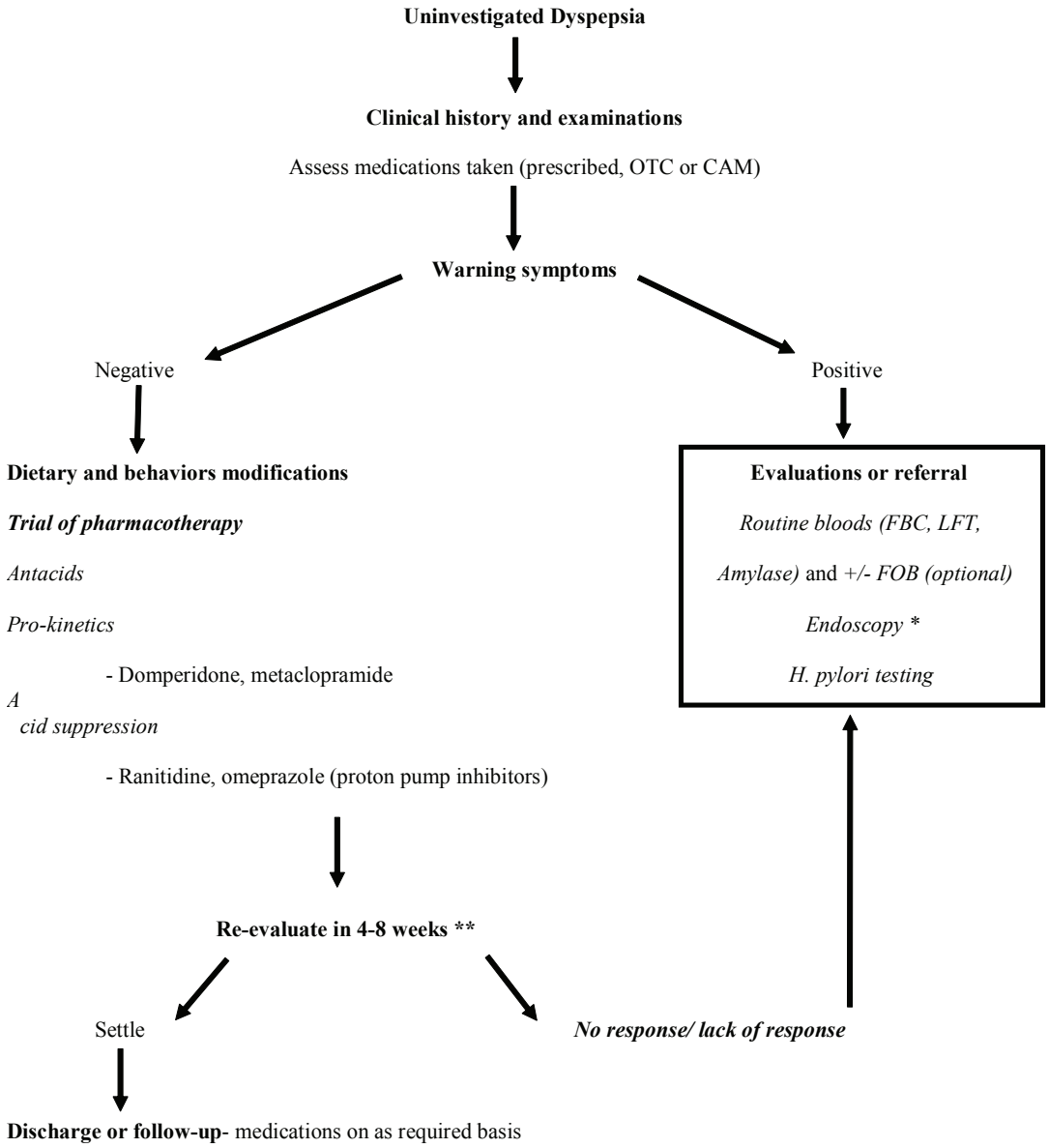
OTC antacids (aluminum, magnesium, calcium carbonate and semithicone based antacids) available in certain shops

In our local setting, the empirical therapy represents a trial of anti-secretory therapy (H2RA or proton pump inhibitors) with or without antacids. Available medications for treatment of dyspepsia are listed in Table 6.

Prompt referral for endoscopy is always indicated if there are any warning symptoms, no response to empiric treatment or concern of serious underlying pathologies. A proposed simple algorithm for the management of uninvestigated dyspepsia in the peripheral clinic setting is shown in Figure 1.

In conclusion, uninvestigated dyspepsia remains a problem commonly encountered in our daily practice and

Figure 1. Algorithm for management of uninvestigated dyspepsia



OTC- Over the counter

* Endoscopy represents an important part of evaluation and referral should be prompt if any warning symptoms or failure to response to empirical therapy

** evaluate sooner if there is concern

need to be managed appropriately. Functional or non-ulcer dyspepsia represents the main subset of uninvestigated dyspepsia and their management can be challenging. Empirical therapies are recommended especially for those who do not have any warning symptoms; however they should be monitored for treatment responses. Patient should undergo prompt endoscopy if there is no response to empiric therapies or if there are warning symptoms. It is hope that this review will give guidance to the front line physicians on the management of uninvestigated dyspepsia that they come across in their daily practice.

References

1. Drossman DA, Corazzairi E, Talley, NJ 2000. The functional gastrointestinal disorders. In: Diagnosis, Pathophysiology and Treatment: a Multinational Consensus, 2nd edition. Degon Mclean, Virginia, USA.

2. Westbrook JI, McIntosh JH, Talley NJ 2000. The impact of dyspepsia definition on prevalence estimates: a consideration for future researchers. Scand J Gastroenterol 35: 227-33.

3. Talley NJ, Stanghellini V, Heading R, et al 1999. Functional gastroduodenal disorders. Gut 45: 137-142.

4. British Gastroenterology Society. Dyspepsia management guideline 2002. http://www.bsg.org.uk/pdf_word_docs/dyspepsia.doc. Accessed 15th August 2006.

5. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, Barkun A, et al (2000). An evidence based approach to the management of uninvestigated dyspepsia in the era of H. pylori. CMAJ 152: S3-23.

6. Talley NJ, Silverstein MD, Agréus L, Nyrén O, Sonnenberg A, Holtmann G 1998. AGA technical review: evaluation of dyspepsia. Gastroenterology 114: 582-95.

7. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, et al. 1993. US householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 38: 1569-80.

8. Talley NJ 2002. Review article: dyspepsia: how to manage and how to treat. Aliment Pharmacol Ther 16: 95-104.

9. Holtmann G, Goebell H, Talley NJ 1994. Dyspepsia in consulters and non-consulters: prevalence, health care seeking behaviour and risk factors. Eur J Gastroenterol Hepatol 5: 917-24.

10. El-Serag HB, Talley NJ 2004. Systematic review: the prevalence and clinical course of functional dyspepsia. Aliment Pharmacol Ther 19: 643-54.

11. Hu WH, Wong WM, Lam CL, Lam KF, Hui WM, Lai KC, Xia HX, Lam SK, Wong BC 2002. Anxiety but not depression determines health care seeking behaviors in Chinese patients with dyspepsia and irritable bowel syndrome: a population based study. Aliment Pharmacol Ther 16: 2081-8.

12. Ho KY, Kang JY, Seow A 1998. Prevalence of gastrointestinal symptoms in a multiracial Asian population, with particular reference to reflux-type symptoms. Am J Gastroenterol 93: 1816-22.

13. Chong VH, Zinna HS 2005. Prevalence of gastrointestinal symptoms among patients undergoing hemodialysis in Suri Seri Begawan Hospital. Brunei Int Med J 4:55-59.

14. Chong VH, Wang CL 2008. Higher prevalence of gastrointestinal symptoms among patients with rheumatic disorders. Singapore Med J 49:419-24.

15. Chong VH, Lim KC, Rajendran N 2008. Prevalence of active Helicobacter pylori infection among patients referred for endoscopy in Brunei Darussalam. Singapore Med J 49:42-6.

16. Samsom M, Verhagen MA, VanBerge Henegouwen GP, Smout AJ 1999. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. Gastroenterology 116: 515-20.

17. Tack J, Peissevaux H, Coulie B, Caenepeel P, Janssens J 1998. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 115: 1346-52.

18. Frissora CL, Koch KL 2005. Symptom overlap and comorbidity of irritable bowel syndrome with other conditions. Curr Gastroenterol Rep 7:264-71.

19. Dickman R, Feroze H, Fass R 2006. Gastroesophageal reflux disease and irritable bowel syndrome: a common overlap syndrome. Curr Gastroenterol Rep 8:261-5.

20. Talley NJ 2006. A unifying hypothesis for the functional gastrointestinal disorders: really multiple diseases or one irritable gut? Rev Gastroenterol Disord 6:72-8

21. Locke GR 3rd, Zinsmeister AR, Fett SL, Melton LJ 3rd, Talley NJ 2005. Overlap of gastrointestinal symptom complexes in a US community. Neurogastroenterol Motil 17:29-34.

22. Johnsen R, Bernersen B, Straume B, Forde OH, Bostad L, Burhol PG 1991. Prevalences of endoscopic and histological findings in subjects with and without dyspepsia. Br Med J 302: 749-52.

23. Chey WD, Moayyedi P 2004. Review article: uninvestigated dyspepsia and non-ulcer dyspepsia- the use of endoscopy, and the role of Helicobacter pylori eradication and antisecretory therapy. Aliment Pharmacol Ther 19: 1-8.

24. Chong VH, Rajendran N 2006. Referral for unsedated upper gastrointestinal endoscopy in RIPAS Hospital: Patient's perception. Brunei Int Med J 5:71-5.

25. Chong VH, Rajendran N, Wint Z 2008. Prevalence and predictive factors for complementary and alternative medicine use in Brunei Darussalam. Singapore Med J 49:1012-6.

26. Ernest E 2000. Prevalence of use of complementary/ alternative medicine: a systematic review. Bull WHO 78: 252-7.

27. Coon JT, Ernest E 2002. Systematic review: herbal medicinal products for non-ulcer dyspepsia. Aliment Pharmacol Ther 16: 1689-99.

28. Nyrén O, Adami HO, Bates S, Bergström R, Gustavsson S, Lööf L, Nyberg A 1986. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. N Engl J Med 314: 339-43.

29. Gotthard R, Bodemar G, Brodin U, Jönsson KA 1988. Treatment with cimetidine, antacids, or placebo in patients with dyspepsia of unknown origin. Scand J Gastroenterol 23: 7-18.

30. Hansen JM, Bytzer P, Schaffalitzky de Muckadell OB 1998. Placebo-controlled trial of cisapride and nizatidine in unselected patients with functional dyspepsia. Am J Gastroenterol 93: 368-74.

31. Champion MC, MacCannell KL, Thomson AB, Tanton R, Eberhard S, Sullivan SN, et al. 1997. A double-blind randomized study of cisapride in the treatment of nonulcer dyspepsia. The Canadian Cisapride Nud Study Group.. Can J Gastroenterol 11: 127-34.

32. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, Barkun A, Thomson A, et al. 2005. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study. Am J Gastroenterol 100:1477-88.

33. Dobrilla G, Comberlato M, Steele A, Vallaperta P 1989. Drug treatment of functional dyspepsia. A meta-analysis of randomized controlled clinical trials. J Clin Gastroenterol 11: 169-77.

34. Tally NJ. Drug treatment of functional dyspepsia 1991. Scand J Gastroenterol 26 S182: 47-60.

35. Redstone HA, Borrowman N, Veldhuyzen van Zanten SJ 2001. H2-receptor antagonists in the treatment of functional (non-ulcer) dyspepsia: a meta-analysis of randomized controlled clinical trials. Aliment Pharmacol Ther 15: 1291-301.

36. Meineche-Schimdt V, Krag G 1997. Antisecretory therapy in 1017 patients with ulcer-like or reflux-like dyspepsia in general practice. Eur J Gen Prac 3: 125-30.

37. Mason I, Millar LJ, Sheikh RR, Evans WM, Todd PL,

Turbitt ML, et al..1998. The management of acid-related dyspepsia in general practice. A comparison of an Omeprazole versus and an antacid-alginate/ranitidine management strategy. Aliment Pharmacol Ther 12: 263-71.

38. Jones RH, Baxter G 1997. Lansoprazole 30 mg daily versus ranitidine 150 mg b.d in the treatment of acid-related dyspepsia in general practice. Aliment Pharmacol Ther 11: 541-6.

39. Johannessen T, Petersen H, Kristensen P, Kleveland PM, Dybdahl J, Sandvik AK, et al. 1993. The intensity and variability of symptoms in dyspepsia. Scand J Prim Health Care 11:50-55.

40. Talley NJ, Weaver AL, Tesmer DL, Zinsmeister AR 1993. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. Gastroenterology 105: 1378-86.

41. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. 1991 Helicobacter pylori infection and the risk for gastric carcinoma. N Engl J Med 325: 1127-31.

42. Wotherspoon AC, Ortiz Hidalgo C, Falzon MR, Isaacson PG 1991. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet 338: 1175-6.

43. Chong VH, Jalihal A 2006. Prevalence of Helicobacter pylori amongst expatriates from the Indian subcontinent in Southeast Asia. Indian J Gastroenterol 25: 45-6.

Findings among patients referred for endoscopy in Brunei Darussalam with special reference to dyspepsia

Vui Heng Chong

Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Bandar Seri Begawan BA 1710, Negara Brunei Darussalam.

Abstract

Dyspepsia is a frequent gastrointestinal complaint and a common reason for endoscopy. This study assessed the spectrum of findings among patients referred for endoscopy, particularly those with dyspepsia. All patients referred for endoscopy (n = 2,066) for the first time over a two year period in at RIPAS hospital in Brunei Darussalam were retrospectively reviewed. Dyspepsia represented the commonest indication (53.3%). Patients with dyspepsia were younger compared to the non-dyspepsia group (44 ± 16.1 vs. 50.3 ± 18.7 years old, $P<0.001$). The commonest findings were gastritis/duodentitis (41.8%), normal findings (26.9%), peptic ulcer disease (9.9%) and isolated oesophagitis (6.4%). Malignancies accounted for 0.8% (gastric, n = 8 and oesophagus, n = 1). The prevalence of *Helicobacter Pylori (H. pylori)* infection among this group was 27.5% being higher in male patients ($P<0.001$). Among all indications, the *H. pylori* prevalence was 26.2%, also higher in male patients ($P<0.001$). Sixty-four percent of patients with peptic ulcer disease did not have dyspepsia as the main complaint. Prevalence of *H. pylori* among peptic ulcer disease were lower than expected; duodenal ulcer (45%), gastric ulcer (40.0%) and gastric/duodenal ulcers (33.3%). Overall, malignancies were detected in 1.3% (oesophagus, n = 5, and stomach, n = 21 [adenocarcinoma, n = 19 and lymphoma, n = 2]). Sixty-two percent of gastric malignancies (n = 13/21) did not have dyspepsia as a main complaint. However, all had warning symptoms. In conclusion, endoscopic findings among Bruneian patients with dyspepsia are comparable to published findings. However, only a third of gastric malignancies had dyspepsia. The prevalence rates of *H. pylori* among those with peptic ulcer diseases are lower that expected, probably due to overall declining prevalence of this infection.

Keywords: Brunei, dyspepsia, endoscopy, Helicobacter pylori, peptic ulcer disease

1. Introduction

Dyspepsia is one of the commonest gastrointestinal (GI) complaints encountered in the daily clinical practice and represents a significant burden on the health care system [1-3]. This occurs despite a large proportion of patients with dyspepsia that self-medicate and do not present for evaluations [4]. Endoscopy is an important tool in the evaluation of dyspepsia and is recommended, particularly for those patients who are over the age of 45 with new onset symptoms, non-response to empiric therapies or presence of warning symptoms [5-7]. Endoscopy is the most effective investigation as it allows direct visualisation of the upper GI tract, sampling and testing for *Helicobacter pylori* infection and also permits therapies to be instituted if required, particularly for GI bleeding.

It is useful to have the background knowledge of the spectrum of findings amongst this group of patient as published data is scarce. This will greatly help in assessing which patients are likely to need endoscopy or require urgent endoscopy as the number of referred cases is likely to increase. The knowledge will also make a change in the spectrum of findings to be detected as the spectrum of gastrointestinal disorders changes, particularly with the declining prevalence of *H. pylori* infection. The aim of the present study was to characterize the findings amongst patients referred for endoscopy, particularly those with dyspepsia.

Correspondence:
Vui Heng Chong, MRCP, FAMS,
Gastroenterology Unit,
Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA 1710
E-mail: chongvuih@yahoo.co.uk

2. Methods

2.1 Setting

The Endoscopy Unit in the local setting, is the main unit that provides endoscopic services to three (Brunei-Muara, Tutong and Temburong districts) of the four districts in Negara Brunei Darussalam. The other district (Kuala Belait) has a small unit within in the district general hospital. The Endoscopy Unit serves a population of approximately 294,400. The unit has an open access referral systems for upper GI endoscopy and lists are performed daily in the morning. The waiting time for endoscopy averages two to three days.

2.2 Procedures

Endoscopy was carried as per normal routine with topical anaesthesia. We only use intravenous sedations if patients requested or patients were very anxiously and likely to undergo repeat procedures. During the procedure, we routinely obtain antral or body biopsies for *H. pylori* testing with either rapid urease test (*CLOTest*, Delta West Ltd, Bentley, West Australia) or histology (Half Gram stain) or both. A positive test was taken as either test or both test being positive.

2.3 Patients

All patients who had undergone endoscopy over a twenty four months period (January 2003 to December 2004) were identified from the endoscopic register. During this two years period, there were 2,530 upper GI endoscopies performed. Repeat endoscopies or patients who previously had endoscopy or incomplete/missing records were excluded. Only patients who had undergone endoscopy for all indications for the first time (n = 2,066) were evaluated.

2.4 Definitions

Dyspepsia was taken as any abdominal discomfort that is centred in the epigastrium. All subtypes of dyspepsia such as 'ulcer like', 'heartburn like' or 'dysmotility like' were categorized as one. Gastroesophageal reflux was taken as any retrosternal burning chest pain with or without radiation up ward or regurgitation.

Findings were considered significant if they were; peptic ulcer disease (PUD) either active or healed, presence of bleeding, neoplasms (benign or malignant), portal hypertensions related findings, significant reflux oesophagitis (Los Angeles Classification grade C and D, shown in Table 1 [8], vascular malformations or infections related pathologies such as *Candidiasis*.

Table 1. Los Angeles classification for endoscopic reflux oesophagitis (LA Classification)

Grades	Definition
A	One mucosal break less than 5 mm in length
B	One or more mucosal break more than 5 mm in lengths
C	Mucosal breaks that cover up to less than 75% of the circumference
D	Complicated reflux oesophagitis (> 75% circumference/ ulceration/stricture)

2.5 Statistics

Data were coded and entered into the SPSS (SPSS Version 10.0, Chicago, IL, USA) for analysis. The Chi-squared or Fisher's Exact tests were used for categorical variables. The Student's *t*-test and ANOVA were used for comparisons of continuous variables. Findings were considered significant for p values < 0.05.

3. Results

During this period, dyspepsia represents the commonest indication for referral for endoscopy accounting for 53.3% of all procedures. The indications for endoscopy are shown in Table 2.

Table 2. Indications for endoscopy (n = 2,066)

Indications	n (%)
Dyspepsia	1,101 (53.3)
Gastrointestinal bleeding	263 (12.7)
Evaluation of anaemia	263 (12.7)
Heartburn	166 (8.0)
Vomiting	67 (3.2)
Dysphagia	41 (1.9)
Weight loss	33 (1.6)
Loss of appetite	19 (0.9)
Others	120 (5.8)

3.1 Patients with dyspepsia

The mean age of patients with dyspepsia was 44.6 ± 16.1 years. There was no difference between the genders (male: female, 45.5 ± 16.0 vs. 43.8 ± 16.3 yrs old, p = 0.072). The commonest findings encountered were; gastritis/duodentitis (41.8%), oesophagitis/gastritis/duodenitis (10.8%), PUD (9.9%) and isolated oesophagitis (6.4%). Endoscopy was normal in 26.9%.

Significantly more male patients had more significant findings and *H. pylori* infection (33.2% vs. 22.2%, $p <$ 0.001). These significant findings were reflux oesophagitis (21.6% vs. 13.0%, $p < 0.001$) and PUD (13.1% vs. 6.8%, $p < 0.001$). Female had significantly more normal findings (34.8% vs. 18.5%, $p < 0.001$). All three cases of Barrett's detected were in male patients.

The dyspepsia group was significantly younger and there were more expatriate population. Demographic of patients with dyspepsia is shown in Table 3.

Table 3. Demographic of patients with dyspepsia compared to other indications

		Dyspepsia (n = 1,101)	Non-dyspepsia (n = 965)	*P* value
Age (yrs)		44.6 ± 16.1	50.3 ± 18.7	<0.001
Gender				
	Male	540 (49.1)	476 (49.3)	ns
Race				
	Malay	782 (71.0)	739 (76.6)	ns
	Chinese	135 (12.3)	126 (13.1)	ns
	Indigenous	43 (3.9)	33 (3.4)	ns
	Others	141 (12.8)	67 (7.0)	< 0.05

Age expressed in mean and standard deviation
Gender and ethnic breakdown expressed in absolute and percentage (bracket)
ns: non significant ($P > 0.05$)

The spectrum of endoscopic findings is shown in Table 4.

Table 4. Endoscopic findings among patients with or without dyspepsia

	Dyspepsia (n = 1,101) n (%)	Non-dyspepsia (n = 965) n (%)	Overall (n = 2,066) n (%)
Findings			
Normal	296 (26.9)	210 (21.8)	506 (24.5)
Gastritis/Duodenitis	579 (52.6)	402 (41.6)	981 (47.5)
Oesophagitis	210 (19.1)	187 (19.4)	397 (19.2)
Grade A/B	204 (18.5)	172 (17.8)	376 (18.2)
Grade C/D	6 (0.5)	15 (1.6)	21 (1.0)
Peptic ulcer disease	110 (9.9)	196 (20.3)	305 (14.8)
GU	27 (2.5)	72 (7.4)	99 (4.8)
DU	72 (6.5)	100 (10.4)	172 (8.3)
DU/GU	11 (1.0)	24 (2.5)	35 (1.7)
Malignancies	9 (0.8)	17 (1.8)	26 (1.3)
Oesophageal	1 (0.1)	4 (0.4)	5 (0.2)
Gastric	8 (0.7)	13 (1.4)	21 (1.0)

GU: Gastric ulcer, DU; Duodenal ulcer
Oesophagitis based on LA classification: Grade A/B (mild) and Grade C/D (severe)

The prevalence of *H. pylori* infection amongst this group was 28.1%. Male patients had higher incidence of significant findings ($p < 0.001$) and *H. pylori* infection rates ($p < 0.001$). The prevalence of *H. pylori* infection was significantly less in the older age group (> 40 yrs, 31.4% vs. 25.3%, $p = 0.032$). Overall significant findings were seen in 13.7% with a trend towards significance in the > 40 years old group (11.9% vs. 16.1%, $p = 0.054$).

3.2 Overall indications

Among all indications, the *H. pylori* prevalence was 26.2%. This was significantly higher in male patients. Overall, there were 306 patients (14.7%) with evidence of peptic ulcer diseases. However, 64% (n = 196) of patients with endoscopic evidence of PUD did not have dyspepsia listed as the main complaint. The main presentations of patients with endoscopic evidence of PUD listed in the request are shown in Table 5.

Table 5. Main presentations of patients with endoscopic peptic ulcer diseases (n = 306)

	GU (n = 99) n (%)	DU (n = 172) n (%)	GU/DU(n = 35) n (%)
Dyspepsia	27 (27.3)	72 (41.9)	11 (31.4)
Evaluation of anaemia	25 (25.2)	17 (9.9)	5 (14.3)
Gastrointestinal bleeding	36 (36.4)	66 (38.4)	18 (51.4)
Reflux symptoms	3 (3.0)	4 (2.3)	0 (0)
Loss of appetite	0 (0)	2 (1.2)	0 (0)
Weight loss	1 (1.0)	4 (2.3)	0 (0)
Vomiting	1 (1.0)	2 (1.2)	0 (0)
Dysphagia	3 (3.0)	0 (0)	0 (0)
Others	3 (3.0)	5 (2.9)	1 (2.9)

GU: Gastric ulcer, DU; Duodenal ulcer

Off the patients with PUD, only 216 (70.5%) had *H. pylori* testing done at initial endoscopy. The prevalence rates of *H. pylori* among PUD were; GU 40% (n = 24/60), DU 45% (n = 61/135) and GU/DU 33.3% (n = 7/21).

Overall, malignancies were detected in 26 patients (oesophagus [n = 5], and stomach [n = 21; adenocarcinoma [n = 19] and lymphoma [n = two]). Two patients were younger than 45 years old. Eighty percent with oesophageal carcinoma presented with dysphagia. Sixty-two percent of patients with gastric malignancies did not have dyspepsia as a main complaint. However, all had warning features at presentations. Patients' details are shown in Table 6.

Table 6. Details of patients with malignancies

	Oesophageal (n = 5) n (%)	Gastric (n = 21) n (%)
Median Age (yrs) **	66 (54-86)	67 (32-83)
Male	2 (40)	15 (68.2)
Indication for endoscopy		
Dysphagia	4 (80)	0 (0)
Dyspepsia	1 (20)	8 (38.1)
Anaemia/blood loss	0 (0)	6 (28.6)
Gastrointestinal bleed	0 (0)	2 (9.5)
Loss of weight	0 (0)	2 (9.5)
Loss of appetite	0 (0)	1 (4.8)
Others	0 (0)	2 (9.5) *

* Evaluation of liver metastasis (n = 1) and epigastric mass (n = 1)

** Age expressed in median and range due to small number of patients

Discussion

In the Brunei setting, dyspepsia represented the most common indication for endoscopy and the spectrums of findings are comparable to published findings [9, 10]. Majority of the findings consisted mainly of non-specific gastritis and duodenitis. No abnormal finding was seen in 26.9% of procedures. These findings, approximately 72% represented the subset of patients who will be categorized as non-ulcer dyspepsia or functional dyspepsia [11]. The overall spectrum of indications for referral for endoscopy is also comparable to other endoscopic studies. Importantly, the overall ethnic breakdown of the patients is consistent with the national breakdown and hence the results obtained can be assumed to be representative of the population.

Patient with dyspepsia were significantly younger than their non-dyspepsia counterpart. There were also significantly more expatriates in the dyspepsia group. One possible reason for this is that the expatriate group is usually of reasonable health and unlikely to have any significant health problems. They would have had compulsory medical screening before being employed. Furthermore, those with significant medical problems were likely to have had their investigations and treatment back in their homeland. Endoscopic reflux oesophagitis is also very common among Bruneian patients with dyspepsia (19.2%). However majority were mild consisting of LA grade A and B oesophagitis. Interestingly, this is more than the findings of a questionnaire study done locally where the prevalence of reflux disorders among control was reported to be 9.5% [12]. This suggests that a proportion of these patients were only mildly symptomatic or asymptomatic with their gastro-oesophageal reflux disorders.

The main aim of endoscopy is to assess for significant causes of dyspepsia such as peptic ulcer diseases, malignancies, portal hypertension related or significant reflux diseases (LA classification grade C and D). This was seen in approximately 15% of patients. Duodenal ulcers were more common than gastric ulcer. Dyspepsia, anaemia and suspected gastrointestinal bleeding accounted for majority of indications among those found to have PUD. However, the study also showed that a small proportion of those with PUD had unexpected indications such as dysphagia. An important finding is that only a third of patients with PUD had dyspepsia as their main complaint, indicating that a large proportion were at risk of adverse PUD events without any typical symptoms. They may present with complications of PUD such as gastrointestinal bleeding, perforation or gastric outlet obstruction. Fortunately, complicated PUD is uncommon. The large proportion of PUD patients not experiencing any dyspepsia may be due to use of NSAIDs or anti-platelets agents. These medications are known to induce ulcerations without much clinical symptoms. Unfortunately, we were not able to assess this correlation as the data on their use were not routinely recorded in the endoscopic sheet.

Malignancies, which is the most important aspect of endoscopy evaluation accounted for only 1.3% of the overall findings. Similar to those of PUD, a large proportion of patients with underlying malignancies also did not have dyspepsia as the main complaint. However, all the patients had warning symptoms at presentations. New onset dyspepsia, presence of anaemia or weight loss was the commonest indication among this group. Studies have shown that presence or absence of alarm symptoms have poor correlations with malignancies [13-15]. Unfortunately most had advanced disease at diagnosis making curative therapy less possible. Only two patients in this study were younger than the age of 45 years old, the age currently taken as a cut off for referral for endoscopy. Hence following the international recommendations, trial of therapy among those under the age of 45 years old without any warning symptoms would have missed these two patients. The age threshold for referral for endoscopy continued to be debated [16-19]. Some have recommended the cut off age for uncomplicated dyspepsia for endoscopy to be increased to 55 years old. However, the age of prompt endoscopy also depends on the local incidence of upper gastrointestinal malignancies [14, 20]. PUD and *H. pylori* infection are still common in our local setting and it is important to identify such cases early and managed appropriately to avoid possible future complications. Hence we routinely offer endoscopy to all patients.

The prevalence of *H. pylori* infection is lower than previously reported. However, consistent with recent reports [21, 22], there is a declining trend of overall *H. pylori* infection and also among those with PUD. This has also been

attributed to increasing use of NSAIDs. These findings are important as we need to assess for other causes of PUD, particularly use of NSAIDs and anti-platelets agents that patients may have taken without informing their doctors. Another explanation for the lower prevalence of *H. pylori* may be due to the fact that rapid urease tests were mostly used for detection. It is known that sensitivity and specificity of rapid urease tests can be poor [23].

In conclusion, the spectrum of findings among patients with dyspepsia referred for endoscopy is consistent with published reports. A large proportion of patients with significant pathologies such as PUD and malignancies did not complaint of dyspepsia. However, all had warning features at presentations.

References

1. Knill-Jones RP 1991. Geographical differences in the prevalence of dyspepsia. Scand J Gastroenterol 182:17-24.

2. Penston JG, Pounder RE 1996. A survey of dyspepsia in Great Britain. Aliment Pharmacol Ther 10:83-89.

3. Sihvo S, Hemminki E 1999. Self medication and health habits in the management of upper gastrointestinal symptoms. Patient Educ Couns 37:55-63.

4. Furu K, Straume B. 1999. Use of antacids in a general population: the impact of health-related variables, lifestyle and sociodemographic characteristics. J Clin Epidemiol 52:509-516.

5. Ryan J, Murkies A 2006. Diagnosis of upper gastrointestinal malignancy. Aust Fam Physician 35:200-201.

6. British Gastroenterology Society. North of England Dyspepsia Guideline Development Group. 1st August 2004. Evidence based clinical practice guideline. Dyspepsia: managing dyspepsia in adults in primary care. http://www.nice.org.uk/nicemedia/pdf/CG017fullguideline.pdf (accessed 29th March 2008)

7. Talley NJ, Silverstein MD, Agreus L, et al.1998. AGA technical review: evaluation of dyspepsia. Gastroenterology 114: 582-595.

8. Armstrong D, Bennett JR, Blum AL, Dent J, De Dombal FT, Galmiche JP, et al. 1996. The endoscopic assessment of esophagitis: a progress report on observer agreement. Gastroenterology 111:85-92.

9. Wai CT, Yeoh KG, Ho KY, Kang JY, Lim SG 2002. Diagnostic yield of upper endoscopy in Asian patients presenting with dyspepsia. Gastrointest Endosc 56:548-551.

10. Hu WH, Lam SK, Lam CL, Wong WM, Lam KF, Lai KC, et al. 2006. Comparison between empirical prokinetics, Helicobacter test-and-treat and empirical endoscopy in primary-care patients presenting with dyspepsia: a one-year study. World J Gastroenterol 12:5010-5016.

11. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, et al. 2006. Functional gastroduodenal disorders. Gastroenterology 130:1466-1479.

12. Chong VH, Wang CL 2008. Higher prevalence of gastrointestinal symptoms among patients with rheumatic disorders. Singapore Med J 49:419-424.

13. Meineche-Schmidt V, Jørgensen T 2006. 'Alarm symptoms' in patients with dyspepsia: a three-year prospective study from general practice. Scand J Gastroenterol 37:999-1007.

14. Boldys H, Marek TA, Wanczura P, Matusik P, Nowak A 2003. Even young patients with no alarm symptoms should undergo endoscopy for earlier diagnosis of gastric cancer. Endoscopy 35:61-67.

15. Maconi G, Kurihara H, Panizzo V, Russo A, Cristaldi M, Marrelli D, et al. Italian Research Group for Gastric Cancer. 2003. Gastric cancer in young patients with no alarm symptoms: focus on delay in diagnosis, stage of neoplasm and survival. Scand J Gastroenterol 38:1249-1255.

16. Phull PS, Salmon CA, Park KG, Rapson T, Thompson AM, Gilbert FJ 2006. Age threshold for endoscopy and risk of missing upper gastrointestinal malignancy--data from the Scottish audit of gastric and oesophageal cancer. Aliment Pharmacol Ther 23:229-233.

17. Sundar N, Muraleedharan V, Pandit J, Green JT, Crim-

mins R, Swift GL 2006. Does endoscopy diagnose early gastrointestinal cancer in patients with uncomplicated dyspepsia? Postgrad Med J 82:52-54.

18. Gillen D, McColl KE 1999. Does concern about missing malignancy justify endoscopy in uncomplicated dyspepsia in patients aged less than 55? Am J Gastroenterol 94:75-79.

19. Canga C 3rd, Vakil N 2002. Upper GI malignancy, uncomplicated dyspepsia, and the age threshold for early endoscopy. Am J Gastroenterol 97:600-603.

20. Liou JM, Lin JT, Wang HP, Huang SP, Lee YC, Shun CT, et al. 2005. The optimal age threshold for screening upper endoscopy for uninvestigated dyspepsia in Taiwan, an area with a higher prevalence of gastric cancer in young adults. Gastrointest Endosc 61:819-825.

21. Wong SN, Sollano JD, Chan MM, et al. 2005. Changing trends in peptic ulcer prevalence in a tertiary care setting in the Philippines: a seven-year study. J Gastroenterol Hepatol 20:628-632.

22. Ho KY, Chan YH, Kang JY 2005. Increasing trend of reflux esophagitis and decreasing trend of Helicobacter pylori infection in patients from a multiethnic Asian country. Am J Gastroenterol 100:1923-1928.

23. Xia HH, Wong BC 2002. Gastric biopsy-based rapid urease tests for the detection of Helicobacter pylori: progress, advantages and limitations. J Gastroenterol Hepatol 17:629-632.

Bronchoscopic management of malignant airway obstruction in RIPAS hospital

Chee Fui Chong [1], Babu Sukumaran [2], Zulaidi Abdul Latif [3], Mohd Syafiq Abdullah [2]

[1]*Cardiothoracic Unit, Department of General Surgery,*
[2]*Oncology Unit, Department of Internal Medicine,*
[3]*Critical Care Unit, Department of Anaesthesia,*
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Bandar Seri Begawan BA 1710, Brunei Darussalam

Abstract

Lung cancer is the leading cause of cancer deaths in the world. Only about 25% of patients diagnosed with lung cancer are amenable to curative surgery. The majorities are in advances stages of the disease by the time of diagnosis and are open only to palliative treatment. Obstruction of major airways by such tumours occurs in 30% of cases and they often present with symptoms of dypsnoea, stridor, obstructive pneumonia and impending suffocation which can be life threatening. Management of this group of patients can be very challenging and requires emergency relief of the obstruction. We describe two cases of major airway obstruction secondary to advanced malignancies in Brunei Darussalam and discuss the emerging bronchoscopic therapy available to deal with this life threatening condition.

Keywords: airway obstruction, airway stenting, endobronchial tumour, lung cancer

Introduction

Only 20-25% of patients diagnosed with lung cancer are amenable to surgical resection [1]. The majority are in advanced stages of the disease by the time of diagnosis and can only be treated palliatively. Malignant airway obstruction secondary to lung cancers occurred in 30% of cases and can result in incapacitating and life threatening symptoms which requires urgent relieve of airway obstructions [2].

Conventional chemotherapy and radiotherapy have limited roles in the management of acute malignant airway obstruction. Endobronchial therapy such as intraluminal brachytherapy, bronchoscopic laser resection combined with endobronchial stenting has evolved into an effective alternative therapy albeit a palliative option [3]. This form of bronchoscopic therapy has only recently become available in Brunei Darussalam. We report here the first two cases of endobronchial therapy with diathermy tumour resection and airway stenting using Ultraflex self-expanding nitinol stents (Boston Scientific; Natick, MA), in two patients with malignant airway obstruction at RIPAS Hospital.

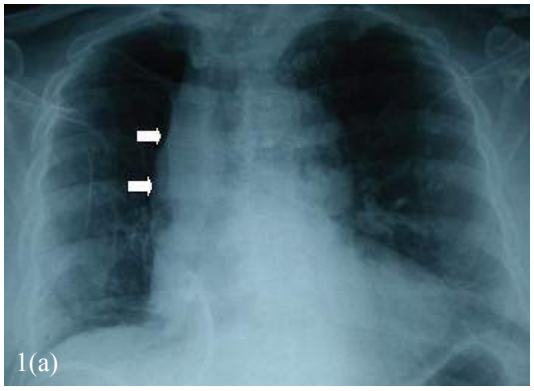
Correspondence:
Mr. Chee Fui Chong,
Consultant Cardiovascular & Thoracic Surgeon,
Thoracic Unit, Department of General Surgery,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA1710, Brunei Darussalam.
Email: chong_chee_fui@hotmail.com

Case Reports

Case 1

In March 2007, a 78-yr old Chinese female with a past medical history of frontal hygroma and dementia, was admitted with to the medical ward with fever and shortness of breath. Routine chest radiograph taken on admission showed a right mediastinal mass lesion (Figure 1a) with right lower lobe lung consolidation. Computed tomography (CT) scan confirmed right paratracheal lymphadenopathy measuring 5 x 3 x 3cm, extending to the level of the carina causing obstruction to both right upper and lower lobe bronchus with complete collapse of the right lower lobe (Figure 1b).

A CT guided FNAC of the right paratracheal mediastinal mass was performed which was complicated by a moderate size pneumothorax. A 12ch pigtail catheter was inserted under radiology guidance but this failed to resolve the pneumothorax and the catheter was kept for several days, resulting in right pleural space infection and empyema.



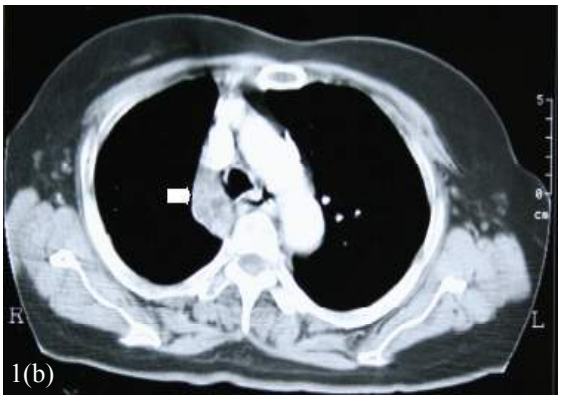
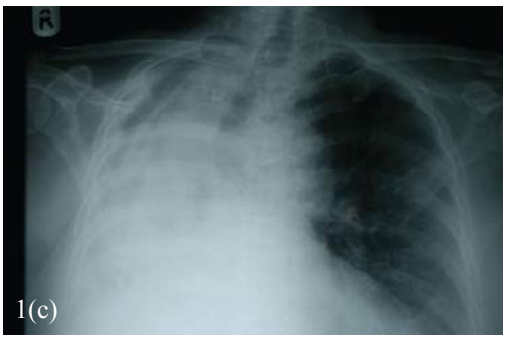


Figure 1. (a) Chest x-ray showing right mediastinal mass lesion as indicated by the white arrows, which is confirmed on CT scan to be a right paratracheal mass with multiple cystic areas (b).

She underwent video assist-thoracoscopic (VATs) decortication for the right empyema. Although the surgery was successful in resolving the empyema, the whole of her right lung collapsed as a result of the tumour compressing on the right upper and lower lobe bronchi (Figure 1c). A rigid bronchoscopy was carried out and confirmed compression of the right intermediate bronchus to a slit-like opening. This was successfully dilated with a 40mm x 12mm uncovered Ultraflex self-expanding nitinol bronchial stent (Boston Scientific, Natick, MA). Post procedural chest radiograph confirmed expansion of the right lung and the stent can be easily seen on the x-ray. She was subsequently discharged home by the first week of May 2007 and follow-up chest radiograph has confirmed patency of the stent (Figure 1d). Flexible bronchoscopy was performed two weeks after discharge, which showed significant amount of secretion in the stent with in growth of bronchial tissue over the stent (Figure 1e). She was still alive although house bound at her last follow-up in August 2007.



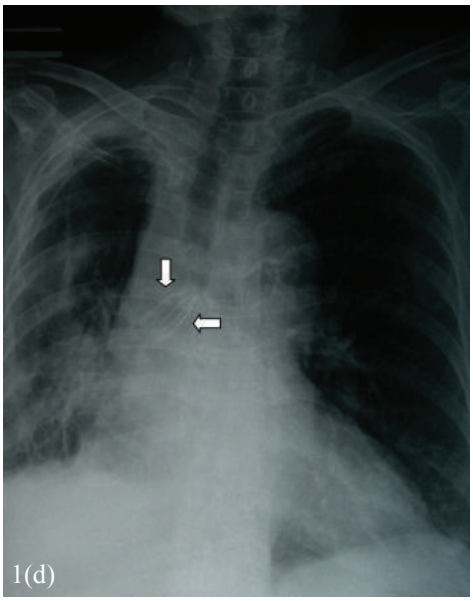


Figure 1. (c) Complete collapse of the right lung following right VATs decortication procedure. Following endobronchial stenting with a 40mm x 12mm Ultraflex self expanding nitinol uncovered stent (white arrows), the right lung is reexpanded (d).

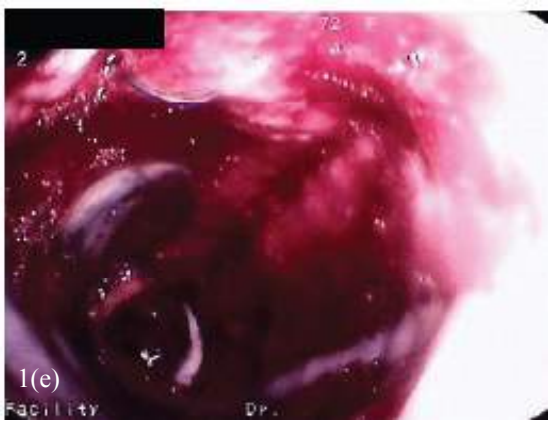
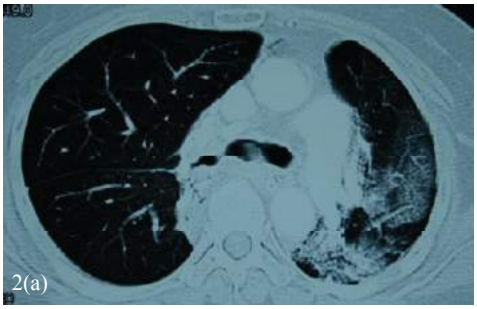


Figure 1(e). In-growth of epithelium over the uncovered Ultraflex nitinol stents with poor clearance of secretion.

Case 2

In October 2007, a 51-yr old Chinese female with a past medical history of hepatitis B/C, left lower lobectomy for stage 3A non small cell lung cancer (NSCLC) performed in September 2004, was admitted to Ward 19 at RIPAS Hospital with haemoptysis and dyspnoea. Following her initial surgery, she underwent four courses of Mitomycin, Vinblastine, Cisplastin (MVP) chemotherapy. She developed local recurrence of her disease in the mediastinum in December 2005, confirmed on PET scan. She was treated with chemoradiation 50Gy/25# followed by three courses of Cis-diamminedichloroplatinum (CDDP). This was followed by Taxotere for three weeks. She was well until December 2006 when biopsy of a right supraclavicular lymph node confirmed recurrence. She again underwent ten courses of localized radiotherapy for the supraclavicular disease.

CT scan was performed which confirmed recurrence of subcarinal tumour with invasion into the right main bronchus and partially occluding the lumen (Figure 2a). An urgent rigid bronchoscopy was performed on the 23rd October 2007 and endobronchial diathermy resection of the tumour was performed (Figure 2b). However due to excessive bleeding and difficulty in ventilation due to air trapping in the right lung, the procedure was abandoned after resecting only 10% of the tumour.



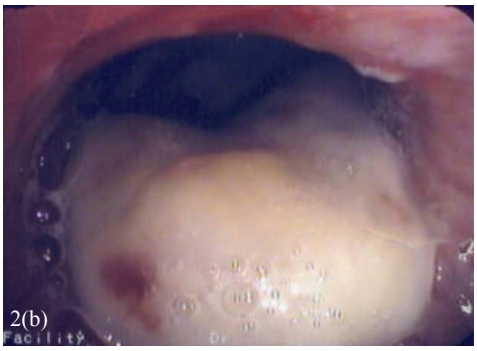
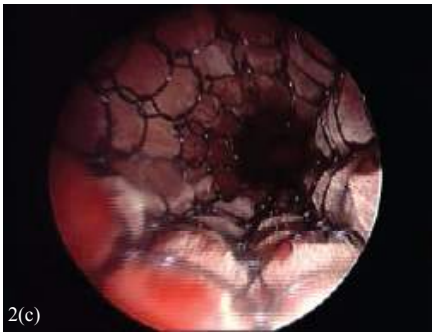


Figure 2. (a) CT scan showing recurrence of subcarina tumour with invasion and near total occlusion of the right main bronchus, (b) regrowth of the tumour 2 weeks after diathermy resection to obstruct about 60% of the right main bronchus lumen.

She again underwent another rigid bronchoscopic resection of the tumour two days later and we were able to remove 80-90% of the tumour. Histology from the first resection confirmed a poorly differentiated metastatic squamous cell carcinoma from her previous NSCLC. Due to the highly malignant nature of the tumour, she underwent 2 other bronchoscopic resections of the tumour during a course of a month and an endobronchial Ultraflex self-expanding covered nitinol stent (60mm x 14mm; [Boston Scientific; Natick, MA]) was inserted into the right main bronchus on the 4th December 2007 (Figure 2c & d). She was extubated the next day and transferred to the general ward a few days later, but died in 2 days later from acute respiratory insufficiency and hypotension.



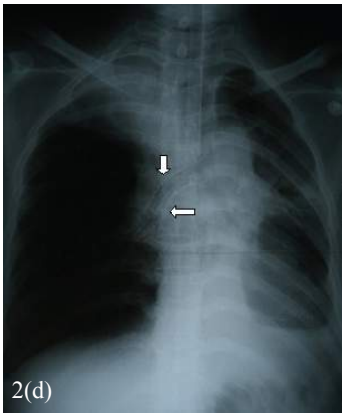


Figure 2. (c) Covered Nitinol selft-expanding stent after deployment into the right main bronchus. (d) Chest x-ray showing a fully expanded covered Ultraflex self-expanding Nitinol stent with full expansion of the right lower lobe.

Discussion

Patients presenting with large airway obstruction secondary to a malignant tumour are often unwell with symptoms of dypsnoea, stridor, obstructive pneumonia and impending suffocation which can be life threatening as shown by the two cases above [2]. Primary surgical resection and reconstruction of the airway provides the best opportunity for definitive management but however majority of patients present at a very late stage when curative resection is no longer possible. Palliative relief of the obstruction can be achieved with endobronchial therapy which is a fast evolving treatment aimed at achieving a patent airway and improvement of the quality of life for the patient [3].

The essential principles of endobronchial therapy for malignant airway obstruction have been well described by Mathisen and Grillo [4], which are, 1) initial resection of the intraluminal tracheobronchial tumour in order to re-establish airway patency and 2) to maintain airway patency by insertion of a stent to hold the airway open and to inhibit further in-growth of tumour into the lumen.

Bronchoscopic intra-luminal tumour resection can be achieved by several modalities such as mechanical coring out using diathermy probe [5], which was done for our second case, cryotherapy resection [6], photodynamic therapy (PDT) [7] and Nd:YAG laser ablation [8]. The latter three modalities are as yet not available in RIPAS Hospital.

Cryotherapy is a cytotoxic method that spares collagen containing structures [6]. It's mode of action is by direct contact effect with a cryoprobe which freezes and destroys the tumour cells [6]. The probe is usually inserted through the bronchoscope. Three cycles of freezing is usually required, each for about 20-30 seconds with a thawing period in between [6]. It is a safe and cost-effective therapy but does not bring about an immediate relieve of the airway obstruction. The subsequent eschar formation from cellular necrosis may cause obstruction when it finally detaches from the wall [8].

Similarly PDT has also been widely applied for treatment of tracheobronchial tumours. This modality uses a light of certain wavelength to activate light sensitive photochemicals known such as hemato-porphyrins [7]. Clinical PDT is a two-phase process. Phase one involves presensitization of the tumour tissues with photosensitizers which is delivered topically or systemically. Photosensitizers are chosen for their ability to accumulate in the tumour tissues rather than in normal tissues. In phase two, the tumour is exposed to a light of appropriate wavelength, usually delivered through a bronchoscope and will activate photosensitizers in the presence of oxygen to produce free oxygen radicals and other cytotoxic mediators resulting in direct tumour cell injury and vascular shutdown [7]. Recent evidence has also shown the immune and inflammatory responses to play a role in tumour cytotoxicity following PDT [9].

This is a very well proven technique and is a safe and effective therapeutic method for advanced lung cancer with important endobronchial presentation [10]. However, PDT requires complex equipment and the photosensitization of the patient implies increased costs and lengthening of hospitalization. The photo sensitizer may also predispose the patient's skin to light sensitivity resulting in incidence of 8-28% of sunburn [10]. Furthermore, just like cryotherapy, a delayed result is seen rather than an immediate relief of obstruction.

Nd:YAG laser ablation is another modality that is very effective and uses laser to coagulate and vaporise the tumour and provide immediate relieve of the airway obstruction [8]. However unlike diathermy resection which provide a shorter mean interval between resection of 29 days, Nd:YAG laser ablation can achieved a much longer duration between resection of 102 days [8]. This is because with the Nd:YAG laser, there is possibly a cytocide effect deep within the tumour even after resection has been completed [8]. However, cost of the equipment is an issue as well as training of staffs.

There are different types of commercially available airway stents, which can be subdivided into two groups, silicone and metal stents as shown in table one. The silicone stents such as Dumon, and Hood have flexible but fixed shape and have the advantage that they are easily removed and repositioned or changed as many times as possible [11,12]. They are more commonly indicated for the temporary relief of benign airway obstruction such as tracheobronchial malacia or benign strictures where they

can be later removed once the problem has been resolved [13]. Their disadvantages are that they required rigid bronchoscopy for placement and due to their fixed shape, they do not conform well to the anatomy of the airway and can be dislodged just as easily resulting in stent migration [11,12].

Polyflex is a newer self expanding thin wall silicone based stents made of polyester mesh covered with silicone [14]. It is more flexible than the Dumon and Hood and can also be folded into a much more compact size and hence can be delivered via a catheter. Like the other two silicone stents, Polyflex stents can be easily removed and repositioned. However, because of its smooth surface, stent migration has been reported to occur in 100% of cases, particularly in cases of benign tracheobronchial stenosis [14]. For treatment of malignant strictures, polyflex stent has been proven to be more promising [15].

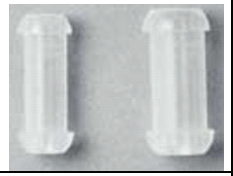
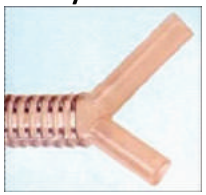
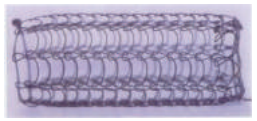
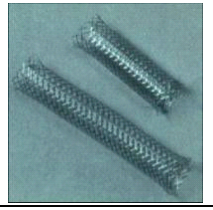
The self-expanding metal stents (Ultraflex and Wallstent) however are available in sterilised prepacked 8F catheter sheath where they are tightly compressed around the catheter [16]. Hence they can be easily delivered via a flexible bronchoscope with fluoroscopic control under local anaesthetic agents. Their flexibility and radial force provided by the struts conforms better to the airway [16]. They come in either uncovered or covered with silicone rubber or polyurethane coating. Uncovered self expanding metal stents are commonly used as in case one for airway obstruction secondary to extrinsic compression by malignancy. They have the advantage of preserving patency of lobar branches as well as mucociliary clearance. Uncovered stents are eventually incorporated within the airway wall with neoepithelization within 3 to 6 weeks after insertion as shown in Figure 1e [17].

Covered self-expanding metal stents however are indicated for treatment of malignant strictures where there is in-growth of tumour into the tracheobronchial lumen [16]. However about 1cm of either ends of the covered stents are bare and hence neoepithelization can occurred at these sites. Self-expanding metal stents have the disadvantages that they are permanent once neoepithelization occurs and removal is extremely difficult, if not impossible [17]. Adjustment is only possible during the early stages prior to full deployment but once the stents are fully expanded, it is difficult to adjust and fluoroscopy is required during placement in most cases.

The complications related to airways stents shown in Table 1, are increased sputum secretion and retention, obstruction of stents from sputum or in-growth of granulation tissue, stent migration particularly with silicon stents and erosion of airways due to excessive radial force of an oversized self-expanding metal [11, 13-16, 18]. However, in cases where endobronchial stents are inserted for malignant airway obstruction such as with both our cases, complications may not arise as most patients succumbed to their malignant disease before.

In conclusion, endobronchial airway stenting is safe and effective in providing immediate albeit palliative relief from malignant major airway obstruction. Because of their poor prognosis, most patients succumbed to their malignant disease before any major complications arise from insertion of these stents.

Table 1. Types of commercially available airway stents.

	Silicon Stents			Self Expanding Stents		
Stent Type	**Dumon** 	**Hood** 	**Dynamic** 	**Polyflex** 	**Ultraflex** 	**Wallstent** 
Manufacturer	Novatech	Hood Corp	Rush Inc.	Rush Inc.	Boston Scientific	Boston Scientific
Construction	Molded silicon rubber	Molded silicon rubber	Silicone with anterolateal steel struts	Polyester mesh covered with silicone	Single strand woven nitilol With/without silicone coating	Woven cobalt/chrome alloy monofilament coated with silicone
Size (mm)	9 x 20 – 18 x 70 + Y	6 x 13 – 18 x 70 + Y	13, 15, 17 (trachea)	6 x 20 – 22 x 80	8 x 20 – 20 x 80	8 x 20 – 24 x 60
Advantages	Easily adjustable and removable, can be repositioned and changed as many times as required. no ingrowth and no reaction of the airway mucosa.			Compressible nature means small delivery catheter. Can be delivered via flexible bronchoscopy with radiological control, hence easily deployed under light sedation and local anaesthetic. Radial tension ensures stable position with minimal migration. Uncovered stents allow also ventilation of lobar bronchi through the interstices of the metal mesh.		
Disadvantages	Rigid fixed shape. Need for rigid bronchoscopy placement. Smaller inner diameter hence can be easily occluded by thick secretions. Potential for dislodgement and distortion.			Difficult to remove once fully deployed except polyflex stent. Ingrowth of tissue in uncovered stents may lead to future obstruction. Sputum retention due to disturbance in ciliary clearance especially in covered stent. Covered stent may obstruct lobar bronchii. Can cause compression necrosis if over distended.		

References

1. Sioris T, Jarvenpaa R, Kuukasjarvi P, Helin H, Saarelainen S, Tarkka M 2003. Comparison of computed tomography and systematic lymph node dissection in determining TNM and stage in non-small cell lung cancer. Eur J Cardiothorac Surg 23:403-408.

2. Ginsberg RJ, Vokes EE, and Ruben A 1997. Non-small cell lung cancer. DeVita VT, Hellman S, and Rosenberg SA. Cancer principles and practice of oncology 5th ed, Philadelphia: Lippincott-Raven. 858-911.

3. Wood DE 2002. Management of malignant tracheobronchial obstruction. Surg Clin North Am 82:621-642.

4. Mathisen DJ, Grillo HC 1989. Endoscopic relief of malignant airway obstruction. Ann Thorac Surg 48:469-473.

5. Stephens KE, Jr., Wood DE 2000. Bronchoscopic management of central airway obstruction. J Thorac Cardiovasc Surg 119:289-296.

6. Bertoletti L, Elleuch R, Kaczmarek D, Jean-Francois R, Vergnon JM 2006. Bronchoscopic Cryotherapy Treatment of Isolated Endoluminal Typical Carcinoid Tumor Chest 130:1405-1411.

7. Moghissi K 2004. Role of bronchoscopic photodynamic therapy in lung cancer management. Curr Opin Pulm Med 10:256-260.

8. Cavaliere S, Foccoli P, Toninelli C, Venuta F, La Face B 1996. Endoscopic treatment of malignant airway obstructions in 2008 patients. Chest 110:1536-1542.

9. Dougherty TJ 2002. An update on photodynamic therapy applications. J Clin Laser Med Surg 20:3-7.

10. Moghissi K, Dixon K 2003. Is bronchoscopic photodynamic therapy a therapeutic option in lung cancer? Eur Respir J 22:535-541.

11. Dumon JF 1990. A dedicated tracheobronchial stent. Chest 97:328-332.

12. Bolliger CT, Probst R, Tschopp K, Soler M, Perruchoud AP 1993. Silicone stents in the management of inoperable tracheobronchial stenoses. Indications and limitations. Chest 104:1653-1659.

13. Martinez-Ballarin JI, az-Jimenez JP, Castro MJ, Moya JA 1996. Silicone stents in the management of benign tracheobronchial stenoses. Tolerance and early results in 63 patients. Chest 109:626-629.

14. Gildea TR, Murthy SC, Sahoo D, Mason DP, Mehta AC 2006. Performance of a self-expanding silicone stent in palliation of benign airway conditions. Chest 130:1419-1423.

15. Wassermann K, Koch A, Muller-Ehmsen J, Reuter M, Michel O, Eckel HE 1997. Clinical and laboratory evaluation of a new thin-walled self-expanding tracheobronchial silicone stent: progress and pitfalls. J Thorac Cardiovasc Surg 114:527-534.

16. Saad CP, Murthy S, Krizmanich G, Mehta AC 2003. Self-expandable metallic airway stents and flexible bronchoscopy: long-term outcomes analysis. Chest 124:1993-1999.

17. Dasgupta A, Dolmatch BL, bi-Saleh WJ, Mathur PN, Mehta AC 1998. Self-expandable metallic airway stent insertion employing flexible bronchoscopy: preliminary results. Chest 114:106-109.

18. Miyazawa T, Yamakido M, Ikeda S, Furukawa K, Takiguchi Y, Tada H, Shirakusa T 2000. Implantation of ultraflex nitinol stents in malignant tracheobronchial stenoses. Chest 118:959-965.

Prevalence of gastrointestinal symptoms in Brunei Darussalam

Vui Heng Chong,

Gastroenterology Unit, Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital, Bandar Seri Begawan BA 1710, Brunei Darussalam

Abstract

Gastrointestinal (GI) complaints have been shown to be particularly common among female and those with comorbid conditions. However these studies have mainly come from the West. The present study assesses the prevalence of GI symptoms in the Bruneian setting. Relatives (n = 607) visiting the wards of a referral hospital were interviewed regarding GI symptoms experienced in the past 12 months. Psychosomatic symptoms of depression were also enquired (anxiety, backache, depression, headache and insomnia). Overall, upper GI symptoms were reported by 33.4%; nausea (9.6%), vomiting (1.3%), reduced appetite (2.1%), dysphagia (0.5%), odynophagia (0.8%), early satiety (10.2%), heartburn (9.8%) and dyspepsia (18.8%), and lower GI symptoms in 20.1%; abdominal bloating (10.2%), abdominal pain (11.5%), irregular bowel habit (2.6%) and bleeding per rectum (5.6%). Female experienced significantly more dyspepsia, early satiety, abdominal pain, and psychosomatic symptoms of depressions (anxiety, headache and insomnia) (all p values <0.05). Presence of any co-morbidity was also significantly associated with the presence of any upper (nausea, early satiety and dyspepsia) and lower GI (abdominal pain and bloating) symptoms, and psychosomatic symptoms of depression (all p values <0.05). Only a small proportion has undergone any endoscopic evaluations. In conclusions, GI symptoms are more common amongst female and those with any co morbid conditions. They also had significantly more psychosomatic symptoms of depression, suggesting functional elements to these complaints.

Keywords: abdominal pain, dyspepsia, heartburn, prevalence in Brunei

Introduction

Gastrointestinal (GI) complaints are one of the most common indications for consultations. GI complaints account for up to 10% of general practice work load in the United Kingdom [1]. Most are self limiting without requiring any investigations. The prevalence of GI symptoms has been reported to be higher in females and patients with numerous chronic comorbid conditions [2-7]. On investigations with endoscopies and radiological imaging, there are often the absence of any significant pathologies and these are considered as functional GI disorders [8, 9]. Such a conclusion is also supported by the fact that female have more psychosomatic complaints. Patients with chronic co morbid conditions have been shown to have higher prevalence of GI complaints [10-12].

Currently, there is no data available in the Bruneian setting. Similar to what have been reported, we hypothesized that female gender and the presence of comorbid conditions may also be important factors associated with GI complaints in our local population. This cross sectional questionnaire study was conducted to assess the: i) prevalence of both upper and lower GI symptoms, ii) to assess if gender and the presence of any underlying comorbid conditions are associated with higher prevalence of GI symptoms.

Correspondence :
Vui Heng Chong, MRCP, FAMS
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA 1710,
Brunei Darussalam
Tel: 673 2232111 ext 3303
Fax: 673 2242690
E mail: chongvuih@yahoo.co.uk

Methods

Relatives visiting the five medical wards (Wards 4, 19, 20, 21 and 22) in the main referral hospital (RIPAS Hospital) were interviewed regarding GI symptoms experienced within the previous 12 months. Subjects were randomly approached on most working hours over a twelve month period. Explanations of the purpose of the survey were

given and verbal consent was obtained prior to the face to face interviews. Data collected included demographic data, background medical conditions, medications use, self medication, GI symptoms (nausea, vomiting, appetite, early satiety, heartburn, dyspepsia, abdominal bloating, abdominal pain, bowel habit and bleeding per rectum) and previous experience with endoscopy. Psychosomatic symptoms of depressions (anxiety, backache, depression, headache and insomnia) were also enquired.

The interviews were conducted by the author in several languages (Malay, English and Chinese) depending on the background of the persons being interviewed. Dyspepsia is described as an abdominal discomfort centered in the epigastrium. No distinctions were made to differentiate the type of dyspepsia (ulcer like, dysmotility like or heartburn like). Heartburn is taken as a retro-sternal burning feeling that radiates upward associated with sour taste in the throat/mouth and regurgitation. Both heartburn and dyspepsia can be described by few terminologies. Similarly, there are various terminologies describing anxiety and depression. Backache, headache and insomnia have well defined terminologies. As various terminologies exist for these various symptoms or complaints, only the commonly used terminologies were used in the questionnaire.

Data were coded and entered into the SPSS (Version 10.0, Chicago, IL USA) program for analysis. The Student-*t* test and chi-square test were used where appropriate. Comparisons were made between the gender and those with and without any comorbid conditions. Association of GI symptoms and presence of any psychosomatic symptoms of depression were tested. Continuous variables were presented as mean and standard deviation (SD). The test was considered statistically significant when p was less than 0.05.

RESULTS

There were a total of 607 subjects who participated in this questionnaire study and the subjects demographic and clinical profiles are shown in Table 1. Overall, there were slightly more female and more Malay subjects who participated in this study. The average age of subjects was 40.5 years.

Table 1. Demographic and clinical profiles of subjects (n = 607)

Gender		
	Male	244 (40.2)
	Female	363 (59.8)
Race		
	Malays	516 (85.0)
	Chinese	43 (7.1)
	Indigenous	7 (1.2)
	Others	41 (6.8)
Co-morbid conditions		221 (36.4)
	Cardiovascular disorders	20 (3.5)
	Diabetes mellitus	63 (11.1)
	Hypertension	112 (19.7)
	Hyperlipidemia	49 (8.6)
	Neurological disorders	23 (4.0)
	Respiratory disorders	23 (4.0)
	Others	45 (7.9)
Smoker		96 (15.8)
Use of prescribed medications		190 (31.3)
Self medicating *		147 (24.2)

Figures presented as absolute number and percentage (parentheses)

* Use of non-prescribed medications including over the counter medications and complementary and alternative medications

The prevalence of upper and lower GI symptoms experienced over the previous 12 months are shown in Table II. Overall 43.5% (n = 264) had reported experiencing any GI symptoms with 33.4% (n = 203) experiencing any upper GI symptoms and 20.1% (n = 120) experiencing any lower GI symptoms. The mean number of upper GI symptoms and lower GI experienced were 1.6 (0.9) and 1.2 (0.5) symptoms respectively.

Table 2. Prevalence of gastrointestinal (GI) symptoms experienced within the last 12 months

Symptoms	n (%)
Upper GI symptoms	203 (33.4)
Nausea	58 (9.6)
Vomiting	8 (1.3)
Dysphagia	3 (0.5)
Odynophagia	5 (0.8)
Reduced appetite	13 (2.1)
Heartburn	60 (9.8)
Early satiety	62 (10.2)
Dyspepsia	114 (18.8)
Lower GI symptoms	122 (20.1)
Non epigastrium abdominal pain	70 (11.5)
Bloating	62 (10.2)
Irregular bowel habit	16 (2.6)
Bleeding per rectum	34 (5.6)

Overall, compared to male subjects, female reported significantly higher prevalence of overall upper GI symptoms (38.3% vs. 26.2%, $p = 0.002$), especially early satiety and dyspepsia. There was no significant difference in the overall lower GI symptoms (22% vs. 17.2%, $p = 0.146$) but there was a significantly higher prevalence of non-dyspepsia abdominal pain. This is shown in Figure 1.

Female also reported significantly more psychosomatic symptoms of depression, in particularly anxiety (8.0% vs. 3.3%, $p = 0.017$) and headache (43.8% vs. 24.6%, $p < 0.001$).

The presence of any comorbid conditions was significantly associated with the presence of any upper GI symptoms (41.6% vs. 28.8%, $p = 0.001$) especially nausea, dyspepsia and early satiety (Figure 2). They also had significantly more of any lower GI symptoms (25.8% vs. 16.8%, $p = 0.008$) especially non-epigastric abdominal pain and bloating. Subjects with comorbid conditions also experienced more psychosomatic symptoms of depressions (anxiety [10.9% vs. 3.4%, $p<0.001$], backache [27.1% vs. 13%, $p<0.001$], depression [2.7% vs. 0.5%, $p = 0.022$], headache [44.3% vs. 31.3%, $p = 0.001$] and insomnia [21.7% vs. 9.1%, $p<0.001$].

In total, 6.3% (n = 38) and 1.8% (n = 11) of subjects had previously undergone upper GI and lower GI endoscopy respectively for evaluation of their GI complains. None had any significant findings based on what patients could remember.

Discussion

This study showed that GI symptoms are common in our population with over 40% of subjects ever experiencing some GI complaints within the previous 12 months, with a third having had upper GI complaints and one fifth having lower GI symptoms. The most common upper GI symptom in our study was dyspepsia followed by early satiety, nausea and heartburn. These are also comparable to what have been reported from other countries [2-7, 13]. In an earlier review of ten studies from the West, the prevalence of upper abdominal pain ranged from 8 to 54% and heartburn ranged from 10 to 48% [14]. A study in Hong Kong showed that the prevalence of uninvestigated dyspepsia was 18.4%.

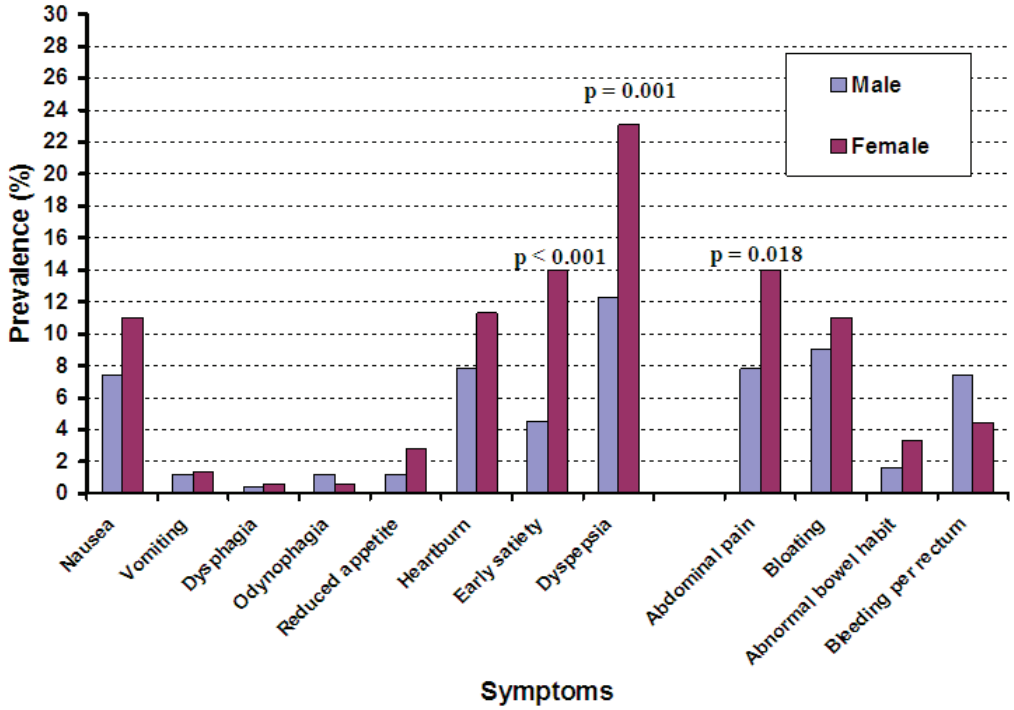


Figure 1. Prevalence of GI symptoms between male and female

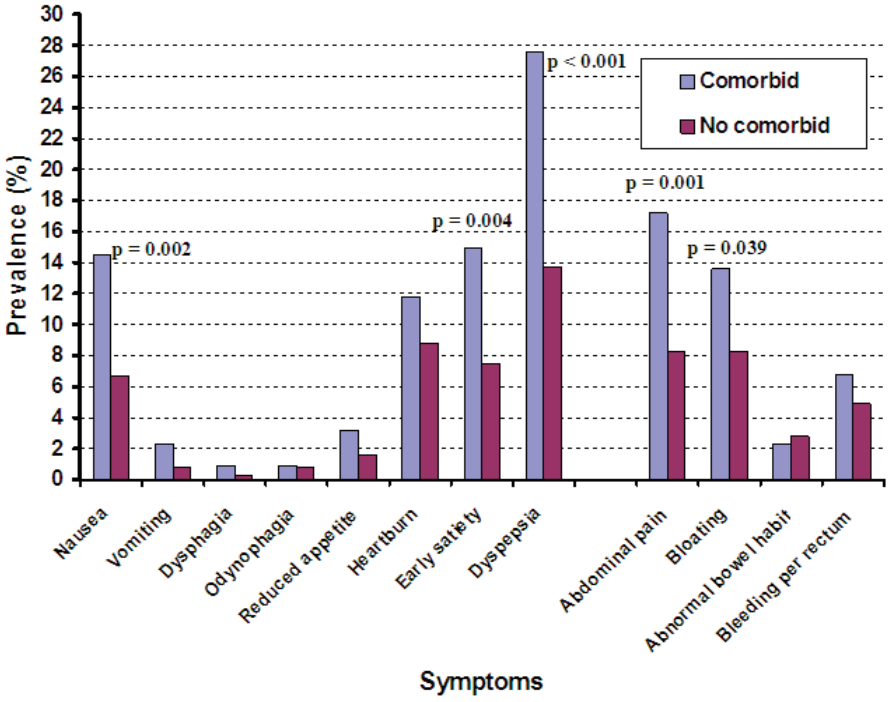


Figure 2. Prevalence of GI symptoms between those with and without co morbid conditions.

[15] Similarly the prevalence of heartburn or GORD is comparable to what have been reported both in the East and West.

The prevalence of lower GI symptoms is also comparable. Abdominal bloating and non-epigastric abdominal pain were equally common. Importantly, 5.6% had experienced bleeding per rectum and only 1.8% had undergone lower GI evaluations. This suggests that most of these complaints were probably self-limiting not requiring any consultations.

Female had higher prevalence of both upper and lower GI symptoms compared to male in our local setting. This again is comparable to what have been reported [8, 9]. Our female subjects generally experienced more GI complaints but this was only significant for early satiety, dyspepsia and abdominal bloating. More male experienced bleeding per rectum. Consistent to what have been shown, our female subjects also had significantly more psychosomatic symptoms of depression. The higher prevalence suggests that the GI complaints were most likely to be functional in origin. This is further supported by the fact that only a small proportion of subjects ever had endoscopies for the GI complaints.

Presence of any comorbid condition was significantly associated with both upper and lower GI symptoms. Numerous studies have shown increased prevalence of GI symptoms in patients with chronic non-psychiatric disorders. Not unexpectedly, presence of any comorbid condition was also significantly associated with psychosomatic symptoms of depression. Such findings are not unexpected as chronic disorders have been shown to be associated with significantly more functional complaints, including functional GI disorders [10-12,16]. However, other studies have not found such association. One study failed to show any difference in GI symptoms between type I diabetes mellitus patients compared to control [17]. These differences may be due to difference in the methologies, symptoms definitions and also duration of symptoms enquiry. However, certain co morbid conditions have underlying pathogenesis that predispose to GI symptoms. Conditions such as chronic renal failure and diabetes have been shown to be associated with motility disorders and bacterial overgrowth that can results numerous numbers of GI symptoms [18, 19].

Despite the high prevalence of GI symptoms reported, only a minority of the subject interviewed actually had any endoscopic investigations. Although no details of the endoscopic findings were available, none of the subjects who had endoscopic evaluations had any significant findings such as neoplasms or peptic ulcer diseases. This suggest that majority of the complaints were mild and perhaps self-limiting. This is also reflected by the fact that 24.2% of our subjects had actually practiced self-medication for various complaints or ailments. The strong association with psychosomatic symptoms of depression also suggests functional elements of these GI complaints.

In clinical practice, it important to know the prevalence and the changing trends of medical disorders so that health care provisions can be improved to manage these disorders appropriately. At present, data on the prevalence of GI symptoms is lacking in our local setting and this study will provide useful information for clinicians managing these disorders. However, the findings of this study were based on sampling of subjects visiting a tertiary referral centre and as such the results may not be generalisable to the general population. Despite this, the differences are likely to be small as the ethnic break down of the samples is comparable to the population break down. However further studies are required.

In conclusion, GI complaints were more common amongst female and in those with comorbid conditions in our local setting. They also had significantly more psychosomatic symptoms of depression suggesting functional elements. Despite, the higher prevalence of any GI complaints, only a small fraction had undergone any endoscopic evaluation indicating that these symptoms were generally mild and self-limiting.

References

1. Jones R 2008. Primary care research and clinical practice: gastroenterology. Postgrad Med J. 84: 454-8.

2. Holtman G, Goebell H, Talley NJ 1994. Dyspepsia in consulters and non-consulters: prevalence, health seeking behaviour and risk factors. Eur J Gastroenterol Hepatol 5: 917-24.

3. El-Serag HB, Talley NJ 2004. Systematic review: the prevalence and clinical course of functional dyspepsia. Ailment Pharmacol Ther 19:643-54.

4. Van Kerkhoven LA, Eikendal T, Laheij RJ, van Oijen MG, Jansen JB 2008. Gastrointestinal symptoms are still common in a general Western population. Neth J Med. 66: 18-22.

5. Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, Locke GR 3rd, Rodriguez-Artalejo F 2004. Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. Aliment Pharmacol Ther 19: 95-105.

6. Locke GR 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd 1997. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 112:1448-56.

7. Lim SL, Goh WT, Lee JM, Ng TP, Ho KY 2005. Community Medicine GI Study Group - Changing prevalence of gastroesophageal reflux with changing time: longitudinal study in an Asian population. J Gastroenterol Hepatol 20: 995-1001.

8. Welén K, Faresjö A, Faresjo T 2008. Functional dyspepsia affects women more than men in daily life: a case-control study in primary care. Gend Med 5: 62-73.

9. Flier SN, Rose S 2006. Is functional dyspepsia of particular concern in women? A review of gender differences in epidemiology, pathophysiologic mechanisms, clinical presentation, and management. Am J Gastroenterol 101: S644-53.

10. Altay M, Turgut F, Akay H, Kanbay M, Babali A, Akcay A, et al. 2008. Dyspepsia in Turkish patients on continuous ambulatory peritoneal dialysis. Int Urol Nephrol 40: 211-7.

11. Delgado-Aros S, Locke GR 3rd, Camilleri M, Talley NJ, Fett S, Zinsmeister AR, et al. 2004. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Am J Gastroenterol 99: 1801-6.

12. Niklasson A, Strid H, Simren M, Engstrom CP, Bjornsson E 2008. Prevalence of gastrointestinal symptoms in patients with chronic obstructive pulmonary disease. Eur J Gastroenterol Hepatol 20: 335-41.

13. Kang JY, Ho KY 1998 Different prevalences of reflux oesophagitis and hiatus hernia among dyspeptic patients in England and Singapore. Eur J Gastroenterol Hepatol 11: 845-50.

14. Heading RC 1992 Prevalence of upper gastrointestinal symptoms in the general population: a systematic review. Scand J Gastroenterol Suppl 231: 3-8.

15. Hu WH, Wong WM, Lam CL, Lam KF, Hui WM, et al. 2002. Anxiety but not depression determines health care seeking behaviours in Chinese patients with dyspepsia and irritable bowel syndrome: a population based study. Aliment Pharmaco Ther 16: 2081-8.

16. Stanghellini V 1999 Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in the general population: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol Suppl 231: 29-37.

17. Maleki D, Locke GR 3rd, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C, et al. 2000. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. Arch Intern Med 160: 2808-16.

18. Strid H, Simren M, Stotzer PO, Ringstrom G, Abrahamsson H, Bjornsson ES 2003. Patients with chronic renal failure have abnormal small intestinal motility and a high prevalence of small intestinal bacterial overgrowth. Digestion 67: 129-37.

19. Hirako M, Kamiya T, Misu N, Kobayashi Y, Adachi H, Shikano M, Matsuhisa E, et al.2005. Impaired gastric motility and its relationship to gastrointestinal symptoms in patients with chronic renal failure. J Gastroenterol 40: 1116-22.

Health of our patients based on body mass index

Vui Heng Chong and Muhd Arif bin Abdullah,

Department of Medicine, Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA 1710, Negara Brunei Darussalam

Abstract

Many countries, including the developing ones, are reporting increases in the prevalence of obesity with improvements in the standard of living. This has great implications as overweight and obesity are strongly associated with many chronic disorders. The aim of this study was to assess the prevalence of weight problem among patients in Brunei Darussalam. The World Health Organisation classification body mass index (BMI) (kg/m^2) for weight disorders was used: (underweight) ≤18.5, (normal) 18.5-24.99, (overweight) ≥ 25.00 and (obese) ≥ 30.00. The overall prevalence of overweight and obesity were 35.0% and 27.7% respectively. Underweight was seen in 3.7% of patients. The mean BMI was 27.30 (12.95 to 66.03). The highest BMI was seen in the 40-49 year age group. Overall, the 20-69 year age groups were overweight. There was no significant difference in the mean BMI between male and female patients (27.26 ± 5.72 vs 27.28 ± 5.76, p=0.967). Among the various racial groups, the Malays had significantly higher BMI (27.57) compared to Chinese (25.14, p<0.001) and the 'Others' (25.04, p=0.005) but not the Indigenous group (26.09, p=0.769). Patients with diabetes (p<0.001), hypertension (p<0.001) and hyperlipidemia (p<0.001) had significantly higher BMI. Weight disorders are common among our patients population, especially the Malays. More needs to be done to address this problem.

Keywords: Co-morbidities, overweight, obesity, prevalence

Introduction

As the standard of living improves, the prevalence of overweight and obesity is increasing at an alarming rate [1]. Obesity rates are highest among some of the developed nations but increasing trends are also seen in developing nations [2, 3]. The prevalence of obesity is 17.3% in men and 21.2% in women in the UK and 22.5% of adults in the US [2, 3]. This is said to be doubling every 5 to 10 years in industrialized countries. In the Southeast Asia setting, the Singapore National Health Survey conducted in 1998, showed that obesity was highest among the Malays (16.2%) compared to Indian (12.2%) and Chinese (3.8%) [4]. A national nutritional status survey that was done in 1997 based on the World Health Organization body mass index (BMI) classification showed that the prevalence of overweight and obesity in Brunei Darussalam was 33.8% and 11.2% for males and 31.3% and 12.8% for females respectively. The mean BMI for males and females were 24.9 kg/m^2 and 24.7 kg/m^2 respectively [5]. Recently, a newer BMI classification for the Asia-Pacific Region had been developed [6].

Weight disorders are linked to the changes in diets and sedentary lifestyles [7-9]. With the increasing prevalence of weight problems, we will see an increase in the associated co-morbid conditions [10-16] and this will place a big constraint on the health care services. Obesity has also been shown to have a linear relationship with cancer occurrence; particularly at a number of sites including breast, colon, prostate, endometrial, kidney and gallbladder [16]. This study aims to assess the prevalence of weight problems based on the WHO classification among patients attending the various medical clinics throughout the country. The WHO classification was used in this study so that a comparison could be made with results of previous studies.

Correspondence:
Vui Heng Chong, FAMS, MRCP,
Specialist Physician, Department of Medicine,
Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital,
Bandar Seri Begawan BA 1710, Negara Brunei Darussalam
E-mail: chongvuih@yahoo.co.uk

Methods

Patients attending the various medical clinics (Hepatology, Gastrointestinal and Endoscopy, Endocrine, Diabetes, General physician and Rheumatology clinics) in the different hospitals (RIPAS Hospital-Brunei Muara, Suri Seri Begawan Hospital-Kuala Belait, Pengiran Isteri Hajah Mariam Hospital-Temburong and Pengiran Muda Mahkota Pengiran Muda Hj Al Muhtadee Billah Hospital-Tutong) were included in this study. Patients (n = 961) consisted of those who were newly referred for evaluations or were already on follow-up for various medical disorders. The racial breakdown was consistent with the population make-up (Malays - 75.4%, Chinese - 14.5%, Indigenous - 3.4% and 'Others' - 6.4%). There were more females than males at 60.3%. Among all the patients, diabetes was present in 42.8%, hyperlipidemia - 41.4%, hypertension - 53.5% and documented ischemic heart diseases - 5.3%. The low prevalence of ischemic heart disease was because patients from the Cardiology clinic were not surveyed.

The BMI was calculated by dividing the weight in kilogram by the square of the height in meter [BMI = Weight (kg)/Height (m^2). The weight was measured in kilogram to the nearest two decimal places using standardized weighing machines (SECA ®, Germany) and the height in meters (SECA ®, Germany) measured to the nearest two decimal places. Measurements were made with patients standing straight facing forward without their shoes or others accessories. Demographic data on age, gender, race and associated medical disorders were recorded. Patients with fluid retaining disorders such as renal failure on renal replacement therapy, cardiac failure, nephrotic syndrome and end stage liver disease were excluded. Weight disorders (BMI) were classified according to the World Health Organization classification: underweight - (BMI ≤ 18.5), normal - (BMI 18.50-24.99), overweight - (BMI 25.00-29.99) and obese (BMI ≥ 30). Obesity is divided into three grades (Grade I, BMI 30.00-34.99, Grade II, BMI 35.00-39.99 and Grade III or morbid obesity, BMI ≥ 40) [16]. This is the same classification used in the National Nutrition Status Survey-1997.

All data are entered into the SPSS program (Version 10.0) for analysis. Analysis of Variance (ANOVA), t-test and Mann-Whitney test were used to compare for differences between different gender, racial backgrounds and associated co-morbid conditions (diabetes, hypertension, hyperlipidemia and ischemic heart disease). Bonferroni's tests were used for post hoc pair-wise comparisons between the different subgroups. Significance was assumed when p was less than 0.05 (2-tailed).

Results

The mean age of the patients was 50.2 years (range 10 to 90) with a mean BMI of 27.30 kg/m^2 (12.95 to 66.03). The prevalence of overweight and obesity were 35.0% and 27.7% respectively, giving an overall prevalence of overweight disorder of 62.7% in the patient population. Underweight was seen in 3.7%. The prevalence of BMI is shown in Table 1. The highest BMI was seen in the age group 40-49 years old. Overall, the age groups 20-29, 30-39, 40-49, 50-59 and 60-69 years old were overweight. This is shown in Table 2. Patients with significant co-morbid conditions had significantly higher BMI (27.82 [S.D 5.29] vs. 25.07 [S.D 5.65] kg/m^2, p<0.001).

Table 1. Body Mass Index (BMI) distributions (World Health Organization classification)

BMI (kg/m^2)	Prevalence (%)
≤ 18.5 (underweight)	3.7
18.5 to 24.99 (normal)	33.0
25.0 to 29.99 (overweight)	35.0
≥ 30.0 (obesity)	
Grade 1 (30.0 to 34.99)	19.8
Grade 2 (35.0 to 39.99)	6.0
Grade 3-morbid obesity (≥ 40.0)	2.5

Table 2. Overall Body Mass Index (BMI) across the different age groups

Age group (years)	Mean BMI (kg/m^2)
10-19	24.98 (9.06)
20-29	27.17 (7.77)
30-39	27.64 (5.58)
40-49	28.81 (5.88)*
50-59	27.62 (4.88)
60-69	26.32 (5.48)
70-79	24.69 (4.62) **
≥ 80	24.89 (4.34)

* Age group 40-49 had significantly higher BMI compared to age group 60-90 and 70-79 (p<0.05)
** Age group 70-79 has significantly lower BMI compared to age groups 30-39, 40-49 and 50-59 (p <0.05)

Comparison between gender in the different age groups

There were no significant differences between male s and females in age (51.16 [S.D 15.26] vs. 49.59 [S.D 15.12] years old, p=0.124) and BMI (27.26 [S.D 5.72] vs. 27.28 [S.D 5.76] kg/m^2, p=0.967). However, male patients were significantly heavier and taller than female patients; (71.24 [S.D 16.77] vs. 61.89 [S.D 14.13] kg, p<0.001) and (1.63 [S.D 0.08] vs. 1.51 [S.D 0.07] m, p<0.001) respectively. The age groups with high BMI (BMI ≥ 25.00) are seen in the 20-29, 30-39 and 40-49 years old groups for male and in the female group, all different age groups had mean BMIs of over 25.00 kg/m^2. This is shown in Table 3.

Comparison between racial groups

Malay patients had higher BMI compared to the other racial groups. This was significant compared to the Chinese (p<0.001) and the 'Others' group (p=0.005). This is shown in Table 4.

Table 3. Difference in Body Mass Index (BMI) between the racial groups

	BMI kg/m^2
Malay	27.56 (5.67)*
Chinese	25.14 (4.48)
Indigenous	26.09 (5.98)
Others	25.04 (4.35)

Data presented as mean and standard deviation (in parentheses)
*Malay group has significantly higher BMI compared to the Chinese (p<0.001)and 'Others' (p=0.005)

Table 4. Differences in BMI between the age groups of males and females

Age group (years)	Male	Female
10-19	24.01 (10.57)	25.57 (8.59)
20-29	8.07 (8.99)	26.27 (6.69)
30-39	28.76 (5.29)	27.26 (5.71)
40-49	29.16 (4.41)	28.54 (5.93)
50-59	27.10 (4.41)	28.07 (5.26)
60-69	26.51 (5.23)	26.21 (5.72)
70-79	24.23 (4.90)	25.10 (4.49)
≥ 80	23.42 (4.23)	26.05 (4.54)

Data presented as mean and standard deviation (in parentheses)
No significant differences between the different male and female age groups

Comparison between patients with and without co-morbid conditions

Patients with diabetes (p<0.001), hypertension (p<0.001) and hyperlipidemia (p<0.001) were signifi-

cantly older and had significantly higher BMI. Patients with ischaemic heart disease were significantly older (p<0.001); however there was no significant difference in the BMI (p=0.294). This was probably due to small sample size of patients with ischaemic heart disease. This is shown in Table 5.

Discussion

This study shows that weight problems are very common among the patient population, particularly among the Malay patients attending the various medical clinics. This finding is in agreement with the findings of the Singapore National Health Survey with the Malays having the highest prevalence of weight problems. The overall prevalence of weight problem was 67.0% (including 3.7% underweight), with only 33.0% being in the normal BMI range. A higher overall prevalence of weight disorder of 76.6% was seen if the new classification of BMI for Asians (overweight if BMI ≥ 23.0 and obese if BMI ≥ 25.0 kg/m^2) was adopted, with obesity prevalence of 63.4% [6]. This result is consistent with a previous study done that showed prevalence of obesity (BMI ≥ 25.0 kg/m^2) at 72% and 75% for male and female patients with diabetes respectively [17]. However, this is far higher than the national figures and has great implications as these patients are at risk of weight related chronic disorders [15]. In addition, higher mortality has been associated with being overweight. This is of great concern especially with the prediction that the prevalence of weight problem is expected to increase [1].

Most observational studies have shown a 'U' or 'J-shaped' relationship between BMI and mortality, with individuals at very low and very high weights at increased risk. Such a relationship is found even after attempts are made to adjust for confounding factors, such as smoking or preexisting illness [18]. Chronic disorders that have been associated with being overweight or obesity include ischemic heart diseases, diabetes, respiratory, metabolic, musculoskeletal and psychological disorders and certain malignancies. Also in agreement with published observations, patients with diabetes, hypertension and lipid disor-

Table 5. Comparisons between those with and without co-morbid conditions

	Age (years)	*P* value	BMI (kg/m^2)	*P* value
Diabetes				
Yes	54.05 (13.08)	<0.001	28.38 (5.32)	<0.001
No	47.21 (16.00)		26.47 (5.93)	
Hypertension				
Yes	55.89 (13.59)	<0.001	27.86 (5.37)	<0.001
No	43.23 (14.03)		26.07 (5.59)	
Hyperlipidemia				
Yes	53.01 (13.86)	<0.001	28.51 (5.20)	<0.001
No	48.35 (15.68)		26.01 (5.54)	
Ischaemic heart disease				
Yes	61.72 (14.95)	<0.001	27.87 (5.00)	0.294
No	49.54 (14.79)		26.98 (5.56)	

Data presented as mean and standard deviation (in parentheses)

ders in this study were significantly more overweight [9, 11, 14, 15]. The low incidence of ischemic heart disease seen in this study was probably due to the fact that patients from the cardiology clinic were not surveyed. In addition, no formal cardiovascular evaluations are routinely done unless patients were symptomatic or found to have electrocardiogram changes suggestive of ischemic heart disease. Hence, patients with milder disease remained undetected. Often patients may present for the first time with acute coronary syndrome.

This study also showed that weight problems have a linear relationship with age, particularly in the female groups. This is most likely related to decrease in physical activities and sedentary lifestyles. There are other factors, such as genetics or cultural factors to account for the high in prevalence among the Malay population. Changes in the diets are important factor. These represent the modifiable risk factors. In addition to these, the mindset of seeing 'chubby' as being healthy or prosperous particularly with the older generations is also a factor that makes overweight and obesity being seen as the norm.

In addition to the increasing trend in the adult population, increasing concerns are reports of increasing obesity seen in the adolescents and the children population [19]. A survey done by the Ministry of Education (2003) presented in the National Convention for Health Promotion 2004, showed that one in three children aged below 12 years was overweight or obese.

Overall, the main emphasis of weight management is the prevention of overweight and obesity [20]. Sustained weight loss would be the ideal end point. Increasing awareness of overweight, obesity, associated disorders, improvement in dietary habits and increasing physical activities are the main measures in the management strategy. Preventing childhood weight problem is probably the best management strategy especially with the increasing trend of childhood obesity.

Treatments currently available for overweight and obesity are limited and have major limitations. Treatment available include medical and surgical in conjunction with life style changes. Currently, there are few available medications for management of weight disorders. Sibutramine (Reductil® Abbott) and Orlistat (Xenical® Roche) have been shown to be effective compared to placebo but the weight loss achieved is only marginal. Weight is usually regained upon stopping the medications. Furthermore, the side effects are limiting factors. Orlistat is currently licensed for treatment up to four years whereas Sibutramine for one year [21]. Newer medication such as the cannabinoid receptor antagonist, rimonabant (Acomplia, Sanofi-Aventis®) which suppresses appetite has been withdrawn due to the increased risk of psychiatric adverse events, including suicidality. There are currently numerous weight reducing remedies or programs available but none of these have been proven. Generally, medications have high failure rate as most patients fail to realize that success requires combinations of sustained motivation and life style modifications.

Apart from medications, other methods include gastric balloon or surgery. Gastric balloon is poorly tolerated and results have been disappointing. Furthermore, the balloon is only licensed for use up to six months. Bariatric surgeries such as bypass surgery or gastric banding have been shown to be superior to medical managements and weight loss is usually sustained. Other surgeries include gastroplasty, biliopancreatic diversion or duodenal switch. All these modalities have been shown to be associated with effective weight loss. Surgery is currently only indicated for those who are severely obese. Unfortunately, the older weight reducing surgeries had been associated with other long term complications such as liver disease and nutrition imbalance. Furthermore, surgeries in obese patients are associated with increased risk for complications. Bariatric surgery, specifically laparoscopic adjustable gastric banding has just been introduced in Brunei Darussalam and experience remains limited. Generally, laparoscopic gastric banding is considered the most effective surgical intervention with the least risk involved.

For patients who have weight problems that cannot be managed with life-style changes, dietary or medications, surgery should be considered. For those patients who do not warrant a surgical option, they should be enrolled into a strict weight management program with the aims of preventing further weight gain and promoting weight loss if possible. Currently, the Obesity clinic is run by as multi disciplinary team consisting of the endocrinologists, surgeons, dietitian, nurses and counselors. The benefits ob-

tained from weight maintenance and weight loss, even if not achieving the target can be substantial. Overall, patients' understanding of their conditions, aims of the management program, commitment and motivations are paramount.

One main limitation of this study is that nutritional status was based only on BMI, which may not correlate with the true nutritional statuses of some patients. However, BMI is widely used and accepted in clinical practice as a simple indicator of nutritional status. Use of waist circumference has also been shown to be a reliable indicator of excess adipose tissue. We had chosen to use the WHO classification instead of the newly developed classification for several reasons. The Asia Pacific classification had just been introduced when the study was carried out and many clinicians were still unaware of this newer classification. Second, in order to compare the prevalence with published reports, we had to use similar BMI classification. Finally, our study subjects were patients followed in the various hospital clinics, therefore our results may not be generalized to the overall population or patients followed in the non hospital clinics. The results of this study clearly show that weight problems are common among the patient population.

In conclusion, weight disorder is very common among our patients population and this is particularly so among Malays, the middle aged groups and female patient populations. More needs to be done to address this problem as weight disorder is known to be associated with significant co-morbidities. Public educations are particularly important to increase awareness prevalence and dangers associated with weight disorders.

References

1. Obesity: preventing and managing the global epidemic 2000. Report of a WHO consultation. World Health Organ Tech Rep Series 894; i-xii, 1-253.

2. Health survey for England: Cardiovascular disease '98. Vol 1. Findings. 1999; 8.

3. Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL 1998. Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obesity 22(1):39-74.

4. Epidemiology and Disease Control Department of Ministry of Health. National Health Survey 1998 Singapore. Singapore: Ministry of Health, 1998.

5. National Nutritional Status Survey-1997. Ministry of Health- Negara Brunei Darussalam.

6. WHO Expert Consultation 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363(9403):157-63.

7. Jeffery RW, Utter J 2003. The Changing Environment and Population Obesity in the United States. Obesity Res 11:12S-22S.

8. Matsushita Y, Yoshiike N, Kaneda F, Yoshita K, Takimoto H 2004. Trends in Childhood Obesity in Japan over the Last 25 Years from the National Nutrition Survey. Obesity Res 12:205-214.

9. Manson JE, Skerrett PJ, Greenland P, VanItallie TB 2004. The Escalating Pandemics of Obesity and Sedentary Lifestyle. Arch Intern Med 164:249-258

10. National Task Force on the Prevention and Treatment of Obesity 2000. Overweight, Obesity, and Health Risk. Arch Intern Med 160:898-904.

11. Pi-Sunyer FX 1993. Medical hazards of obesity. Ann Intern Med 119:655-60.

12. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB 2003. Years of Life Lost Due to Obesity. JAMA 289:187-193.

13. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB 1999. Annual Deaths Attributable to Obesity in the United States. JAMA 282:1530-1538.

14. Harris ML, Flegal KM, Cowie CC, et al. 1998. Prevalence of diabetes, impaired fasting glucose, and imparted glucose tolerance in US adults: the Third National Health and Nutri-

tion Examination Survey, 1988-94. Diabetes Care 21:518-524

15. Eckel RH. 1997. Obesity in heart disease. Circulation 96:3248-3250.

16. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO 2001. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 91(3):421-30.

17. Dash RJ 1999. A glimpse of Diabetes Mellitus in Brunei Darussalam. Brunei Int Med J 1: 241-247.

18. Troiano RP, Frongillo EA Jr, Sobal J, Levitsky DA. 1996. The relationship between body weight and mortality: a quantitative analysis of combined information from existing studies. Int J Obes Relat Metab Disord 20:63-75.