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CONTENTS



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"True courage is like a kite; a contrary wind raises it higher."

John Petit-Senn (1792 – 1870)
French poet

Editorial

- 1 **Evidence-balanced Medicine: "Real" Evidence-based Medicine in the Elderly**
[Wee Shiong Lim](#), [YY Ding](#)

Original Articles

- 6 **A Novel "Box Lesion" Minimally Invasive Totally Thoracoscopic Surgical Ablation for Atrial Fibrillation**
[Qiu Zhe Guo](#), [Da Zhu](#), [Zhi Xuan Bai](#), et al
- 13 **Anaerobic Bacteraemia Revisited: Species and Susceptibilities**
[Lily SY Ng](#), [Lee Ling Kwang](#), [Suma Rao](#), [Thean Yen Tan](#)
- 19 **Safety and Effectiveness of Improving Carbapenem Use via Prospective Review and Feedback in a Multidisciplinary Antimicrobial Stewardship Programme**
[Christine B Teng](#), [Tat Ming Ng](#), [Michelle W Tan](#), et al
- 26 **Schizophrenia as a Lifelong Illness: Implications for Care**
[Jimmy Lee](#), [Gary Remington](#)

Please see inside Contents for the full list of articles.

Evidence-balanced Medicine: “Real” Evidence-based Medicine in the Elderly

Wee Shiong Lim,^{1,2} MRCP, MHPed, FAMS, YY Ding^{1,2} MBBS, FRCP, FAMS

Case History

Case 1: An 85-year-old male with past history of hypertension is otherwise healthy and enjoys his daily walks and good food. During a health screening, he was found to be hyperlipidaemic (LDL 3.4 mmol/L; HDL 1.0 mmol/L). He was started on simvastatin 20 mg nocte by his physician. He developed muscle pain and weakness that interfered greatly with his ability to exercise and quality of life.

Case 2: An 85-year-old female with advanced Alzheimer’s dementia who is bedbound and on nasogastric tube feeding has been newly diagnosed with chronic kidney disease stage 3. Her blood pressure is 125/80 mmHg. Her physician is wondering whether she will benefit from angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in preventing progression to end-stage renal disease (ESRD).

Developed countries around the world (including Singapore) are aging at an unprecedented rate. Against this backdrop, the above case scenarios have now become increasingly commonplace in daily “real” clinical practice. Often, the clinician is confronted with an elderly patient who does not fit the classical bill of the typical “surreal” patient recruited in randomised controlled trials (RCTs), either in terms of age, comorbidities, functional status or vulnerability to adverse drug reactions.¹⁻⁴

Our first case developed significant side effects after a seemingly “standard” dose of statin, while in the second case, there is hesitancy as to whether the preventive benefits seen in more robust younger patients can be extrapolated to frail older adults with multiple comorbidities and limited life expectancy. Given the medical complexity, heterogeneity and diverse sociocultural background of the elderly, how does one realistically apply evidence-based medicine (EBM) so that care is customised to their unique needs?^{1,5} Or is the pursuit of good EBM practice an elusive dream in the “real” world of frail elderly patients?

Premise and Promise of EBM (Advent from Eminence-based Medicine)

To understand EBM thoroughly, it is important to review its history and the environment in which EBM arose (Fig. 1).⁶ Up to the early 1970s, it was thought that medical decisions made by physicians were by far appropriate. Through medical education, continuing education, journals, individual clinical experience and interaction with other colleagues, it was assumed that physicians “always thought the right thoughts and did the right things”.⁶ However, over the following 2 decades, wide practice variations were documented⁷ and surprisingly, large proportions of procedures performed by physicians were judged by experts to be inappropriate.⁸ In addition, the well known assertion that only 15% of medical practices were based on clinical trials was made.^{6,9}

EBM was born into this environment in 1991 when Guyatt first coined the term “evidence-based medicine”.¹⁰ The following year, he used this term again in another paper in the Journal of the American Medical Association (JAMA)

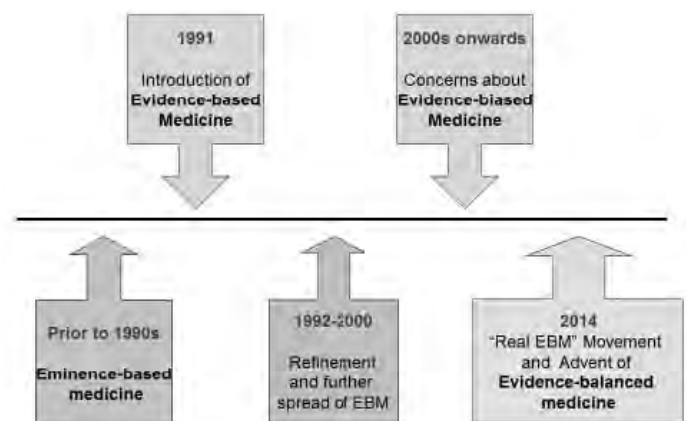


Fig. 1. Key milestones in evidence-based medicine.

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entitled “Evidence-based Medicine: A New Approach to Teaching the Practice of Medicine”.¹¹ The tradition, anecdote, and theoretical reasoning of “eminence-based medicine” would be replaced by the use of available research evidence to guide clinical decisions rather than relying on the opinion of clinical experts.¹¹ The initial introduction of EBM did not see much mention of patient values. Over the ensuing 5 years, patient values and preferences were incorporated into the concept of EBM. The most widely cited definition of EBM that emphasised “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” was put forth by Sackett, who is widely regarded as the “father of EBM”.¹² Sackett further developed this definition to explicitly include patient values by stating that “EBM is the integration of best research evidence with clinical expertise and patient values”.¹³ From there, the rest is history. Use of hierarchies of evidence, adoption of clinical practice guidelines based on research evidence, and widespread teaching of EBM were among some of its impressive results. To say that EBM has revolutionised the way many physicians including ourselves practise medicine would be a gross understatement.

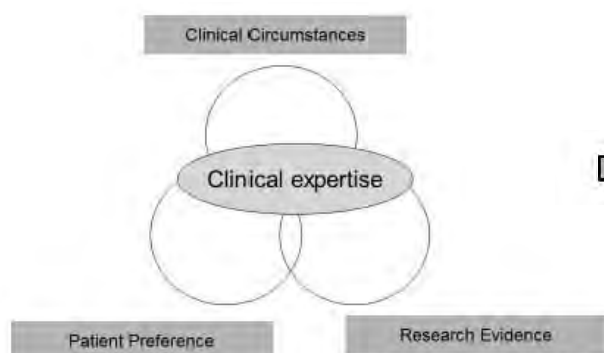
Caveats of EBM

Yet, as with all good things, there is often a downside that is often only discovered later on. While it is clear that EBM has gone a long way in improving rational clinical practice, it has its pitfalls that we need to be cognisant about. Overly rigid application of evidence and clinical guidelines in routine patient care results in the practice of “cookbook” medicine and over-standardisation of clinical practice.⁵ This could lead to inappropriate and suboptimal care where some patients may be harmed in the process. Furthermore, discouragement and eventual downgrading of good clinical

reasoning and judgment on the part of physicians may sadly result.¹⁻³ As mentioned, most randomised clinical trials (RCT) and consequently, clinical practice guidelines based on them reflect the best available evidence albeit for the “average” patient. More pointedly, since older and sicker patients have been excluded from reference clinical trials, many older people encountered in real life clinical practice simply do not fit the description of the “average” patient.^{1,4} The unthinking application of clinical guidelines and rules in older people can adversely influence the clinical benefit-risk ratio of the intended intervention. For older, sicker, and more complex patients, the simplistic way of using EBM could result in “evidence-biased medicine” (Fig. 2).³ The latter has been likened to “using evidence in the manner of the fabled drunkard who searched under the streetlamp for his doorkey because that is where the light was, even though he had dropped the key somewhere else”. In other words, it’s applying the inappropriate evidence to older frail people just because that’s the only evidence available.

So clearly, uncritical application of EBM in older persons can result in failure to individualise the care of heterogeneous patients seen on a daily basis.^{2,3} Specific pitfalls relate to the failure to take into account their unique medical, functional and social aspects. Among medical aspects, multimorbidity and multiple medications may increase potential risks while remaining life expectancy may influence the anticipated benefits of the treatment in question. Physical and cognitive function may influence the selection of treatment options. Social aspects such as the home environment and availability of caregivers could also differentially weight the appropriateness of different treatment options. Over and above these points, the stated aspiration of EBM has been to take into account patient values and preferences in decision making.^{2,5} We are of the opinion that this is often forgotten in the single-minded

Evidence-based Medicine (EBM)



Evidence-biased Medicine (EBiM)



Fig. 2. Comparison of evidence-based medicine (EBM) vs evidence-biased medicine (EBiM). In EBM, clinical judgment is exercised in integrating the research evidence with clinical context and patient values and preferences. In contrast, EBiM emphasises the supremacy of evidence over other considerations, resulting in dogmatic rigid adherence to guidelines and cookbook medicine.

application of EBM-directed clinical guidelines in busy clinical practice. Eliciting values and preferences require a conversation with older patients and their caregivers that goes beyond technical care aspects and may involve some form of shared decision making.^{2,5} Nevertheless, we are struck by the possibility that many of these pitfalls may be avoided when the true spirit of EBM envisioned by its founders is adhered to, particularly the emphasis on the individual patient and the need to account for patient values and preferences. There should also be a greater willingness to recognise that in many clinical situations involving care of frail older patients, no applicable research evidence really exists because they are so far removed from the “average” patient in RCTs.^{1,4} In these instances, physicians must sail in uncharted territory.

Renaissance of EBM (Advent of Evidence-balanced Medicine)

There are exciting developments in recent years in response to the repeated calls for EBM to emphasise person-centredness and retain relevance in the “new normal” of frail older adults who now form the “core business” of health services.^{2,3} These include the “Choosing Wisely” campaign to promote discussions about the safety and appropriateness of medical tests, medications and procedures;¹⁴ updated Beers Criteria for potentially inappropriate medication use in older adults;¹⁵ development of elderly-friendly guidelines for specific diseases;^{16,17} dedicated forums to discuss the application of EBM in the elderly;¹⁸ and the recently launched “Campaign for Real EBM.” This campaign aims to address concerns with ersatz EBM by

refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment.² This advent of evidence-balanced medicine (EBLM) is congruent with developments elsewhere,¹⁹ and heralds a return to the original spirit of EBM.

We would therefore like to propose the “PCR triangle” of EBLM to advance its application and practice in geriatrics care (Fig. 3), comprising the three-pronged approach of patient at the apex, and supported at the base by clinician and research. The hallmark of EBLM is ethical person-centric care that embraces the complexity and diversity of frail older adults through an individualized approach.^{2,3} Thoughtful application of preventative intervention such as cancer screening or primary prevention of cardiovascular diseases should incorporate an estimation of the older person’s life expectancy as well as the preventative intervention’s lag time to benefit to avoid overdiagnosis and overtreatment.^{1,5} An individual’s health preference is another factor that should influence decisions about preventative interventions.^{1,3} When deliberating about intensive or invasive treatments for serious illnesses, older persons are often less concerned with the chances of dying (mortality outcomes) compared with the prospect of surviving with disability (functional, cognitive and quality of life outcomes).³ As illustrated by our first case example, their willingness to take medications for primary prevention of cardiovascular disease is often less related to potential benefits than to potential adverse effects.²⁰ Our task is to present the evidence in a format that older persons can understand so as to enable them to make informed decisions about what treatment they want.²

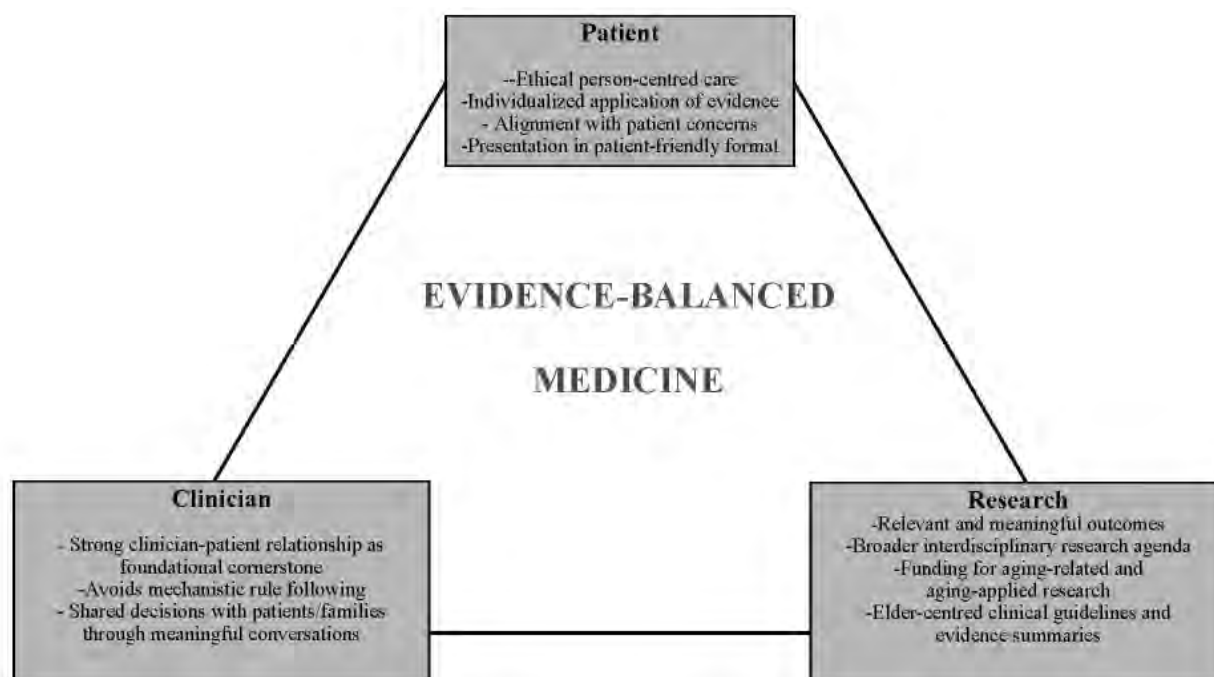


Fig. 3. The PCR triangle of evidence-balanced medicine (Adapted from Greenhalgh T, Howick J, Maskrey N, Evidence Based Medicine Renaissance Group. Evidence based medicine: a movement in crisis? *BMJ* 2014;348:g3725)

Clinicians therefore need to build upon a strong clinician-patient relationship as the foundational cornerstone to practice EBM.² Evidence should be individualised rather than applied mechanistically as inflexible rules or technology-driven prompts, as appropriate care decisions may not necessarily match what “best (average) evidence” seems to suggest.² The utility of EBM is ultimately dependent on expert judgment that combines context and patient preference in drawing valid analogy.^{2,3} To this end, we propose the “ESCAPE” communication model to guide meaningful conversations with patients and their families in shared decisions about investigations and treatments (Table 1). By considering the benefits (number needed to treat, NNT), adverse effects (number needed to harm), actual costs of treatment, contextual factors, and patient concerns and preferences, clinicians can establish consensus about care decisions that are in the patient’s best interest. In our second case illustration, evidence suggests that the magnitude of benefit of ACEIs and ARBs in preventing ESRD seen in RCTs of younger participants is less well extrapolated to elderly patients (NNT: 9 to 25 to prevent 1 case of ESRD over 3 years versus greater than 1000 in many elderly subgroups).²¹ Weighing the limited benefit against the potential harms of treatment (renal impairment, hyperkalaemia, and hypotension), the clinician may opt not to start ACEI or ARB in this patient with limited life expectancy.

To address this gap between clinical trials and the real world, it is imperative that we build up the evidence base to guide decision-making in elderly care.²²⁻²⁴ Research in older adults should incorporate clinically relevant and meaningful outcomes such as quality of life, cognition, physical function and psychosocial consequences.¹⁻³ Given the importance of lag time to benefit in determining whether a preventative treatment is appropriate for an older adult, it is recommended that future research on preventative interventions should report the lag time to benefit (“When will it help?”) along with the magnitude of benefit (“How much will it help?”).⁴ There should be a shift in emphasis beyond reductionist positivist study designs such as RCTs

and meta-analyses to embrace a broader research agenda that is interdisciplinary and encompasses plurality of methods (including the rich diversity of qualitative methods) to answer use-inspired Pasteur’s quadrant research questions that matter.^{2,25} This raises the need to create independent sources of funding for aging-related research (e.g. frailty, sarcopenia, delirium, geriatric rehabilitation, and end-of-life care)^{26,27} and aging-applied research (e.g. models of care, lifestyle interventions, technology in healthcare, and interprofessional education).^{28,29} For implementation studies, funding policy should look beyond chronological age as a crude criterion of aging research by delinking it from functional and cognitive age, and frailty status. We should also encourage the development of elder-centred clinical guidelines and evidence summaries.^{30,31}

Conclusion

EBM has come a long way since it was introduced more than 20 years ago as a “new paradigm” to counterbalance the then prevailing practice of eminence-based medicine. The ongoing discourse about the need to guard against evidence-biased medicine is timely and especially salient in the context of elderly care. While not amounting to a paradigm shift in the strictest sense, the return to real EBM in the elderly upholds the original ethos of providing best quality care that is undergirded in evidence, clinical judgment, context and patient preference.² As aptly put by Evans when describing EBM, “the name is crass but the idea is worthy.”³ Evidence-balanced medicine in the elderly provides a way forward if EBM is to truly live up to its name.³²

Table 1. ESCAPE Communication Model to Promote Shared Decisions with Patients/Families

1.	Efficacy
2.	Side effects
3.	Cost of treatment
4.	Apply to context
5.	Patient preference and concerns
6.	Establish consensus

Steps 1 to 5 are iterative and need not be applied in a particular order. They provide the basis for the ultimate step of establishing consensus on care decisions with patient/family.

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A Novel “Box Lesion” Minimally Invasive Totally Thoracoscopic Surgical Ablation for Atrial Fibrillation

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Abstract

Introduction: Minimally invasive surgical ablation is an emerging alternative method to catheter ablation and the full surgical maze procedure for nonpharmacologic treatment of atrial fibrillation (AF). We present a totally thoracoscopic “box lesion” radiofrequency ablation procedure in patients with paroxysmal or persistent AF. **Materials and Methods:** From June 2011 to October 2012, 14 patients with lone paroxysmal (n = 7) or persistent AF (n = 7) were enrolled in this study. Procedures were performed through 3 5-12 mm holes on each side of the chest wall. A bipolar ablation device was used to create a box lesion in the posterior wall of the left atrium that encircled the 4 pulmonary veins (achieving bilateral pulmonary vein/posterior left atrial wall isolation). Perioperative complications were recorded for all patients. Freedom from AF was assessed by 24-hour Holter monitoring every 3 months or during symptoms of arrhythmia. **Results:** The ablation was successfully performed in all patients, with median operation time of 128 minutes (range, 45 to 180 minutes). No operative mortality or morbidity were noted during the study period. Freedom from AF was achieved in 12 patients (85.7%) during follow-up (median follow-up 9 months). One patient with persistent AF was shifted to paroxysmal AF. No atrial flutter or atrial tachycardia was noted during the follow-up. **Conclusion:** These early results show that totally thoracoscopic surgical ablation using a unique “box lesion” procedure for persistent or paroxysmal AF is a feasible and effective method with good short-term results. Further study is necessary to validate this result.

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Key words: Arrhythmia therapy, Flutter, Surgery, Thoracoscopy

Introduction

Atrial fibrillation (AF) is the most common and severe cardiac arrhythmia. It affects 0.4% to 1% of the general population, and the prevalence of AF,¹ which increases with age, is 8% in people aged over 80. About three-quarters of the cases are non-valvular AF. The risk for stroke in AF patients is 5 times higher than that of the non-AF population. Maintaining sinus rhythm has been shown to be superior to heart rate control in this arrhythmia in reducing the incidence of stroke and other cardiovascular events. But the success rate of drug-only therapy or catheter ablation in maintaining sinus rhythm in AF patients does not exceed 60%.² The traditional surgical “cut-and-sew” Cox maze III procedure is the most successful treatment

for the management of AF, and has a cure rate of 95%.³ But this procedure requires sternotomy, cardiopulmonary bypass (CPB), and a complex series of incisions into the myocardium. The complexity of this technique and the risks involved in its use have prevented wide application of the procedure.

As substitutes for the Cox maze III procedure, a variety of surgical ablation procedures that rely on minimally invasive techniques to achieve isolation of the pulmonary veins, the primary source of ectopic foci in AF, have been developed.^{4,5} Unfortunately, none of these procedures are likely to be as effective as the traditional Cox maze III procedure. One reason is that isolation of the posterior left

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atrial wall is not included, and the posterior left atrial wall, in addition to the pulmonary veins, is considered to play a significant role in the initiation and maintenance of AF.⁶ In the present study, we report our initial experience with, and short-term results for, a newly developed minimally invasive technique for treatment of AF that uses a bipolar radiofrequency device to create a transmural box lesion that surrounds the posterior left atrial wall and encompasses the pulmonary veins—a procedure that separates the pulmonary veins and posterior left atrial wall as a whole from the rest of the atrium.

Materials and Methods

Patient Enrolment

This study was approved by Clinical Research and Biomedical Ethical Committee of West China Hospital Sichuan University. Patients with lone AF (paroxysmal, persistent or permanent) and who had underwent minimally invasive totally thoracoscopic surgical ablation in our hospital were enrolled in the study. The patients involved were all from our clinic and voluntarily chose to undergo surgery after the different treatment options were introduced and explained to them. The classification of paroxysmal and persistent AF followed the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) definitions.⁷ All patients fulfilling either of the following criteria were included in this study: (1) recurrent episodes of AF, and (2) AF refractory to antiarrhythmic drugs. Exclusion criteria were (1) previous pulmonary and cardiac surgery, (2) underlying cardiovascular or pulmonary diseases other than AF, (3) atrial thrombi or persistent left superior vena cava confirmed by transoesophageal echocardiogram. Coronary angiographic analysis was performed if necessary to rule out coronary artery disease. Informed written consent was obtained from all patients.

Surgical Procedure

Procedures were conducted under general anaesthesia under CPB standby conditions. Patients were intubated with a double lumen endotracheal tube in order to achieve lung isolation, and were placed in a supine position with both upper arms dorsiflexed 15° and slightly flexed along the body to facilitate the exposure of the lateral side of the chest wall. A transoesophageal echocardiogram was performed to confirm the absence of left atrial thrombi and persistent left superior vena cava.

After deflation of the right lung, a 5-mm trocar was introduced into the fourth intercostal space in the anterior axillary line and CO₂ insufflation was delivered at approximately 8 to 12 mmHg. A 0° thoracoscope was then

introduced through this port. Two other 5-mm ports were introduced in the third and fifth intercostal space at the anterior axillary line, respectively. The first 5-mm port was then replaced by a 12-mm port which served as the working port (Fig. 1a). The pericardial sac was opened from the superior vena cava (SVC) to the inferior vena cava (IVC) about 2 cm anterior and parallel to the phrenic nerve (Fig. 2). Blunt dissection was performed underneath the SVC and IVC to establish access to the transverse and oblique sinuses, respectively. Two Cardioblade Navigators (Medtronic, Minneapolis, MN, USA) were then put through the sinuses and the right lung was re-inflated (Figs. 2 and 3).

Left-sided Ablation

The left lung was deflated and the same ports as those on the right chest wall were developed on the left chest wall. The pericardium was opened and the tips of the 2 navigators were delivered through the working port (Fig. 1b). Two jaws of the Cardioblade Gemini-s bipolar radiofrequency isolator (Medtronic, Minneapolis, MN, USA) were attached to the tips of the navigators. Under the guidance of the navigators, the 2 jaws of the isolator were then delivered smoothly into the transverse and oblique sinuses respectively (Figs. 2 and 3). When the correct position was achieved, repetitive radiofrequency pulses were applied about 3 to 5 times to achieve transmural ablation. The isolator was then retrieved.

Right-sided Ablation

After re-inflating the left lung and collapsing the right lung, the ablation procedure was repeated by introducing the isolator into the right side of the transverse and oblique sinuses under the guidance of navigators through the right working ports. Repetitive radiofrequency ablations were then applied. When ablations on both sides were completed, a continuous box lesion surrounding the pulmonary veins and posterior left atrial wall was created (Figs. 2 and 3). A single 28-French chest tube was placed in each pleural space through the most inferior ports. The patient was then transferred to the intensive care unit for recovery.



Fig. 1. Location of the ports on each side of the chest wall.

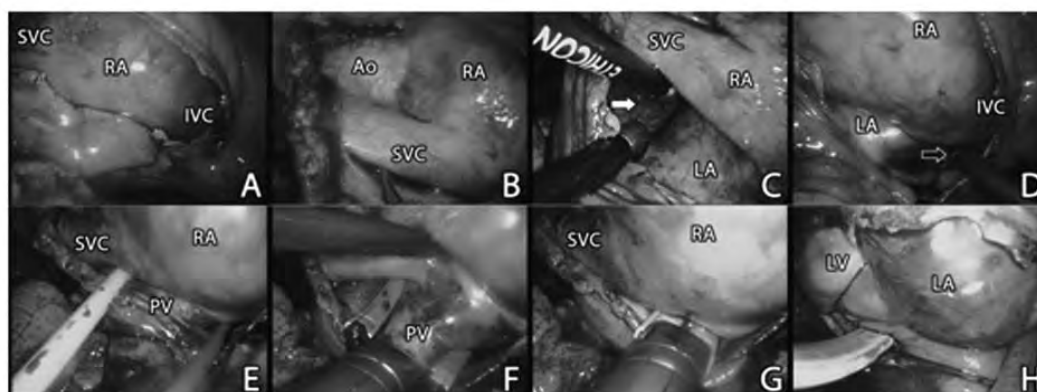


Fig. 2. Continuous intraoperative endoscopic view of the ablation procedure. (a, b) The pericardial sac was opened from the superior vena cava to the inferior vena cava anteriorly and parallel to the phrenic nerve. (c, d) Blunt dissection of the transverse (indicated by the white arrow) and oblique sinuses (black arrow). (e) Two navigators were delivered through the 2 sinuses. (f, g) Right side ablation. (h) Left side ablation. Ao: Aorta; IVC: Inferior vena cava; LA: Left atrium; LV: Left ventricle; PV: Pulmonary vein; RA: Right atrium; SVC: Superior vena cava.

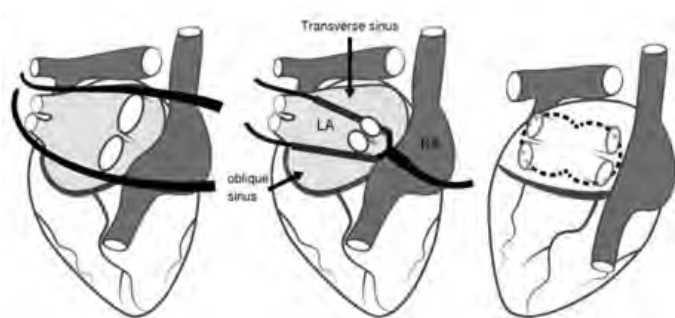


Fig. 3. Schematic drawing of the posterior aspect of the heart. Two navigators were positioned in the transverse and oblique sinuses to guide the ablation device. The dashed line in the figure shows the box lesion created after ablation on both sides. LA: Left atrium; RA: Right atrium

Postoperative Management

Cardiac rhythm was continuously monitored for 48 hours. Thereafter, daily 12-lead electrocardiograms (ECGs) were performed for the duration of hospitalisation. All patients were given amiodarone (or sotalol if amiodarone was not tolerated) for at least 3 months. In patients who were in stable sinus rhythm, the antiarrhythmic agent was stopped at 3 months. Those who developed persistent AF during the hospital stay underwent cardioversion within 24 hours.

Follow-up

Electrocardiographic follow-up was undertaken at 1 month, 3 months, 6 months, and 1 year after the surgery. A 24-hour Holter test was requested at 3 and 6 months after the surgery, or at any time for patients with normal ECG but symptomatic evidence of recurrence of AF.

Results

Patient Demography and Characteristics

Patient demographic data and characteristics are listed in Table 1 and Table 2. From June 2011 to October 2012, 14 patients (8 male and 6 female) with lone paroxysmal ($n = 7$) or persistent AF ($n = 7$) who had undergone totally thoracoscopic surgery in our hospital were enrolled in the

study. All patients had been unresponsive to or did not tolerate antiarrhythmic drugs. Four patients had had a recurrence of AF after a prior transcatheter endocardial ablation. The median age of patients and median duration of AF were 62 years (range, 41 to 76 years) and 36 months (range, 12 to 204 months) respectively. On echocardiography, the median left atrial diameter was 42 mm (range, 32 to 56 mm) in the parasternal long axis view.

Perioperative Data

The procedure was successfully completed in all patients, with no conversions to sternotomy or thoracotomy. The median procedure time was 128 minutes (range, 45 to 180 minutes). Procedure length was significantly shortened after the first few cases, and the last 3 procedures were completed within 90 minutes. All patients were awakened in the intensive care unit. Thirteen patients were successfully extubated within 6 hours after surgery. A prolonged intubation time occurred in 1 patient with a long history of smoking and deterioration in lung function, and this patient was not extubated until 18 hours after the completion of surgery. The median postoperative stay was 7 days. Eight patients had a postoperative stay of 7 days, and the others had postoperative stays of 8 to 12 days (Table 3).

Table 1. Patient Demography and Characteristics (n = 14)

Characteristics	n (%)
Gender	
Female	6 (42.9)
Male	8 (57.1)
Age (years)	62 (41, 76)
AF type	
Paroxysmal	7 (50.0)
Persistent	7 (50.0)
AF duration (months)	36 (12, 204)
Left atrial diameter (mm)	42 (32, 56)
Previous catheter ablation	4 (28.6)
Preoperative AADS	
IC II	1 (7.1)
II	2 (14.3)
III	2 (14.3)
No	9 (64.3)

AADS: Antiarrhythmic drugs; AF: Atrial fibrillation

Table 3. Perioperative Data and Surgical Outcomes

Surgical Outcomes	n = 14
Procedure time (range, minutes)	128 (45 to 180)
Extubation time (range, hours)	5 (3 to 18)
Postoperative hospitalisation time (range, days)	7 (7 to 12)
Cardioversion (n, %)	2 (14.3%)
Postoperative sinus rhythm (n, %)	12 (85.7%)
Sinus rhythm at 6-month follow-up* (n, %)	9 (90.0%)
Follow-up (range, months)	9 (1 to 12)

*Four subjects' with follow-up period less than 6 months were excluded. Continuous data are summarised by median and full range. Categorical data are summarised by count and percentage.

Table 2. Patient Demography and Characteristics

Patient No.	Gender	Age (Years)	Atrial Fibrillation Type	Atrial Fibrillation Duration (Months)	LAD (mm)	Previous Catheter Ablation	Preoperative AADS
1	Female	41	Paroxysmal	48	42	Yes	No
2	Female	66	Paroxysmal	120	32	Yes	IC II
3	Female	59	Persistent	204	51	No	No
4	Male	76	Persistent	60	42	No	No
5	Female	51	Paroxysmal	12	40	No	No
6	Male	67	Paroxysmal	36	42	Yes	III
7	Male	62	Persistent	36	41	No	No
8	Male	62	Persistent	24	40	No	No
9	Male	69	Paroxysmal	36	56	No	III
10	Male	62	Persistent	12	51	No	II
11	Male	56	Persistent	12	39	No	No
12	Female	47	Paroxysmal	36	32	No	No
13	Female	56	Paroxysmal	24	39	No	No
14	Male	63	Persistent	96	48	Yes	II

AADS: Antiarrhythmic drugs; LAD: Left atrial diameter

A complication occurred in 1 patient who was readmitted 2 weeks after the surgical intervention due to a medial right pleural effusion shown on x-ray. This patient was then treated with pleurocentesis. There were no perioperative deaths, and no reintubations, blood product infusions or pacemaker insertions were required during follow-up.

Surgical Outcome

Twelve of the 14 patients (85.7%) converted to sinus rhythm immediately after the procedure. The 2 patients who did not convert received electrical cardioversion during hospitalisation and were restored to sinus rhythm. All patients (100%) were in sinus rhythm at discharge and

1 month follow-up. Of the 10 patients who completed 6 months follow-up, 9 (90%) patients were in sinus rhythm. One patient who suffered persistent AF before the surgery had a recurrence of paroxysmal AF at this time. No atrial flutter or atrial tachycardia was observed during the follow-up. The median follow-up time was 9 months (range, 1 to 12 months).

Discussion

This report describes the early results of the first series of patients who had underwent a completely thoracoscopic box lesion procedure for the treatment of AF. This procedure was both safe and effective. A pleural effusion in 1 of the 14 patients was the only adverse effect, and the 6-month follow-up showed a 90% success rate.

AF is an increasingly common disease that affects patient morbidity and mortality. Over the years, hypertension and coronary artery disease have replaced rheumatic heart disease as the major causes of AF. In addition, about 30% of AF cases are not associated with an underlying heart disease. For these reasons, catheter ablation and minimally invasive surgical ablation have emerged as promising new treatment strategies.

Advantages and Disadvantages of Different Energy Sources

Over the past decade, different energy sources for causing ablation have been used to replace the “cut and sew” technique during AF surgery, and they include bipolar and unipolar radiofrequency, cryotherapy, microwave, laser and ultrasound. Of these energy sources, bipolar radiofrequency has been shown to be the most safe and effective in creating transmural linear lesions.⁸ Unipolar radiofrequency ablation has favourable plasticity and can be used in some special areas such as the mitral isthmus, but the continuity and transmural of the lesion cannot be assured. Cryotherapy is less likely to cause thrombosis and damage to the surrounding tissues than other techniques, but treatment using this energy source is time-consuming and has poor efficacy. Microwave ablation has favourable plasticity and is also less likely to cause damage to the surrounding tissues, but the transmural of microwave ablation is poorer than that of bipolar radiofrequency ablation. High-intensity focused ultrasound ablation has favourable transmural, but is likely to cause damage to the surrounding tissues and carries a risk for oesophageal injury. Bipolar radiofrequency ablation, the technique used in this study, can be used for transmural ablation with high efficiency and is less likely to cause damage to surrounding tissues than other techniques. Its disadvantage is that some special areas, such as the mitral isthmus, are difficult to access.

Development of Minimally Invasive Ablation Technique

In 2003, Saltman et al⁹ reported the first totally endoscopic microwave ablation procedure for paroxysmal AF, and a variety of minimally invasive techniques emerged after that. Wolf et al⁴ reported their initial experience of video-assisted thoracoscopic AF surgery in 2005, using bipolar radiofrequency to perform bilateral pulmonary vein isolation. Totally thoracoscopic radiofrequency pulmonary vein isolation was performed by Yilmaz in 2007.⁵ A hybrid procedure combining electrophysiology (EP) mapping, epicardial and endocardial ablation was introduced recently and good success rate in eliminating AF freedom rate was reported.¹⁰

Advantages of Our Procedure in Comparison with Other Minimally Invasive Procedures or Catheter Ablation

The 6-month sinus rhythm restoration rate (90.0%) seen in our study is similar to, or even higher than the results reported in other studies.^{11,12} The main reason for this acceptable result is that we combined the advantages of both bipolar RF and box lesion isolation.

Isolated endocardial and epicardial techniques have the following advantages and disadvantages. Isolated endocardial ablation can be performed percutaneously, is less invasive, and can be performed in regions where epicardial ablation is not feasible. It has favourable repeatability and is not influenced by pericardial or pleural adhesions. However, the continuity and transmural of the lesion cannot be assured, single ablation has a low success rate, radiation damage due to x-ray exposure can occur along with complications such as thrombosis, pulmonary venous stenosis, and atrial oesophageal fistula. Continuity and transmural can easily be accomplished with isolated epicardial ablation, and this method is less likely to cause thrombosis, pulmonary venous stenosis, and atrial-oesophageal fistula. But, epicardial ablation is more invasive than endocardial ablation and requires general anesthesia and endotracheal intubation. In addition, an incision on each side of the chest and alternating one-lung ventilation should be done.

Continuity and transmural of the lesion sets are critical for the therapeutic effect,⁸ and histopathological studies have shown that lesions produced by bipolar RF ablation are more likely to be uniformly transmural than those produced by other energy devices.^{13,14} During our minimally invasive procedure, atrial tissue was clamped by the 2 jaws of the bipolar RF device, and saline irrigation between the compressed tissue and the electrode was performed by the device during delivery of radiofrequency energy in order to cool the tissue and increase the effectiveness of the ablation. The achievement of transmural ablation

was directly detected by a feedback system contained in the device. Compared to other completely thoracoscopic box lesion procedures using microwave or high-intensity focused ultrasound (HIFU),^{9,15} our procedure has a higher single-ablation success rate and fewer complications.

Our box lesion procedure isolated the left posterior atrial wall as well as the pulmonary veins. Cui et al,¹² using bilateral thoracoscopic pulmonary vein isolation, ablation of ganglionic plexi, and left atrial appendage removal, reported a 78.6% success rate 6 months after surgery. However, the left posterior atrial wall was not isolated. The existence of non-pulmonary foci has been correlated with recurrence of AF, and the left posterior atrial wall is the critical site in which these foci are located.⁶ The activation of epicardial ganglionic plexi (GP), which are found primarily in fatty epicardial tissues and ligament of Marshall (LOM), has been implicated as a trigger of lone AF. Additional ablation of GPs and LOM may increase freedom from AF.¹⁶ Some GPs located away from the pulmonary vein-atrial junction are difficult to isolate by bilateral pulmonary isolation but can be included in the box lesion ablation. In addition, the roof line of the box lesion is critical in blocking the LOM. Isolating the entire posterior left atrium with a box lesion in the Cox maze procedure has been shown to produce a higher response rate than making only a single connecting lesion between the pulmonary veins.¹⁷ A high clinical success rate of a box-shaped isolation in the posterior left atrium has also been reported in catheter ablation procedures.¹⁸ Doty et al¹⁹ have used a procedure including the destruction of autonomic ganglia, box lesion RF ablation, and removal of the left atrial appendage, but their procedure is not totally endoscopic and requires thoractomy on each side of the chest. A few studies have reported a less invasive procedure which needs only 3 ports on one side of the chest. However those techniques either did not use bipolar radiofrequency or did not perform a box lesion.

No bleeding, conversion to open procedures, stroke, pulmonary vein stenosis and oesophageal damage was observed during follow-up in our study. In our procedure, radiofrequency energy was delivered through the epicardium and the ablation device was not in contact with the endocardium, therefore thrombus formation was not likely to occur. Pulmonary veins stenosis was also avoided as the ablation was not performed on the pulmonary vein orifice.

Underlying Disadvantages

The hybrid procedure is capable of overcoming the shortcomings of both surgical and catheter ablation techniques and is therefore likely to be more effective, because the conduction block can be confirmed by EP mapping and additional ablation can be performed as

necessary. However, the hybrid procedure will not avoid damage caused by radiation and contrast medium, and its financial cost is higher. In mainland China, patients need to pay part of the hospitalisation cost, and the lower cost procedure of our procedure is therefore an advantage. The major disadvantage of our procedure is that no EP mapping was included. Bidirectional block of the lesion set could only be guaranteed by the feedback system of the device and repeated isolation. But, we have provided a less invasive and more economical way to achieve an acceptable result and avoid the damage caused by radiation and contrast medium of an extra catheter ablation.

One possible disadvantage of our technique is that electrophysiological changes that occur after the procedure might enable the formation of a macro-reentry circuit around the box lesion set. The underlying possibility of atrial flutter was taken into consideration in our study, but was not observed during follow-up.

Another possible disadvantage (but also a possible advantage) of our method is that it does not include amputation of the left atrial appendage. In non-rheumatic AF, most of the thrombus is located in the left atrial appendage.²⁰ Eliminating the appendix will reduce the risk of release of thrombotic emboli. But elimination of the appendix also has disadvantages. According to the study of Kamohara et al,²¹ left atrial appendage exclusion may affect the function of the left atrial reservoir. Also, atrial appendectomy by the maze procedure has been shown to reduce atrial natriuretic peptide secretion and the ability of kidneys to handle fluid load early after surgery.²² And, in studies of minimally invasive epicardial ablation techniques combined with left atrial appendage amputation, the incidence of bleeding and conversion to open procedures has been closely associated with left atrial appendage amputation.^{23,24} In our procedure, no left atrial appendage amputation was performed and this may be one of the reasons for the low complication rate seen. Also, in spite of the fact that the left atrial appendage was left intact, no thromboembolic event occurred during the follow-up.

Study Limitations

Our result reflects our experience on a relatively small number of patients, in a rather limited time period. Only 7 patients were able to finish the 1-year follow-up because the procedure was first used in June 2011. In addition, it was hard to detect every asymptomatic episode of AF using single ECG or Holter tests. However, the study is still ongoing, and more patients will be enrolled and followed for a longer duration, incorporating Holter monitoring for all patients at 6-months and 1-year.

Conclusion

We presented the early results of a new, completely thorascopic, minimally invasive surgery for treatment of AF by creating a unique box lesion around the pulmonary veins that includes the left posterior atrial wall. This procedure is safe, easy to perform and appears to be effective in short-term follow-up. It might be an attractive alternative to antiarrhythmic medication therapy and catheter ablation. Continued long-term follow-up on a large group of patients is still required to establish the sufficiency of the treatment.

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Anaerobic Bacteraemia Revisited: Species and Susceptibilities

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Abstract

Introduction: This retrospective study was performed to evaluate the frequency of anaerobic bacteraemia over a 10-year period, and to provide updated antibiotic susceptibilities for the more clinically relevant anaerobes causing blood stream infection. **Materials and Methods:** Data were retrieved from the laboratory information system for the period 2003 to 2012. During this time, blood cultures were inoculated in Bactec™ Plus vials (BD, USA) and continuously monitored in the Bactec™ 9000 blood culture system (BD, USA). Anaerobic organisms were identified using commercial identification kits, predominantly API 20A (bioMérieux, France) supplemented with Vitek ANC cards (bioMérieux, France) and AN-Ident discs (Oxoid, United Kingdom). A representative subset of isolates were retrieved from 2009 to 2011 and antimicrobial susceptibilities to penicillin, amoxicillin-clavulanate, clindamycin, imipenem, moxifloxacin, piperacillin-tazobactam and metronidazole were determined using the Etest method. **Results:** Anaerobes comprised 4.1% of all positive blood culture with 727 obligate anaerobes recovered over the 10-year period, representing a positivity rate of 0.35%. The only significant change in anaerobe positivity rates occurred between 2003 and 2004, with an increase of 0.2%. The *Bacteroides fragilis* group (45%) were the predominant anaerobic pathogens, followed by *Clostridium* species (12%), *Propionibacterium* species (11%) and *Fusobacterium* species (6%). The most active in vitro antibiotics were imipenem, piperacillin-tazobactam, amoxicillin-clavulanate and metronidazole, with susceptibilities of 95.0%, 93.3%, 90.8% and 90.8% respectively. Resistance was high to penicillin, clindamycin and moxifloxacin. However, there were apparent differences for antibiotic susceptibilities between species. **Conclusion:** This study indicates that the anaerobes comprise a small but constant proportion of bloodstream isolates. Antibiotic resistance was high to some antibiotics, but metronidazole, the beta-lactam/beta-lactamase inhibitors and carbapenems retained good in vitro activity.

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Key words: Antibiotic resistance, *Bacteroides*

Introduction

Over the last 2 decades, the importance of anaerobic bacteraemia has undergone various shifts in opinion. Early studies in the 1970s reported that anaerobes accounted for 2% to 20% of bacteraemia.^{1,2} However, by the mid 1980s, multiple centres reported declining rates of anaerobic bacteraemia,³⁻⁵ and several authors suggested that the routine inoculation of anaerobic blood cultures should be discontinued. The rationale for this argument was that the inoculation of 2 aerobic blood cultures would increase the yield of obligate aerobes,^{6,7} and that antimicrobial susceptibilities of anaerobes were also predictable. The late 1990s saw several studies reporting a resurgence of

anaerobic bacteraemia,^{8,9} although this was also clearly dependent on local epidemiology.^{10,11}

Antibiotic therapy for anaerobes is usually empiric. Anaerobic susceptibility testing is not performed routinely, as it is both costly and methodologically demanding, and time consuming. Nonetheless, the prevalence of antibiotic resistance in anaerobes is increasing, both to commonly used antibiotics (e.g. metronidazole and clindamycin)¹² and broad-spectrum antibiotics (e.g. the carbapenems).¹³ Clinical data suggest that antibiotic resistance impacts both microbiological cure and patient mortality for patients with anaerobic bacteraemia.¹⁴

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There is little susceptibility data for anaerobic infections in Singapore. Our laboratory first published data on antibiotic susceptibilities for anaerobes isolated from diabetic foot infections in Singapore.¹⁵ However, the sample size was small and data from soft tissue infections may not be representative of invasive bloodstream isolates. The Clinical Laboratory Standards Institute (CLSI) recommends that at least 50 to 100 strains should be tested to obtain accurate representation of the susceptibility pattern of local isolates. Reliable antibiotic data is required to guide antibiotic choices for both empiric and definitive treatment for anaerobic bacteraemia.

This study was performed in an 800-bed hospital that provides medical, surgical, orthopaedic and geriatric medical care to the eastern region of Singapore. The aims of the study were to determine the relative frequency of anaerobic bacteraemia over a 10-year period, to analyse the relative distribution of anaerobic species isolated from blood cultures and to determine the antibiotic susceptibilities of a representative panel of anaerobes.

Materials and Methods

Bacterial species identification and basic patient epidemiological data were extracted from the laboratory information system. Duplicate isolates from the same patient (defined as similar isolates within a 30-day period) were excluded from analysis. During the period from 2003 to 2012, standard clinical practice in the hospital included routine aerobic and anaerobic blood cultures which were performed using BACTEC™ Plus Aerobic/F and Plus Anaerobic/F vials (BD, USA). Blood cultures were incubated for 5 days in a continuous monitoring blood culture system (Bactec 9000 series, BD, USA). Anaerobic vials which flagged positive for growth were subcultured on to blood agar with 5% sheep blood (BD, USA), MacConkey agar (Oxoid, UK), chocolate agar (BD, USA) and CDC anaerobe 5% sheep blood agar (BD, USA). Blood agar and MacConkey agar were incubated at 35°C in ambient atmosphere, while chocolate agar and CDC anaerobe were incubated in 5% CO₂ and anaerobic conditions, respectively. Media were routinely incubated for 2 days, with additional incubation for up to 4 days if a slow growing anaerobe was suspected. Initial tests performed on suspected anaerobic isolates included confirmatory aerotolerance testing for strict anaerobic growth and Gram-stain. Further speciation by commercial identification kits was performed, supplemented by additional phenotypic tests, where required. The primary identification kit used was the API 20A (bioMérieux, France), with additional AN-Ident discs¹⁶ (Oxoid, United Kingdom) used from 2003 to 2007. From 2008, isolates were predominantly identified using Vitek® ANC identification cards tested on the Vitek® Compact system supplemented with API 20A, where necessary.

Antibiotic susceptibility testing was performed on a retrospective collection of 119 anaerobic isolates from blood culture, collected from 2008 to 2010. Banked isolates were stored at -70°C in commercial cryovials, and retrieved from initial storage by subculture on CDC anaerobe 5% sheep blood agar (BD, USA). Isolates were passaged by subculture at least twice before further testing was performed. The isolates included *Bacteroides* spp. (n = 69), *Clostridium* spp. (n = 28), *Fusobacterium* spp. (n = 9) and other species.¹³ These were chosen to represent the most common and/or most pathogenic anaerobic isolates from blood cultures. Antimicrobial susceptibility testing was performed by Etest, according to manufacturer's instructions.¹⁷ Testing was performed on Brucella agar with 5% sheep blood, vitamin K and hemin (BD, USA), with inoculating suspensions prepared using Brucella broth (BD, USA). The antibiotics tested were amoxicillin-clavulanate, clindamycin, imipenem, metronidazole, moxifloxacin, penicillin and piperacillin-tazobactam. All testing media was pre-reduced anaerobically overnight to achieve optimal conditions. Plates were incubated at 35°C in an anaerobic workstation system to achieve rapid anaerobiosis. Etest results were read after 48 to 72 hours, with the duration of incubation depending on the time required to achieve satisfactory confluent growth. Antibiotic susceptibilities were interpreted according to current CLSI breakpoints.¹⁸

Results

During the 10-year period, 421,185 blood culture vials were processed in the laboratory (49.6% comprising of anaerobic blood cultures). A total of 727 obligate anaerobes were recovered from these cultures, representing a positivity rate of 0.35%. Anaerobes comprised 4.1% of 17,800 organisms recovered from blood cultures over the same period (Table 1). The only significant change in anaerobe positivity rates occurred between 2003 and 2004, with an increase of 0.2% ($P < 0.01$).

The most frequent anaerobic isolates were the *Bacteroides fragilis* group (n = 328; 45%), *Clostridium* species (n = 89; 12%), *Propionibacteria* species (n = 80; 11%) and *Fusobacterium* species (n = 42; 6%). The proportion of bacteraemia cases caused by the *B. fragilis* group decreased over the 10-year period, from 44% to 49% of all cases in the first 7 years to a low of 35% in 2010 (Table 2). The proportion of *Clostridium* species and *Fusobacterium* species stayed relatively constant over the study time period. The last 3 years of the study seemed to indicate a greater diversity of anaerobic species, with other species (*Veillonella*, *Peptoniphilus*, *Eggerthella*, *Actinomyces*, *Bifidobacteria*, *Porphyromonas* and *Eubacterium*) accounting for 16% to 17% of annual anaerobic bacteraemias.

Table 1. Anaerobic Bacteraemia Over Time

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Anaerobes										
Number of anaerobes	31	54	72	72	78	94	83	93	75	75
By all blood cultures	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
By anaerobic blood cultures	0.1%	0.3%	0.4%	0.4%	0.4%	0.4%	0.3%	0.4%	0.3%	0.3%
As percentage of all blood culture isolates	2.1%	3.8%	5.0%	4.7%	4.6%	4.8%	4.4%	4.2%	3.6%	3.4%
Rate /1000 admissions	0.84	1.33	1.75	1.84	1.83	2.19	2.02	2.44	1.93	1.85
Aerobic Bacteria										
Number of anaerobes	1419	1368	1378	1459	1622	1853	1787	2105	1980	2102
Rate/1000 admissions	38.65	33.78	33.57	37.29	37.95	43.22	43.41	55.16	50.84	51.79
Candida Species										
Number of aerobes	14	27	20	19	25	33	27	25	18	18
Rate/1000 admissions	0.38	0.67	0.49	0.49	0.58	0.77	0.66	0.66	0.46	0.44

Table 2. Frequency of Anaerobic Species from Blood Cultures

Year of Analysis	Number of Isolates* (% of Total for the Year)										Total
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	
<i>Bacteroides fragilis</i> group	19 (61%)	24 (44%)	35 (49%)	33 (46%)	38 (49%)	46 (49%)	42 (51%)	33 (35%)	28 (37%)	30 (40%)	328
<i>Clostridium</i> species	4 (13%)	6 (11%)	8 (11%)	10 (14%)	7 (9%)	12 (13%)	7 (8%)	16 (17%)	11 (15%)	8 (11%)	89
<i>Propionibacterium</i> species	2 (6%)	4 (7%)	8 (11%)	6 (8%)	11 (14%)	12 (13%)	9 (11%)	8 (9%)	6 (8%)	14 (19%)	80
<i>Fusobacterium</i> species	-	8 (15%)	6 (8%)	-	4 (5%)	4 (4%)	6 (7%)	4 (4%)	6 (8%)	4 (5%)	42
Anaerobic Gram-positive bacilli (others)	-	4 (7%)	4 (6%)	5 (7%)	6 (8%)	5 (5%)	7 (8%)	6 (6%)	3 (4%)	-	40
<i>Peptostreptococcus</i> species	2 (6%)	3 (6%)	4 (6%)	10 (14%)	2 (3%)	6 (6%)	3 (4%)	4 (4%)	1 (1%)	-	35
<i>Prevotella</i> species	-	-	3 (4%)	5 (7%)	1 (1%)	-	1 (1%)	-	4 (5%)	2 (3%)	20
Other anaerobes†	4 (13%)	5 (9%)	4 (6%)	3 (4%)	9 (12%)	9 (10%)	8 (10%)	18 (19%)	16 (21%)	17 (23%)	93

*As % of total for the year.

†*Lactobacillus* spp. (n = 20), anaerobic Gram-negative bacilli (not identifiable) (n = 15), *Veillonella* spp. (n = 15), *Peptoniphilus* spp. (n = 11), Anaerobic Gram-negative cocci (not identifiable) (n = 8), *Eggerthella* spp. (n = 8), anaerobic Gram-positive cocci (not identifiable) (n = 7), *Actinomyces* spp. (n = 5), *Porphyromonas* spp. (n = 2), *Eubacterium* spp. (n = 1), and *Bifidobacterium* spp. (n = 1).

Imipenem, piperacillin-tazobactam, amoxicillin-clavulanate and metronidazole remained the most active antibiotics, with in vitro susceptibility rates of 95.0%, 93.3%, 90.8% and 90.8% respectively (Table 3). Susceptibilities to penicillin (30.3%), clindamycin (53.8%) and moxifloxacin (51.3%) were much lower. Within these overall results, there was individual variation in antibiotic susceptibilities for specific anaerobic species. *Bacteroides* spp. were uniformly

resistant to penicillin, and susceptibilities to moxifloxacin (44.1%) and clindamycin (51.5%) were variable. The most effective in vitro antibiotics for *Bacteroides* spp. were metronidazole, imipenem and the beta-lactam/beta-lactamase inhibitors. *Clostridium* spp. demonstrated lowest susceptibility to moxifloxacin (44.1%), clindamycin (51.5%) and variable susceptibility to metronidazole (78.6%), but were uniformly susceptible to the beta-lactam/

Table 3. Antibiotic Susceptibilities of Selected Anaerobes

Antibiotic	Genus	R (%)	I (%)	S (%)	MIC90 (mg/L)
Penicillin	<i>Bacteroides</i> spp. (n = 69)*	98.5	0	1.5	>256
	<i>Clostridium</i> spp. (n = 28)†	14.3	7.1	78.6	96
	<i>Fusobacterium</i> spp. (n = 9)‡	11.1	0	88.9	>256
Amoxicillin/Clavulanic acid	<i>Bacteroides</i> spp.	5.9	5.9	88.2	6
	<i>Clostridium</i> spp.	0	3.6	96.4	2
	<i>Fusobacterium</i> spp.	11.1	0	88.9	>256
Piperacillin/Tazobactam	<i>Bacteroides</i> spp.	5.9	1.5	92.6	24
	<i>Clostridium</i> spp.	0	3.6	96.4	6
	<i>Fusobacterium</i> spp.	11.1	0	88.9	>256
Imipenem	<i>Bacteroides</i> spp.	1.5	0	98.5	0.75
	<i>Clostridium</i> spp.	10.7	0	89.3	32
	<i>Fusobacterium</i> spp.	22.2	0	77.8	64
Moxifloxacin	<i>Bacteroides</i> spp.	25	30.9	44.1	64
	<i>Clostridium</i> spp.	28.6	3.6	67.9	64
	<i>Fusobacterium</i> spp.	44.4	11.1	44.4	64
Clindamycin	<i>Bacteroides</i> spp.	42.6	5.9	51.5	>256
	<i>Clostridium</i> spp.	35.7	10.7	53.6	>256
	<i>Fusobacterium</i> spp.	33.3	11.1	55.6	12
Metronidazole	<i>Bacteroides</i> spp.	2.9	0	97.1	1.5-
	<i>Clostridium</i> spp.	17.9	3.6	78.6	>256
	<i>Fusobacterium</i> spp.	0	0	100	0.38

**Bacteroides fragilis* (n = 40), *Bacteroides thetaiotaomicron* (n = 12), *Bacteroides distasonis* (n = 7), *Bacteroides vulgatus* (n = 4), *Bacteroides ovatus* (n = 3), *Bacteroides uniformis* (n = 2), *Bacteroides stercoris* (n = 1).

†*Clostridium perfringens* (n = 11), *Clostridium* spp. (n = 8), *Clostridium ramosum* (n = 4), *Clostridium difficile* (n = 1), *Clostridium bifermentans* (n = 1), *Clostridium tertium* (n = 1), *Clostridium clostridioforme* (n = 1), *Clostridium glycolium* (n = 1).

‡*Fusobacterium varium* (n = 4), *Fusobacterium mortiferum* (n = 2), *Fusobacterium necrophorum* (n = 2), *Fusobacterium nucleatum* (n = 1).

Table 4. Antibiotic Susceptibilities for *Bacteroides* Species

	Susceptible (%)			
	<i>Bacteroides Fragilis</i> (n = 40)	<i>Bacteroides Thetaiotaomicron</i> (n = 12)	<i>Bacteroides Distasonis</i> (n = 7)	Other <i>Bacteroides</i> Species* (n = 10)
Penicillin	0	0	0	10
Amoxicillin/Clavulanic Acid	87.5	91.7	71.4	100
Piperacillin/Tazobactam	95	100	71.4	90
Imipenem	97.5	100	100	100
Moxifloxacin	52.5	25	57.1	20
Clindamycin	60	41.7	14.3	50
Metronidazole	100	100	71.4	100

**B. vulgatus* (n = 4), *B. ovatus* (n = 3), *B. uniformis* (n = 2), *B. stercoris* (n = 1)

beta-lactamase inhibitors. Metronidazole and penicillin remained highly active against *Fusobacterium* species, with susceptibilities of 100.0% and 88.9% respectively. Interestingly, the lowest susceptibility to imipenem was seen in *Fusobacterium* spp. (77.8%).

Antibiotic resistance was lower in *B. fragilis* than for other *Bacteroides* species in the *fragilis* group (Table 4). Moxifloxacin resistance was higher in *B. thetaiotaomicron*, while *B. distasonis* was more likely to be resistant to the beta-lactam/beta-lactamase inhibitors and clindamycin. Two strains of *B. distasonis* were resistant to metronidazole; one with high-level resistance (minimum inhibitory concentration (MIC) >256 mg/L) and the other with low-level resistance (MIC = 32 mg/L). One multiresistant isolate of *B. fragilis* was present, with high-level resistance to all tested antibiotics except for metronidazole. Two unusually multiresistant isolates of *Fusobacterium* were also detected, with one strain of *F. mortiferum* showing high-level resistance to all tested beta-lactams but remaining susceptible to metronidazole.

Discussion

This is the first study to report on anaerobic bacteraemia with antibiotics susceptibilities in Singapore. The data suggest that anaerobes comprise 2.1% to 5.0% of all blood culture isolates, and this proportion has remained constant over the past decade. In comparison to other reported studies,^{8,10} the rate of positivity for anaerobic vials was at the lower end of the reported range of 0.5% to 7.0%.¹¹ *Bacteroides* spp. accounted for nearly half of all bacteraemias, followed by *Clostridium* spp. and propionibacteria. Both *Bacteroides* and *Clostridium* spp. are considered to represent clinically significant bacteraemia, which may be associated with crude mortalities of 20% to 30%.^{19,20} However, propionibacteria are much less likely to be associated with clinically significant infections.²¹ Over the 10-year period, our data suggests a reduction in bacteraemia caused by *Bacteroides* species. The increasing diversity of anaerobes in this study contrasts with results from other investigators, which report an increase in the proportion of bacteraemia caused by *Bacteroides* species.^{10,11}

Susceptibility testing indicates that the carbapenems, beta-lactam/beta-lactamase inhibitors and metronidazole generally retain excellent in vitro activity against anaerobes. Conversely, resistance to penicillin, clindamycin and moxifloxacin are high, which suggests that these antibiotics are no longer suitable for empiric treatment of anaerobic bacteraemia. A prospective study in the United States demonstrated similar trends in clindamycin and moxifloxacin resistance over a 3-year period, with differentially higher rates of resistance in non-*Bacteroides fragilis* isolates.²² A Taiwan study reported higher rates of

carbapenem resistance (up to 12% in *B. fragilis*) over a 10-year period, but conversely, lower rates of resistance to moxifloxacin.¹³ As with antibiotic resistance in aerobes, this serves to highlight the importance of local epidemiology and data, as regional differences in susceptibility are inevitable.

There are several limitations to this study. Firstly, the data is generated from a single institution and may not be representative of other healthcare centres. This institution does not provide solid organ transplant, haematology, oncology, paediatric or obstetrics/gynaecology services, while provision of outpatient renal dialysis only commenced in 2010. The relative lack of severely immuno-compromised patients may account for the lower rate of anaerobic bacteraemia reported in our patient population. Secondly, phenotypic identification of anaerobes was performed by different test methods over the study period. However, the performance of the test methods used has been reported to be roughly equivalent, based on existing data.^{23,24} Phenotypic identification of anaerobic bacteria by conventional methods remains challenging. Most commercial kits reliably identify anaerobic Gram-negative bacilli, including *Bacteroides* spp.,^{25,26} but generate less reliable results for non-perfringens clostridial species and anaerobic Gram-positive bacilli. Finally, antibiotic susceptibility testing was performed using a gradient-diffusion method (Etest) rather than the reference agar dilution method. However, there is evidence to suggest that results by Etest are comparable to the reference test method.^{27,28}

In summary, this study demonstrated a low but constant rate of anaerobic bacteraemia over a 10-year period, with the *Bacteroides fragilis* group as the predominant pathogen. Overall antibiotic resistance was high for penicillin, clindamycin and moxifloxacin but there were species-specific resistance patterns.

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Safety and Effectiveness of Improving Carbapenem Use via Prospective Review and Feedback in a Multidisciplinary Antimicrobial Stewardship Programme

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Abstract

Introduction: Antimicrobial stewardship programmes (ASP) can reduce antibiotic use but patient safety concerns exist. We evaluated the safety of prospective carbapenem review and feedback and its impact on carbapenem use and patient outcomes. **Materials and Methods:** After 3 months implementation of our ASP, we compared patients with and without acceptance of ASP recommendations on the use of carbapenems. Primary outcome was 30-day mortality. Secondary outcomes included duration of carbapenem use, length of hospitalisation, clinical response, microbiological clearance, 30-day re-admission and mortality at discharge. **Results:** Of 226 recommendations for 183 patients, 59.3% was accepted. De-escalation, switching to oral antibiotics and antibiotic cessation comprised 72% of recommendations. Patients with acceptance of ASP recommendations had lower 30-day mortality and higher end-of-therapy clinical response despite shorter carbapenem duration ($P < 0.05$). Predictors of 30-day mortality were Pitt bacteremia score (adjusted odds ratio [aOR] 1.39, 95% confidence interval [CI], 1.11 to 1.74; $P = 0.004$) and non-acceptance of ASP recommendations (aOR 2.84, 95% CI, 1.21 to 6.64; $P = 0.016$). **Conclusion:** Our prospective carbapenem review and feedback mainly comprising of reducing carbapenem use is safe.

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Key words: De-escalation, Multifaceted strategies, Pharmacists

Introduction

Multidrug-resistant (MDR) bacteria coupled with a rapidly diminishing antimicrobial pipeline has made antimicrobial resistance an international public health problem.¹⁻⁴ Control strategies of MDR bacteria include infection control and antimicrobial stewardship programmes (ASP).² The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have proposed guidelines for ASP.⁵ A recent Cochrane Review demonstrated the effectiveness of ASP in reducing antimicrobial usage and incidence of MDR Gram-negative and *Clostridium difficile* infection.⁶

In Singapore, healthcare-associated infections secondary to MDR bacteria, especially methicillin-resistant *Staphylococcus aureus* and MDR Gram-negatives, is a major concern.⁷ Tan Tock Seng Hospital (TTSH), a 1400-

bed university teaching hospital in Singapore, established its ASP in January 2009. At the end of 2008, 49% of *Staphylococcus aureus* were methicillin resistant, extended-spectrum beta-lactamases (ESBLs) was detected in 29% of *Escherichia coli* and 40% of *Klebsiella pneumoniae*, and carbapenem resistance was detected in 17% of *Pseudomonas aeruginosa* and 70% of *Acinetobacter baumannii*. A 1-day point prevalence audit of carbapenem use in the 3 largest public hospitals in Singapore including TTSH revealed inappropriate use in 38%. These included failure to de-escalate to a narrow spectrum antibiotic in 36% and non-compliance with hospital carbapenem use criteria in another 30%.⁸

One of the key measures adopted by our ASP is prospective review and feedback on all new carbapenem orders. However, carbapenems are often used in the treatment

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of serious healthcare-associated infections, and ESBLs are prevalent among healthcare-associated *E. coli* and *K. pneumoniae*, 2 common Gram-negative bacteria in TTSH. Against this background of endemicity with ESBL-producing Enterobacteriaceae with high baseline rates of empiric carbapenem usage, an ASP strategy of prospective review and feedback on carbapenems needs to demonstrate effectiveness and safety. While the Cochrane Review on ASP demonstrated diminished MDR Gram-negative and *C. difficile* infection rates, 4 of 5 studies reporting mortality as a clinical outcome found a non-significant trend towards increased mortality.⁶

In this study, we aim to evaluate the acceptance and safety of ASP recommendation on prospective review and feedback on all carbapenems in our institution.

Materials and Methods

Description of Our Multifaceted, Multidisciplinary ASP

Our ASP was approved by the TTSH Medical Board in January 2009. An ASP committee comprising members from every clinical department, pharmacy, microbiology, infectious diseases (ID), information technology and clinical quality was formed. Our ASP initiatives include: (1) hospital empiric antibiotic guideline for 56 common or important ID conditions, with recommendations for first and second-line antibiotics, criteria for intravenous to oral conversion, total duration of antibiotic(s) and oral antibiotics for de-escalation with negative microbiological cultures, (2) antibiotic renal dose adjustment guidelines, (3) criteria for carbapenem and piperacillin-tazobactam use, (4) criteria for intravenous to oral conversion for highly bioavailable antibiotics, (5) criteria for meropenem to imipenem conversion, and (6) surgical antibiotic prophylaxis guidelines. These guidelines were drafted by an ASP team which comprised 3 ID physicians and 2 ASP pharmacists. They were then reviewed by the Department of ID and endorsed by the TTSH Drug and Therapeutics Committee. All these guidelines are accessible on our intranet via an icon on every hospital computer desktop.

At the inception of the programme, our ASP team visited every clinical department to explain and seek input on the ASP guidelines. Subsequently, ongoing activities include quarterly departmental reports of selected antimicrobial usage and incidence of MDR bacteria sent to heads of departments. An annual ASP update is also presented at a hospital grand round. In addition, an annotated hospital antibiogram is emailed to every hospital doctor annually and made available on our intranet along with the ASP guidelines. Our ASP was developed and implemented according to the IDSA/SHEA 2007 ASP guideline.⁵

As guidelines without active intervention may not be followed widely,⁹ we implemented prospective review

and feedback on all carbapenems available in TTSH, namely ertapenem, imipenem and meropenem, from April 2009. We reviewed all carbapenem orders according to our criteria for carbapenem use (Table 1). With pertinent positive microbiological cultures, the most narrow-spectrum antibiotic with in vitro activity appropriate for the site of infection is recommended. If patient improves with negative microbiological cultures, de-escalation to narrower spectrum intravenous or oral antibiotic(s) is recommended for the likely ID condition. De-escalation is recommended once patient fulfills pre-specified criteria for clinical stability (Table 1). Patients who fail to improve despite use of carbapenems are referred to the ASP ID physician and recommendations on alternative diagnoses, further investigations and treatment are provided.

Overview of the Prospective Review and Feedback Workflow

The carbapenem order is reviewed initially by the ward pharmacist who performs the initial intervention as indicated. This is escalated to the ASP pharmacist, and subsequently the ID physician, when initial recommendations are not accepted. The ward pharmacists (1 to 2 on each ward), ASP pharmacists (2 full-time equivalents, (FTE)) and ID physicians (0.5 FTE, 1 out of 3 on duty each day) conduct reviews and provide recommendations on every week day during office hours (8 am to 5 pm). Cases that require ID physician review are presented by ASP pharmacists during daily ASP rounds. These rounds usually last for 2 to 3 hours in the afternoon and take place in the patients' wards so as to facilitate individual patient review and discussion with the primary care team. This review and escalation process takes place daily from the day of carbapenem initiation, unless it falls on a weekend or public holiday in which case the review will take place on the next working day, provided the patient is still receiving a carbapenem. Complicated cases may be referred directly to the ASP pharmacist or ID physician. Our ASP reviews the indication for antimicrobial use, renal dose adjustment, opportunity for culture-guided de-escalation, duration of therapy, conversion of meropenem to imipenem, and the need for formal ID consultation. Additional differential diagnoses, investigations, and adjunctive therapy (for example, removal of urinary or central venous catheters, drainage of infected collections) are also recommended, if applicable. All recommendations are entered into the patient's chart and often followed with discussion via telephone or in person with the primary care team.

Evaluation of Acceptance and Safety of Prospective Carbapenem Review and Feedback

To assess the acceptance and safety of ASP recommendation on prospective review and feedback on all carbapenems, we

Table 1. Criteria for Carbapenem Use and Clinical Stability

Empiric Use	Culture-Guided Use
Appropriate criteria A 1. Evidence of sepsis or septic shock (fever >38°C, increased white cell >10x10⁹/L, or increased C-reactive protein) and 2. Clinically unwell (drowsy/confused, oxygen saturation <92%, systolic blood pressure <90 mmHg or respiratory rate >30 breaths/min) and 3a. Onset of infection: (i) Nosocomial (>48 hours after admission) or (ii) Healthcare-associated (previous admission ≤3 months) or 3b. Isolation of the following within last 3 months: (i) Extended spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria or (ii) AmpC beta-lactamase-producing Gram-negative bacteria (e.g. <i>Enterobacter</i>, <i>Serratia</i>, <i>Citrobacter freundii</i>, <i>Proteus vulgaris</i>, <i>Providencia</i>, <i>Morganella</i>) or (iii) Gram-negative bacteria sensitive to only carbapenems	Appropriate criteria A 1. ESBL-producing Gram-negative bacteria or 2. Gram-negative bacteria sensitive only to carbapenem or 3. Non-ESBL-producing bacteria resistant to ceftriaxone and ceftazidime or 4. AmpC beta-lactamase-producing Gram-negative bacteria (e.g. <i>Enterobacter</i>, <i>Serratia</i>, <i>Citrobacter freundii</i>, <i>Proteus vulgaris</i>, <i>Providencia</i>, <i>Morganella</i>) with either: (i) Positive cultures at non-sterile sites resistant to ciprofloxacin and co-trimoxazole (ii) Positive cultures at sterile sites (blood, cerebrospinal fluid, bone) sensitive or resistant to ciprofloxacin and/or co-trimoxazole
Appropriate criteria B 1. Where carbapenem is recommended for empiric therapy in hospital empiric antibiotic guideline	Appropriate criteria B 1. Infections by susceptible organisms but use of penicillins and/or cephalosporins is precluded due to allergy and/or intolerance
Criteria of Clinical Stability for De-escalation: Consider de-escalation to narrower-spectrum intravenous or oral antibiotic(s) (according to microbiology results or hospital antibiotic guideline) when patient fulfills the following criteria: 1. Afebrile (temperature <38°C for 24 hours) 2. Inotropes are ceased if previously on inotropes 3. Systolic blood pressure returned to baseline or ≥100 mmHg 4. Off mechanical ventilations or fraction of inspired oxygen ≤0.4 5. Respiratory rate <25 breaths/minute and oxygen saturation >92% on room air 6. Reduction in white cell count (if available) 7. Reduction in C-reactive protein (if available)	

collected the following data prospectively on every patient with a carbapenem order reviewed by the ASP team from 1 April to 30 June 2009: age, gender, comorbidities for Charlson's comorbidity score,¹⁰ clinical data for Pitt bacteraemia score at start of carbapenem use,¹¹ ID diagnosis as assessed by the primary medical team, admission and discharge dates, start and stop dates of carbapenems, dosing as well as reasons for use of carbapenems, renal function, microbiological and radiological reports, ASP recommendations and acceptance, adverse events from carbapenems, and mortality.

We compared patients with and without acceptance of ASP recommendations. The primary outcome was 30-day mortality from start date of carbapenem use, and secondary outcomes included (1) duration of carbapenem use, (2) length of hospitalisation from start of carbapenem use to discharge, (3) clinical response defined as improvement or resolution of signs and symptoms of initial infection at day 7 and end of therapy, (4) microbiological clearance at day 7, (5) 30-day re-admission, and (6) mortality at hospital discharge.

Statistical Analysis

Descriptive data was presented as mean ± standard

deviation (SD), median and range, or percentages, as appropriate. Baseline patient variables and endpoints were compared between groups using Student t-test or Mann-Whitney U test for continuous variables, Chi-square or Fisher exact test for categorical variables, as appropriate. Univariate analysis was performed to evaluate predictive factors for 30-day mortality. Any variable with $P < 0.20$ on univariate analysis was included in a logistic regression model to determine independent associations with 30-day mortality. Statistical analysis was performed using SPSS software version 19. All tests were 2-tailed and a P value <0.05 was regarded as statistically significant. This study was approved by our Institutional Review Board.

Results

In the 3 months after implementation of ASP, 656 courses of carbapenems were ordered, of which 498 were reviewed. Among these, there were 226 ASP recommendations by ward or ASP pharmacists or ID physicians for 183 patients. Our ASP recommendations included de-escalation in 54%; stopping antibiotic, optimising antibiotic and meropenem-to-imipenem conversion in 12% each; and switching to oral

antibiotics in 6% (Table 2). Mean acceptance rate of ASP recommendations was 59.3% (134/226 recommendations for 130/183 patients). The 3 most accepted recommendations pertained to antibiotic optimisation (with additional antibiotics to broaden coverage), de-escalation and switch to oral antibiotics at 66.7%, 65% and 61.5%, respectively.

Baseline demographic and clinical data including age, gender, Charlson's comorbidity and Pitt bacteraemia scores, and ID conditions were similar between patients with and without acceptance of ASP recommendation (Table 3). Patients with acceptance of ASP recommendation had significantly shorter median duration of carbapenem use (3 [range, 1 to 47] vs 7 [range, 1 to 36] days, $P < 0.001$), higher end-of-therapy clinical response (116/130 [89.2%] vs 41/53 [77.4%], $P = 0.04$) and lower 30-day mortality (15/130 [11.5%] vs 14/53 [26.4%], $P = 0.012$) (Table 4).

There was no significant difference between patients without and with acceptance of ASP recommendation in 7-day clinical response (36/53 [67.9%] vs 98/130 [75.4%], $P = 0.301$), mortality at hospital discharge (16/53 [30.2%] vs 24/130 [18.5%], $P = 0.082$) and median duration of hospitalisation (15 [range, 1 to 236] vs 16 [range, 3 to 230] days, $P = 0.564$). After excluding patients who died within 30 days after discharge, rate of 30-day re-admission was similar between the 2 cohorts (11/37 [29.7%] vs 32/106 [30.1%], $P = 0.958$). Repeat microbiological culture was performed in 14 cases without acceptance of ASP recommendation and 27 cases with acceptance; the 7-day microbiological clearance rate was similar (10/14 [71.4%] vs 19/27 [70.4%], $P = 0.876$) (Table 4).

In the multivariate analysis for predictors of 30-day mortality, Pitt bacteraemia score (adjusted odds ratio [aOR] 1.39, 95% confidence interval [CI], 1.11 to 1.74; $P = 0.004$) and non-acceptance of ASP recommendation (aOR 2.84, 95% CI, 1.21 to 6.64; $P = 0.016$) were independently associated with increased risk of 30-day mortality. In the subgroup of patients whose ASP recommendation comprised

de-escalation ($n = 107$), switch to oral antibiotics ($n = 8$) and stopping antibiotics ($n = 19$), 30-day mortality was 14/98 (14.3%) with acceptance of ASP recommendation versus 7/36 (19.4%) without acceptance of ASP recommendation ($P = 0.467$).

Discussion

Our ASP showed significant impact in improving appropriate carbapenem use which was associated with improved patient outcomes. This improvement occurred before the start of our computerised decision support system for electronic antibiotic prescription in September 2009.¹² A Cochrane Review documented the effectiveness of ASP in modifying antibiotic prescribing. These comprised 6 of 8 studies that increased active antibiotic treatment with controlled before-and-after (CBA) and randomised controlled trial (RCT) design, and 10 of 14 studies with CBA, cluster controlled trial and RCT design, and 26 of 33 studies with interrupted time series (ITS) design which decreased antibiotic use.⁶

The improved clinical outcome from our ASP is highly encouraging. Comparison of patients with and without acceptance of ASP recommendation in our prospective carbapenem review and feedback showed that patients with acceptance of ASP recommendation had higher end-of-therapy clinical response and lower 30-day mortality despite shorter duration of carbapenem use. Illness severity and non-acceptance of ASP recommendation were found to be independent predictors of 30-day mortality. These findings are in contrast to the Cochrane Review, where there was a trend to higher mortality in 4 of 5 studies and significantly higher re-admission in 1 of 4 studies that decreased antibiotic use.⁶ The difference in mortality outcomes could be due to different target patient population, antibiotics and specific interventions studied. For example, all patients included in the study by Singh et al¹³ were in intensive care units (ICUs), and 20% of patients included in the study by Fraser

Table 2. Types of ASP Recommendations and Acceptance Rates

Type of Recommendation	Ward Pharmacists n = Accepted/Total (%)	ASP Pharmacists n = Accepted/Total (%)	ID Physicians n = Accepted/Total (%)	Total n (% Total)	Total n = Accepted/Total (%)
Total	59/94 (62.8)	42/74 (56.8)	33/58 (56.9)	226 (100)	134/226 (59.3)
De-escalation	33/49	31/49	16/25	123 (54)	80/123 (65.0)
Stopping antibiotics	1/4	2/10	5/12	26 (12)	8/26 (30.8)
Antibiotic optimisation	10/17	5/6	3/4	27 (12)	18/27 (66.7)
Meropenem to imipenem conversion	11/17	0/1	4/8	26 (12)	15/26 (57.7)
Switch to oral antibiotics	1/2	3/6	4/5	13 (6)	8/13 (61.5)
Others	3/5	1/2	1/4	11 (5)	5/11 (45.5)

ASP: Antimicrobial stewardship programme; ID: Infectious disease

Table 3. Baseline Demographic and Clinical Characteristics of Patients with and without Acceptance of ASP Recommendations

Baseline Parameters	Not Accepted (n = 53)	Accepted (n = 130)	P Value
Median age, years (range)	70 (34 – 94)	74 (17 – 98)	0.311
Male gender, n (%)	26 (49.1)	63 (48.5)	0.942
Median Charlson's comorbidity score (range)	5 (0 – 12)	5 (0 – 12)	0.890
Median Pitt bacteremia score (range)	0 (0 – 5)	0 (0 – 12)	0.776
Critically ill (Pitt bacteraemia score ≥ 4), n (%)	4 (8)	8 (6)	0.747
Comorbidities, n (%)			
Hypertension	30 (57)	82 (63)	0.415
Diabetes mellitus	24 (45)	59 (43)	0.990
Dyslipidaemia	17 (32)	53 (41)	0.272
Site of infections, n (%)			
Respiratory	16 (30)	45 (35)	0.564
Intra-abdominal	2 (4)	8 (6)	0.726
Skin/soft tissue	4 (8)	6 (5)	0.479
Hepatobiliary	1 (2)	11 (8)	0.103
Urinary	26 (49)	55 (42)	0.404
Sepsis of unknown source	3 (6)	2 (2)	0.147
Others	1 (2)	3 (2)	0.990

Data are number (%) of patients, unless otherwise indicated. For median values, minimum and maximum values are in parentheses.
ASP: Antimicrobial stewardship programme

Table 4. Outcomes of Patients with and without Acceptance of ASP Recommendations

Outcomes	Not Accepted (n = 53)	Accepted (n = 130)	P Value
Median days of index carbapenem (range)	7 (1 – 36)	3 (1 – 47)	<0.001
7-day clinical response, n (%)	36 (67.9)	98 (75.4)	0.301
End of therapy clinical response, n (%)	41 (77.4)	116 (89.2)	0.040
7-day microbiological response, n (%)	10/14 (71.4)	19/27 (70.4)	0.876
Mortality at hospital discharge, n (%)	16 (30.2)	24 (18.5)	0.082
30-day mortality, n (%)	14 (26.4)	15 (11.5)	0.012
30-day re-admission,* n (%)	11/37 (29.7)	32/106 (30.1)	0.958
Median days of hospitalisation (range)	15 (1 – 236)	16 (3 – 230)	0.564

*Excluded patients who died within 30 days after discharge

et al¹⁴ were haematology-oncology patients. However, only 7.7% of our patients were in ICUs and none were haematology-oncology patients. Reassuringly, our study did not find higher risk for 30-day re-admission.

Despite prospective review and feedback by an ID physician, overall acceptance of our ASP recommendation was relatively low at 59.3%. Anecdotally, many doctors were concerned about the safety of stopping carbapenems in their sick patients. Our evaluation showed that, to the

contrary, in patients who achieved clinical stability, it was safe to de-escalate carbapenems when usage is not indicated by microbiological data. Interestingly, while it was not surprising that acceptance rate was more reasonable when we recommended antibiotic optimisation (66.7%) and substitution of meropenem with imipenem (57.7%), acceptance was higher when we advised de-escalation to a narrower spectrum intravenous antibiotic (65%) or oral antibiotic (61.5%) versus cessation of antibiotic (30.8%).

Strategically, ASP may be more effective if short-course de-escalation is adopted similar to the 3-day ciprofloxacin for patients at low risk of ventilator-associated pneumonia.¹³

Prospective review and feedback has been found to be a highly effective strategy in changing prescribing behaviour, albeit labour-intensive.¹⁴⁻¹⁷ We invested in extensive educational efforts in developing and disseminating our ASP guidelines with the hope of achieving earlier appropriate carbapenem use. Inadequate empiric antibiotic is a risk factor for mortality in serious infections in a recent meta-analysis of prospective observational studies.¹⁸ With high rates of ESBLs in our Enterobacteriaceae, early empiric carbapenem in sick septic patients may be appropriate, followed by de-escalation or discontinuation with clinical improvement and microbiological results.¹⁹ Increasingly shorter duration of antibiotics may be adequate for nosocomial pneumonia,²⁰⁻²² procalcitonin-guided antibiotic therapy in community-acquired pneumonia^{23,24} and sepsis in ICUs.^{25,26}

Our study suggest the effectiveness of non-specialised ward pharmacists in implementing ASP using clearly defined criteria in ASP guidelines developed with broad consultation and endorsement by hospital senior management and medical heads of department. The acceptance rate of ward pharmacists' ASP recommendations was 62.8% (Table 2). ASP pharmacists and physicians are scarce resources. We run our hospital-wide ASP with only 2 full-time ASP pharmacists. Specialised pharmacists have been effective in ASP,^{27,28} anticoagulation service²⁹ and heart failure clinics.³⁰ Our study provided evidence that non-specialised ward pharmacists may be supported to run ASP with a smaller number of ASP pharmacists and ID physicians.

We were able to achieve a 76% review rate of all carbapenem prescribed in the study period. We did not capture specific reasons for courses that were not reviewed. However, due to the inherent workflow of our ASP, a possible reason was the initiation of carbapenems over the weekend or after office hours; patients were no longer receiving the carbapenem when ASP review was to take place during the next working day.

A strength of our study is that we adjusted for potential confounders for comorbidity and illness severity for 30-day mortality by using Charlson's comorbidity and Pitt bacteraemia scores respectively. Pitt bacteremia score has been validated against APACHE II in sepsis in intensive care.¹¹ Although one of the key rationales for ASP is reducing antibiotic resistance and collateral damage from inappropriate antibiotic use, a limitation of our study is that we did not collect such data. We hope to be able to assess these outcomes in future studies.

Conclusion

Our study showed that a multidisciplinary ASP with core strategies of evidence-based ASP guidelines and prospective review and feedback of carbapenem use led to appropriate and shorter duration of carbapenem use with better clinical response and lower mortality. Importantly, de-escalation of carbapenem appeared to be safe in patients who achieved clinical stability.

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Schizophrenia as a Lifelong Illness: Implications for Care

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The management of schizophrenia has advanced considerably since the term was first coined in 1911, with Kraepelin's early pessimism tempered by more recent evidence examining outcome.¹ The discovery of antipsychotics represented a major breakthrough in the treatment of schizophrenia, while more recently we have witnessed promising initiatives such as the early intervention and recovery movements.

The early intervention initiative began in the 1990s, premised on the notion that reducing duration of untreated psychosis (DUP) through early intervention would translate to better long-term outcomes. There was evidence already in place to support this rationale; for example, the International Study of Schizophrenia (ISoS) had reported that initial 2-year course patterns were the strongest predictor of 15-year functional outcomes.² Evidence since has, indeed, confirmed that early intervention leads to improved 1- and 2-year clinical and functional outcomes,³ as well as cost-effectiveness in the first 18 months.⁴ However, recent reports on longer term follow-up of the early intervention cohorts paint a different picture, noting no differences in course of illness or a diminution of early gains compared to those who did not receive early intervention.^{5,6}

Further to this point, when we compare studies examining the clinical course of schizophrenia before and after the adoption of early intervention, the proportion remaining symptomatic appears similar (Table 1). Results from the OPUS trial, a landmark trial comparing early intervention versus treatment as usual in Denmark, showed that 3 years after a 2-year early intervention programme, there were no significant differences in the symptomatic proportion between early intervention and treatment as usual groups (59% vs 57% respectively).⁷ In a follow-up study of the same cohort, stable rates of symptom remission and recovery were reported at 2-, 5- and 10-years, again with no differences between early intervention and treatment as

usual groups.⁵ When we examine recovery rates between ISoS, EPPIC (Early Psychosis Prevention and Intervention Centre in Melbourne, Australia), and OPUS, results are similar; 16.3% vs 14.9% vs 14%, respectively.^{2,5,8} Despite perceived advances in the care of schizophrenia, a recent meta-analysis reported no significant increase in rates of recovery for schizophrenia over the past 60 years.⁹

As important as it is to be optimistic, it is also essential that we remain realistic and these findings cannot be ignored. Antipsychotics and early intervention have fundamentally changed the way we manage schizophrenia, but they are by no means panaceas.^{6,10} Evidence indicates that the illness has varied outcomes ranging from a single episode with full recovery to a chronic deteriorating illness course; however, for the large majority, schizophrenia is a chronic and lifelong condition^{11,12} exacting significant burden beyond the initial years following diagnosis.¹³

Also arising from the early intervention work has been the notion of 'clinical staging' for schizophrenia, with 3 major categories (at-risk; first-episode; incomplete response), each with specialised care services.¹⁴ While such an approach has advantages in understanding the illness, its progression, and need for different treatments, it also runs the risk of fostering a silo approach to care that belies the illness' chronicity. Challenging management issues (e.g. continued service engagement, treatment adherence, medication side effects, suicide and comorbid psychiatric disorders) persist for schizophrenia's duration, with new challenges such as treatment resistance and chronic medical conditions frequently arising over time.^{15,16}

The World Health Organisation (WHO) defines a chronic disease as one that is of long duration and generally slow progression (e.g. diabetes mellitus). Arguably, labeling schizophrenia as "chronic" connotes pessimism and ignores that subgroup who demonstrates a good outcome;¹ however, for many this is not the case and for others they move in and

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Table 1. Comparison of Course Types and Recovery Rates for Studies on Schizophrenia in the Pre-early Intervention (ISoS) Cohort, the Early Intervention Cohort (EPPIC) and in a Randomised Trial of Early Intervention Versus Standard Treatment (OPUS)

	Psychotic Illness Course, %			Recovery, %	Duration of Follow-up, Years
	Episodic	Continuous	Never Psychotic		
ISoS*	16.6	33.6	42.8	16.3	15 and 25 years
EPPIC†	18.8	40.7	40.4	14.9	7
OPUS‡					5
Early intervention programme	14	45	41	16	
Standard treatment	13	44	43		

*International Study of Schizophrenia: rates from incident schizophrenia cohort, n = 502

†Early Psychosis Prevention and Intervention Centre in Melbourne, Australia. Includes schizophrenia and schizophreniform, n = 276

‡Intervention in the OPUS trial lasts for 2 years. Illness course data reported here is for the 3 years post OPUS trial. Recovery rates are for combined early intervention and standard treatment arms. Early intervention programme, n = 151; standard treatment, n = 150.

out of recovery over the illness' course.⁵ In reality, the vast majority is afflicted with recurrent or persistent symptoms,¹² and framing schizophrenia as a chronic condition may offer advantages in terms of management strategies.

As an example of this, diabetes is an illness where outcomes have improved over time after the implementation of a chronic disease management framework.¹⁷ Early detection and intervention strategies have certainly been promulgated in diabetes care, but its persistence is both acknowledged and embraced in establishing longer term care from the outset. So too is its complexity, with aspects of care ranging from regular monitoring of blood sugar to diabetic complications, dietary and lifestyle advice. The management strategy is one of prevention and health promotion built upon close and collaborative care coordination between the different treatment components, an over-arching philosophy for all chronic conditions.

Adopting a chronic care model (CCM) in the management of schizophrenia is not new,¹⁸ but an approach that we perhaps have lost sight of based on shifts in treatment that have not necessarily lived up to expectations. Current clinical care is often administered in an ad hoc, time-limited approach that is not appropriate for a chronic illness. Components of the CCM remain evident in established early intervention programmes, examples including self-management and support through psychoeducation, implementation of treatment algorithms as decision support tools, and assertive community treatment to enhance community integration.¹⁹ Unfortunately, though, these services may be tied to the programme and withdrawn when the individual is no longer deemed to be 'first-episode'. The early intervention model of care should be extended and adapted to as long as the individual requires psychiatric care, and expanded to integrate with medical care. Clinicians need to find ways to hold on to and build upon the early gains from early intervention.

The stark reality remains that schizophrenia is a chronic illness that for most individuals waxes and wanes over the years. However, chronic illness and poor outcome are not inextricably linked. As noted for diabetes, gains can be made in embracing chronicity and integrating a multifaceted, long-term approach to care delivery that fosters optimal outcomes.²⁰ Identifying schizophrenia as a chronic illness acknowledges clinical reality, does not preclude good outcome, and in shaping service delivery accordingly should actually enhance this possibility. Therefore, just as healthcare and research resources have been increasingly allocated to early intervention and to the understanding of pre-psychotic phases of the illness, we argue that the research and development of a feasible CCM for schizophrenia is an equally important need.

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A Follow-up Longitudinal Survey on a Cohort of Undergraduate Medical Students' Attitudes towards Radiology

Dear Editor,

As a follow-up to an earlier study comparing the attitudes of first year undergraduate medical students following the introduction of a new radiology curriculum in 2008 with their clinical seniors who did not have an early exposure to radiology;¹ we again surveyed this same cohort of first year students who are now in their fifth year in 2013 to see if their attitudes towards radiology have changed.

Introduction

Revision of the first-year curriculum with 13 1-hour formal radiology lectures was done in 2008/9. This came about as we realised that radiology was not a popular specialty for undergraduate student electives or postgraduate training amongst students from a local undergraduate medical school.¹ For example, out of the May and November 2007 intakes of the first-year radiology medical officers (MOs), only 1 in 5 (20%) MOs was a graduate from the local undergraduate medical school.² The rest were graduates from overseas medical schools.

Our primary aim is to attract more local students to join the radiology residency and our secondary aim is for the rest of the students to appreciate radiology and to learn how to optimally utilise radiology services for patient management. Earlier studies have shown that early exposure of first-year medical students to radiology improved their impression of radiology as a specialty.³

Our initial survey in 2009 showed that early exposure of first-year medical students to radiology increased their interest in the subject.¹ Further changes were made to their radiology curriculum in subsequent years: second year – 8 formal lectures; third and fifth year – small group tutorials; and fourth year – 1-week radiology department attachment. Given that this is the first batch of students to have continued exposure to radiology throughout all the 5 years, and that we wanted to evaluate as to whether the interest in radiology that we saw in this cohort during their first year is sustained to their fifth year, we decided to survey this same cohort of students.

Materials and Methods

The same hard copy anonymous 6-question survey

that was administered to these students in their first year (2009) was administered to them in their fifth year (2013). Exemption from full Institutional Review Board (IRB) review was sought and approved by the National University of Singapore (NUS) IRB. Survey forms were distributed to students at the start of their lecture and collected at the end. Survey responses were tabulated and students' attitudes whilst they were in their first and fifth years were compared using the Mann-Whitney rank sum tests.

Results

The response rate to the survey was 118 out of 270 students. Figure 1 summarises the results comparing the same cohort of students' response to the same administered survey whilst they were in year 1 and year 5 of medical school.

Non-parametric statistically testing was used for data analysis as the responses were not a continuous variable, and the differences between responses were not equal. The two surveys done in 2009 and 2013 were also considered to be independent samples as the respondents were not identifiable.

Students' response to Question 1 (How much do you know about radiology?) showed a statistically significant difference in response when they were in year 1, compared to when they were in year 5 (P = value for median was 0.007, P -value for distribution was 0.044).

Students' response to Question 2 (How much radiology have you been exposed to?) showed 57% of students attending lectures and study sessions when they were in year 5, compared to 1.9% when they were in year 1.

Students' response to Question 3 (How interesting is the subject matter in radiology?) showed 50% of students found radiology to be interesting in its own right in year 5, compared to 30.3% when they were in year 1.

This, however, did not translate into more students considering radiology as a career (Question 4) or as an elective (Question 5). In fact, there were more polarised responses with respect to radiology as a career, with more students adopting a negative disposition.

There was also a more polarised response to the impact of radiology on other areas of medicine (Question 6), with a tendency towards radiology playing a more conservative role.

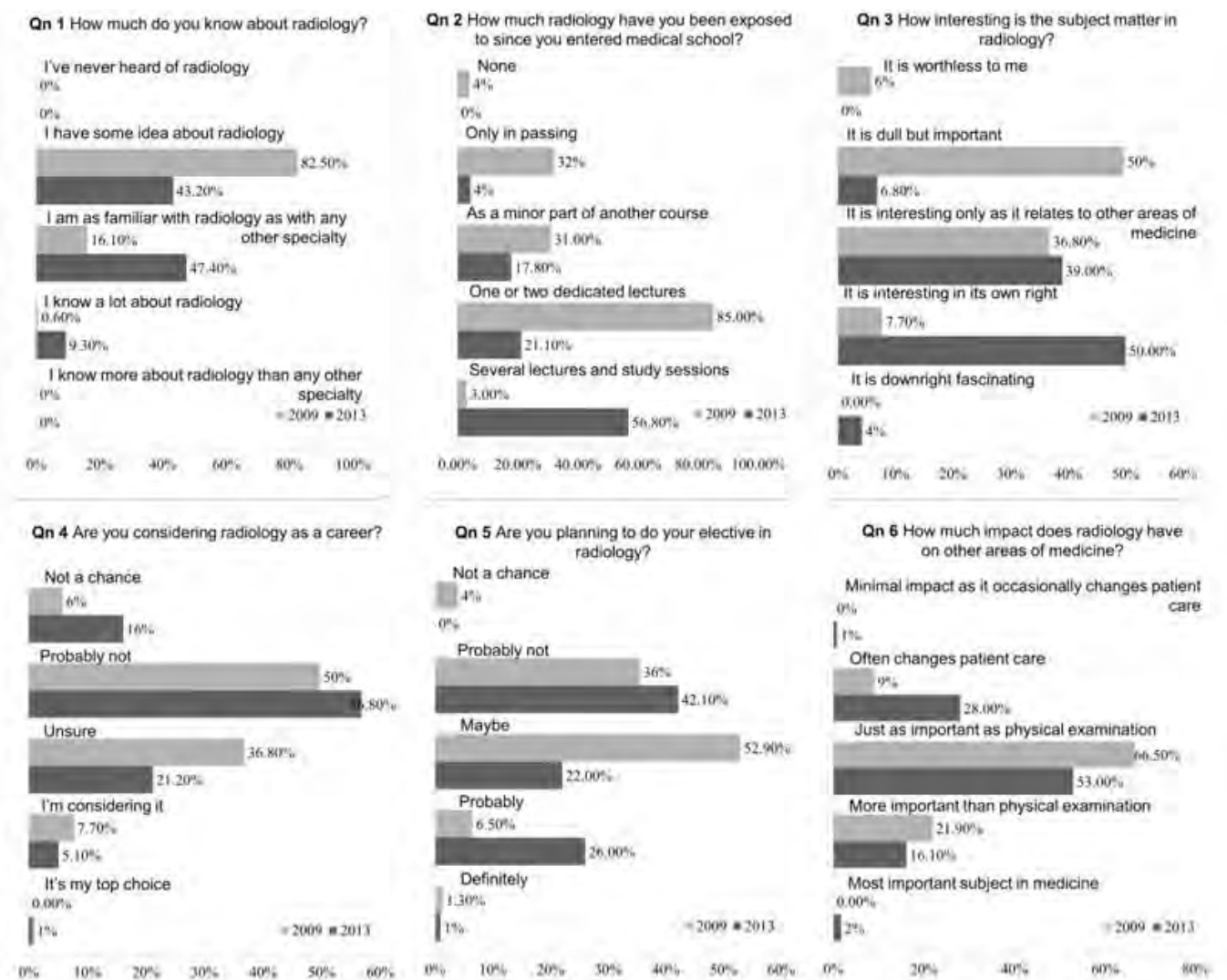


Fig. 1. Survey questions and comparison of results of the same cohort in 2009 (year 1) and 2013 (year 5).

Discussion

Although the survey results did not achieve our main aim of increasing the popularity of radiology as a student elective or career choice, we managed to demonstrate a significant increase in students feeling familiar with radiology as with other specialties, a higher percentage of students attending radiology teaching sessions, and an increase in the percentage of students feeling that radiology was interesting in its own right.

Since the start of the Accreditation Council of Graduate Medical Education-International (ACGME-I) Diagnostic Radiology Residency in 2011, we have also been trying to engage local medical students through other channels; for example, holding Open House and tea-sessions for final-year medical students with one-on-one meetings with the faculty for career development.

On the ground, we have been seeing the fruits of our labour. In 2008, we only had 1 out of 5 (20%) radiology residents who were graduates from our local undergraduate medical school. Since the start of the ACGME-I Diagnostic Radiology residency and our repeated attempts to increase the profile of radiology in our local undergraduate medical school, our residency intake with graduates from the local medical school has increased to between 60% to 75% and are as follows: 2011: 3 out of 4 residents; 2012: 3 out of 4 residents; 2013: 3 out of 5 residents.

Conclusion

Early and continued exposure of students to radiology increases their interest and appreciation of this subject. Although this longitudinal survey is not reflective of increased popularity of radiology as a student elective or

career choice (which was our primary aim), on the ground, we are seeing more local graduates join the radiology residency system in our institution. It would, however, be interesting to know the application rates from the local medical school before and after the revised medical school curriculum, something that is beyond the scope of our study.

Our secondary aim for students to appreciate and learn how to optimally use the radiology department has been achieved, given that it is so important for all doctors to appreciate the utility of various imaging modalities, and to refer patients appropriately for radiological investigations.

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The Root of Unprofessionalism

Dear Editor,

The editorial written by Caroline CPong and Nigel CK Tan published in the November 2014 issue on professionalism of doctors and how to counter unprofessionalism, directs our attention to an aspect which we tend to overlook.

Many laymen think that doctors still take the Hippocratic Oath on graduation and are therefore bound for life to professionalism and ethics. I feel that even if we have taken the outdated oath or a modern version of the oath, it would not make any difference to our behaviour because it would have come too late to have any influence.

In attempts to instill professionalism and ethics in doctors, I believe that the law of diminishing returns applies. In other words, the success of altering personal behaviour diminishes progressively as the student becomes a junior doctor and advances to a senior position. Childhood and early youth are the periods when one is most susceptible to the influence of teaching, indoctrination or brainwashing, or whatever we choose to call it. Doctors are not any different from members of any other profession or occupation in psychological makeup.

The Chinese sage Confucius believed that men were born benign and innocent but needed to be guided to the right path in order not to go wayward. Thus, the classic 'Three-worded Jing', a compulsory study for all Chinese schoolchildren from the Song dynasty to the late Qing dynasty, began with these opening remarks:

Men are born good and similar in nature.
They become different by influence of nurture.
Men's nature goes wayward with neglect of teaching.
Full attention is needed for proper upbringing.
Jade that is not carved does not rate as jewellery.
Man who is unlearned is ignorant of morality.

Some 200 years after Confucius, Xun Zi, an outstanding Confucian scholar, disagreed with the Old Master. He was known for his opinion that men were born bad, and that

the character needed to be moulded by teaching in order to become good and benevolent. He was among the first to emphasise the importance of childhood upbringing. His views led to the emergence of the Chinese legalist school.

For admission to the medical school, we can only select adult students by their scholastic records and not by their earlier upbringing. It is difficult to modify the character once it is formed. The multifaceted approach of cultivating professionalism put forth by Dr Ong and Dr Tan in the editorial is valid and important. However, I am pessimistic that it may be of limited effectuality at such a late stage.

There are 3 ways to make a person conform to generally accepted social norms—teaching and indoctrination from young, instilling fear of supernatural beings, and enforcement of strict law, or a combination of all 3. It is rare to see an unprofessional doctor mend his way willingly. It is sad and unfortunate that our medical profession may have to rely increasingly on rule enforcement.

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Reply from Author: Missing the Forest for the Trees

We thank Dr Ong Siew Chey for his sincere comments. He opines that professional behaviour is a reflection of an innate character trait, that behaviour is shaped early and is difficult to modify later, and that there are 3 ways of making doctors conform to professional norms. We would like to reframe the issue as this traditional view oversimplifies and limits the appreciation of the complex problem of professionalism.

Firstly, the pessimistic notion that ethical/moral behaviours are hard to change with increasing seniority is fortunately refuted by evidence. Advances in moral reasoning increase with age throughout a person's lifespan, and this progression in adulthood is correlated with education.¹

Secondly, even though character traits do influence professional behaviour, these traits are but one of several factors influencing professionalism when we take a systems perspective.^{2,3} Organisational culture is another component of the system influencing professional behaviours.³ In psychology, the phenomenon of "moral elevation" describes how others are motivated to behave ethically when they see others doing likewise.⁴ Regardless of a person's traits, an institutional culture of ethical behaviour is another system component that can promote professional behaviour in both senior and junior doctors.

Finally, there is evidence that professionalism can be shaped and improved. Dr Ong feels that reciting the Hippocratic Oath or the modern physicians' pledge does not change professional behaviour. The pledge is an example of a moral reminder. Experimental psychology studies have shown that such moral reminders do alter ethical behaviour by reducing cheating during tests.⁵ Within the field of medicine, a recent randomised trial at the Mayo clinic⁶ demonstrated that it was possible to promote professionalism using a targeted intervention. Notably, the participants were already qualified specialists, showing that seniority was not an impediment to improving professionalism.

These are just some examples of how elements within our system can be used to improve professionalism. By taking a systems viewpoint,³ instead of focusing on fixed character traits, we see the forest, not just the trees. Extant evidence^{1,4-6} provides grounds for hope; we remain optimistic that professional behaviours can be shaped using a multifaceted systems approach.

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24th Seah Cheng Siang Lecture*: Seeing Better, Doing Better—Evolution and Application of Gastrointestinal (GI) Endoscopy

Khean Lee Goh, ¹MBBS (Mal), MD (Mal), FRCP (Glasg, London)

Abstract

Gastrointestinal (GI) endoscopy has evolved tremendously from the early days when candlelight was used to illuminate scopes to the extent that it has now become an integral part of the practice of modern gastroenterology. The first gastroscope was a rigid scope first introduced by Adolf Kussmaul in 1868. However this scope suffered from the 2 drawbacks of poor illumination and high risk of instrumental perforation. Rudolf Schindler improved on this by inventing the semiflexible gastroscope in 1932. But it was Basil Hirschowitz, using the principle of light conduction in fibreoptics, who allowed us to “see well” for the first time when he invented the flexible gastroscopy in 1958. With amazing speed and innovation, instrument companies, chiefly Japanese, had improved on the Hirschowitz gastroscope and invented a flexible colonoscope. Walter McCune introduced the technique of endoscopic retrograde cholangiopancreatography (ERCP) in 1968 which has now evolved into a sophisticated procedure. The advent of the digital age in the 1980s saw the invention of the videoendoscope. Videoendoscopes have allowed us to start seeing the gastrointestinal tract (GIT) “better” with high magnification and resolution and optical/digital enhancements. Fusing confocal and light microscopy with endoscopy has allowed us to perform an “optical biopsy” of the GI mucosa. Development of endoscopic ultrasonography has allowed us to see “beyond” the GIT lumen. Seeing better has allowed us to do better. Endoscopists have ventured into newer procedures such as the resection of mucosal and submucosal tumours and the field of therapeutic GI endoscopy sees no end in sight.

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Key words: Fibreoptics, History, Videoendoscopy

The Early Beginnings

Man’s innate curiosity to study the internal organs of the human body dates back to the time of Hippocrates where basic speculums were invented to peer into the buccal cavity and vagina. The first instruments used to intubate the oesophagus and stomach in the 16th and 17th centuries were designed for the purpose of extracting foreign bodies stuck in the oesophagus (or pushing them down into the stomach).

The first scopes used candlelight for illumination (Bozzini, 1806) and subsequently gasogen which is a mixture of alcohol and turpentine (Desormeux, 1853).¹ These scopes were, however, mainly designed as urethro-cystoscopes. Desormeux was the first to call such instruments, “endoscopes”.¹

Development of Rigid Scopes

Adolf Kussmaul is credited with inventing the first gastroscope in 1868. Taking the cue from sword swallows who were popular entertainers at that time, Kussmaul attempted to insert a long rigid hollow tube into a professional sword swallower at a meeting of the Society of Naturalists in Freiburg, Germany. Illumination was provided by a gasogen lamp but it was poor and as a result, the examination was unsatisfactory.¹ Water-cooled and electrically-heated wire platinum loops were then used by Nietze for providing light but these were found to be cumbersome and impractical. The “enlightenment” of endoscopy followed Edison’s invention of the incandescent lamp in 1879. A miniaturised or “mignon” light bulb was

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used with oesophagoscopes by Leiter and Mickulicz (1887).¹ Despite much effort at developing a gastroscope by many workers, the first fully usable rigid gastroscope was produced by Elsner in 1911. Rudolf Schindler, who more than anyone else had popularised upper gastrointestinal (GI) endoscopy at that time, called the Elsner instrument “the mother of all instruments”. He himself modified this rigid scope in 1922 by adding an air-channel into the scope to clean the lens. Through numerous examinations and assiduous recording by colour drawings, he published his classic book, “Lehrbuch und Atlas der Gastroskopie” (Textbook and Atlas of Gastroskopy) in 1923.¹

Rudolf Schindler and the Semiflexible Gastroscope

But the rigid scope had serious drawbacks. Instrumental perforations were not uncommon and as a result, the initial enthusiasm for the procedure waned. Schindler set about to invent a semiflexible gastroscope with the collaboration of a Berlin instrument maker, Georg Wolf. Working on the optical principle proposed by Hoffmann in 1911 that lenses attached to a flexible wire at short focal intervals from one another would bend light, Wolf and Schindler produced such a scope in 1932.^{2,3} It had a flexible distal 30-cm tip which was made of a bronze wire spiral and which incorporated a number of short convex lenses. This instrument was a major advance at that time, as not only was it much safer, it also provided significantly more information about the stomach. Despite the temporary setback of World War II and the incarceration of Schindler himself in a Nazi concentration camp, the semiflexible scope gained many ardent followers. This was in no small measure due to Schindler who was an enthusiastic and indefatigable teacher. Following his release from prison in 1934, Schindler and his family emigrated to the United States, where he was given an academic position at the University of Chicago. He continued his good work there and Chicago soon became a mecca for gastroenterologists and endoscopists. In 1941, Schindler started, at a meeting in his own house, the American Gastroscopic Club, the forerunner of the American Society of Gastrointestinal Endoscopy (ASGE). The ASGE chose to recognise his exceptional contributions in 1962 by creating the Schindler Award, the society’s highest tribute for contributions to the field of gastrointestinal endoscopy.⁴

Dawn of a New Era: Fibreoptic Endoscopy—Seeing Well

The Schindler-Wolf semiflexible gastroscope was the standard bearer for gastroscopes until 1957 when a further dramatic innovation, that of fibreoptics, was introduced into endoscopes. The inspiration for the making of a fibrescope was a 1954 paper appearing in *Nature* entitled “A flexible fibrescope using static scanning” coauthored by Harold

Hopkins and Nirmal Kapany.⁵ In this paper, Hopkins and Kapany showed that light could be transmitted through a single glass fibre based on the principle of total internal reflection. Basil Hirschowitz who was then a GI fellow at Ann Arbor, University of Michigan with Professor Marvin Pollard, was fascinated about the possibility of using fibreoptics in endoscopes and with the encouragement of his former mentor, Sir Francis Avery Jones of Middlesex Hospital, London, he paid a visit to Hopkins and Kapany at the Imperial College, London. On his return, Hirschowitz enlisted the help of Wilbur Peters, a physicist, and Larry Curtis, a sophomore student at the University of Michigan. Working feverishly with his coworkers, Hirschowitz was able to develop the first fibreoptic gastroscope, which he presented to the American Gastroscopic Society in Colorado Springs in May 1957. Before the year was out, the American Cystoscopic Makers Inc (ACMI) contracted to manufacture fibrescopes under license and in October 1960, the ACMI 4990 Hirschowitz gastroduodenal fibrescope was available for sale and use. Hirschowitz reported his initial experience with the fibreoptic scope in the *Lancet* in 1961.⁶ By the late 1960s, fibreoptics had almost completely displaced lens-optic gastroscopes. The Olympus Optical Company’s (Tokyo, Japan) first fibre gastroscope was introduced in 1968. ACMI produced the panendoscope in 1970. Japanese and American manufacturers rapidly and competitively improved fibreoptic instruments. In the words of Hirschowitz, “There seemed to be no end to the ingenuity of endoscopists and instrument makers and the application of fibreoptic instruments to diagnosis and therapy”⁷ (Professor Basil Hirschowitz, circa 2004, Fig. 1).

While developments were taking place in the United States, Dr Tatsuno Uji and engineers from the Olympus Optical Company, Japan, had developed a gastrocamera in 1952. In essence, it consisted of a miniaturised intragastric camera which could take high quality pictures. It was presented to Western endoscopists at the World Congress in Washington DC in 1958. Olympus Optical Company

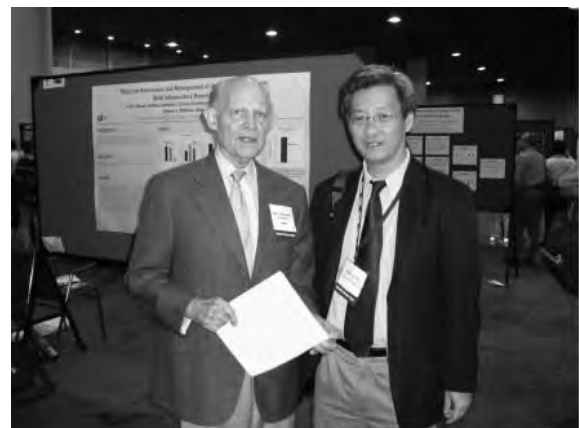


Fig. 1. Professor Basil Hirschowitz with author, May 2004, Digestive Disease Week, New Orleans, USA.

subsequently developed a model incorporating fibrescope and a gastrocamera in 1963 and this was used widely in Japan for mass screening for gastric cancer. But the gastrocamera had already by then, been quickly rendered obsolete by fibreoptic scopes.⁸

Fibreoptics was soon introduced for the examination of organs other than the upper gastrointestinal tract (GIT). Bergein Overholt, who also worked in the University of Michigan, Ann Arbor, presented his experience with the first fibreoptic sigmoidoscopy in 1967 at the ASGE meeting.¹ Subsequently in 1969 fiber optic colonoscopy and shortly thereafter, endoscopic polypectomy was performed by Wolff and Shinya in New York.⁹ Colonoscopy opened up a whole unexplored field of endoscopy. This was particularly significant in the face of widespread skepticism at that time. Comments included: “It requires a tricky skill that few will be able to acquire”, “It will tell you nothing a good radiologist couldn’t show” etc. Time has however, proven otherwise.

Further Innovations—Seeing More

One of the most exciting and elegant innovations of fibreoptic endoscopy was the cannulation of the ampulla of Vater. WC Watson of Glasgow in 1966 reported in the *Lancet*, his observations of the ampulla of Vater with a flexible duodenoscope and concluded that “endoscopic examination of the ampulla of Vater could be helpful in the diagnosis of biliary and pancreatic disorders”. McCune and colleagues from George Washington University reported in 1968 the first successful cannulation of the pancreatic duct using an Eder duodenoscope with a makeshift housing for a canula.¹⁰ But the Japanese were responsible for developing the endoscopic retrograde cholangiopancreatography (ERCP) as a standard diagnostic procedure. Itaru Oi, and Kunio Takagi and colleagues, together with engineers from the Machida Manufacturing Company and Olympus Optical Company, developed specially designed ERCP scopes: the FDS and JF and JFB-2 models respectively.^{11,12} Peter Cotton reported on his series of patients undergoing ERCP in 1972.¹³ In 1973, Keichi Kawai from Japan and Meinhard Classen and Ludwig Demling from Germany simultaneously reported endoscopic electrosurgical sphincterotomy of the papilla for the non-operative extraction of common bile duct stones.^{14,15} In 1980, Nib Soehendra from Hamburg, Germany introduced stenting of the biliary system with plastic tubes.¹⁶ The range of innovations that have come out in this field from pioneer ERCP-dedicated endoscopists such as Kees Huibregtse from Amsterdam have been truly amazing.¹⁷

Endoscopic ultrasonography, a more recently developed innovation in the late 1980s combines the diagnostic

capability of an ultrasound probe and that of a fibreoptic scope. Lutz and Rosch from Germany was the first to report on a transgastroscopic ultrasonography¹⁸ and subsequently Strohm et al¹⁹ and Eugene DiMagno from Mayo Clinic²⁰, improved on the applicability of these instruments. The first mechanical sector scanning instruments for endoscopic ultrasound displayed 180° images. The subsequent introduction of a full 360° image endoscope, the Olympus GF-UM3, provided the first commercially available echoendoscope.

Videoendoscopy—Seeing Better

Videoendoscopy provided perhaps the latest innovation in GI endoscopy. It is certainly not a new technique of performing endoscopy but a new way of viewing, acquiring and storing images in the digital form. The mechanical control and internal lumen subsystems remained essentially unchanged. Videoendoscopy is made possible following the discovery of the charged couple device (CCD) or electronic chip as it is commonly called.²¹ The first videoendoscope system was developed by Welch Allyn Incorporated (Skaneateles, USA) and exhibited at the ASGE meeting in 1983 and the first clinical report on its use in colonoscopy by Sivak and Fleischer in 1984.²² It drew little interest then as the prevailing attitude was “why replace something that is perfectly good with one that provided an image of lesser definition and at greater cost?”. Again, time has been the best judge. With further development and refinement of the system predominantly by the Japanese companies—Olympus Optical Company, Pentax and Fujinon—videoendoscopy has achieved not only “supra-maximum” quality imaging with ease of storage and transfer of images, it has also become the standard system for all forms of endoscopy today.

Videoendoscopy has also meant that endoscopists have now moved away from viewing through an “eyepiece” and to viewing images on a “television” screen (Fig. 2). This has made it ergonomically better for endoscopists as well as improving visualisation, and has also made teaching of endoscopy trainees more efficient.

Seeing Even Better

Videoendoscope instruments with even better imaging reaching a million pixels have been produced. Magnifying endoscopes and chromoendoscopy have enhanced the details of the GI mucosa. Recent innovations by the instrument companies included enhanced optical and digital modalities including narrow band imaging (Olympus, Optical company, Tokyo, Japan), Flexible spectral imaging colour enhancement (Fuji Film, Japan) and i-scan technology (Pentax, Hoya Corporation, Japan)²³ (Fig. 3).



Fig. 2. Fiberoptic gastroscope using an eyepiece (left); videoendoscope using a television monitor (right) with a trainee and instructor by his side.

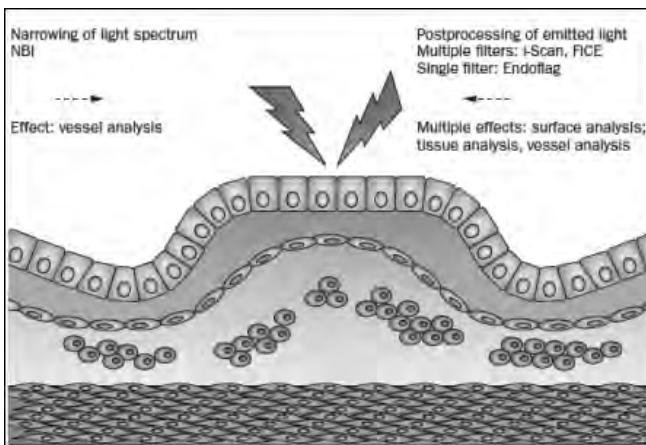


Fig. 3. This figure explains the principles of digital or virtual chromoendoscopy. NBI uses distinct filters to narrow the light that is emitted to the tissue. The ‘blue’ light leads to improved visualisation of surface vessel architecture. Emitted light from the tissue can be postprocessed, with many different effects modulated. FICE: Fuji intelligent chromoendoscopy; NBI: Narrow band imaging. Figure reproduced with permission from Elsevier[®]. Sauk J, Hoffman A, Anandasabapathy S, Kiesslich R. High-definition and filter-aided colonoscopy. *Gastroenterol Clin North Am* 2010;39:859-81.

Several technologies have now emerged that allow high resolution examination of the GI mucosa. These innovations have enabled an “optical biopsy” of the GI mucosa at the cellular and even the subcellular level. These technologies include confocal endoscopy, endocytoscopy and optical coherence tomography endoscopy.

Confocal endoscopy is perhaps the best established of these techniques and is already in routine clinical use. Essentially, it is a fusion of endoscopy and confocal microscopy techniques and was originally invented by Pentax as a scope-based technology.²⁴ In more recent years Mauna Kea Technologies has introduced a probe-based confocal endoscopy.²⁵ Endocytoscopy (EC) can be simply described as the application of a light microscope on the lining of the GIT and provides an ultra-high magnification of cells of the GI epithelium.²⁶ Again this technology can be scope-based or probe-based. Currently however, it is only available in prototype forms. Optical coherence tomography techniques for the GIT borrows the application

from examination of the retina in ophthalmology and relies on the back scattering of light to obtain cross-sectional image of tissues.²⁷ Again, this technology is still in the prototype form. These examinations are carried out in vivo with real-time image display. These optical biopsy techniques would be most useful in diagnosing dysplasia in patients with Barrett’s oesophagus and ulcerative colitis for example, and allows an immediate decision to be made on endoscopic therapy.

Miniaturisation of electronic components may allow the construction of new types of endoscopes that no longer require external wires, cables, or optical fibres. A “video pill” would allow the operator to perform a “drive through” endoscopy. The invention of capsule endoscopy in 2000 by Iddan et al²⁸ opened up the examination of a whole new frontier of the GIT—all 6 metres of the small intestine. Again, various technological advances over time have gradually allowed better capsule endoscopy imaging and more complete capture of images.

Seeing Better, Doing Better

Seeing better has inevitably allowed us to do better. New generation and braver endoscopists have ventured into procedures such as resection of mucosal and submucosal tumours, and the field of therapeutic endoscopy sees no end in sight. Endoscopic submucosal dissection was first described for early gastric tumours by Japanese endoscopists in 2001²⁹ and is now an established technique for early cancers of the oesophagus, stomach and the colon.³⁰ Submucosal tunneling can now be performed safely and confidently, and experts like Haruhiro Inoue have described the technique of per-oral endoscopic myotomy (POEM) for achalasia of the cardia.³¹ Braver endoscopists now routinely perform endoscopic dissection and removal of submucosal tumours, and there have been reports of full thickness endoscopy resection of GI tumours done together with laparoscopy or by endoscopy alone.³²

Visualisation of the biliopancreatic tracts have improved with the introduction of ultrathin scopes or probes directly into the bile duct and pancreatic ducts. The “mother-baby” ERCP scope set up has been in use for a long time but recent innovations utilising an intraductal biliary balloon by Moon et al has allowed ultrathin gastroscopes to be introduced directly into the bile duct.³³ This has allowed biopsy of biliopancreatic tumours, and in the bile duct, it has permitted the use of electrohydraulic and pulsed laser therapies to fragment large stones and to remove stones from intrahepatic ducts.

Epilogue—What of the Future?

The development and the subsequent widespread use and application of GI endoscopy ranks as one of the landmarks in the annals of medicine. GI endoscopy is indispensable to the field of gastroenterology and GI surgery. The “endoscope” has evolved from a candlelit instrument in the early 19th century to its current state of sophistication. Procedures are now performed in well planned dedicated endoscopy units (Fig. 4). Training, credentialing, audit, retraining and maintenance of standards of practice are important issues. The field of GI endoscopy has developed into a distinct and separate field, with journals, workshops, international meetings and a global fraternity of its own. With continuing advances and technical sophistication, GI endoscopy will remain an exciting field stimulating further research and spearheading advances in the diagnosis and treatment of GI diseases. Man’s ingenuity in the development of endoscopy has brought gastroenterology into the forefront of diagnosis and treatment of human diseases.



Fig. 4. A modern therapeutic endoscopy room with a digital fluoroscopy unit, University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia, 2014. The GI Endoscopy unit at the UMMC has been accorded the Centre of Excellence Award, by the World Endoscopy Organization from 2008 to 2014, an award which has now been renewed from 2015 to 2020.

Postscript

Professor Seah Cheng Siang, whom I did not have the chance to meet in his lifetime, was a teacher, doctor and pioneer gastroenterologist par excellence. Above all, he was a humane man who contributed immensely to the development of medicine and gastroenterology in Singapore. Many Malaysian doctors benefited from his teaching in the earlier days, as the only medical school then was the University of Malaya, which was based in Singapore before it moved to Kuala Lumpur, Malaysia in 1962. It is truly a privilege to deliver this lecture in his name in 2014. Younger physicians and gastroenterologists have been fortunate and as Sir Isaac Newton quoted, “[they] could see further by standing on the shoulders of giants”—a giant such as Professor Seah.

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