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CME ARTICLE

The diagnosis and management of *H. pylori* infection in Singapore

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Jonathan, a 22-year-old undergraduate, has been troubled by dyspepsia in the past few weeks. He initially attributed it to stress from studying for his upcoming university examinations. However, when the symptom persisted, he decided to seek advice from his family physician. He was positive for H. pylori *on serological testing and was started on seven-day clarithromycin-based triple therapy. Upon its completion, Jonathan returned for repeat serology, which remained positive. As his symptoms were persistent, his family physician referred him to a gastroenterologist for further management.*

HOW RELEVANT IS THIS TO MY PRACTICE?

Helicobacter pylori (*H. pylori*) is a common chronic bacterial infection that is present in over 50% of the world's population, although its prevalence has been gradually declining in the Asia-Pacific region.[1] In Singapore, the seroprevalence rate is 31%.[2]

The majority of people infected with *H. pylori* never experience any symptoms or complications. However, the increasing use of *H. pylori* serology by family physicians during health screening prompts further investigation for *H. pylori*. Symptoms include dyspepsia, bloating, and nausea or vomiting. Colonisation with *H. pylori* is a major risk factor for peptic ulcer disease, as well as gastric malignancies such as gastric adenocarcinoma and lymphoma involving mucosa-associated lymphoid tissue.[3] Successful eradication is essential for primary and secondary prevention of peptic ulcer disease and gastric malignancy.[4,5]

WHAT CAN I DO IN MY PRACTICE?

Diagnosis of *H. pylori* infection

In managing patients with dyspepsia, primary care physicians can take a stepwise approach (Fig. 1). Endoscopy is the first-line investigation in patients with dyspepsia. It can diagnose peptic ulcer disease, gastric malignancies and *H. pylori* infection through biopsy-based tests such as the rapid urease test and histology. While endoscopy has a high diagnostic yield, its disadvantages include the need for referral to a specialist (i.e. for open-access gastroscopy or formal specialist review), cost, procedure-related risk and the discomfort experienced by patients. General practitioners and family physicians serve an important role in the first-line treatment for such patients, as they can use a noninvasive diagnostic strategy: 'test and treat'. This is a reasonable option in younger patients without alarm features such as anaemia, loss of weight, anorexia, recent onset of progressive symptoms, melaena or haematemesis, and dysphagia.[6-10] The age threshold depends on the local prevalence of gastric malignancies. In Singapore, the 'test-and-treat' strategy is a reasonable option for patients who are aged 40 years and below.

As its name suggests, this strategy is based on investigating for the presence of *H. pylori* and its subsequent eradication when detected. The patient is assessed for symptom resolution and no further diagnostic evaluation (with endoscopy or referral) is needed if the symptoms have fully resolved. The carbon urea breath test (C-UBT) is considered the best approach for the initial diagnosis and subsequent confirmation of the cure, as it has high sensitivity and specificity, excellent performance, and is cost-effective.[11,12] C-UBT is based on the principle that *H. pylori* will hydrolyse orally administered labelled urea to produce carbon dioxide that is isotopically labelled and can be measured in exhaled breath. As *H. pylori* is the most common urease-containing gastric pathogen, the presence of urea hydrolysis confirms a *H. pylori* infection. Two types of C-UBT are available: ^{13}C-UBT and ^{14}C-UBT. ^{13}C-UBT is preferred as it is non-radioactive and based on mass spectrometry, whereas ^{14}C-UBT is radioactive.

Routine 'test and treat' is not recommended for patients with gastro-oesophageal reflux disease.[13] An alternative to C-UBT is stool antigen testing, which is particularly useful for children who may not be able to comply with C-UBT. The monoclonal stool antigen test has high sensitivity and specificity, and has been shown to be the most effective noninvasive test for children.[14,15] For adults, C-UBT is preferred.

Serological assays are inexpensive and easy to conduct in the primary care setting.[16,17] However, the performance of these tests is dependent on the antigenic composition of circulating strains

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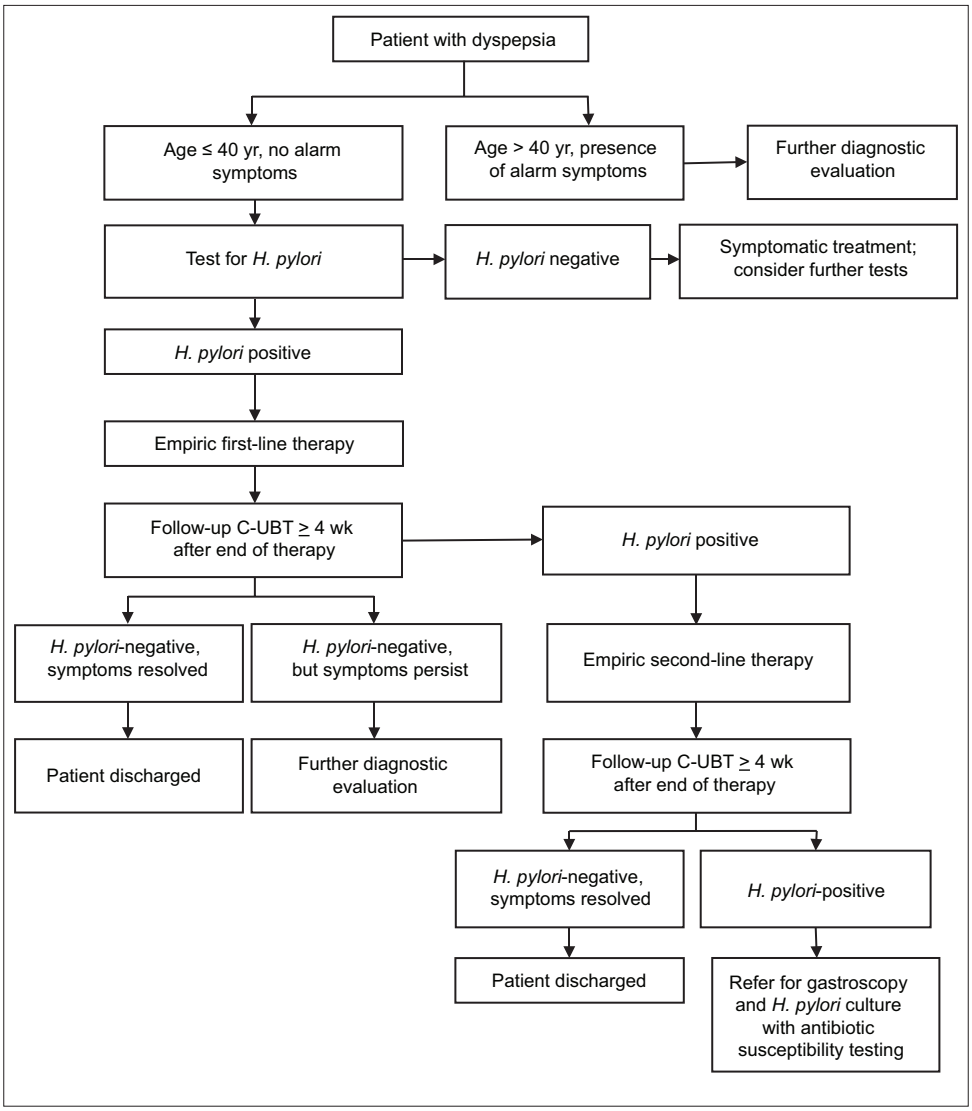

Fig. 1. Flow chart shows the stepwise approach to management of *H. pylori*-associated dyspepsia in the primary care setting. C-UBT: carbon urea breath test

and thus, they need to be validated for the local population. Furthermore, as these tests cannot differentiate between active and past infection, they are not recommended for diagnosis of active infection or confirmation of eradication. False positive tests may result in overuse of antibiotics and potentially contribute to antimicrobial resistance.[4,18]

Empiric first-line treatment

The determinants of treatment efficacy are adequate treatment duration, at least two different antibiotics, potent acid suppression, compliance to treatment and antibiotic resistance. When the first set of Ministry of Health Clinical Practice Guidelines for *H. pylori* treatment was published, one-week triple therapy was recommended, comprising twice-daily proton pump inhibitor (PPI), amoxicillin and clarithromycin.[19] These guidelines are now obsolete and have been withdrawn. Since then, studies have shown that a two-week clarithromycin-containing triple-therapy regimen increases cure rates compared to both ten-day and one-week therapy regimens.[20] Potent acid suppression is an important element of triple therapy. Twice-daily PPI therapy increases the efficacy of triple therapy, because *H. pylori* enters a replicative state after gastric pH is raised and thus, becomes more susceptible to amoxicillin and clarithromycin.[21-24] However, compliance to treatment is very important and clinicians must educate patients on the consequences of noncompliance; a compliance rate of less than 80% has been shown to lower treatment efficacy.

An important cause of treatment failure is *H. pylori* antibiotic resistance, which is increasing in most parts of the world.[25] Resistance to clarithromycin, in particular, is responsible for a decrease in the efficacy of current triple-therapy regimens.[25-27] As antibiotic resistance profiles vary across geographical regions, knowledge of local resistance patterns and treatment outcomes is important.[26,28] A recent study of *H. pylori* resistance profiles in Singapore found that in the time periods of 2000–2002 and 2012–2014, resistance rates to clarithromycin (7.9% to 17.1%), metronidazole (24.8% to 48.2%) and levofloxacin (5.0 to 14.7%) have increased, whereas resistance to amoxicillin (3.0% to 4.1%) and tetracycline (5.0% to 7.6%) remained low. Multidrug resistance rates were low during these periods.[2]

The recently published Maastricht V/Florence Consensus Report recommended that in areas of high clarithromycin resistance (> 15%), bismuth quadruple therapy or a non-bismuth

quadruple therapy called concomitant therapy (PPI, amoxicillin, clarithromycin and a nitroimidazole) be recommended.[4] It is also generally regarded that in the context of quadruple therapies, the effect of metronidazole resistance can be overcome if a higher dose of 500 mg three times a day is used for two weeks.[4] The Toronto Consensus Report further clarified the issue by including outcome data, stating that to continue using clarithromycin-containing triple therapy, the clarithromycin resistance rate should either be less than 15%, or there should be local data demonstrating high eradication rates (> 85%).[29]

A recent randomised controlled study in Singapore compared concomitant (PPI, amoxicillin, clarithromycin and metronidazole), sequential (PPI, amoxicillin for the first five days, followed by PPI, clarithromycin and metronidazole for the subsequent five days) and triple (PPI, amoxicillin and clarithromycin) therapies for ten days. All three regimens achieved high eradication rates of more than 90% even though the rate of clarithromycin resistance in Singapore had risen to 17.1% during the study period.[30] This suggests that two-week clarithromycin-containing triple therapy is currently a viable first-line empiric treatment option in Singapore, despite the rise in the clarithromycin resistance rate. However, the efficacy is likely to decrease should clarithromycin resistance rates increase further and exceed 20%.

Other first-line options include concomitant therapy and bismuth quadruple therapy. Sequential therapy is not recommended. Interestingly, in countries with high antibiotic resistance rates, the addition of bismuth to standard triple therapy further increased treatment efficacy due to the bactericidal properties of bismuth, although no local data is available.[31] Issues with these alternative regimens include added costs and lower patient tolerability. Vigilance and follow-up C-UBT are important when triple therapy is used. In cases of penicillin allergy, it is theoretically possible to replace amoxicillin with metronidazole in clarithromycin-containing triple therapy, but this is not ideal given the high local antibiotic resistance rates, and bismuth quadruple therapy should be preferred. The options for empiric first-line treatment in Singapore are summarised in Box 1.

Testing for *H. pylori* eradication

C-UBT is the test of choice for confirming successful eradication of *H. pylori* infection after treatment. False negative C-UBT results can occur in patients taking PPI and antibiotics.[32] Therefore, it is advisable to perform C-UBT at least four weeks after completion of antibiotic therapy; patients should also have discontinued PPI therapy for at least two weeks.[33] As with diagnosis of *H. pylori*, the stool antigen test is an acceptable alternative. However, serological testing should not be used for confirmation of eradication, as the levels will remain positive.[4]

WHEN SHOULD I REFER FOR GASTROSCOPY?

Referral for gastroscopy should be considered when patients present with alarm symptoms, or when the 'test-and-treat' strategy is unsuccessful and persistent infection is suspected. There are several endoscopy-based biopsy tests for *H. pylori* infection. Among these, the rapid urease test is recommended as a first-line test, as it has a high sensitivity and specificity of 90% and 95%–100%, respectively, and results are quickly confirmed.[34,35] If the test is positive, treatment can be started immediately after endoscopy. Biopsies can also be obtained for histology, for diagnosis of *H. pylori* infection and topographical mapping of the extent and severity of gastritis, including the presence and severity of gastric atrophy and intestinal metaplasia. This information allows risk stratification for development of subsequent gastric dysplasia.[36,37,38] However, histology is not routinely required nor performed, given the additional costs involved and longer turnaround time. Biopsies from both the antrum and corpus are recommended to increase the sensitivity of the rapid urease test.[39]

When patients are referred for gastroscopy and a rapid urease test is likely to be performed, they should be advised to avoid taking antibiotics or bismuth for four weeks and PPI therapy for two weeks.[4] When there is a concern that the rapid urease test might return a false negative due to recent use of PPI or antibiotics, additional biopsies for histology can be obtained.

WHAT ARE THE SECOND-LINE TREATMENT OPTIONS?

Second-line treatment may be prescribed empirically in primary care or specialist settings. If endoscopy is scheduled, gastric biopsies may be obtained for *H. pylori* culture and antibiotic susceptibility testing to guide the choice of antibiotic therapy.[4]

For patients who fail treatment with clarithromycin-containing triple therapy, clarithromycin resistance should be suspected, and second-line therapy should be considered.[4] Bismuth quadruple therapy or levofloxacin-containing therapy (PPI, amoxicillin and levofloxacin) are both acceptable second-line therapies for these patients.[40] However, high resistance rates to levofloxacin in the local setting may affect the efficacy of levofloxacin-based regimens.[2,41]

For patients who fail initial treatment with non-bismuth quadruple therapy, meta-analyses have shown PPI-levofloxacin-amoxicillin therapy to be the most effective rescue therapy, with a 78% eradication rate.[4] However, the efficacy of this regimen is reduced in the presence of fluoroquinolone resistance,[41] which appears to be rising in Singapore.[2] A quadruple regimen with the addition of bismuth has been shown to be useful, likely due to the synergistic effect of bismuth with antibiotics in overcoming clarithromycin and levofloxacin resistance.[42,43] The options for empiric second-line treatment in Singapore are summarised in Box 2.

Failure of second-line treatment

Referral to a specialist for assessment and antibiotic susceptibility testing is indicated for patients who fail second-line treatment. Gastroscopy will have to be performed and biopsies obtained for *H. pylori* culture.[44,45] It is important that treatment compliance is explored with these patients and any barriers to compliance are addressed.

As treatments for *H. pylori* infection are constantly evolving, there is a need to maintain an up-to-date approach in our

Box 1. Options for empiric first-line treatment of *H. pylori*.

Treatment should be for two weeks to maximise efficacy (ten days may suffice if patients are unable to complete two weeks of treatment).

(a) No penicillin allergy

1. Clarithromycin-containing triple therapy (PPI BID, amoxicillin 1 g BID, clarithromycin 500 mg BID)
2. Concomitant therapy (PPI BID, amoxicillin 1 g BID, clarithromycin 500 mg BID, metronidazole* 500 mg TID)
3. Bismuth quadruple therapy (PPI BID, bismuth subcitrate 240 mg BID or bismuth subsalicylate 1,050 mg BID/525 mg QID, metronidazole* 500 mg TID, tetracycline 500 mg QID)
4. Clarithromycin-containing triple therapy (PPI BID, amoxicillin 1 g BID, clarithromycin 500 mg BID) with addition of bismuth (bismuth subcitrate 240 mg BID or bismuth subsalicylate 1,050 mg BID/525 mg QID)

(b) Penicillin allergy

Bismuth quadruple therapy (PPI BID, bismuth subcitrate 240 mg BID or bismuth subsalicylate 1,050 mg BID/525 mg QID, metronidazole* 500 mg TID, tetracycline 500 mg QID)

*Good evidence for QID dosing of metronidazole is lacking, but would be acceptable in cases where only a 400-mg dose is available.[29] BID: twice a day; PPI: proton pump inhibitor; QID: four times a day; TID: thrice a day

Box 2. Options for empiric second-line treatment of *H. pylori*.

(a) After failure of first-line clarithromycin-containing triple therapy

1. Bismuth quadruple therapy (PPI BID, bismuth subcitrate 240 mg BID or bismuth subsalicylate 1,050 mg BID/525 mg QID, metronidazole 500 mg TID, tetracycline 500 mg QID)
2. Levofloxacin-containing triple therapy (PPI BID, amoxicillin 1 g BID, levofloxacin* 500 mg BID)

(b) After failure of first-line concomitant therapy

1. Bismuth quadruple therapy (PPI BID, bismuth subcitrate 240 mg BID or bismuth subsalicylate 1,050 mg BID/525 mg QID, metronidazole 500 mg TID, tetracycline 500 mg QID)
2. Levofloxacin-containing triple therapy (PPI BID, amoxicillin 1 g BID, levofloxacin* 500 mg BID)

(c) After failure of first-line bismuth quadruple therapy

Levofloxacin-containing triple therapy (PPI BID, amoxicillin 1 g BID, levofloxacin* 500 mg BID)

*The dose of levofloxacin used in published studies was 250 mg BID, 500 mg QD and 500 mg BID. BID: twice a day; PPI: proton pump inhibitor; QD: once a day; QID: four times a day; TID: thrice a day

management. The profile of antibiotic resistance in Singapore should be re-evaluated at regular intervals, as it may affect the efficacy of empiric first-line treatment regimes. For instance, recent data revealed that the clarithromycin resistance in Singapore is above the threshold level of 15%, suggesting that the use of clarithromycin as first-line empirical therapy may need to be reconsidered.[2] However, despite this increase in the resistance rate, clarithromycin-containing triple therapy was demonstrated to achieve eradication rates of more than 90% in the local context in a randomised controlled study. Hence, it can still be recommended as first-line therapy.[30] Post-treatment C-UBT must be performed routinely in all patients at least four weeks after treatment to confirm the cure, as no regimen can consistently achieve a 100% treatment success rate.

CONCLUSION

Generally, vaccination is the best public health measure against infections. In the context of *H. pylori* infection, vaccination is not universally available and the efficacy is limited, although a promising field trial in China has recently been reported.[46] In the primary care setting, one can adopt a stepwise approach to the management of *H. pylori*-associated dyspepsia (Fig. 1). The 'test-and-treat' strategy can be considered in younger patients without alarm symptoms; however, further evaluation must be performed should symptoms persist. Clarithromycin-containing triple therapy for two weeks can still be an empiric first-line therapy for *H. pylori* infection in Singapore. For patients unable to tolerate two-week therapy, ten days may suffice in the local context.[30] Other options for empiric first-line treatment include bismuth quadruple therapy and concomitant therapy. Referral for gastroscopy is indicated in patients with alarm symptoms or those with persistent infection. Confirmation of eradication is mandatory for all patients after treatment. Patient education is important and clinicians should reinforce the importance of treatment compliance and educate patients on the risks and complications of persistent *H. pylori* infection.

TAKE HOME MESSAGES

1. *H. pylori* infection is a common condition, and treatment is important for the primary and secondary prevention of complications, which range from peptic ulcer disease to gastric malignancy.
2. 'Test and treat' is an acceptable strategy for younger patients who have uninvestigated dyspepsia without alarm symptoms. C-UBT has high sensitivity and specificity for active infection.
3. Patients with alarm symptoms or persistent infection should be referred for gastroscopy.
4. Clarithromycin-containing triple therapy for two weeks is an acceptable first-line empirical treatment for *H. pylori* infection in Singapore. Patients who fail to respond to treatment should be prescribed bismuth quadruple therapy. C-UBT should be performed at least four weeks after treatment to confirm the cure.
5. Bismuth quadruple therapy and concomitant therapy are recommended first-line treatment options in regions of high clarithromycin resistance.
6. Local antibiotic resistance patterns must be re-evaluated at regular intervals to guide the choice of empiric treatment. Compliance to treatment is important and clinicians must reinforce this by actively educating and engaging the patient.

Jonathan underwent gastroscopy, which showed non-erosive antral gastritis. Biopsies were taken and the rapid urease test confirmed the presence of persistent H. pylori *infection. Upon further questioning, Jonathan revealed that he had not been compliant to the initial course of clarithromycin-based triple therapy, as he had often forgotten to take his medications when he was studying. He was counselled on the risks of persistent* H. pylori *infection and agreed to start on bismuth-based quadruple therapy for 14 days. A repeat carbon urea breath test performed by his family physician confirmed successful eradication of* H. pylori.

ABSTRACT *Helicobacter pylori (H. pylori)* is an infection that has a role in causing dyspepsia and complications such as peptic ulcer disease and gastric malignancies. In the primary care setting, one can adopt a stepwise approach with the 'test-and-treat' strategy to manage *H. pylori*-associated dyspepsia in young patients without alarm symptoms. Empiric first-line therapies should be for a two-week duration; options include clarithromycin-containing triple therapy alone or with the addition of bismuth, concomitant therapy and bismuth quadruple therapy. Post-treatment carbon urea breath test must be performed at least four weeks after the end of treatment to confirm the cure. Options for empiric second-line treatment include bismuth quadruple therapy and levofloxacin-containing triple therapy. Patients with persistent or alarm symptoms should be referred for further evaluation. Patients with persistent infection should be referred for gastroscopy so that gastric biopsies can be obtained for *H. pylori* culture and antibiotic susceptibility testing.

Keywords: acid suppression, antibiotic resistance, dyspepsia, H. pylori

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201705A)

	True	False
1. *Helicobacter pylori* (*H. pylori*) infection is a cause of peptic ulcer disease and gastric cancer.	☐	☐
2. *H. pylori* infection is a cause of gastro-oesophageal reflux disease.	☐	☐
3. A 'test-and-treat' strategy can be applied to all patients.	☐	☐
4. *H. pylori* serology is useful for diagnosis and post-treatment follow-up.	☐	☐
5. Stool antigen is useful to diagnose active *H. pylori* infection in children.	☐	☐
6. The carbon urea breath test may be falsely negative if the patient is taking proton pump inhibitors.	☐	☐
7. For confirmation of cure, the carbon urea breath test is repeated two weeks after the end of antibiotic treatment.	☐	☐
8. Potent acid suppression is important for successful *H. pylori* therapy.	☐	☐
9. A treatment compliance rate of less than 80% has been shown to decrease treatment efficacy.	☐	☐
10. There has been an increase in *H. pylori* antibiotic resistance rates and this may affect treatment efficacy.	☐	☐
11. Empiric first line *H. pylori* therapies should generally be for two weeks.	☐	☐
12. Clarithromycin-containing triple therapy is obsolete in Singapore and should never be prescribed.	☐	☐
13. For patients with an allergy to amoxicillin, substitution of amoxicillin with metronidazole in a triple therapy regimen will not reduce treatment efficacy.	☐	☐
14. The effect of metronidazole resistance can be overcome with a higher dose and longer treatment duration when used in context of bismuth-based quadruple therapy.	☐	☐
15. Local studies have shown that the efficacy of sequential therapy is superior to that of triple therapy.	☐	☐
16. In regions with a high clarithromycin resistance rate of 20%, suitable empiric first-line therapies include bismuth-based quadruple therapy and concomitant therapy.	☐	☐
17. The addition of bismuth to standard triple therapy may increase treatment efficacy, as it can help overcome the effect of clarithromycin resistance.	☐	☐
18. In the context of failed first-line therapy using triple therapy, empiric two-week bismuth-based quadruple therapy can be prescribed.	☐	☐
19. Antibiotic susceptibility testing can be considered after failure of empiric first-line therapy if gastroscopy is being planned.	☐	☐
20. Antibiotic susceptibility testing should be performed after failure of empiric second-line therapies.	☐	☐

Doctor's particulars:

Name in full : _____

MCR number : _____ Specialty: _____

Email address : _____

SUBMISSION INSTRUCTIONS:

(1) Visit the SMJ website: http://www.smj.org.sg/current-issue and select the appropriate set of questions. (2) Provide your name, email address and MCR number. (3) Select your answers and click "Submit".

RESULTS:

(1) Answers will be published online in the SMJ July 2017 issue. (2) The MCR numbers of successful candidates will be posted online at the SMJ website by 30 June 2017. (3) Passing mark is 60%. No mark will be deducted for incorrect answers. (4) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council. (5) One CME point is awarded for successful candidates.

Deadline for submission: (May 2017 SMJ 3B CME programme): 12 noon, 23 June 2017.