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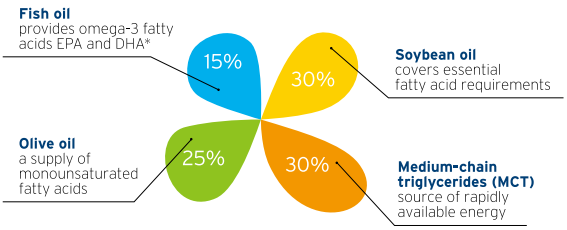

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The Cover Shot

Bird watching is getting more and more popular in recent years as people are looking to connect more with nature. However, many beginners believe that they have to use expensive and high-powered equipment to enjoy this hobby which is not true. A pair of affordable, entry-level binoculars is the most important piece of gear needed for this hobby. "6 x 32" and "8 x 42" are some popular choices. Handy birding apps help quickly identifying birds you see on your treks, while the superzoom camera allows you to begin wildlife photography on a budget.

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It is our honour to be invited by the Federation of Medical Societies of Hong Kong to be the co-issue editors of this May 2021 issue of the Hong Kong Medical Diary, an issue on Intensive Care.

In 2021, what does the name "Intensive Care Unit (ICU)" imply to you? The ICU concept started as finding a geographical location to put together the sickest patients needing ventilator support for better care. Compared with many other time-honoured specialities, we would say this concept, which started in the 1950s overseas, and in the late 1960s in Hong Kong, is relatively "young". Not only does the ICU put together the sickest patients, but it also puts together doctors, nurses and allied health professionals. In the early ICUs in Hong Kong, care was provided by doctors of the original departments. In most Hong Kong ICUs today, two specialities contribute to the ICU medical expertise, namely, critical care medicine of the physicians' stream and intensive care medicine of the anaesthesiologists' stream, with additional inputs from doctors of other specialities.

ICU is an indispensable part of a modern hospital, where one will find the most avant-garde paraphernalia to support each organ. In this issue, readers will get updated on advances in acute respiratory failure, resuscitation and sepsis. While the quintessence of future ICU development must be ever-advancing technology, good administration is also needed to coordinate and steer the development most appropriately and efficiently. This issue covers what data-driven management is, what to expect in a future ICU, and the rapidly growing University of Hong Kong-Shenzhen Hospital under the good leadership and collaboration of Hong Kong and the Mainland. Hence, although we were young, we are still young, and we will forever be young, in terms of our liveliness, energy and creativity.

Last but not least, we would like to thank the authors and the Hong Kong Medical Diary Editorial Board, and the Federation's Secretariat team. We are confident that this issue will impart new medical knowledge and information to the broad readership of the Hong Kong Medical Diary.

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Advances in Sepsis Management

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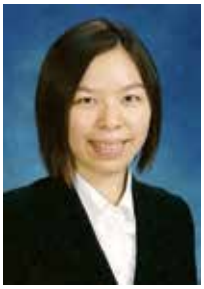
Dr May MY MAN

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2021.

INTRODUCTION

Sepsis is the leading cause of death in hospitalised patients worldwide. In 2017, it was estimated that 48.9 million suffered from sepsis; 11 million sepsis-related death were recorded.[1] According to the international prevalence of sepsis study (EPIC III), more than 54% of patients admitted to an intensive care unit (ICU) had a proven infection associated with significant hospital mortality up to 30%.[2] Ongoing efforts have been made in the past decade to improve the care of septic patients in the following aspects: early identification of sepsis, timely resuscitation and de-resuscitation of the critically ill, optimisation of antimicrobial agents and development of sepsis adjuncts. In this paper, we will review each of these aspects.

ROLE OF RAPID DIAGNOSTIC TESTS IN CRITICAL CARE

Early identification of infective micro-organisms that caused sepsis remains the cornerstone in managing patients with severe sepsis and septic shock. Early identification allows early commencement of appropriate antimicrobial therapy, timely de-escalation of broad-spectrum antibiotics, thus reducing potential side effects and averting the development of resistance. The Surviving Sepsis Campaign recommended that early antibiotics should be given within one hour from the time of presentation[3], and research showed each and every hour's delay in antibiotics administration would result in an extra 7.6% mortality.[4]

Conventional cultures, identification of causative organisms and antibiotic susceptibility testing remain the gold standard in diagnosing bacterial infection. It is, however, labour-intensive and time-consuming. Recently, newer molecular diagnostic techniques have been developed and employed to identify causative organisms.

Automatic cartridge-based systems extract and purify nucleic acids from the clinical sample and perform nested multiplex polymerase chain reaction (PCR) in stages. It shortens the turnaround time from 72 hours to 2 hours. Approved by the Food and Drug Administration, PCR systems detect bacteria, viruses and resistance genes in clinical samples such as respiratory, cerebrospinal fluid and blood cultures. Studies have demonstrated a positive correlation of more than 90% between the multiplex PCR system and conventional cultures.[5] Feasibility study in the critically ill population showed up to 77% switching of antimicrobial therapy after the employment of multiplex PCR technique, with the majority of the switch being de-escalation.[6]

A pilot study involving 47 patients was undertaken in our unit in November 2020. It showed that along with the incorporation of multiplex PCR testing and multidisciplinary stewardship under the microbiologist, switching of antibiotics was noted in 29 patients (61.7%), among whom 96.6% was de-escalation. The decision to switch antibiotics was shortened by 1.2 days, thanks to the multiplex PCR testing.

Nevertheless, one should exercise clinical judgement when interpreting these molecular tests. Owing to the lack of consensus on diagnostic threshold, these tests carry limited ability to differentiate among previous infections, colonisation and genuine infections. Moreover, several bacteria such as *Stenotrophomonas, Citrobacter, Morganella* and *locally prevalent M. \tuberculosis* species, have not been included. Furthermore, although the panel covers commonly seen resistance genes, clinically important inducible resistance, i.e. the AmpC β-lactamase gene has not been included.

Joining hands with clinical decision-care algorithms and antibiotic stewardship programmes, these rapid diagnostic techniques brought from bench to bedside bode well for improving patient outcome.

OPTIMISATION OF ANTIMICROBIAL TREATMENT TO MINIMISE RESISTANCE SELECTION

Optimising antimicrobial use includes optimising the pharmacokinetics and pharmacodynamics, choosing the appropriate agents or combination therapies and routes, and using the right dosage by therapeutic drug monitoring (TDM) in critically ill patients.

Meta-analysis has shown that extended infusion, or even continuous infusion of β-lactams, which carry time-dependent killing properties, improved clinical outcome when compared with bolus injections.[7] Aminoglycosides, given their concentration-dependent

killing properties, should be given as a single daily dose to achieve high peak antibiotics concentration. While the combination of antibiotics, in theory, may serve synergistic effects and provide a broader coverage empirically, a meta-analysis showed that the benefit was only apparent in those with severe sepsis carrying an expected mortality > 25%.[8] Routine combination therapy in all patients may not offer additional benefit.

The long debate on the alternative route of antibiotics administration remains inconclusive. Nebulised antibiotics has been shown to enhance clinical cure by providing high concentration at the site of infection, reducing systemic toxicity, and suppressing biofilm formation.[9] However, no difference was observed in the ICU mortality and length of stay. Low-efficiency drug delivery systems (jet and ultrasonic and vibrating mesh devices) have been criticised for their asynchrony with ventilatory cycles.[10] The recently published INHALE trial did not show mortality benefit over standard intravenous therapy in mechanically ventilated patients with gram-negative pneumonia, despite using synchronised inhalational system.[11]

In critically ill patients, renal function is often affected due to several reasons. On the one hand, septic acute kidney injury and hypotension may impair renal function; on the other hand, subgroups of patients may have augmented renal clearance (ARC).[12] Increased cardiac output in response to sepsis caused the increase in renal blood flow and glomerular filtration rate, leading to increased clearance of renal-excreting antimicrobials. Literature suggested giving 1.5 times the usual doses as a loading dose in ARC and monitor drug levels.[13] TDM allows fine titration of antibiotics in accordance with changes in the liver and renal functions and is particularly important in patients receiving extracorporeal therapies, including various renal replacement therapy modalities and extracorporeal membrane oxygenation.[13] However, rapid, cost-effective TDM is not yet widely available in public hospitals, and this should be an important development area in the coming years.

NEW 'BIG GUNS' IN THE PIPELINE

The emergence of multi-drug resistant (MDR) organisms, particularly carbapenem-resistant (CR) organisms, has imposed a great challenge to intensivists. Several new antibiotics have been approved and made available for the treatment of gram-negative complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI) and hospital-acquired pneumonia (HAP).

Ceftolozane/tazobactam (C/T) is a novel oxyimino-cephalosporin/β-lactamase inhibitor that shows activities against MDR *Pseudomonas aeruginosa* (attributed to the ceftolozane component) and extended-spectrum β-lactamase (ESBL)-producing organisms (attributed to the tazobactam component). Randomised trials have proved the non-inferiority of C/T (in combination with metronidazole) to carbapenems in treating cIAI[14] and HAP (given at higher doses)[15]. C/T has also been found to be superior to levofloxacin in treating cUTI.[16] However, C/Thas demonstrated limited activity towards carbapenemase-producing Enterobacteriaceae (CPE) and carbapenem-resistant *Acinetobacter baumannii*(CRAB).

Ceftazidime/avibactam shows a broad range of coverage towards class A, AmpC, class D β-lactamase-producing organisms and *Pseudomonas aeruginosa*. Similar to Ceftolozane/tazobactam, it was approved as a treatment option for cIAI, cUTI[17], HAP and ventilator-associated pneumonia[18], with non-inferiority shown compared with the best available treatment. However, resistance has been reported in KPC-producing organisms.[19]

Vaborbactam, a cyclic boronated β-lactamase inhibitor, protects meropenem from serine β-lactamase. The meropenem/vaborbactam (M/V) combination shows activity against class A, AmpC and ESBL-producing organisms. TANGO I and II trial showed M/V was superior to piperacillin/tazobactam in treating cUTI and was better than the best available treatment for CRE infections.[20] However, M/V holds limited activity against class B β-lactamase-producing organisms and CRAB.

Imipenem/cilastatin-relebactam is comparable to imipenem/colistin combination in treating imipenem-nonsusceptible cUTI and cIAI[21], and is non-inferior to piperacillin/tazobactam in HAP/VAP in RESTORE-IMI 1 and 2 trials respectively.[22] The novel β-lactamase inhibitor, Relecbactam, restores imipenem activity against imipenem-resistant *Enterobacteriaceae* and *Pseudomonas*.

Other new antibiotics targeting MDR gram-negative organisms and their spectrum of activities are listed in table 1.

Table 1. showed a summary of new antibiotics and their trials (Developed by authors)

Antimicrobials	Antibiotic class	Spectrum against organisms Effective	Ineffective	Indication
Ceftolozane/ tazobactam	Cephalosporin/ β-lactamase inhibitor	MDR *P. aeruginosa* ESBL and AmpC producing-Enterobacteriaceae	CRE CRAB	cIAI[14] cUTI[16] HAP[15]
Ceftazidime/ avibactam	Cephalosporin/ β-lactamase inhibitor	ESBL, AmpC, Class A and D Enterobacteriaceae, *P. aeruginosa*	Class B β-lactamase producing-CRAB	cIAI, cUTI[17] HAP, VAP[18]
Meropenem/ vaborbactam	Carbapenem/ β-lactamase inhibitor	ESBL, AmpC and Class A β-lactamase producing-Enterobacteriaceae	Class B β-lactamase producing-MDR P. aeruginosa CRAB	cUTI[20]
Imipenem/ cilastatin +relebactam	Carbapenem/ β-lactamase inhibitor/ dehydropeptidase inhibitor	AmpC and Class A β-lactamase producing-Enterobacteriaceae *P. aeruginosa*	Class B, D β-lactamase producing-Enterobacteriaceae CRAB	cIAI cUTI[21] HAP, VAP[22]
Eravacycline	Tetracycline	Enterobacteriaceae (including ESBL, CRE) CRAB	*P. aeruginosa Burkholderia spp.*	cIAI[23]
Plazomicin	Aminoglycoside	Enterobacteriaceae	CRAB MDR *P. aeruginosa*	cUTI[24]
Cefiderocol	Cephalosporin	Class A, B, AmpC and Class D producing-Enterobacteriaceae MDR *P. aeruginosa* CRAB *Stenotrophomonas maltophilia Burkholderia spp.*		cUTI HAP, VAP BSI[25]
Murepavadin	Outer Membrane Protein Targeting Antibiotics	*P. aeruginosa*	CRE CRAB	Phase III trials terminated for cIAI, cUTI HAP, VAP (NCT03409679)

MDR: multi-drug resistant; ESBL: extended-spectrum β-lactamase; *P. aeruginosa*: Pseudomonas aeruginosa; CRE: carbapeneme-resistant enterobacteriaceae; CRAB: carbapenem-resistant *Acinetobacter Baumanni*; cIAI: complicated intra-abdominal infection; cUTI: complicated urinary tract infection; HAP: hospital-associated pneumonia; VAP: ventilator-associated pneumonia; BSI: blood stream infection

SEPSIS BUNDLES – WHERE ARE WE NOW?

River et al. showed significant mortality improvement in early goal-directed therapy.[26] The subsequent patient-based meta-analysis did not demonstrate a mortality benefit in routine protocol-driven therapy in septic patients.[27] The management paradigm has since shifted from protocolised to individualised therapy.

Updates in the Surviving Sepsis Campaign 1-hour bundle in 2018 highlighted the importance of obtaining cultures, early administration of appropriate antibiotics, measurement and reassessment of lactate if elevated, appropriate fluid therapy and vasopressor use to maintain mean arterial pressure of 65 mmHg.[3] Lactate is produced during cellular hypoxia and serves as a marker of tissue hypoperfusion, constituting part of the definition of septic shock.[28] Both the absolute lactate level and the delay in lactate clearance are associated with increased mortality.

In the place of a pre-defined amount of aggressive fluid therapy, the concept of Resuscitation, Optimisation, Stabilisation and Evacuation/De-escalation (ROSE) has been applied in fluid management.[29] Early adequate fluid resuscitation, dynamic assessment of fluid responsiveness and a late conservative approach should be adopted. The use of a balanced solution may be beneficial in septic patients than the use of sodium saline.[30]

Mean arterial pressure (MAP) of 65 mmHg has been adopted after the SEPSISPAM study[31]; while it may apply to some population, attention should be paid to particular subgroups. Studies have shown that permissive hypotension in older patients (age > 65) did not increase mortality.[32] In contrast, those with pre-existing hypertension had fewer acute kidney injury when aiming for a higher MAP. Close monitoring of organ perfusion, i.e. lactate trend, urine output and capillary refill, etc. and regular review of usual blood pressure may allow blood pressure targets to be individualised.

BLOOD PURIFICATION AND SEPSIS ADJUNCTS

Extracorporeal blood purification therapies might improve the clinical outcome of patients with severe sepsis with or without acute kidney injury (AKI), as the removal of Pathogen and Damage Associated Molecular Patterns (PAMP & DAMP) from circulation could modulate the inflammatory responses and mitigate organ damage. Various techniques have been developed, including haemoperfusion/haemoadsorption, high adsorption haemofiltration, high volume haemofiltration, high cut-off membrane haemofiltration/haemodialysis, plasma exchange, and coupled plasma filtration adsorption (Table 2). Despite the fact that haemodynamic improvement has been commonly demonstrated with the use of these sepsis adjuncts, none of them provided sustainable mortality benefits. Applying these novel techniques should be individualised, and routine use in septic shock patients is not recommended.

Table 2: Comparison between major blood purification techniques (Developed by authors)

Therapy	Mode of Action	Comments
Polymyxin B haemoperfusion	Endotoxin haemoadsorption	Reduce endotoxin, improve haemodynamic, controversy on survival benefit[33]
Cytosorb	Cytokine haemoadsorption	Reduce cytokine, improve haemodynamic, controversy on survival benefit[34]
Oxiris haemofilter	Endotoxin and cytokines haemoadsorption	Reduce cytokine and endotoxin, improve SOFA score[35]
HA-330	Cytokine haemoadsorption	Improve haemodynamic and organ function[36]
HVHF	Cytokine haemofiltration	No survival or haemodynamic benefits[37]
High cut off haemofiltration/ haemodialysis	Cytokines haemofiltration/ haemodialysis	No survival benefits[38]
Plasmapheresis	Cytokines haemofiltration	Controversy on survival benefit, loss of vital blood component[39]
CPFA	Cytokines haemofiltration and haemoadsorption	No survival benefits[40]

CPFA: coupled plasma filtration adsorption, HVHF: High volume haemofiltration

CONCLUSION

In summary, there have been substantial advances regarding sepsis management in the past decade. However, one size does not fit all. The pendulum has shifted from protocol-driven treatment to individualised therapy. With the development of rapid diagnostic technologies, wiser use of existing antibiotics in conjunction with the incorporation of antimicrobial stewardship programmes and sepsis adjuncts, we aim to "hit fast and hard" to reduce the morbidity and mortality in sepsis.

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DYNASTAT ABBREVIATED PRESCRIBING INFORMATION

1.TRADE NAME: Dynastat **2.**PRESENTATION: 40 mg powder vial: Each vial contains 40 mg parecoxib (present as 42.36 mg parecoxib sodium) for reconstitution. After reconstitution, the final concentration of parecoxib is 20 mg/ml. When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Dynastat contains approximately 0.44 mmol of sodium per vial. **3.**INDICATIONS: short-term treatment of postoperative pain. **4.**DOSAGE: 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. Dynastat should be used at the lowest effective dose for shortest possible time. **5.**CONTRAINDICATIONS: hypersensitivity to the active substance or to any of the excipients; history of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulphonamides; active peptic ulceration or gastrointestinal (GI) bleeding; patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors; third trimester of pregnancy and breastfeeding; severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10); inflammatory bowel disease; congestive heart failure (NYHA II-IV); treatment of post-operative pain following coronary artery bypass graft (CABG) surgery; established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease. **6.**WARNINGS & PRECAUTIONS: Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used; limited clinical experience with Dynastat treatment beyond three days; COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term; NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal; in patients with cardiovascular disease; patients with significant risk factors for cardiovascular events should only be treated with parecoxib sodium after careful consideration; not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effects; co-administering with warfarin and other oral anticoagulants; may mask fever and other signs of inflammation; monitor the incision for signs of infection in surgical patients; increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal; caution is advised in treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, selective serotonin reuptake inhibitors, patients ingesting alcohol or patients with a prior history of gastrointestinal disease; further increase in the risk of gastrointestinal adverse effects, when parecoxib sodium is taken concomitantly with acetylsalicylic acid (even at low doses); serious skin reactions, including erythema multiforme, exfoliative dermatitis, and Stevens-Johnson syndrome (some of them fatal); should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity; patients with a history of sulphonamide allergy may be at greater risk of skin reactions; in patients with impaired renal function or hypertension, or in patients with compromised cardiac or hepatic function or dehydration or other conditions predisposing to fluid retention; not recommended in patients with advanced renal disease; caution in patients with moderate hepatic impairment (Child-Pugh score 7-9). If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of parecoxib sodium therapy should be considered. **7.**INTERACTIONS: fluconazole, angiotensin-converting enzyme (ACE inhibitors), angiotensin II inhibitors, diuretics, beta blockers, ciclosporin, tacrolimus, warfarin or other anticoagulants, NSAIDs, including selective COX-2 inhibitors, lithium, rifampicin, phenytoin, carbamazepine, dexamethasone, methotrexate, substrates of CYP2C19 (e.g. omeprazole, phenytoin, diazepam, or imipramine) and CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol). **8.**PREGNANCY AND LACTATION: contraindicated in the third trimester of pregnancy; increased risk of miscarriage when used in early pregnancy; should not be used during the first two trimesters of pregnancy unless clearly necessary; must not be administered to women who breast-feed. **9.**COMMON SIDE EFFECTS: dizziness, abdominal pain, vomiting, constipation, hyperhidrosis, anaemia post-operative, hypokalaemia, agitation, insomnia, hypoaesthesia, hypertension, hypotension, respiratory insufficiency, pharyngitis, alveolar osteitis (dry socket), dyspepsia, flatulence, pruritus, back pain, oliguria, oedema peripheral, blood creatinine increased.

Reference: HK PI (version date May 2017)

Date of preparation: Feb 2019

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Advances in Sepsis Management" by Dr SHUM Hoi-ping and Dr May MY MAN and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Surviving Sepsis Campaign recommends early antibiotics should be given within one hour of presentation.**
2. **Multiplex PCR techniques provide a quick clue to causative organisms, and conventional cultures are no longer needed.**
3. **Stenotrophmonas maltophilia can be identified by the currently available multiplex PCR cartridge.**
4. **Rapid PCR technique helps to differentiate colonisation from true infection.**
5. **Aminoglycoside killing is concentration-dependent.**
6. **In septic patients, causes of renal function derangement include septic acute kidney injury and hypotension.**
7. **Ceftolozane/tazobactam and ceftazidime/avibactam offer adequate protection for resistant Acinetobacter infections.**
8. **Aggressive fluid replacement is the mainstay in the management of sepsis.**
9. **Blood pressure target should be individualised, and close monitoring of organ perfusion is essential.**
10. **Blood purification techniques may improve haemodynamics but did not demonstrate mortality benefits.**

ANSWER SHEET FOR MAY 2021

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Advances in Sepsis Management

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to April 2021 Issue

Parasomnia- an Update on Approach and Management

1. F 2. F 3. F 4. T 5. T 6. F 7. F 8. F 9. T 10. T

ONCE-A-DAY

INVANZ®

(ertapenem, MSD) IV/IM

1 vial 1 gram ONCE Daily*

Indicated for:[1]

Treatment

- ✓ Complicated Urinary tract infections
- ✓ Complicated acquired Pneumonia
- ✓ Complicated intra-abdominal infections
- ✓ Complicated skin and skin structure infections
- ✓ Acute pelvic infections

Prophylaxis

- ✓ Prophylaxis of Surgical site infection following elective colorectal surgery

Covering a wide range of bacteria included:[1]

Gram-positive

- ✓ Staphylococcus aureus
- ✓ Streptococcus agalactiae
- ✓ Streptococcus pneumoniae
- ✓ Streptococcus pyogenes

(Note: Methicillin-resistant staphylococci are resistant to INVANZ®. Many strains of Enterococcus faecalis and most strains of Enterococcus faecium are resistant.)

Gram-negative

- ✓ **Escherichia coli** (+/- ESBL^)
- ✓ **Klebsiella pneumoniae** (+/- ESBL^)
- ✓ Haemophilus influenzae (including β-lactamase producing strains)
- ✓ Moraxella catarrhalis
- ✓ Proteus mirabilis

Anaerobes

- ✓ Bacteroides fragilis
- ✓ Clostridium spp (excluding C difficile)
- ✓ Eubacterium spp
- ✓ Peptostreptococcus spp
- ✓ Prevotella spp
- ✓ Porphyromonas asaccharolytica

^ESBL = Extended Spectrum β-lactamase *For adult (aged 13 and older)

Reference: 1. Hong Kong INVANZ Product Circular

INVANZ® Selected Safety information

Indications:

- *INVANZ®* is indicated for the treatment of patients with moderate to severe infections caused by susceptible microorganisms, as well as initial empiric therapy prior to the identification of causative organisms in the infections listed below:
  - Complicated Intra-Abdominal Infections
  - Complicated Skin and Skin Structure Infections, including diabetic foot infections without osteomyelitis
  - Community Acquired Pneumonia
  - Complicated Urinary Tract Infections including pyelonephritis
  - Acute Pelvic Infections including postpartum endomyometritis, septic abortion and post-surgical gynecologic infections
- *INVANZ®* is indicated in adults for the prophylaxis of surgical site infection following elective colorectal surgery.

Contraindications:

- *INVANZ®* is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to betalactams.
- Due to the use of lidocaine HCl as a diluent, *INVANZ®* administered intramuscularly is contraindicated in patients with a known hypersensitivity to local anesthetics of the amide type and in patients with severe shock or heart block (Lidocaine HCl is the diluent for intramuscular administration of *INVANZ®*).

Precautions:

- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams. These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with another beta-lactam. Before initiating therapy with *INVANZ®*, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams and other allergens. If an allergic reaction to *INVANZ®* occurs, discontinue the drug immediately. **Serious anaphylactic reactions require immediate emergency treatment.**
- Seizures and other CNS adverse experiences have been reported. Seizures, irrespective of drug relationship, occurred in 0.5% of patients during therapy plus 14 day follow-up period. Most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. Close adherence to dosage regimen is urged in patients with factors predispose to convulsive activity. Anticonvulsant therapy should be continued. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and the dosage of *INVANZ®* re-examined to determine whether it should be decreased or discontinued.
- The concomitant use of ertapenem and valproic acid/divalproex sodium is generally not recommended. Anti-bacterials other than carbapenems should be considered to treat infections in patients whose seizures are well controlled on valproic acid or divalproex sodium.
- As with other antibiotics, prolonged use of *INVANZ®* may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.
- Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ertapenem, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
- Caution should be taken when administering *INVANZ®* intramuscularly, to avoid inadvertent injection into a blood vessel.

Adverse Events:

- Most adverse experiences reported in clinical studies were described as mild to moderate in severity. The most common drug –related adverse experiences reported during parenteral therapy in patients treated with ertapenem were diarrhea, infusion vein complication, nausea and headache. Other common side effects include: phlebitis/thrombophlebitis, vomiting, infusion site erythema, infusion site pain, infusion site swelling, rash, etc.
- For detailed adverse events, please consult the prescribing information.

Before prescribing INVANZ®, please read the Full Prescribing Information.

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Updates on the Management of Acute Respiratory Failure

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INTRODUCTION

Acute respiratory failure is a frequent cause of hospital admission and indication for intensive care. While treating the cause, such as timely and appropriate antibiotic(s) for pneumonia, is of paramount importance, such patients frequently require support to ensure adequate oxygenation and ventilation. This article will discuss the latest updates on the support of acute respiratory failure.

OXYGENATION TARGET

Supplemental oxygen reverses tissue hypoxia; but an excess use has been associated with harm.[1] Possible mechanisms of harm include direct toxicity to the lungs by reactive oxygen species, absorption atelectasis, and systemic arterial vasoconstriction. Clinicians are generally less aware of an excessive use of oxygen, as exemplified by a prevalence ranging from 23.9 to 30% in mechanically ventilated patients in whom the arterial partial pressure of oxygen (P_aO_2) was found to be greater than 100-103 mmHg.[2,3]

Recent multicentre randomised controlled trials (RCT) investigated the optimal use of oxygen in the critically ill. The ICU-ROX trial recruited mechanically ventilated adult intensive care unit (ICU) patients.[4] Oxygen saturation measured by pulse oximetry (S_pO_2) was kept above 90% in all patients. In the conservative oxygen group, S_pO_2 was kept below 97% using the lowest inspired oxygen fraction (F_iO_2), whereas in the usual oxygen group, there was no upper S_pO_2 limit, and F_iO_2 below 0.3 was discouraged. There were no between-group differences in the number of ventilator-free days or mortality. However, in the subgroup of patients with hypoxic-ischemic encephalopathy, outcomes favoured conservative oxygen therapy with a lower 180-day mortality and better neurological outcomes. Two trials recruited moderate-to-severely hypoxaemic patients with a median P_aO_2/F_iO_2 around 120 mmHg: While the HOT-ICU trial found no between-group difference in mortality at 90-day or the number of serious adverse events, the LOCO2 trial was terminated prematurely for safety because the conservative oxygen group showed significantly higher 90-day mortality and mesenteric ischemic events.[5,6] The conservative oxygen group in the LOCO2 trial allowed a lower P_aO_2 target of 55 mmHg compared to 60 mmHg in the HOT-ICU trial, and a lower S_pO_2 limit of 88%.

Suffice to say, the dosage of oxygen prescribed should be titrated like all drugs. Hyperoxia should be avoided, especially in patients with hypoxic encephalopathy. The lower S_pO_2 limit may be taken at 90%; monitoring arterial blood gases is indicated to avoid hypoxaemia (P_aO_2<60 mmHg), which in turn may result in harm such as mesenteric ischemia.

NON-INVASIVE RESPIRATORY SUPPORT

While non-invasive ventilation (NIV) has been around since the start of this century, high flow nasal oxygen (HFNO) is the latest modality that has rapidly gained a place in the last decade. HFNO delivers warmed humidified oxygen/air mixture in high flow (30-60 L/min, up to 100 L/min depending on the device) via nasal cannulae. In addition to delivering a fixed F_iO_2 up to 1.0, flow higher than the 15 L/min achieved by conventional oxygen therapy (COT) carries physiological advantages of increasing carbon dioxide (CO_2) clearance by dead-space washout, and decreasing respiratory rate and the work of breathing. While most of the effect on CO_2 clearance is obtained at 30 L/min, airway pressure and end-expiratory lung volume (EELV) increase linearly with gas flow, thus effecting alveolar recruitment and improving oxygenation (P_aO_2/F_iO_2).[7] Hence it is reasonable to start at a higher flow of 60 L/min in patients with hypoxaemic respiratory failure and a lower flow of 30 L/min for hypercapnoeic patients without hypoxaemia.

In acute hypoxaemic respiratory failure, HFNO, compared to facemask NIV and COT, significantly reduced intubation rates in a post-hoc subgroup with P_aO_2/F_iO_2 < 200 mmHg.[8] The 90-day mortality and patient comfort at one hour were also improved. The use of NIV in the same setting is more controversial, and no recommendation was made in international guidelines.[9] Post-hoc analysis of the FLORALI study identified that in the NIV group, an exhaled tidal volume greater than 9 ml/kg of predicted body weight at one hour predicted the need for intubation and 90-day mortality.[10] The larger tidal volume consequent to great inspiratory effort on top of positive pressure support could result in patient self-inflicted lung injury (P-SILI).[11] This is concurrent with the observation that hypoxaemic patients failing NIV suffered a higher mortality rate than those intubated.[12] The NIV interface used may also make a difference: Helmets, compared to facemasks, provide a better seal around the neck with less leakage; higher positive end-expiratory pressure (PEEP) can

be achieved, which has been shown to mitigate the injurious effect of excessive spontaneous efforts by lung recruitment.[13] In support of this hypothesis, a single-centre RCT showered that helmet over facemask NIV improved intubation rates and 90-day mortality among acute respiratory distress syndrome (ARDS) patients.[14] Future trials comparing the use of HFNO and helmet NIV in acute hypoxaemic respiratory failure are much anticipated.

NIV remains the first-line treatment for patients with acute hypercapnoeic respiratory failure secondary to exacerbation of chronic obstructive pulmonary disease and cardiogenic pulmonary oedema.[9] The ability of HFNO to increase CO_2 clearance makes it an attractive alternative when NIV is not tolerated or as a complementary therapy during NIV breaks. Ongoing and future studies will reveal definitive clinical outcomes and clarify the role of HFNO in acute hypercapnoeic respiratory failure.

INVASIVE MECHANICAL VENTILATION

When non-invasive respiratory support fails, intubation and invasive mechanical ventilation (MV) should not be delayed. The aim is to relieve respiratory muscles and maintain gas exchange while the body recovers from the initial cause of respiratory failure. During this period, it is essential to minimise further insults to the respiratory system, including ventilator-induced lung injury (VILI) and myotrauma.

Protective Lung Strategy: Limiting Tidal Volume and Pressure

More than two decades ago, the ARMA trial has shown a mortality benefit approaching 9% by reducing tidal volume from the then-standard 12 to 6 ml/kg of predicted body weight (PBW). Plateau pressure (P_{plat}) should be kept below 28 - 30 cmH_2O. The driving pressure (P_{plat} minus PEEP) reflects tidal volume scaled to the respiratory system's compliance, and a value above 15 cmH_2O was associated with increased mortality in ARDS patients.[15,16] Hypercapnoeia is permitted in the absence of raised intracranial pressure or right heart failure.

PEEP

The purpose of a higher PEEP above 10 cmH_2O in the open lung approach is to maximise alveolar recruitment and protect against the shear stress of cyclic closing and re-opening of alveoli and small airways during tidal breaths (atelectrauma). Therefore, higher PEEP only benefits when the lungs are recruitable with resultant reduction in driving pressure. In non-recruitable lungs, higher PEEP causes harm by over-distending non-dependent alveoli and causing acute corpulmonale. The severity of ARDS provides an initial guide to lung recruitability. In a meta-analysis, higher PEEP was associated with mortality reduction only in patients with moderate-to-severe ARDS (P_aO_2/F_iO_2 < =200 mmHg), while patients with mild disease experienced harm.[17] Analysing quasi-static (slow flow) pressure-volume (P-V) curves using software on designated ventilators, de-recruited lung volume with PEEP reduction (the recruitment-to-inflation ratio), and use of lung ultrasound or electrical impedance technology (EIT) allow further selection of patients who may benefit from an open lung approach.[18] It is essential that patients are fluid resuscitated to avoid detrimental cardiovascular collapse when higher PEEP is coupled with initial recruitment manoeuvre.

In patients with recruitable lungs who will benefit from a higher PEEP, finding the optimal PEEP is the next step. There is currently no consensus as to the best method, and the choice depends on the availability of equipment and the clinician's preference. Methods include following the ARDS network's PEEP-F_iO_2 escalation table, finding the best compliance with decremental PEEP titration or stress index, finding the inflexion points on quasi-static PV curves, tailoring to end-expiratory transpulmonary pressure (PL) using an oesophageal balloon catheter, or imaging techniques with lung ultrasound or EIT.

SAFE SPONTANEOUS BREATHING

Spontaneous breathing efforts in mechanically ventilated patients offer the advantages of increasing end-expiratory lung volume by contraction of the dependent parts of the diaphragm, improving ventilation/perfusion matching, improving hemodynamic status, reducing the need for deep sedation, avoiding delirium and ventilator-induced diaphragmatic dysfunction (VIDD) from disuse atrophy. On the other hand, vigorous breathing can cause alveolar overdistension from increased transpulmonary pressure, breath-stacking from patient-ventilator asynchrony, over-stretching of dependent lung regions due to pendelluft phenomenon, and increased vascular transmural pressure and permeability with resultant pulmonary oedema.[11] This lung injury has been termed P-SILI. Apart from causing injuries to the lungs, vigorous breathing also causes load-induced diaphragm injury (myotrauma). In order to control spontaneous efforts within safe limits, such efforts should be monitored during mechanical ventilation. Oesophageal pressure (P_{es}) is a surrogate of pleural pressure. Pes is the gold standard in monitoring respiratory efforts, but its measurement requires the insertion of an oesophageal balloon catheter. Other valuable bedside tools include P_{plat}, driving pressure, airway occlusion pressure at 0.1 second($P_{0.1}$), and pressure generated by respiratory muscles predicted from end-expiratory airway occlusion pressure swing.[19]

The harmful effects of vigorous breathing are more pronounced in patients with severe ARDS compared to milder disease.[20] Although the ACURASYS trial found lower 90-day mortality with the use of 48-hour continuous neuromuscular blockade in early moderate-to-severe ARDS, this finding was not reproduced in the recent ROSE trial.[21] The difference between the two trials is that the control group in the ROSE trial received higher PEEP and lighter sedation. There is increasing evidence that higher PEEP renders spontaneous breathing less injurious in severe ARDS.[13] In patients who continue to exhibit intense inspiratory effort despite optimizing sedation and ventilator settings, intermittent pharmacological paralysis may be necessary.

PRONE POSITIONING

When supine, the dorsal dependent lung is compressed by the mediastinum and abdominal organs and receives less ventilation, resulting in ventilation/perfusion mismatch. Prone positioning recruits the dorsal lung and decreases hyperinflation of the ventral lung. Ventilation is more homogenous, thus minimisingVILI. This benefit was confirmed by the PROSEVA trial, which significantly reduced 28-day mortality in patients with severe ARDS by early continuous (≥ 16 hours per day) prone ventilation.[22]

The current COVID-19 pandemic has led to a growing interest in proning non-intubated hypoxaemic patients (awake prone). While it is a low-cost, low-risk intervention, the evidence is conflicting in terms of reducing the need for intubation.[23,24]

VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION (VV-ECMO)

The EOLIA trial is a multicentre controlled trial that randomised severe ARDS patients with refractory hypoxaemia or hypercapnoeia despite optimal MV and rescue therapies to VV-ECMO or conventional MV.[25] Although the ECMO arm had an absolute 11% (35% vs 46%) reduction in 60-day mortality, it did not reach statistical significance, and the trial was prematurely terminated for futility. However, 35 (28%) patients from the control group crossed over to ECMO. Fifteen of them survived, which would not have been possible without ECMO, given their degree of desaturation(median S_aO_2 of 77%). During ECMO, tidal volume, P_{plat}, and respiratory rate were all reduced while PEEP was maintained as the gas exchange took place in the extracorporeal circuit. As a result, VILI was minimised. Thus, when conventional MV fails, and adequate gas exchange cannot be achieved within safe limits, ECMO provides a last resort rescue, allowing for ultraprotective MV while the lungs rest and heal, and preserving diaphragmatic activity within safe limits.

CONCLUSION

Over the past decades, there has been great advancement in the support of patients with acute respiratory failure, from setting an appropriate oxygenation target, using non-invasive support in the hope of avoiding complications of invasive ventilation, fine-tuning invasive MV by protecting the lungs and diaphragm, to allowing lung rest with the use of extracorporeal oxygenation in the most severe patients (Table 1). We await with eagerness results of future trials that will further improve precision in caring for the individual patient who requires acute respiratory support.

Table 1: Summary of current evidence in acute respiratory support (Developed by authors)

Oxygenation target	• S_pO_2 90-96% • P_aO_2≥ 60 mmHg • Actively titrate and use minimal oxygen to achieve target range	
Non-invasive support	Acute hypoxemic failure	• HFNO: start at a total flow of 60 L/min. Titrate F_iO_2 to achieve oxygenation target. • Alternative: Helmet NIV
	Acute hypercapnoeic failure, especially AECOPD, cardiogenic pulmonary oedema	• NIV is first-line therapy. • Alternative: HFNO if NIV is not tolerated and/or during NIV breaks
Invasive mechanical ventilation	Avoid excess stress and strain	• Tidal volume: 6-8 ml/kg of PBW. • P_{plat}<28-30 cmH_2O • Driving pressure ≤15 cmH_2O
	Permissive hypercapnoeia	• Remove unnecessary instrumental dead space (catheter mount and end-tidal CO_2 monitor, changing passive to active humidification) to facilitate low tidal volume ventilation • Hypercapnoeia allowed in the absence of raised intracranial pressure or right heart failure
	Avoid atelectrauma	• Higher PEEP >10 cmH_2O is to be used in moderate to severe ARDS patients with recruitable lungs. • PEEP titration method depends on the availability of equipment and physician's preference.
	Safe spontaneous breathing	• Encourage spontaneous breathing efforts within safe limits by targeting light sedation and avoiding over-ventilation. At the same time, monitor for excessive efforts: • Oesophageal balloon catheter: end-inspiratory P_L≤20 cmH_2O, negative P_{es} swing 3-8 cmH_2O • P_{plat}<28-30 cmH_2O • Driving pressure ≤15 cmH_2O • $P_{0.1}$ 1.5-3.5 cmH_2O • Respiratory muscle pressure <13 cmH_2O[a] • Consider sedation + intermittent pharmacological paralysis in injurious breathing pattern despite optimizing PEEP
Prone positioning	• Consider early use in severe ARDS (P_aO_2/F_iO_2<150 mmHg with F_iO_2≥0.6) • Prone continuously for ≥16 hours • Evidence inconclusive for awake prone	
Extracorporeal membrane oxygenation	• Rescue therapy for severe hypoxaemia or hypercapnoeare fractory to all of the above measures	

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; CO_2, carbon dioxide; F_iO_2, inspired oxygen fraction; HFNO, high flow nasal oxygen; NIV, non-invasive ventilation; $P_{0.1}$, airway occlusion pressure at 0.1s; P_aO_2, arterial partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P_{es}, oesophageal pressure; PL, transpulmonary pressure; P_{plat}, plateau pressure; S_pO_2, oxygen saturation measured by pulse oximetry.
[a]Predicted respiratory muscle pressure = -3/4 x (pressure swing when airway occluded at end-expiration)

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Dermatology Quiz

Dermatology Quiz

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Dr Lai-yin CHONG

Fig.1: An indurated nodule with yellowish tint at the scrotum

This 25-year-old man presented with one year's history of a solitary asymptomatic yellowish hard nodule of one centimetre in diameter at his scrotum (Fig. 1). There were no skin lesions elsewhere. His past health was good.

Questions

1. What is your diagnosis, and what are the differential diagnoses?
2. What is the possible underlying cause?
3. Are laboratory tests useful?
4. What is your treatment for this condition?

(See P.40 for answers)

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Advances in Resuscitation: Mechanical Circulatory Support (eCPR), Targeted Temperature Management, and Post-Resuscitation Care

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INTRODUCTION

A century ago, cardiac massage was performed with the open chest approach. The survival rate was very low, as only those resuscitated in the operation room might survive. This invasive approach was abandoned only after the 1960s when Guy Knickerbocker, an electric engineer, discovered a rise in arterial blood pressure when he accidentally pressed the electrode paddles on a patient's chest wall during his research on defibrillation. This discovery was further modified by William Kouwenhoven and James Jude and is known as external chest compression. Cardiopulmonary resuscitation (CPR) has evolved from a skill-based procedure to a team-based protocol. Timely and high-quality CPR is the mainstay of treatment. Post-resuscitation care has become the fifth link of the chain of survival for cardiac arrest since 2010. Patients who received post-resuscitation care had higher hospital survival rate and better neurological outcomes.[1] This article will discuss the use of mechanical circulatory support in CPR, the post-cardiac arrest syndrome, and the strategy of targeted temperature management (TTM) in post-resuscitation care.

ADVANCES IN MECHANICAL CIRCULATORY SUPPORT

Despite recent advances in resuscitation sciences and improvement in techniques of CPR, the overall hospital survival rates of the in-hospital cardiac arrest (IHCA) and the out-of-hospital cardiac arrest (OHCA) are between 10% and 20%.[2,3] The hospital survival rates of OHCA and IHCA patients were even lower in Hong Kong (around 1.5% and 4.5% respectively).[4,5] Resuscitation Outcomes Consortium studies discovered that most healthcare workers who were taught basic life support and advanced life support had, during conventional CPR, chest compressions performed at rates and depths outside of the recommended range of the American Heart Association guidelines.[6] Moreover, it has been demonstrated that the conventional cardiac compression (manual or mechanical) can achieve less than 30% of the original cardiac output.[7] During chest compression, the heart is refilled only in the decompression phase. However, this refilling process is extremely inefficient during CPR as the passive recoiling of the chest wall provides the only force. Mechanical automated chest compression device improves the quality of chest compression by providing consistent rate and depth during chest compression. Active compression-decompression (ACD) device that can actively lift up the chest wall with a suction cup during the decompression phase can theoretically improve the venous return and cardiac output during CPR. However, extracorporeal membrane oxygenation (ECMO) is the only device that can provide full circulatory support. Extracorporeal cardiopulmonary resuscitation (E-CPR) is the application of a mechanical pump and a circuit, usually by peripheral cannulation of a femoral vein and a femoral artery, to provide blood flow in the systemic circulation when patients have cessation of cardiac mechanical activity. The ECMO-facilitated resuscitation is a high-risk and invasive procedure that should only be performed by fully trained medical staff.

The CHEER trial reported that OHCA patients resuscitated with E-CPR and subsequent immediate TTM as post-resuscitative care had better survival and neurological outcomes compared to conventional CPR,[8] and the findings were supported by a recent prospective controlled study.[9] According to Extracorporeal Life Support Organization (ELSO) registry, the hospital survival rate of E-CPR is about 30%, and it is near 40% in our locality.[10] The favourable ECMO outcomes may be potentially explained by the selection criteria for patients receiving E-CPR. The selection criteria may vary according to different hospital settings, ECMO experience, and readiness of E-CPR deployment. In general, candidates selected for E-CPR are usually young, have immediate bystander CPR, short arrest-to-ECMO duration, and no major comorbidities.[11] Despite the much better outcome than conventional CPR, a systemic review of 15 OHCA studies and 7 IHCA studies found there had been neither strong high quality evidence to support nor refute the use of E-CPR for OHCA and IHCA.[12] American Heart Association (AHA) recommends E-CPR as a rescue therapy for selected patients when conventional CPR fails.[13]

Cardiac arrest is a time-sensitive disease. The optimal time point to transition from conventional CPR to E-CPR is still controversial. Obviously, a shorter "low-flow time" results in a shorter period of ischemia and is associated with improved survival. Delaying E-CPR treatment may jeopardise the potential benefit from the intervention by increasing the risk of organ ischemia, and the risk of the systemic insults of reperfusion after prolonged cardiac arrest. The observation study suggested that the target to set up E-CPR should preferably be less than 40 minutes when possible.[14]

POST-RESUSCITATION CARE

Patients who survive cardiac arrest will develop post-cardiac arrest syndrome, consisting of ischemic brain injury, myocardial ischemia, systemic ischemic-reperfusion response, and persistent precipitating pathology. Post-cardiac arrest syndrome leads to damages to multiple organs and plays a significant role in mortality after the regain of spontaneous circulation (ROSC). Its severity correlates with the duration of ischemia, cause of cardiac arrest, and the patient's past medical comorbidities. The pathophysiology is related to spontaneous circulation resumption (reperfusion) after a period of cessation of blood flow (ischemia). Formation of free radicals and inflammatory cytokines, disturbance of coagulation cascade, disruption of calcium homeostasis, mitochondrial injury and activation of cell-death signalling pathways are the proposed mechanisms of the injuries.[15]

Post-resuscitation care is a critical part of the whole resuscitation process. It includes identification and treatment of the precipitating cause of cardiac arrest, treatment to alleviate systemic damages due to ischemic-reperfusion injury of the post-cardiac arrest syndrome, avoidance of further brain insults by optimising the oxygen concentration and carbon dioxide concentration in blood, and targeted temperature management that confers neuroprotection. Patients who receive post-resuscitation care are usually managed in the critical care setting as management is resource-demanding, and the patients resuscitated from cardiac arrest are usually critically ill. We will focus our discussion on targeted temperature management below.

TARGETED TEMPERATURE MANAGEMENT

The brain is highly susceptible to reperfusion injury, especially after a prolonged period of cardiac arrest. TTM is a treatment that helps to attenuate the anoxic cerebral insults due to cardiac arrest and reperfusion injury secondary to cardiac arrest. It is postulated that controlled hypothermia can reduce the metabolic demand of the sick brain for oxygen and glucose, minimise the production of free radicals and proinflammatory mediators, and prevent the initiation of the apoptotic process.[16] In 2002, both a European multicentre study and an Australian multicentre study showed that targeted hypothermia at 33°C for 12-24 h was associated with improved neurological outcomes in OHCA survivors with a witnessed shockable rhythm. Targeted hypothermia at 32-34°C was the gold standard of TTM until 2013 when Neilson et al. showed similar difference in mortality and neurological recovery rates in OHCA patients irrespective of the initial rhythms between the two targeted temperatures (33°C or 36°C).[17] The pendulum has appeared to swing back to moderate hypothermia (at 33°C) after the HYPERION trial, which favoured targeted temperature at 33°C to normothermia (37°C) in terms of the neurological outcome at day 90 for patients who survived non-shockable cardiac arrest.[18] TTM is recommended by American Heart Association (AHA) as standard management for adults with OHCA with an initial shockable rhythm (strong recommendation) and initial non-shockable rhythm (weak recommendation) who remain comatosed after ROSC. TTM is also recommended for adults with IHCA with any initial non-shockable rhythm (weak recommendation). However, AHA has not taken sides in the targeted temperature. The 2015 and 2020 recommendations only suggest providing TTM at a temperature between 32°C to 36°C for at least 24 hours.[13]

Besides targeted temperature, the quality of TTM is determined by many factors: timing of initiation, method of temperature measurement, cooling of devices, method of rewarming, and post-TTM care. TTM should be initiated as soon as possible to minimise reperfusion injury following ROSC.[19] After major brain insults, brain temperature can be up to 2.0°C higher than core temperature.[20] Core temperature at the closest approximation to the brain should be measured with oesophagus or central venous temperature probes or urinary bladder temperature catheters. Measurement should be continuous or as frequent as possible to avoid overshoot of temperature beyond the target range. Shivering, a frequent side effect of hypothermia during TTM, should be avoided using sedatives or sometimes paralytic agents.

The rewarming phase should be regarded as equally important as the warming phase. According to van't Hoff-Arrhenius law, the biochemical reaction rate is halved for each 10°C decrease in temperature. Rapid rewarming after hypothermia can cause a mismatch of oxygen demand and delivery in the body, production of free radicals and oxidants, and inflammatory cytokines.[21] If left unattended, those patients will end up in rewarming shock,which is a syndrome of acute metabolic acidosis, respiratory failure, hypotension, and cardiomyopathy.[22] Therefore, the rewarming procedure should be performed in a controlled setting at a rewarming rate of less than 0.25°C per hour.

CONCLUSION

Recent studies have shown that the timely application of ECMO during resuscitation in selected patients may improve hospital survival. Post-resuscitation care, particularly targeted temperature management, can improve survival and neurological outcomes. However, ECMO-facilitated resuscitation and post-resuscitation care can only succeed if healthcare providers designated in resuscitation care are familiar with these new technological advances. Hospital administrators and clinical leaders should work together to allocate resources and develop clinical protocols for these new advances in resuscitation.

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9 June, 2021	Routine Mid-trimester morphology scan and common anomalies	Dr. Tak-yuen FUNG Chief of Service Obstetrics & Gynecology Hong Kong Baptist Hospital
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23 June, 2021	Ultrasonography of the fetal heart: from basic to advanced examination	Dr. Ben Chong-pun CHAN Private Obstetrician
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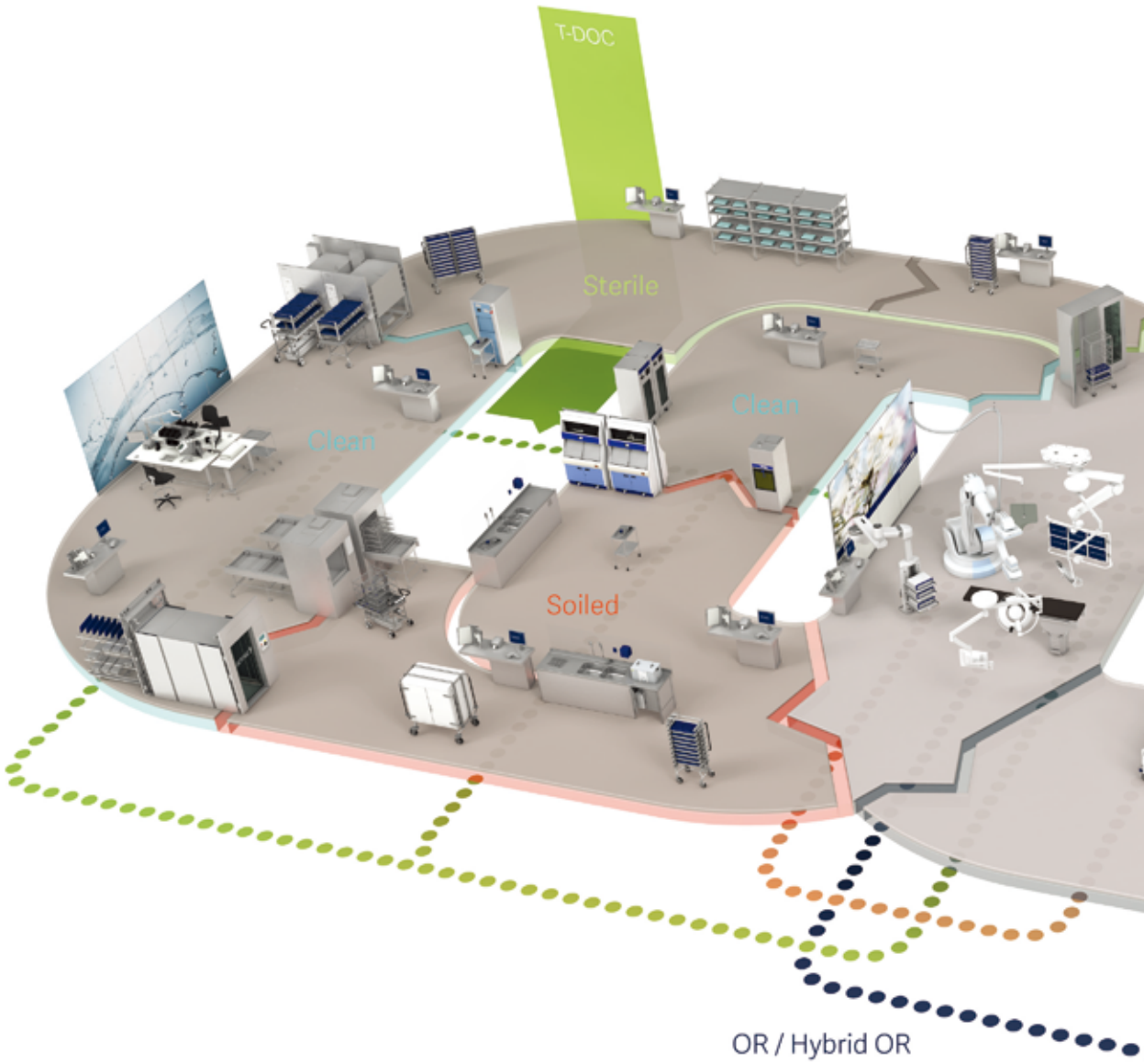

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INTRODUCTION

The Chinese Government launched her healthcare reform plan with updated guidelines in 2009[1]. The reform aimed to provide quality-assured, affordable, and accessible health for her people. The University of Hong Kong-Shenzhen Hospital (HKU-SZH) in the Binhai area of Shenzhen was one of the new hospitals built as part of this reform plan. The Hospital holds 2,000 beds and provides comprehensive inpatient and outpatient services. The Hospital is clinically governed by HKU, with clinical departments headed by professoriate of the Li Ka Shing Faculty of Medicine of HKU. The mission of the Hospital is to contribute to the modernisation of healthcare in China. Given the differences in healthcare financing and in the social system between Mainland China and Hong Kong[2], HKU-SZH undertook changes from and reforms of currently in place HKU and Hospital Authority clinical practices, changes and reforms implemented to adapt to the Mainland Chinese environment in order to maximise effectiveness and to ensure sustainability.

ACHIEVEMENTS OF HKU-SZH

The Hospital commenced services in July 2012. It houses all major clinical departments and units, including Emergency Medicine, Internal Medicine, Surgery, Orthopaedic Surgery, Paediatrics, Neonatology, Obstetrics & Gynaecology, Clinical Oncology, Critical Care Medicine, Anaesthesiology, Radiology, Traditional Chinese Medicine and Dentistry. Over the years, a full spectrum of services have been established. They include toxicology, trauma, infectious disease, cardiac catheterisation, interventional neurology, haemodialysis, hepatobiliary surgery, neurosurgery, ear nose & throat surgery, vascular surgery, thoracic surgery, cardiac surgery, interventional radiology, in-vitro fertilisation, rehabilitation medicine and haemopoietic stem cell transplantation. To further meet the needs of the Shenzhen population, the Hospital will expand the bed number to 3,000 by 2025.

Many changes to improve the quality and safety of clinical care have been introduced since the inception of the new hospital, such as hospital-wide antimicrobial stewardship; halting the routine practice of giving intravenous fluid infusion to attendees at the Emergency Department; usage of unique patient identifiers; scheduling outpatient consultation by appointment; usage of group O unmatched red cells in dire emergency before the type and screen results are available, etc. Most of these good clinical practices have since been adopted by other hospitals in the region.

Furthermore, policies and measures to enhance professionalism and doctor-patient and doctor-relative relationship have been implemented. The Patient Relation Office was established very early on. A system is in place to settle disputes in a fair and open manner. There is zero tolerance for workplace violence. Staff are forbidden to accept monetary gifts from patients and relatives. Many of these newly launched practices require a paradigm shift in habit, mindset and even culture. The successful implementation of these practices is indeed a remarkable achievement.

The Hospital has been dually accredited by the Australian Council on Healthcare Standards and the National Regulation of Hospital Accreditation and Management as a tertiary hospital. The Hospital has been granted a national resident trainee training centre since the year 2017. Moreover, it was recognised as a Guangdong Province High Level Hospital in 2018. In Mar 2021, the Hospital was awarded Extensive Achievement in 14 criteria in the ACHS assessment.

HKU-SZH ICU

The history of intensive care medicine in the Mainland began with the establishment of the first 6-bed general intensive care unit (ICU) in the Peking Union Medical College Hospital in 1982[3]. The first National ICU Construction and Management Standard was issued in 2006. Critical care medicine was officially recognised as a specialty in clinical medicine only after 2009. It is thus still a young and rapidly developing specialty in the Mainland[4].

By design, the ICU of HKU-SZH offers space for 42 beds. The ICU floor is divided into three similarly designed zones. There is one negative pressure isolation room with an anteroom in each zone. The ICU started admission since 2014 when six beds were in operation. Since then, the number of ICU beds has gradually increased to 28 to meet the additional demand from ongoing hospital development. It is the only adult ICU in the Hospital, taking care of all critically ill adult patients from all specialties. A closed system of management has been adopted. There is a dedicated team of staff with admission and discharge rights. Such a set-up differs significantly from ICUs of other hospitals in the Mainland, in which some are specialty ICUs, such as emergency ICU, respiratory ICU, neurology ICU, and surgical ICU, among others.

ICU teams there generally do not have admission and discharge rights, which significantly affect the proper utilisation of ICU resources.

CLINICAL PRACTICES

Shenzhen is a rapidly developing city. The workforce in Shenzhen, including her healthcare workers, largely came from other provinces. There is no formal post-graduate training curriculum for critical care specialists in the Mainland. It is challenging for an Hong Kong-trained ICU specialist to lead a team of staff coming from a heterogeneous background of training and experience. Non-alignment of clinical practices of medical and nursing staff poses hazards to the already sick patients. To ensure safety and quality care, the foremost task at the initial phase of establishing the ICU was to standardise the clinical practices in ICU through extensive in-house training, drills and close supervision. Taking reference from international guidelines, more than 50 ICU clinical guidelines written in simplified Chinese have been formulated with adaptation to local practices. These guidelines form the basis of the clinical practices of all staff. The guidelines are very practical and useful to ICU staff. Some of them have been compiled into a booklet and published in China. Colleagues from other ICUs of Shenzhen are using the guidelines in their daily practice. It is hoped that these guidelines would benefit critical care physicians in the Mainland.

Despite difficulties in the logistics, some of the ICU staff has had the opportunities to visit the ICUs at Queen Mary Hospital and Pamela Youde Nethersole Eastern Hospital in 2017 & 2018. These ICU visits were an eye-opening experience for the Mainland ICU colleagues. They appreciated the differences in practices and went back to discuss and led changes deemed necessary and worthwhile. For examples, nursing colleagues are now responsible for routine wound dressing instead of medical staff; family members can now visit patients at the bedside rather than only along the visitation corridor outside the patient areas. Occasionally, they are allowed to stay overnight to accompany patients in need.

BUILDING A TEAM

Needless to say, communication is key when leading a team. Language and cultural differences were barriers that needed to be overcome. Some department heads were not fluent in Putonghua, while only a minority of our Mainland colleagues spoke Cantonese or English well. To overcome the language barrier in the early days, we relied on additional measures such as written simplified Chinese, body gesture and even drawing. Extra effort and patience were required in the communication process. With time, communication became better and better, and now it is seldom a hindrance at work.

The medical profession is not an attractive career in the Mainland. This lacklustre profession is in part related to a lack of trust between doctor and patient, violence at the workplace and a lack of respect for the profession. In the beginning, there were hostile family members yelling and cursing in the ICU areas, which was indeed a cultural shock to colleagues from Hong Kong. These incidents were carefully analysed. As expected, most of the root causes are related to communication problem - inappropriate communication skills, inadequate preparation, and poor management of expectation. To establish rapport, empathy, knowledge and confidence during the communication process are keys. Much effort has been given to coach the staff on communication skills. Patient-centred care is also an important concept to be emphasised in the Mainland. It is not uncommon to see family members making treatment decisions for an adult patient. Colleagues, as well as family members, both need to be reminded of the principle of patient-centred care in the decision-making process. Thanks to collective efforts, the ICU Team was awarded the Most Caring Team of the Hospital in 2018.

"First do no harm" is the pivotal motto of the medical profession. The importance of reducing iatrogenic damage to patients cannot be over-emphasised. Key performance indicators (KPIs) have been set up, which are benchmarked with those of the Hong Kong Hospital Authority and overseas centres. KPI data are regularly captured and are discussed in monthly team meetings to drive improvements. Such capture and review of KPIs have resulted in the reduction of (1) risk from intra-hospital transfer of critically ill patients, (2) catheter-associated urinary tract infections, (3) ventilator-associated pneumonia, (4) accidental extubation and (5) arterial catheter-associated infection. These ICU continuous quality improvement (CQI) projects have received annual awards in the Hospital.

Rome wasn't built in a day, nor by one pair of hands, for building up the ICU or otherwise. Ongoing engagement of every team member is vital. It is important to align team members to achieve the same goals of supporting the development of the Hospital and of delivering patient-centred care to the critically ill. Our team members have been organised into several functional groups under a clear reporting structure. Each functional group is empowered to contribute to the development of the ICU. Clear job assignment, setting of timeline, and regular reporting and review are essential. Under the respective functional groups, various activities have been set up and have become routine in patient care. These include ventilator bundle, prevention of pressure injury, sedation protocol, enteral feeding protocol, blood glucose protocol, regional citrate continuous renal replacement therapy, prone ventilation, early mobilisation, enhanced recovery after surgery for cardiac surgery patients, among others.

Leading the ICU at HKU-SZH gives one the role of an ambassador representing the ICU of Hong Kong. It demands professional knowledge, clinical acumen, management skills and courage. I am still in the process of learning to refine myself in all these areas. I am grateful that I have been supported by many ICU colleagues in Hong Kong. They provide much help and support, especially in training the Mainland ICU colleagues. Examples are their participation in workshop on extracorporeal membrane oxygenation in the Mainland and Hong Kong, a continuous renal replacement therapy workshop in the Mainland, and

an ultrasound workshop in the Mainland, as well as their delivery of lectures in the annual Shenzhen ICU conferences.

CONCLUSION

No doubt, there are many challenges ahead. Nevertheless, with the commitment of the Chinese Government to reform the healthcare system, and with the willpower of the healthcare professionals, HKU-SZH, including her ICU Team, will continue to contribute to the betterment of healthcare for our people.

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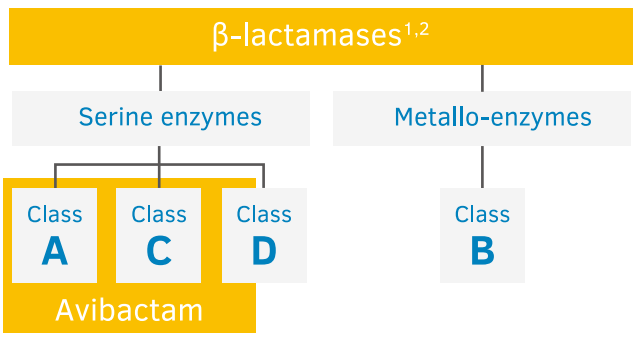

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References: 1. Zavicefta™ (Ceftazidime-avibactam) Prescribing Information. Pfizer Corporation Hong Kong Limited Version October 2018 **2.** Liscio JL, *et al. Int J Antimicrob Agents* 2015;46:266–71

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Data-Driven Management for Hong Kong Intensive Care Units

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INTRODUCTION

Intensive care is an indispensable service in Hong Kong (HK) public health care system, providing critical care to patients with life-threatening illnesses. The ageing population, increasing patient expectations, advances in medical technologies, and increased disease complexities potentially place a greater demand for critical care services in HK. Meanwhile, intensive care is resource-intensive, from personnel to equipment and medication. The provision of intensive care services is a high cost to our healthcare system, and as such data science is essential in the management of intensive care. Data science is defined as "the set of fundamental principles that support and guide the principled extraction of information and knowledge from data."[1] In this day and age, technology has transformed our daily lives. Artificial intelligence, machine learning, deep learning and neural networks embedded into many facets of our lives. This transformation includes the application of data science in healthcare[2]. With data science, healthcare services are expected to be more fast-paced, interconnected and predictable. The implementation of data-driven management in an intensive care unit (ICU) helps to improve healthcare quality, enabling critical care physicians to make more precise clinical decisions, ultimately reducing the cost of care[3].

DATA APPLICATIONS FOR THE MANAGEMENT

Data application originated in 1860 when Florence Nightingale advocated the uniform collection of hospital statistics during the International Statistical Congress, stating that outcomes could be compared by hospital, region, and country to improve healthcare[4]. The collection of information on critically ill patients, their treatment and their outcomes began in the 1950s in an effort to communicate and exchange experiences[5]. In 1977, William A Knaus used individual patient data to develop an objective and mathematical measure of severity which was well known as the Acute Physiology and Chronic Health Evaluation (APACHE) system[6]. ICU is a highly technological environment where thousands of data-points were generated every day. Over the past decades, the data generated was either underused or wasted because of the difficulty in accessing, organising, and analysing from the paper charts (Fig 1)[7]. The value of many treatments and interventions in ICUs is unproven, and high-quality data supporting our practices is sparse[8]. In a recent systematic review, Shillan et al. reported that nearly half of the studies identified in the use of machine learning had been published since 2015, and the collected data was used to predict complications (29.8%) and mortality (27.1%), and to develop prognostic models (16.7%)[9]. More recent machine-learning applications with electronic health data have included gradient-boosted decision trees that can predict acute kidney injury and readmission[10,11], and a reinforcement learning agent that can reinforce treatment decisions in sepsis[12].

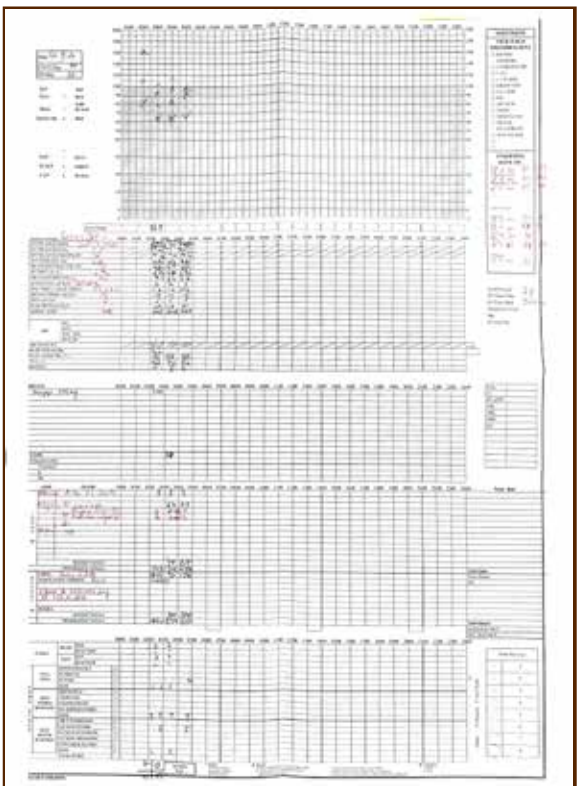

Fig. 1. ICU chart by manual (Photo from personal collection)

In 2020, the coronavirus disease 2019 (COVID-19), the disease resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a worldwide pandemic[13]. By the end of 2020, there have been over 420 adult patients admitted to ICUs, comprising 4.7% of all COVID-19 patients in HK[14]. Facing the pandemic, HK ICUs are under stress in different aspects, from staff, space, supplies of

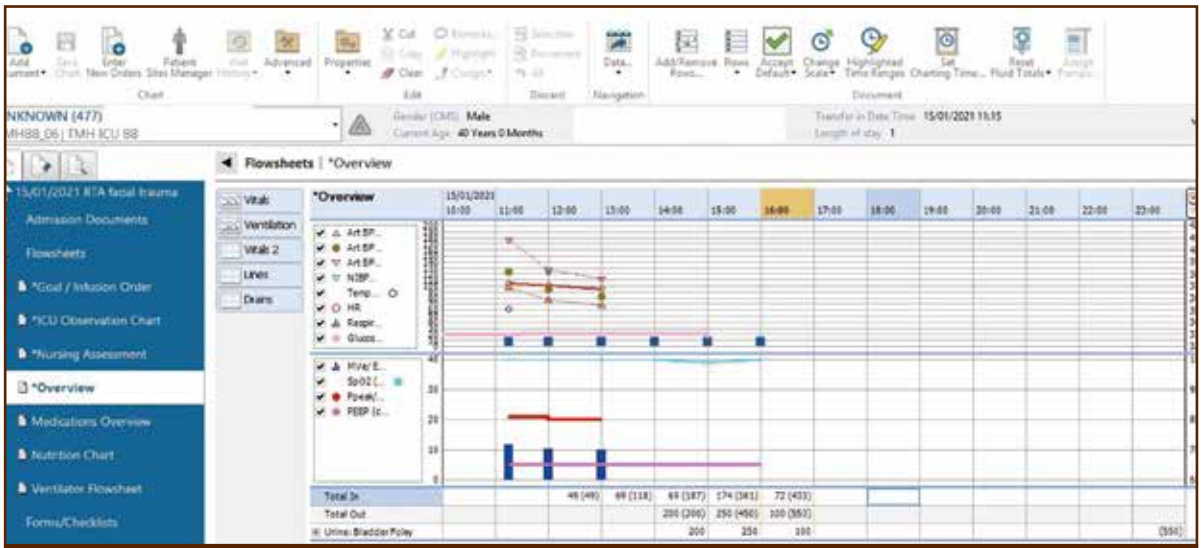

Fig. 2. ICU clinical information system by automation (Photo from personal collection)

equipment to the standard of services. In view of such a huge demand for ICU services, timely, reliable and effective intensive care is mandatory to achieve better outcomes. The use of data in the ICU is serviceable to achieving such aims. The rapid development of electronic medical records, telemedicine, point-of-care testing, connectivity with medical devices, and digitised networking infrastructure have provided advanced and immediate information to the bedside, assisting healthcare workers in managing our critically ill patients based on ICU data. In digitalised ICUs, multiple variables are continuously monitored and stored. Over the last decade, several electronic medical registries have reached national level, such as the Australian and New Zealand Intensive Care Society Adult and Pediatric Database (ANZICS) and the United Kingdom Intensive Care National Audit and Research Centre Case Mix Programme Database (ICNARC). The most common applications of these data to intensive care are predictive and prognostic models.

HK has maintained high standards in developing information technology (IT) industries in recent years, performing particularly well in downstream commercialisation[15]. Currently in HK, 15 ICUs in public hospitals have established an integrated electronic medical registry. The aims of collecting reliable, valid, and comprehensive data are threefold: 1) to develop a reliable local contemporary clinical audit related to critically ill patients in HK ICUs, 2) to measure, review and strengthen the quality of critical care service, and 3) to improve strategic planning of ICU services within HK healthcare system. The registries included critically ill patients in ICUs from all geographical regions of HK, with units in teaching and non-teaching hospitals and wide variations in the size of units. It is expected that this model performs well within our local population. In 2019, there were 15,278 adult intensive care unit (ICU) admissions, an increase of 7.6% since 2016. Upon admission to HK ICUs, over 140 variables (including demographic variables, acute physiology variables, chronic health status, admission source, hours in the hospital before ICU admissions, diagnosis, laboratory results upon hospitalisation) were collected. Most demographic and laboratory data were automatically retrieved from the Hospital Authority (HA) Clinical Medical System (CMS). Physiology variables and therapeutic interventions were also automatically retrieved from various ICUs Clinical Information System (CIS) (Fig 2). In order to provide accurate, consistent and concrete data regarding the data definition and international standard, well-trained independent colleagues were responsible for the data quality checking before engaging in the analysis. The registries have covered an ever expanding dataset since 2016.

In the past four years, a total of around 75,000 ICU admission datasets have been collected. With tremendous support and concerted efforts from different units with data science skills, clinical research expertise and knowledge of the clinical conditions in ICUs, the characteristics of the critically ill patients can be outlined accurately. Statistical analysis was also performed by biostatisticians. Well-refined risk adjusted and contemporary models at 30-day, 90-day, and hospital discharge were separately formulated for four groups of critically ill patients: 1) all patients 2) emergency non-operative patients 3) emergency post-operative patients, and 4) elective post-operative patients to effectively benchmark the ICU performance in HK, in terms of both mortality and length of stay. With regular calibration, these models have achieved good mortality prediction results with the area under the receiver-operating characteristic curve (AUC), ranging between 0.83 and 0.89. Upon the application of data, variations in the performance among different units are identifiable. Specific subgroups were identified to explain some results. These findings have been reported to corresponding units, making evaluation and devising improvement plans feasible.

In 2019, HK provided approximately 3.4 adult intensive care or high dependency beds per 100,000 populations, which were managed by ICU specialists in public hospitals. Despite the limited number of ICU beds

available in our territory, HK consistently provides high-quality and efficient ICU service compared with international standards[16]. Furthermore, multiple hospital-level and patient-level variables involving ICU structure and process of care were applied in the post-hoc analysis. The analysis intended to look for the association between these variables and the risk-adjusted performances of the ICUs. Although these variables were observational and descriptive, which could yet be interpreted as the reasons for the performance discrepancy in the model, the relationship between outcomes and these variables is noticeable. These statistically significant variables are mainly related to ICU staffing and workload. Patients admitted to ICU always receive close monitoring and prompt interventions. Adequate ICU staffing is a prerequisite for safe and quality care. The reasons for the association of lower ICU staffing levels with worse outcomes may include prolonged duration of weaning, increased nosocomial infection, and even critical incidents. Whilst there is a lack of conclusive data about ICU physician staffing in HK, the expansion of intensive care services has not been accompanied by a commensurate increase in the number of intensivists. Additionally, ICU staffing practices need to be tailored to the workload in order to limit the workload's impact on patient outcomes. Thus, caution is needed in designing intensivist staffing models in our supply-limited environment in HK. The registry provides valid, reliable and high-quality information on several aspects of ICUs in HK. It helps to improve professional care with better understanding of patient characteristics, the severity of illnesses, outcomes, process of care, resource utilisation and capacity planning in the short and longer term.

CHALLENGES OF DATA APPLICATION

Data science has played an important role in the management of ICU, albeit with various major challenges in its application.

To begin with, the effectiveness of a data-driven management always goes beyond a measure of statistical performance, such as an AUC or a P-value. Appropriate management is vital to effectively achieve organisational objectives, deploying scarce resources timely in this ever-changing environment. Accordingly, the data are expected to generate actionable outputs for the right patients at the right place and right time.

Secondly, clinical thinking and medical decision making in ICU cannot be solely reproduced by the current data science. The qualitative aspect of clinical decision making, the "art of medicine", is unlikely to be modelled quantitatively. Numerous factors, such as social and personal, not revealed in the data, should not be undermined by critical care physicians. Medical practitioners should not become so obsessed with numbers that we forget our Declaration of Geneva. For this very reason, any output from data-driven management should be carefully collected and interpreted.

Finally, the underdevelopment of cybersecurity poses another barrier. Data security is of paramount importance as it requires the collection, storage, and use of large amounts of personally identifiable health information, much of which may be sensitive and potentially embarrassing[17]. The data is increasingly under threat from hackers. Thus, these growing threats ought to be considered with prudence.

CONCLUSION

"Ideas do not always come in a flash, but by diligent trial-and-error experiments that take time and thought"- Charles K. Kao

The application of data science in intensive care management in HK is just a new start. Our reliable, valid, and high-quality data registry shall endeavour to improve our professional care with better understandings of critically ill patient characteristics, the severity of illnesses, structures, processes of care, outcomes, resource utilisation and capacity planning in the short term and longer term. Yet, its success hinges on cooperation, communication, collaboration and engagement among frontline critical care providers, organisation and the Government; all such stakeholders need to be willing to create a safe, effective and patient-centred care model.

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28 May 2021	Dementia	Dr Pey-chyou PAN Private Psychiatrist
4 June 2021	Insomnia and Management of Sleep Disorders	Dr Yee-him WONG Private Psychiatrist
11 June 2021	Common Psychiatric Disorders in Children and Adolescents	Dr Queenie CHIN Private Psychiatrist
18 June 2021	Psychosocial Approaches in Psychiatry	Dr Lai-wah CHAN United Christian Hospital
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The Future ICU: Innovation, Information and Technology

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INTRODUCTION

The Intensive Care Unit (ICU) is where a hospital concentrated her staff and equipment to meet the demanda of severely ill patients with a reasonable chance of recovery. ICU care involves a complex interplay between patients, multiple medical equipments, various care teams and a health-care environment. For some important therapeutic interventions, patients' family would also be involved in the decision-making process. It is likely that all these inter-linking processes will become more robust and more cost-effective as the art of intensive care advances. While some visionary intensivists have expressed their conceptual views on the future ICU in 30 years[1], I will describe the future ICU in a more technically orientated way.

PATIENTS AND EQUIPMENT

ICU begins with only ventilators as the life support machine and ECG as the physiological monitor. Along with the advances of medical technology, the invasiveness and number of equipments increased dramatically. At present, we could provide comprehensive support for the heart, lungs, kidney, liver, nutrition and blood components. Innovations are toward miniaturisation and reducing the invasiveness of the life support equipment. The benefits are roomier condition around patients and improved safety. The best example of this trend is the catheter-based blood pump for supporting cardiac output. A single 21 French intra-vascular device could provide more than 6 litres of blood flow per minute[2]. The device is connected to an external console, which is only slightly bigger than a toaster. The size of the renal support machine is most challenging to miniaturise, as a large volume of fluid is required to carry away the waste products. New sorbent technology may provide the breakthrough needed for miniaturisation by concentrating waste products before disposal[3].

The final frontier for ICU support is neurological support. The progress is mainly on regenerative medicine, also known as stem cell technology, to replace brain function[4]. There are numerous advances in functional electrical stimulation for the replacement of spinal cord function, which allows patients with spinal cord injury to accomplish functional tasks, such as respiration, micturition or even activities of daily living[5].

For physiological monitoring, monitoring of most, if not all, bodily functions is expected in the future. The sensors used will be less invasive and more comfortable to wear. Multiple sensors will be integrated into one, and the cable connecting the sensor to the monitor will be replaced by wireless technology. An example is the development of cardiac output measurement. In the past, an invasive trans-cardiac pulmonary artery catheter was the standard. Soon, non-invasive cardiac output monitoring using ECG and signal from pulse oximeter will be commercially available, with wireless connections and the size of a wrist watch[6].

BETWEEN EQUIPMENTS

With more equipments, interdependence and hence data exchange become more critical. Different equipments should coordinate their actions to provide optimal care. For example, an infusion pump will adjust infusion rate of vasoactive drugs according to the haemodynamic data provided by the physiological monitor. Two infusion pumps will coordinate their actions so that a near-empty syringe of vasoactive drugs can be replaced by a new one without any consequential fluctuation of haemodynamics. The current solution is having all the required components in a single machine, just as a ventilator is equipped with a built-in oximeter and a continuous carbon dioxide level monitor. Another example is an intra-aortic balloon pump with built-in ECG and continuous blood pressure monitoring. Such data integration approach will increase the costs and complexity of monitoring. Empowered by the development of interoperability standards[7], the future ICU equipments will work as a "team" to provide care for patients.

EQUIPMENTS AND CARE TEAMS

The increasing complexity of technology has made it difficult for the care team to understand all the technologies. One could expect "smart" equipment, a decision support system, to run most routine care. Should an event occur, the machines will integrate all the information and suggest the best action for the caregivers. For less critical issues, the devices may troubleshoot by themselves so that user interventions will be minimised. Such automation will reduce the number of false alarms. Do note that the lower signal to noise ratio of most currently-in-use non-invasive monitors, erroneous data would be more common and frequent false alarm could pose a problem.

New ways of interaction between the caregivers and the devices are expected in the future ICU. In the past, life support machines were controlled with knobs and

switches, while physiological data presented using gauges. When more parameters need to be controlled and presented, a computer menu and screen is typically used as part of the modern ICU equipments. These screens were too small to see from the far end of an ICU bed a few years back. Now, they get so big that precious space around an ICU bed has become overcrowded. Mobile devices have provided the first breakthrough for such a predicament, allowing the information from devices to get close to the care providers. However, this created a new risk of selecting an incorrect patient on the mobile device. Soon into the future, geo-location of care providers can provide an extra layer of safeguard for selecting the right patient. Augmented reality with smart glasses will be the next significant advance to allow the interface between the caregivers and medical devices. These smart glasses will present all critical information when a care-giver approaches a patient or a device[8]. All critical information wiil be presented when a care-giver coming close to and looking at a patient or device. The information will change with different objects we gaze at; a patient's respiratory status, ventilator setting and reading will show up when we look at the ventilator, while electrolytes, dialysis setting and reading will be presented on the dialysis machine.

PATIENT AND CARE TEAMS

Given the relative scarcity of healthcare workers, fewer personnel are expected to run an ICU. To compensate, the care teams have to set up a central monitoring post for patient observation and clinical tasks scheduling. Apart from data originated from medical devices, a live video stream of patients' immediate surroundings would provide key information about patients' condition and care. In the future, computer vision can assist the observation of the multiple video feed, providing information such as the depth of sedation, any clinical seizure, any risk of treatment intervention by patients (pulling off lines or drains), and risk of fall[9]. Before the devices' full interoperability, the computer vision can help integrate the parameters shown on the devices and the alarms they produced. The more sophisticated algorithms would enable the computer vision to recognise clinical procedures. Patient turning or bathing can be documented automatically, or even summoning extra help if someone has started external chest compression for cardiopulmonary resuscitation.

Advancement in robotics will help to mitigate the workforce shortage. Task-specific robots have made much progress in health care. Pilot projects of using robotic carts for transporting equipment has started in public hospitals in Hong Kong. Robotic bronchoscopy[10] and robotic venesection may arrive in the commercial market soon[11]. I believe that we will see the usual ICU procedures, such as intubation or central venous catheter insertion, be performed remotely by robotics within our lifetime.

General-purpose robots or true "robotic doctors", which are human-like robots with versatile arms or hands, are still in their infancy for clinical use. On the other hand, people often refer to workstations for teleconsultation as "robotic doctors". Such workstations are relatively mature and can effectively bring an expert to a clinical challenge, at a low cost. The advantages of tele-ICU have been well described[12], and it is an issue of technology adoption rather than innovation.

BETWEEN CARE TEAMS

In the future, every caregiver will manage a higher number of patients. Coupled with more data gathered from patients, handing over information between different caregivers and different care teams will become more challenging. Case summary or dashboard has long been used for clinical communication and with great successes. However, the burden of preparing case summary and populating the dashboard will be hard to cope with if they continue to be performed manually. An algorithm for "automated journalism" could extract critical information from the vast amount of clinical data and provide a draft clinical summary for the caregiver to edit. Instead of having a single dashboard for the whole ICU, multiple virtual dashboards can be created for a specific care team and a specific caregiver to be viewed on a mobile device. The concise and just-in-time information will help to prevent information overload[13]. Moreover, a central integration of all the dashboards allows scheduling and coordination of care by multiple caregivers.

PATIENT'S FAMILY

The ICU environment has always been difficult for family members of patients. They are highly stressed by patients' critical condition, an unfamiliar environment and lack of control in the care process. Telecommunication technology has allowed their video communication with patients during the COVID-19 epidemic, and this practice will continue into the future. Apart from tele-visits, simple factual information, such as whether there was fever, whether the feeding went well, what procedures have been performed or when an operation is planned, will be provided by "automated journalism" to the family in the future. Such transparency will foster trust in and satisfaction with ICU care. A short pre-recorded video explaining the important aspects of the procedures that have been performed or planned for a specific patient will be provided to the family. Ultimately, the caregiver's time to communicate with the family per patient could be reduced, yet the family will have more information obtained and higher satisfaction.

CARE ENVIRONMENT

The traditional ICU design was a hall with no windows, where there is plenty of open space for accommodating patients and convenient observation. Such arrangement looked more like an aeroplane hangar or a car garage where repair works are to be done. The contemporary design for ICU is more humanistic, with walls or a partition for privacy and plenty of windows for sunlight. If it is structurally impossible, artificial lighting, simulated windows and decorations can be installed to mimic a homey environment. Studies have shown that such an environment may reduce ICU delirium[14]. For mentally alert patients, mobile devices or even virtual reality may help them connect with their familiar environment or even provide them with some therapeutic effect[15].

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Lastly, along with the improved healthcare technologies, a dedicated ICU ward may no longer be necessary, as all the ICU equipments are so handy to move around and expertise so readily available with telecommunication. My dream for the future is that all patients in a hospital will receive wireless ICU monitoring. Should ICU support is required, a life support cart that is no bigger than a current dialysis machine can provide all the necessary support. Considering the home ventilation programme at present, supporting selected patients with multiple organ failure at home may also be a possibility in the future. Of course, such patients' mobility can be maintained with a robotic exoskeleton and functional electrical stimulation, or else moving them home may not carry many benefits.

CONCLUSION

The government has placed great emphasis on innovation and technology as part of the development of the Greater Bay Area. Given the many hospital redevelopment projects ongoing in Hong Kong, it is a golden opportunity to develop the next generation of "Smart Hospital" and "Smart ICU" for the future. Concerted efforts of the practitioners, academia and industries are pivotal to the success of ICU care in the future.

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How to Build a Crystal Clear Aquarium

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Fishkeeping is a great hobby. Having a fish tank with crystal clear water, spectacular aquascape, and happily swimming fishes is the dream of every aquarium hobbyist. However, most of the newcomers turn their aquarium into a cloudy dead zone with algae overgrown, and no matter how frequent you change the water, the situation is still getting worse. Here we share some basic theory on how to maintain your aquarium in good condition.

Before we start, we need to understand the natural waste management system, the so-called "Nitrogen Cycle". It describes how nature breaks down the fish waste so that it can get converted into food again. The Aquarium nitrogen cycle is referring to the specific part of the cycle where the fish waste turns into toxic nitrogen compounds like ammonia, nitrites, and nitrates. It involves 4 phases:

1. The first step is the decay of the waste products of inhabitants (fish, plant)[1] or their dead bodies, and this process will produce ammonia. Ammonia will burn the gills of fish and choke off their oxygen supply. The increase in ammonia level can be observed by the naked eye as wispy, smoke-like cloudy aquarium water.
2. Beneficial bacteria Nitrosomonas consume ammonia and produce nitrite. Nitrite is toxic to the fish by decreasing the oxygen-carrying capacity of the blood, although it is less toxic compared to ammonia.
3. Beneficial bacteria Nitrobacter consume nitrite and release a less toxic chemical - Nitrate. Nitrate can be harmful when it is in a high amount, and excessive nitrate promotes algae growth.
4. Nitrate is removed either by changing water or being consumed by aquarium plants.

"Cycling your aquarium" refers to the process of making sure you have enough biological filtration[2] (e.g., beneficial bacteria and aquarium plants) so that all the ammonia and nitrites get eaten up; this process can take anywhere from a few weeks to months. The length of time depends on the amount of ammonia being produced and the biological filtration efficiency. First of all, make sure you limit the amount of fish to be kept in your aquarium in order to control the production of nitrogenous waste. Secondly, don't overfeed your fishes as the more they eat the more faeces they will produce. Overfeeding will also increase the unconsumed food particle inside the aquarium, where they will decay into nitrogenous waste and contaminate the water. As a rule of thumb, feed your fish daily or once every two days with the amount of which they could consume completely within 2-3 minutes, and decrease the frequency of feeding when the water condition is getting worse. Mechanical filtration serves to remove free-floating waste before it decays into harmful substances, and to be beneficial, the filter material must be cleaned or replaced every two to four weeks.[3]

Thirdly, to have effective biological filtration, we should nurture a steady population of beneficial bacteria. For beneficial bacteria to thrive, oxygen-rich water is needed, as well as a surface that bacteria can attach to, such as rocks, sand[3], filter media, and plants. We can increase our filter volume and add more biological filter media to increase the filter capacity to hold more beneficial bacteria. We can also speed up this process by buying a bottle of live nitrifying bacteria or getting some used filter media from a friend. Another way is to improve biological filtration efficiency is to add more aquarium plants. Plants provide a large surface for the bacteria to attach to; they consume the ammonia and nitrates produced by your fish's waste. Most importantly, oxygen produced during photosynthesis provide oxygen-rich water for the bacteria to grow.

Having a bunch of healthy growing aquarium plants not only makes your aquarium good looking, but also limits the growth of algae inside the aquarium. Both plants and algae compete for nitrate to grow, and algae will overgrow when there is a lack of competition from aquatic plants. It usually happens from the second week onwards, whenbrown and green algae coats come up. Thus, It is important to plant densely right from the beginning, preferably with fast-growing species such as stem plants. In addition, the aquarium plants should also be sufficiently supplied with nutrients, good lighting and CO_2 installation so that they can grow healthily. Adding some algae-eater (such as Amano shrimp and Neritina or Clithon snails) is also important to control algae overgrowth.

An aquarium is an artificial biosystem where water will stay constant unless you change it. Food particles will fall to the bottom where they decay, and urine or faeces from habitants will accumulate in the aquarium and eventually release dissolved chemicals such as nitrate and phosphate after decay. Nitrate and phosphate, having the effect of fertilizers, promote the overgrowth of algae. Changing the water is the best way to keep nitrate and phosphate levels low. [4]

Waste products are not the only reason why water needs to be changed. Trace elements and minerals in the water are important both to the stability of the water chemistry and to your fish and plants. Over time, if the trace elements are not replaced by water changes, the trace elements would either be used up or filtered out;[4] However, too frequent water change or large volume change, especially when accompanied by the change to filter, will disrupt the colonisation of the beneficial bacteria and reduce biological filtering efficiency. For the average aquarium, change only 10 to 15 percent of the water each week. If your tank is heavily stocked, bump that up to 20 percent each week. A lightly stocked aquarium can likely get by for two to four weeks, but this should be the maximum length of time between water changes.[4] When doing a water change, vacuum the substrate to get rid of some of the detritus that is building up. Make sure you don't clean the gravel and the filter on the same day, as both harbour beneficial bacterial colonies.

Similar to managing a critically ill patient, maintenance of a crystal clear aquarium requires a full understanding of the mechanisms essential to achieving a delicate equilibirum, an equilibrium that requires fine tuning and dedicated efforts. It is enjoyable to watch your fish swimming happily in the beautiful habitat you have built following a long day of hard work. I hope everyone would appreciate the joy of aquascraping and start to build your own aquarium today.

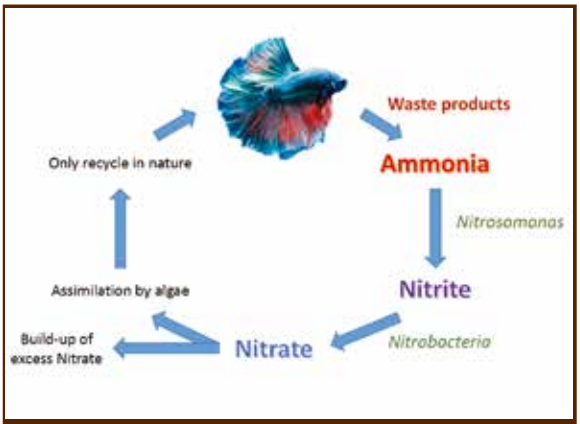

Fig. 2. Aquarium nitrogen cycle (Developed by author)

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4. Water Changes in Your Aquarium (https://www.thesprucepets.com/water-changes-1381886)

Fig. 1. A crystal clear aquarium (Photo from personal collection)

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Year	Guideline	Recommendation
2016	IDSA[2] Invasive aspergillosis	Preferred alternative to standard for invasive *Aspergillus* syndromes
2017	ECIL-6[3] Invasive aspergillosis	**Grade AI** for leukaemia and HSCT
2018	ESCMID-ECMM-ERS[4] Invasive aspergillosis	**Grade AI/II** for IPA in neutropenic non-allo and allo-HSCT recipients, in allo-HSCT without neutropenia or other non-neutropenic patients **Grade AII** for *Aspergillus terreus* infection **Grade BII** for amphotericin B-resistant infections
2019	ECMM-MSG ERC[5] Mucormycosis	**Grade BII** as 1st line for all patients **Grade A** for pre-existing renal compromise **Grade AII** as salvage therapy for refractory disease and in those with toxicity or intolerance to 1st-line treatment

ECIL, European Conference on Infections in Leukaemia; ECMM, European Confederation of Medical Mycology; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HSCT, haematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; IPA, invasive pulmonary aspergillosis; MSG ERC, Mycoses Study Group Education and Research Consortium.

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References: 1. CRESEMBA® (isavuconazole) Prescribing Information. Pfizer Corporation Hong Kong Limited: Version Dec 2018. **2.** Patterson TF, et al. *Clin Infect Dis* 2016;63:e1–e60. **3.** Tissot F, et al. *Haematologica* 2017;102:433–444. **4.** Ullmann AJ, et al. *Clin Microbiol Infect* 2018;24(Suppl 1):e1–e38. **5.** Cornely OA, et al. *Lancet* 2019;S099:1–17. **6.** Maertens JA, et al. *Lancet* 2016;387:760–769. **7.** Miceli T, Maertens J. *J Antimicrob Chemother* 2017;72:i29–i38. **8.** Marty FM, et al. *Lancet Infect Dis* 2016;16:828–837. **9.** Wilson DT, et al. *Ther Clin Risk Manag* 2016;12:1197–1206. **10.** Groll AH, et al. *Clin Pharmacol Drug Dev* 2017;6:76–85. **11.** Natesan SK, Chandrasekar PH. *Infect Drug Resist* 2016;9:291–300.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	★Live Lecture HKMA - HKS&H CME Programme 2021 Topic: Recent advance in GORD (Online) ★Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 4	★Live Lecture Beyond Ordinary Headache: Chronic Migraine Treatment And Prevention Overview - Online ★Certificate Course on Wilderness Medicine 2021 (Video lectures) 5	★Live Lecture Progressive-Fibrosing Interstitial Lung Disease - What Do We Know About the Clinical Course and Management? - Online 6	7	8
9	10	★Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 11	★The Hong Kong Neurosurgical Society Monthly Academic Meeting –Endoscopic skull-base surgery: A systematic evidence-based review ★Live Lecture Envisioning the Future of SGLT2 Inhibitors: Treatment of T2D Patients with Cardiovascular Disease - Online ★Certificate Course on Wilderness Medicine 2021 (Video lectures) 12	13	14	15
16	17	★Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 18	19	★FMSHK Executive Committee Meeting ★FMSHK Council Meeting 20	★Certificate Course on Mental Health 2021 (Video Lectures) 21	22
23	24	★Live Lecture HKMA-GHK CME Programme Topic: Update on renal stone management	★Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)	★Live Lecture Hearing Loss - A Microscopic View - Online 27	★Certificate Course on Mental Health 2021 (Video Lectures) 28	29
30	31	25	26			

Date / Time	Function	Enquiry / Remarks
4 TUE 2:00 PM	**Live Lecture** **HKMA - HKS&H CME Programme 2021** **Topic: Recent advance in GORD (Online)** Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital Speaker: Dr KWONG Wing-hang	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Victor Hip-wo YEUNG	Ms Vienna LAM Tel: 2527 8898
5 WED 2:00 PM	**Live Lecture** **Beyond Ordinary Headache: Chronic Migraine Treatment And Prevention Overview - Online** Organiser: Hong Kong Medical Association Speaker: Dr FONG Ka-yeung	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Axel Yuet-chung SIU	Ms Vienna LAM Tel: 2527 8898
6 THU 2:00 PM	**Live Lecture** **Progressive-Fibrosing Interstitial Lung Disease - What Do We Know About the Clinical Course and Management? - Online** Organiser: HKMA-KLN East Community Network Speaker: Dr Angus Ho-yin LO	Ms. Antonia LEE Tel: 3108 2514 1 CME Point
11 TUE 7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr HUNG Hing-hoi	Ms Vienna LAM Tel: 2527 8898
12 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –Endoscopic skull-base surgery: A systematic evidence-based review** Organiser: Hong Kong Neurosurgical Society Speaker(s): Dr Eric Yuk-hong CHEUNG Chairman: Dr Calvin Hoi-kwan MAK Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
2:00 PM	**Live Lecture** **Envisioning the Future of SGLT2 Inhibitors: Treatment of T2D Patients with Cardiovascular Disease - Online** Organiser: HKMA-Central, Western & Southern Community Network; Speaker: Dr Jacky Kit CHAN	Ms. Antonia LEE Tel: 3108 2514 1 CME Point
7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Kwok-shing LAM	Ms Vienna LAM Tel: 2527 8898
18 TUE 7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Eddie Shu-yin CHAN	Ms Vienna LAM Tel: 2527 8898
20 THU 7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
21 FRI 7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr John SO	Ms Vienna LAM Tel: 2527 8898
25 TUE 2:00 PM	**Live Lecture** **HKMA-GHK CME Programme** **Topic: Update on renal stone management** Organiser: Hong Kong Medical Association Gleneagles Hong Kong Hospital; Speaker: Dr Vera Yeung CHUNG	HKMA CME Department Tel: 2527 8452 1 CME Point
26 WED 7:00 PM	**Certificate Course on Ultrasound Diagnosis of Fetal Anomalies 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Wing-cheong LEUNG	Ms Vienna LAM Tel: 2527 8898
27 THU 2:00 PM	**Live Lecture** **Hearing Loss - A Microscopic View - Online** Organiser: HKMA-New Territories West Community Network; Speaker: Dr Nelson Hui-yui CHEUNG	Ms. Antonia LEE Tel: 3108 2514 1 CME Point
28 FRI 7:00 PM	**Certificate Course on Mental Health 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Pey-chyou PAN	Ms Vienna LAM Tel: 2527 8898

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Answers to Dermatology Quiz

Answers:

1. Idiopathic scrotal calcinosis
   The differential diagnoses include epidermoid cyst, steatocystoma, eccrine epithelial cyst and other benign cysts.

2. Though it was considered an idiopathic condition, it is now believed that the lesion is developed from dystrophic calcification of epidermal cyst, eccrine epithelial cyst, or degenerated dartos muscle in the scrotal skin.

3. Most clinicians will order blood tests of calcium and phosphate because of calcification in the lesion. However, these tests are almost invariably normal and unrewarding.

4. Treatment is surgical removal, but because of its benign nature, surgical removal is recommended only in the presence of local symptoms or aesthetic reasons.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

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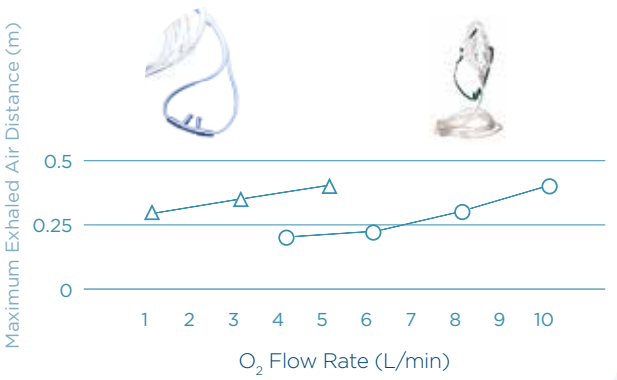
NHF is currently not considered to represent an increased risk of HCW infection via contact, droplet or airborne transmission routes.[5-9]

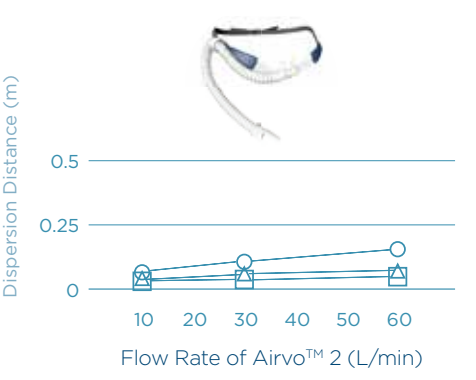
Collated air dispersion results from Hui et al.[10,11]

Changes in Exhaled Air Dispersion**

COT with O_2 Nasal Cannula[10] COT with O_2 Mask[10]



NHF with F&P Optiflow Interface[11]



Human patient simulator setting: ○ Normal △ Mild lung injury ☐ Severe lung injury

** Dispersion distance data shown on the chart is combined from two studies conducted by the same authors.
The experiments were conducted in rooms with different configurations. Not all of the interfaces depicted were directly compared.

FOR MORE LITERATURE ON NASAL HIGH FLOW USE IN COVID-19

*A F&P internal review of studies comprising the body of NHF evidence found the majority used F&P Optiflow™ systems.
This information was drawn from edition 10 of Flow Matters that covers NHF use in COVID-19.
The content of Fisher and Paykel Healthcare's Flow Matters publication is intended for healthcare professionals only.
https://www.fphcare.com/us/hospital/adult-respiratory/optiflow/articles/#fm10

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Patients with type 2 diabetes
should expect more after metformin

REALISE THE POTENTIAL

UP TO

80%

ACHIEVED ADA TARGET OF HbA_{1c}

<7%

VS OTHER DIABETES TREATMENT[1,2,7,8,9#]

OZEMPIC®

The only once-weekly treatment unifying superior efficacy and CV benefits[1-5]

SUPERIOR GLYCAEMIC CONTROL[1,2*]
Up to 1.8% HbA_{1c} reduction[2]

SUPERIOR AND SUSTAINED WEIGHT LOSS[1-3*]
Up to 6.5kg weight reduction[2]

PROVEN CV BENEFITS[1,3 †]
26% CV risk reduction[1,3§]

§ When added to SOC, which included oral antidiabetic treatment, insulin, antihypertensives, diuretics and lipid-lowering therapies.[3]

Other diabetes treatments refer to sitagliptin, dulaglutide, exenatide ER, liraglutide, canagliflozin and glargine U100. Target refers to American Diabetes Association target of HbA_{1c} <7%.

† In SUSTAIN 6, Ozempic® reduced CV risk (CV death, nonfatal myocardial infarction [MI] or nonfatal stroke) versus placebo in patients with type 2 diabetes at high CV risk treated with standard of care.[1]

* Results apply to Ozempic® across SUSTAIN trials, which included placebo, DPP-4I, SGLT-2I, GLP-1 RA and basal insulin.[1,2]

For adults with type 2 diabetes with established ASCVD or indicators of high ASCVD risk
2019 ADA/EASD consensus report recommends a GLP-1 RA therapy with proven CV benefit[6]

CV=cardiovascular; CVD=cardiovascular disease; ADA=American Diabetes Association; EASD=European Association for the Study of Diabetes;
GLP-1 RA=glucagon-like peptide-1 receptor agonist.

Abbreviated prescribing information Ozempic® (semaglutide). Ozempic 0,25 mg solution for injection in pre-filled pen; Ozempic 0,5 mg solution for injection in pre-filled pen; Ozempic 1 mg solution for injection in pre-filled pen. **Consult Summary of Product Characteristics before prescribing. Presentation:** Ozempic 0,25 mg & 0,5 mg solution for injection: Each pre-filled pen contains 2 mg semaglutide in 1.5 ml solution. Ozempic 1 mg solution for injection: One pre-filled pen contains 4 mg semaglutide in 3.0 ml solution. **Uses:** Ozempic® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise as Monotherapy: when metformin is considered inappropriate due to intolerance or contraindications. Combination therapy: in addition to other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see the full Summary of Product Characteristics. **Dosage and administration:** The starting dose is 0,25 mg Ozempic® once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control. Ozempic® is to be administered once weekly at any time of the day, with or without meals. Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. Ozempic® should not be administered intravenously or intramuscularly. When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged. When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. **Elderly:** No dose adjustment is required based on age. Therapeutic experience in patients aged ≥75 years of age is limited. **Renal impairment:** No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience in patients with severe renal impairment is limited. Not recommended for use in patients with end-stage renal disease. **Hepatic impairment:** No dose adjustment is required for patients with hepatic impairment. Experience in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with Ozempic®. **Paediatric population:** The safety and efficacy of Ozempic® in children and adolescents below 18 years have not yet been established. No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Ozempic® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Ozempic® is not a substitute for insulin. There is no experience in patients with congestive heart failure NYHA class IV and Ozempic® is therefore not recommended in these patients. The possibility of gastrointestinal adverse reactions should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea may cause dehydration, which could cause a deterioration of renal function. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Ozempic® should be discontinued; if confirmed, Ozempic® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Patients treated with Ozempic® in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. Consider reducing the dose of sulfonylurea or insulin when initiating treatment with Ozempic®. In patients with diabetic retinopathy treated with insulin and Ozempic®, an increased risk of developing diabetic retinopathy complications has been observed. Caution should be exercised when using Ozempic® in patients with diabetic retinopathy treated with insulin. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. **Interactions:** Ozempic® delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Ozempic® should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. No dose adjustment of paracetamol, oral contraceptives (ethinylestradiol and levonorgestrel), atorvastatin, warfarin, digoxin or metformin is necessary when administered with Ozempic®. For further details of these interaction studies, please see the Summary of Product Characteristics. **Pregnancy and lactation:** Ozempic® should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs during treatment, Ozempic® should be discontinued. Ozempic® should not be used during breast-feeding. Effect of Ozempic® on fertility in humans is unknown. **Driving or using machines:** When Ozempic® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. **Undesirable effects:** The most frequently reported adverse reactions with Ozempic® in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. Adverse reactions by system organ class and absolute frequencies identified in all phase 3a trials listed here as Very common (≥1/10): Hypoglycaemia when used with insulin or sulfonylurea, nausea, diarrhoea; Common (≥1/100 to <1/10): Hypoglycaemia when used with other OADs, decreased appetite, dizziness, diabetic retinopathy complications, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation, flatulence, cholelithiasis, fatigue, increased lipase, increased amylase, weight decreased; Uncommon (≥1/1,000 to <1/100): Dysgeusia, increased heart rate, injection site reactions; Rare (≥1/10,000 to <1/1,000): Anaphylactic reaction.

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