MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

Year Book 2013/2014

MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS YEAR BOOK 2013/2014

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Foreword

It gives me great pleasure to write the foreword of the sixth edition of the Malaysian Society of Anaesthesiologists Year Book 2013/2014. The Year Book serves to update our members on the current advances in the field of anaesthesia, intensive care and pain medicine. The Society is committed in its pursuit to provide continuing professional development activities to our members.

The Year Book 2013/2014 was entrusted to Associate Professor Dr Basri Mat Nor as the editor and the focus is primarily on intensive care medicine.

The Editors have done an excellent compilation of recent developments in clinical research and practices in intensive care medicine. The Year Book comprehensively documents and addresses clinical issues that we regularly encounter not only in intensive care but in the perioperative care of a patient. For many of us who find it difficult to keep abreast with our reading in intensive care and also spending less time in the intensive care unit, this Year Book will definitely come in handy.

The chapters are well written, researched and peer-reviewed by acknowledged experts in their respective fields. The topics cover management of acute liver failure, acute heart failure, biomarkers of AKI, clinical use of lactate monitoring and the use of echocardiography in hemodynamic assessment of the critically ill patient, the ever worrisome multidrug-resistant organism, causes of coagulopathy in the intensive care unit, strategies to improve hypoxaemia in ARDS and the anaesthetic management of pulmonary hypertension in a parturient.

I am extremely grateful to all the authors and peer reviewers for their contribution and commitment to this Year Book.

I am indebted to both the Editors, Associate Professor Dr Basri Mat Nor and Associate Professor Dr Azrina Md Ralib, and thank them for producing the Year Book 2013/2014.

Well done colleagues!

Dr Sushila Sivasubramaniam
President
Malaysian Society of Anesthesiologists

Preface

We would like to thank the Malaysian Society of Anaesthesiologists (MSA) for the trust given to us as Editors for this 6th edition of MSA Year Book for the year of 2013/2014.

The theme for this edition is mainly related on the management of critically ill patients. The articles contained in this yearbook are a compilation of review articles written by experts covering a diverse range of topics of each system of the body. It is our hope that these articles could update clinicians with the latest evidences in managing critically ill patients as a whole.

We would like to thank all authors and reviewers for their valuable time and effort in writing and reviewing the papers. We hope that this effort could be an impetus for future writings in more esteemed peer-reviewed journals. In addition, we hope this would serve as an avenue in developing the skills of the Society members in writing more scientific papers in the future.

Associate Professor Dr Mohd Basri Mat Nor
Associate Professor Dr Azrina Md Ralib
Editors
MSA Year Book 2013/2014

Acknowledgements - Reviewers

We would like to acknowledge the contributions of the following reviewers:

Associate Professor Dr Raha Abdul Rahman
Head and Consultant, Department of Anaesthesiology and Intensive Care, University Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Dr Yip Cheng Bee
Consultant Anaesthesiologist, Royal Perth Hospital, Perth, WA, Australia

Dr Nik Azman bin Nik Adib
Consultant Intensivist, Department of Anaesthesiology and Intensive Care, Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, Malaysia

Dr Rohisham bin Zainal Abidin
Head and Consultant, Department of Anaesthesiology and Intensive Care, Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia

Dr Khairulamir bin Zainuddin
Senior Lecturer and Consultant Cardiothoracic Anaesthesiologist, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Associate Professor Dr Che Rosle Draman
Consultant Nephrologist, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

Dr Laila Kamaliah binti Kamalul Bahrin
Consultant Intensivist, Department of Anaesthesiology and Intensive Care, Hospital Selayang, Selangor, Malaysia

Dr Rafidah binti Atan
Consultant Anaesthesiologist and Senior Lecturer, Jeffrey Cheah School of Medicine and Health Sciences, Monash University Sunway Campus, Johor Bahru, Johor, Malaysia

The Growing Threat of Multidrug-Resistant Organisms in Intensive Care Units

Louisa Chan Yuk Li, MBBS, FCICM
Consultant Intensivist, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

The threat of multidrug-resistant (MDR) organisms in intensive care is real and the need to address this issue urgently is now gaining widespread momentum worldwide. This threat needs to be addressed at many levels: legislative, national policies, practice guidelines, hospital and unit operational procedures and individual prescribing. Educations on current evidence-based practices need to be met by equally effective application of best practices. This is the challenge in present day intensive care practice. The intensive care environment itself exerts a great selection pressure on microbes and invariably will always be exposed to MDR organisms. Infections with MDR organisms increase mortality, morbidity and cost to the already burdened healthcare system. The key to this is managing and containing these organisms. This brief review will cover some aspects a clinician will need to know and apply to manage the microbial environment of the intensive care unit (ICU).

INTRODUCTION

Today we have taken for granted the use of antibiotics for without which many medical advances would not have been possible such as organ transplantation, major surgery and cancer chemotherapy. As microbial resistance accelerates globally, the efficacy of antibiotics will cease and medical treatment will regress if we do not change our behaviour towards the use of antibiotics at all levels of society. It is often said that the golden era of antibiotics will come to a resounding halt. There are fewer effective antibiotics in the pipeline and less interest from the pharmaceutical industry to pursue new antibiotics.

Sepsis is the most common cause of admission to intensive care in Malaysia. And sentinel to the treatment of sepsis is appropriate antibiotics as soon as possible. Often broad-spectrum antimicrobials are deployed and frequently two and occasionally more antimicrobials are administered simultaneously. Compounding this is the protracted prescription of the antibiotics, no positive cultures to guide and fear of de-escalation to narrow spectrum agents that continue to drive antimicrobial resistance.

However other aspects of intensive care practice also perpetuates antimicrobial resistance. The lack of enforcement of infection control practices, staff-patient ratio and budgetary constrains continue to plague our intensive care here. Data from the Malaysian Registry of Intensive Care shows the grip of MDR organisms in ventilator-associated pneumonia (VAP). In 2009, 42% of the causative organisms in VAP were multi-drug resistant.[1] In 2012, the proportion rose to 58% - *Acinetobacter spp, Klebsiella spp and Pseudomonas spp*. being the predominant organisms.[2] This is congruent with many intensive care worldwide where MDR organisms are becoming the predominant infections acquired in the intensive care.

As part of the national initiative to reduce infections across medical and public health spheres, the Ministry of Health released the second edition of Policies and Procedures on Infection Control. This is a collective effort to promote the culture of patient safety and the standardization of best practice. The guide encompasses the setting up of hospital infection and antibiotic control committee, surveillance programmes, infection control and antibiotic stewardship. It also covers infection control in various environmental settings and clinical scenarios including managing the different infections of various MDR organisms.

On a global scale, attempts are now made to educate the public and doctors of the perils of flagrant antibiotic use and looming threat of MDR organisms. In line with the need to educate and

accelerate research and collaboration, some notable international groups such as World Alliance against Antibiotic Resistance, Alliance for the Prudent Use of Antibiotics, Antibiotic Action and Joint Programme Initiative on Antimicrobial Resistance are leading the fight against this threat.

Centers for Disease Control and Prevention (CDC) in America has responded to this problem with a four prong strategy that is useful to adopt in our approach towards MDR organisms: (1) preventing infections and preventing spread of resistant bacteria, (2) tracking resistant bacteria, (3) improving the use of antibiotics and (4) promoting development of new antibiotics and new diagnostic tests.[3]

PREVENTING INFECTIONS

This is the responsibility of every health care worker (HCW) in the intensive care; first do no harm. There is a growing body of evidence as to the methods that may prevent infection which often requires a change in practice culture. Following this, the concept of bundles of care was developed. Bundles of care are not meant to be burdensome and punitive but an attempt to ensure best practice is applied consistently with accountability. The application of bundles of care such as the Ventilator care bundles (VCB) and Central venous catheter (CVC) care bundles are well established here, although some aspects of care may not be directly related to infection prevention. We should strive towards the ideal of zero tolerance against hospital-acquired infections.

Urinary Tract Infection (UTI) Prevention Bundle, Surgical Site Infection (SSI) Prevention Bundle, Pressure Ulcer Prevention Bundle and *C. difficile* Infection Care Bundle are other care bundles relevant to the intensive care practice to reduce mortality, morbidity and cost. UTI Prevention Bundle has been adopted by many centres worldwide with a simple algorithm of reducing use and shortening duration of catheterisation; asepsis and hand hygiene on insertion; use of a closed drainage system that does not back flow or kink and is secured; and vigilant meatal care.[4] The use of UTI Prevention Bundles have recorded good success in centres that have adopted them with drop in urinary catheter usage and UTI infection rates to as low as 0 to 0.5 per 1000 catheter days.[5]

SSI prevention bundle has been promoted as a strategy consisting of no preoperative surgical site hair removal, timely administration of antibiotics, perioperative normothermia and normoglycaemia with meticulous hand hygiene and asepsis.[6] However many surgical centers have modified the bundle according to local needs with additions such as perioperative judicious use of intravenous fluids and supplemental oxygen. There have also been numerous publications of success in the implementation of SSI Prevention bundles.[7]

Once a unit decides to embark on a practice change, there are many resources available to guide the process. This starts with conducting a surveillance study to establish baseline practice and infection rates followed by widespread education and then subsequent implementation. Lastly, monitoring of compliance and further data collection to assess objective changes in the intended outcome completes the process. Feedback is necessary to strengthen the efforts and entrench the new policies.

Here in Malaysia the VCB compliance rate is above target at a rate of 97.5%. Since its inception in 2007 the VAP rates per 1000 ventilator-days had halved in the period of 5 years from 15.4 to 7.2. The CVC care bundle was initiated in 2008 and the compliance rate in 2012 was complimentary with a mean compliance rate of 97.6% . However, the actual beneficial impact of this cannot be ascertained, as under-diagnosis of central venous catheter blood stream infection remains a concern.[2]

The subject of decolonisation as a means to prevent infection remains debatable. There is suggestion of benefit for patients colonised with methicillin-resistant *S. aureus* (MRSA) in the context of perioperative infections, and more recently has been extrapolated to the intensive care. There are fewer trials with Gram-negative organisms, most concentrating on the use of oral non-absorbable antibiotics to reduce extended spectrum beta-

lactamase (ESBL) enterobacteriaceae. It possible reduces carrier state but has no long-term effects. The issues of perpetuating further resistance, drug costs and adverse effects have resulted in inconsistent uptake of this practice.[8]

There is recent interest in chlorhexidine baths for reduction in hospital infections as it is a good broad-spectrum antimicrobial agent. Recent studies have shown to reduce blood stream infections although there was no effect on Gram-negative bacteraemia.[9] Nonetheless chlorhexidine baths have been reported to be implemented as a measure in MDR organism outbreaks. When applied, surveillance for chlorhexidine resistance is necessary. Since the current evidence for decolonisation is present for Gram-positive bacteraemia, units with high rates of coagulase-negative staphylococcal blood stream infections or MRSA infection may benefit from chlorhexidine decolonization attempts.

PREVENTING SPREAD OF INFECTIONS

Infection control measures belong to all who work in the ICU. Taking ownership of this issue is to prevent further transmission of MDR organisms. We have our national 'Consensus Statement on Infection Control Measures in the Intensive Care Unit, 2009' to be adapted for the use of individual units. The effective vectors of spread are the hands of .s, the environment and the visitors.

K. pneumoniae strains spread commonest via contaminated HCWs' hands, whilst environmental contamination (of both wet and dry areas) remains the most important vector for dissemination for *A. baumannii. P. aeruginosa* appears to spread well with both modes, contaminated hands and moist environmental sources.[8]

Basic infection control measures such as hand hygiene need to be made an institutional priority and be monitored. Katherason et al in 2009 observed hand hygiene and use of gloves in 2 ICUs in Malaysia. The authors found that despite 1:1 nurse to patient ratio, the adherence was only 70% before each patient contact with hand washing .The procedure of hand washing was also inadequate. Alcohol hand rubs were used 60% of the time and only 4% staff changed contaminated gloves between patients.[10] This is compelling data to demonstrate the need for ongoing education, behavioural change and accountability. This data dispels any assumptions about hand hygiene practice being routine and inherent in all health-care professionals.

The wearing of gloves without appropriate hand hygiene does not eliminate contamination as may be perceived by some. The HCWs' gloves and hands (after glove removal and before any hand hygiene), is contaminated at a rate of 29.3% and 4.2% respectively with MDR *A. baumannii* and 17.4% and 3.5% with MDR *P. aeruginosa* respectively.[11]

Contact precautions are also part of the strategies to tackle nosocomial spread. This includes individual rooms or cohorting, gowning and gloving upon entry and utilising dedicated/single use equipment. And to further enhance the effectiveness of contact precautions, contact and environmental screening has also been advocated. Studies have quoted the success of employing these strategies in outbreaks especially for Carbapenem-resistant enterobacteriaceae (CRE) and MDR acinetobacter.[12,13] More extreme measures such as separate entrances and medical teams, screening of staff have also been done to stem outbreaks. Well-equipped centers were also able to apply molecular technologies to track and explain the spread of organisms. Upon mapping out the routes of transmission the institutions were able to further refine their infection control policies.[14]

In addition, a fastidious environmental cleaning policy is necessary. This would include types of disinfectants, thoroughness of cleaning, dilutions and contact time. Although always mentioned as part of overall infection control, it has only been proven effective with MRSA, vancomycin-resistant enteroccocus (VRE), *C difficile* and *Acinetobacter spp. P aeruginosa* and *S maltophilia* outbreaks have been reported following contamination from water sources which makes environmental monitoring more complicated.

Although outbreaks in ICU have been contained with combinations of the above strategies, the role of each individual component remains unknown. And the strategies are costly, time and labour consuming and difficult to sustain in the long term if MDR organisms continue to persist. Isolation of patients may result in reduced contact with HCW and thus be subjected to substandard medical care. Surveillance and screening duration, extent (how many sites, environmental areas and HCW to swab) and frequency is not known and results may not return in a clinically relevant time frame to prevent spread. Regular staff meetings, which include non-resident allied health workers, need to be held to enforce, educate and provide feedback. On the extreme, closure of wards/units may be needed if unable to stem an outbreak.

Organisational factors such as inadequate staffing and excessive workloads have been implicated in the spread of infections. In such situations hand hygiene and other infection control measures become compromised, distractions abound and likelihood for errors increase.[15,16] There is also evidence that the level of training also affects infection rates. Alonso-Echanove et al in a prospective multicenter trial involving ICU patients with CVC found that there was an increase risk of CVC associated blood stream infections when patients were cared by 'float' nurses who are not part of the ICU pool of nurses.[17]

TRACKING RESISTANT BACTERIA

This process of tracking resistant organism requires a dedicated team to monitor and to survey across time and geography the pattern of behaviors of these organisms in our local context. At the very least in individual units, a regular antibiogram of organisms have to be made available. This would assist our anticipation of who would be at risk of such organisms, guide empirical antibiotic in at-risk groups and how to better prevent or control outbreaks. MDR organisms do not just arise de-novo in ICU, evidence suggest more ICU patients now are already colonised with these MDR organisms preadmission.

On a national level, there is centralised reporting of ESBL and MRSA organisms whereby data is submitted monthly to the Quality in Medical Care section, Ministry of Health. This process is vital as now the acquisition of MDR organisms can also occur directly from the community again impacting on empirical treatment of antibiotics in the future. There are cases of community acquired MRSA (cMRSA) separate from those acquired in hospital facilities. Fit young people are often the victims to serious skin and soft tissue infections and also necrotizing pneumonias. There are also carbapenem-producing enterobacteriaceae in epidemic proportions in southern Europe, parts of USA and India. And yet in some regions of the world the spread of carbapenemases occurs primarily within the community through unsanitary conditions. In 2007, 79% of E. coli isolates in India, were positive for ESBLs, with similar prevalence in both hospital and community. In this globalised world, migration, travel and trade promote importation of these organisms. [18, 19]

Tracking of sensitivities of food borne organism such as salmonella, campylobacter and cholera are also important. Patients with severe acute infective diarhoeas are admitted to ICU. Standard empirical treatment with ciprofloxacin and ceftriaxone in the future may not be effective as growing resistance starts to occur. Likewise importation of multi-drug resistant tuberculosis and the emergence of malaria resistance to artemisinin-based drugs in parts of Southeast Asia will impact on first-line therapy.

IMPROVING THE USE OF ANTIBIOTICS

This is the one single area that requires commitment from the prescriber to ensure appropriate handling of antibiotics. Studies have shown MDR organisms favour conditions where there is usage of cephalosporins, fluoroquinolones and carbapenems, and where there is protracted use of broad spectrum antibiotics.[20,21,22] Excessive usage also contributes to resistance as was reported in a Spanish insitution with linezolid resulting in an outbreak of linezolid resistant *S aureus*. The outbreak was only terminated when the use of linezolid was restricted.[23]

Appropriate use is also necessary in prophylactic usage and not just established infection. Taking for example the SSI Prevention Bundle, the timing of the first dose of antibiotics prior to skin incision varies according to the different pharmacokinetic (PK) profiles of the drug and care must be taken to ensure prompt redosing intra-op and up to first dose post-op. There is no evidence for protracted courses of prophylactic antibiotics for surgery beyond 24 hours after.

Inappropriate use encompasses not only the wrong class of antibiotics but wrong dosing strategies. Unfortunately PK profiles of drugs in the critically ill patients are complex and more so when extracorporeal therapies are initiated. Hence it remains the onus of the prescriber to continue to keep abreast in developments of drug dosing. Vancomycin is often reported to be poorly administered with inadequate dosing especially if patient is on dialysis. The inability to provide adequate antibiotic levels to the organ affected allows for selection pressure to occur promoting resistance rather than successful eradication of the microbes.

In the era of carbapenem-resistant enterobacteriacae and MDR acinetobacter, drugs like colistin are redeployed and the data of its PK and pharmacodynamic (PD) profile is only beginning to emerge. Colistin has a concentration-dependent bactericidal activity and will need adequate peak levels to minimum inhibitory concentration ratio. Thus to achieve this steady state and given that the volume of distribution in a critically ill patient is larger, there must be an adequate loading dose. The subsequent doses are also recommended to be higher than the traditional dose but in reduced frequency.[24] The current dose recommendations suggests a loading dose of 9 million units followed by 4.5 million units twice a day (to adjust for renal function).[25] The concerns of nephrotoxicity are also now being disputed although the side effect profile of the new high dosing strategies needs to be validated.

Another strategy to preserve antibiotic efficacy and regulate antimicrobial sensitivities is the use of antibiotic cycling or rotation. This method has shown to be of benefit although its use is predominantly for the control of Gram-negatives. Rotating between linezolid and vancomycin for MRSA or enterococcus has not been proven. To further the rational and appropriate use of antibiotics, the involvement of pharmacists, Infectious Diseases Physicians and even computer-based programmes are now starting to establish itself in some ICUs. Computer-based programmes have been found to reduce drug errors, improve antibiotic sensitivity matching, ensure appropriate dosing and duration and in so doing reduce morbidity and cost.[26]

NON-MEDICAL USE OF ANTIBIOTICS

It is also important to note the role of agriculture and animal husbandry in the use of antibiotics. Antibiotics here are used as growth promoters and as mass prophylaxis where animals are subjected to overcrowding and unsanitary conditions. Lack of surveillance, enforcement and political will in the face of powerful industry forces allows the continuation of this practice. In 2005 a case report of community acquired VRE was published.[27] VRE can be found in Malaysian poultry and according to Getachew *et al* in 28% of their isolates of poultry samples in 2006.[28] In 2012, Mansouri-najand et al found that 33% of poultry sampled for campylobacter spp was resistant to at least 4 classes of antibiotics.[29] CDC classifies drug resistant campylobacter with a threat level of serious, in the same category as MDR acinetobacter and VRE. This situation can lead to widespread introduction of resistant strains into the community and may eventually dominate the existing sensitive microbial flora.

DEVELOPMENT OF NEW ANTIBIOTICS AND DIAGNOSTIC TESTS

Microbes are designed to survive. They can mutate, transmit resistant genes, adapt to the environment and finally conquer the host. The ingenuity of microbes requires that we constantly need to discover novel antibiotics. This requires industry support and commitment plus legislative policies that favour research and development. Currently

there are only 2 new classes of antibiotics against the Gram-positive agents, oxazolidinone (linezolid by Pfizer) and cyclic lipopeptide (daptomycin by Cubist) but there are no new classes in phase II or III clinical trials. But more distressing is the fact that there are no new classes of drugs against the major Gram-negative pathogens that are in the late stages of development (phase II or III).This translates to no new classes for the next 10 years.[30]

There is also need to develop more rapid and sensitive test of infection and infection types to allow better use of antibiotics or none at all if infection can be ruled out. The resistant pattern of the organisms also needs to be expedited to reduce broad spectrum usage. Better markers of infection unlike procalcitonin and C-reactive protein are needed to shorten the duration of antibiotic use.

CONCLUSION

There remains much work to be done at all levels to manage the scourge of MDR organisms. MDR organism is a global threat that must not be neglected. Ignore it at our own peril. As doctors working in an environment that is the hotbed for MDR organisms we need to be vigilant of our prescribing habits, infection control practices and must strive to further our knowledge in this area.

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Management of Acute Liver Failure in the Intensive Care Unit

Kamal Bashar Abu Bakar, MBChB (Leeds), MMed (Anaesthesiology) UKM
Lecturer and Clinical Specialist, Department of Anaesthesiology and Intensive Care, University Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Acute liver failure (ALF) is defined as sudden severe hepatic dysfunction manifested as coagulopathy and encephalopathy. It is a rare but a potentially fatal condition. In many developed countries, the commonest cause of ALF is drug induced. Globally however, the most frequent cause is viral hepatitis. This is especially true in developing countries including Malaysia. Treatment is largely supportive with additional specific therapy according to its aetiology. Hepatic and non hepatic organ involvement may occur. Neurological, cardiorespiratory, renal and haematological dysfunctions are seen. Protective measures are taken to prevent such organs involvement. As the disease progresses, steps are taken for temporary organ support while waiting for the liver to regenerate. Early referrals to a liver centre are crucial for safe transport and optimal care. Good intensive care and liver transplantation have improved mortality over the years. Currently, therapies such as hepatocytes transplantations and high plasma exchange are of limited evidence. Similarly, due to lack of evidence, the uses of hepatic assist devices are presently restricted to clinical trials.

INTRODUCTION

Acute liver failure (ALF) is defined as rapid deterioration of liver function manifested by elevated liver enzymes, worsening coagulopathy (International Normalised Ratio (INR) > 1.5) with features of encephalopathy in patients with no pre-existing liver disease.[1] The exact time course differentiating acute and chronic liver failure varies. However, a cut-off point of less than 26 weeks is commonly used to distinguish ALF from chronic liver failure.[1,2] Acute hepatitis B infection, autoimmune hepatitis and Wilson disease can still be considered as ALF even when cirrhosis is present provided the manifestation of ALF is of less than 26 weeks from diagnosis.[1] ALF can be further sub-classified to hyperacute (<7 days), acute (7-21 days), and subacute (>21 days to <26 weeks).[3] The onset of ALF is typically related to its aetiology. For instance, paracetamol poisoning usually presents as hyperacute or acute disease. In contrast, autoimmune hepatitis usually present late as subacute ALF. The complications and prognosis of ALF appears to be associated with the timing of the disease onset although it is more likely to be associated to its aetiologies. Cerebral odema and encephalopathy are more commonly seen in hyperacute and acute cases whereas portal hypertension and renal failure are more frequently observed in subacute cases. Hyperacute and acute illness such as paracetamol poisoning and acute ischaemic hepatitis generally carries better recovery rate compared to subacute illness such as autoimmune and viral hepatitis.[1,4]

EPIDEMIOLOGY

ALF is an uncommon disease. In the United Kingdom, ALF accounts for 1 per million populations whereas the incidence is 10 per million populations in the developing world.[5] A 2008 Malaysian data from a national tertiary referral centre for liver disease showed ALF accounts for only 7% of the overall incidence of liver failure.[6] Females have a three times higher incidence of developing ALF than males. ALF typically affects the younger age group with a mean age of 39 years in females and 32 years in males.[7]

AETIOLOGY

There are numerous causes of ALF. These ranges from common causes such as drug-induced, infection and autoimmune to rare causes such as Budd-Chiari syndrome, haemophagocytic lymphohistiocytosis and heat stroke. In developed countries such as the United States and Europe, more than 50% of ALF is caused by drug-related hepatotoxicity, namely

paracetamol poisoning (42%) and idiosyncratic drug reaction (12%).[3,7] In contrast, for most part of Asia and developing countries, hepatitis A and E are the most common cause for ALF.[8,9] Malaysian data from the year 2001-2009, showed hepatitis B (23.2%), indeterminate cause (20%) and non paracetamol induced hepatotoxicity (18%) as the leading causes of ALF. Acute paracetamol toxicity only accounts for 7% of the overall cause of ALF.[6]

MANAGEMENT

In general, the management entails establishing the diagnosis and aetiology, treating the cause and complications, transplantation in suitable candidates and prevention of recurrence.

Diagnosis and initial assessment

Detailed history and thorough physical examination are the corner stone in establishing diagnosis. Exposure to hepatotoxic agents including illicit drug abuse and traditional medicine, risk of infections such as foreign travel, sexual history and body piercing needs to be carefully elucidated. Family history of liver disease (Wilson disease) is also important. Specific symptoms suggestive of liver failure such as duration of jaundice, pruritis, increasing abdominal girth, right upper quadrant pain and deterioration of mental status are useful to establish diagnosis and a measure of severity. Patients with acute alcoholic hepatitis may present with features similar to ALF. However, these patients typically have a long history of alcohol abuse, hence are considered to have acute-on-chronic liver failure.[10] Differentiating alcoholic hepatitis from ALF is important as their management differs. In addition, patients with alcohol addiction may present with ALF not from heavy drinking but from other causes such as paracetamol overdose. Occasionally, severe encephalopathy is encountered that the history may not be reliable or simply impossible to be obtained. In such cases, history needs to be taken from close friends and family members. Identifying the aetiology of ALF is crucial as it determines subsequent approach to therapy and allows prognostication.

Physical examination

Mental status examination is mandatory to assess the degree of encephalopathy. Hepatic encephalopathy is graded from I to IV.[11] (Table I)

Table I: Degree of hepatic encephalopathy

Grades	Clinical Signs
Grade I:	Changes in behaviour, mild confusion, slurred speech, disordered sleep
Grade II:	Lethargy, moderate confusion Marked confusion (stupor), incoherent speech, sleeping but rousable
Grade III:	Marked confusion (stupor), incoherent speech, sleeping but rousable
Grade IV:	Coma, unresponsive to pain

Asterixis is pronounced in grade II and III encephalopathy but is absent in grade I and IV encephalopathy. Instead, grade IV encephalopathy may exhibits decorticate or decerebrate posturing. Features of raised intra cranial pressure such as systemic hypertension, Cushings reflex and brain stem dysfunction may be present. Pupillary changes occur in the presence of brainstem herniation. Seizure is common yet can be difficult to detect in heavily sedated patients or those receiving paralytic agents. Occurrences of seizures have been reported to be as high as 1 in 3 as detected by electroencephalogram.[12]

Jaundice is often but may be absent at initial presentation. Stigmata of chronic liver disease are usually absent. Inability to palpate the liver may indicate decreased liver volume. An enlarged liver suggest possible underlying malignancy, congestive cardiac failure, Budd Chiari syndrome or early viral hepatitis.

Investigations

Investigations are essentially done for 4 purposes., namely; (1) to ascertain diagnosis, (2) to evaluate severity and complications, (3) to monitor progression, and (4) to decide on further management including suitability for transplantation.

All patients should have prothrombin time and INR measured. A prolonged INR of >1.5 is characteristic of ALF, thus must be present. Liver function test may show an elevated bilirubin level, an elevated liver enzymes especially aminotransferase. Decreasing aminotransferase may indicate spontaneous recovery but could also signify the deterioration of liver function as hepatocytes continue to die. An improving INR and reducing bilirubin level are the hallmark of improving liver failure. It is imperative that coagulopathy not treated unless there is active bleeding or prior to invasive procedure. In fact, it has been shown that despite an abnormal INR, thromboelastography studies only showed hypercoagulable state in 35% of patients with ALF.[13] Other blood tests include routine chemistry especially blood glucose, arterial blood gas, full blood counts and renal function. Additional tests are performed when relevant such as autoimmune screening, acetaminophen levels, drugs and toxicology screen, test for Wilson disease, viral serologies, plasma ammonia and a pregnancy test for females. Urine analysis is done in suspected HELLP (Haemolysis Elevated Liver enzymes Low Platelets) syndrome.

Investigation result have specific pattern according to the causes of ALF. In paracetamol poisoning for instance, a very high aminotranferase (>3500 int. unit/L), low bilirubin and high INR are seen. Ischaemic hepatitis often shows very high aminotransferase (25 to 250 times the upper limit of normal) and an elevated lactate dehydrogenase (LDH). In hepatitis B, the alanine aminotransferase (ALT) is higher than aspartate aminotransferase (AST) whereas in dengue hepatitis, AST levels are higher as compared to ALT. Fulminant Wilson disease can be quickly diagnosed by neither waiting for copper level which takes too long to obtain nor cerulopasmin level which is low in half of ALF patients. A bilirubin to ALP ratio of more than 2 together with AST to ALT ratio of more than 2, low uric acid and progressively worsening renal function makes Wilson disease the most likely diagnosis.[1]

Imaging may reveal malignancy, Budd-Chari syndrome and evidence of cerebral oedema or bleed. An electroencephalogram is indicated whenever subclinical seizures activity is suspected. Liver biopsy, often via transjugular route in the presence of coagulopathy may be required in certain conditions such as autoimmune, malignancy and infection.

PRINCIPLE OF CARE

Despite the numerous aetiologies of ALF, all patients share the similar clinical features; acute loss of hepatocytes function, systemic inflammatory response and multi organ failure. The principle of care is thus unsurprisingly similar for all cause of acute liver failure. Care is essentially steps taken to treat underlying cause of ALF, managing and preventing complication. In addition, certain subgroups of patients may benefit from additional therapy as determined by its aetiology of ALF.[1,4]

General treatment

No single therapy has been found to be useful in all cases of ALF with the possible exception of N-acetylcysteine (NAC).[14,15] Good intensive care practise remains the major factor in determining the outcome of patients with ALF.[1] Patients need to be cared for in an appropriate set up. This is usually the intensive care units (ICU) or some other high dependency units where continuous monitoring can be provided, complications treated and nutritional support maintained. The 2011 American Association for the Study of Liver Diseases (AASLD) guidelines on ALF recommends all patients with grade I-II encephalopathy be admitted to the ward whereas all grade III-IV encephalopathy should be managed in the ICU.[1] Any patient with the potential need for transplant should be transferred to a centre with liver

transplantation program regardless of the degree of encephalopathy as it may be too hazardous for transfer once encephalopathy or disease worsens.

Central nervous system

Cerebral oedema and intracranial hypertension (ICH) are potentially fatal complications of ALF. The pathophysiology of cerebral oedema and ICH is not fully understood. Ammonia is believed to cause cerebral oedema by producing glutamine, a neurotoxic substance in the astrocytes.[14] Indeed; it has been shown that an arterial ammonia level of more than 200µg/dl is strongly associated with cerebral herniation whereas level of less than 75µg/dl is rarely associated with hepatic encephalopathy. Neurological complications in ALF are more likely to be multi factorial. Disturbances in cerebral osmotic pressure, increased cerebral blood flow due to loss of cerebral autoregulation and inflammation are known contributors to this phenomenon. The occurrence of cerebral oedema and ICH correlates with the severity of encephalopathy. Cerebral oedema is seldom observed with grade I and II encephalopathy but the incidence increases dramatically to as high as 65% to 75% in grade IV encephalopathy.[15] As the severity of encephalopathy worsens; head imaging becomes necessary to diagnose cerebral oedema and also to exclude other causes of dropping conscious level such as cerebral haemorrhage.

Lactulose is regularly used in chronic liver failure (CLF) to reduce ammonia level from the gut but recent evidence did not show any difference in the severity of encephalopathy or the overall outcome in ALF patients treated with lactulose. Lactulose on the other hand may cause bowel distension, hence posing technical difficulties during liver transplantation.[16] Sedation is generally avoided as it can mask encephalopathy. Patient with ALF have impaired ability to clear also sedatives resulting in its prolonged and unpredictable effect. However, in patients with severe agitation and restlessness, short acting benzodiazepines, barbiturates and propofol are preferred over opioids, as opioids decrease seizure threshold. Seizures are common in ALF and must be treated quickly to avoid ICH and cerebral oedema. Phenytoin is considered as first line therapy as compared to sedative agents due to impaired drug clearing ability in ALF.[1] Short acting benzodiazepines may be used in phenytoin refractory seizures. Prophylactic use of phenytoin has not been shown to be useful.[17]

Intracranial pressure (ICP) monitoring is controversial. There are 4 types of invasive ICP catheters, namely epidural, subdural, parenchymal and intraventricular catheters. An epidural catheter carries the least risk of bleeding but unfortunately is also the least accurate.[18] Non invasive ICP monitoring such as transcranial Doppler ultrasonography and infra red spectrophotometry are either unreliable or not widely available. ICP monitoring allows an objective and targeted therapy. Clinical features of raised ICP such as Cushing's reflex and papillary changes are not always present or present very late in the disease progression. The downside however, is the risk of bleeding and infection which may be catastrophic in ALF. Non-randomised studies suggest invasive ICP monitoring can be safely inserted and provide information to guide management but did not show an overall benefit as compared to those managed without an ICP monitoring.[19] Measures to avoid and treat ICH and cerebral odema are generally supportive. The only definitive treatment for ICH is transplantation. Neuroprotective measure includes placing patients in a quiet environment with minimal stimulation with the patients' head elevated at 30 degrees in neutral position. Recommended haemodynamic targets are ICP below 20-25 mm Hg, mean arterial pressure (MAP) of 75mmHg or above and cerebral perfusion pressure (CPP) above 50-60 mmHg.[1] Hyperventilation to achieve paCO2 of 25-30mmHg causes cerebral vasoconstriction thus reducing ICP. Nevertheless, this effect is not sustainable and there is possibility of hypoxia thus worsening cerebral oedema. Based on current evidence, hyperventilation may be useful acutely in impending herniation but of is of no role as routine management.[20]

In the event of ICH and cerebral odema, osmotic diuretic mannitol has been used to decrease ICH. Administration of intravenous mannitol as a bolus

of 0.5-1.0 g/kg is recommended as first line therapy and repeated as long as serum osmolality is less than 320mOsmol/L.[21] However; mannitol may cause fluids overload, hyperosmolality, hypernatremia and hypertension. Furthermore, the effect is transient and is not effective in severe ICH (ICP > 60mmHg). Prophylactically targeting a serum sodium of 145-155 mEq/L in patients with high risk of developing cerebral oedema with hypertonic saline showed lower incidence of ICH but its benefit in established ICH has not been demonstrated.[23] When all else fail, a barbiturate coma may be considered. Barbiturates decreases ICP but causes systemic hypotension and may result in prolonged sedation due to impaired drug clearance in ALF.

The pathophysiology of haemodynamic derangement in ALF is similar to that in sepsis. ALF causes a low systemic vascular resistance resulting in relative hypovolemia. Fluids resuscitation should be attempted before initiation of vasopressors. Normal saline is the fluids of choice for fluids resuscitation and changed to half saline if hyperchlorremic acidosis develops. Dextrose containing crystalloids can be added in hypoglycaemia. Hypovolemia decreases CPP and induces organ ischemia while over hydration worsens ICH and systemic oedema. Haemodynamic restoration should be attempted with fluids therapy before initiation of vasopressors. There is no evidence to support the use of any particular vasopressor.[23] Noradrenaline however appears to be the choice of agent for most centres. Vasopressin and its analogues are considered as second line agents due to its highly potent vasoconstrictive effect and potential to cause tissue ischaemia.

Hypothermia has been shown in animal models to be effective in preventing cerebral oedema.[24] While there are some evidences to suggest its benefits with moderate hypothermia, hypothermia also increases the risk of infection, cardiac arrhythmias and bleeding. Due to the limited evidence and serious complications, hypothermia is currently recommended only as a bridging therapy to liver transplant.[1]

Steroids are used in ICH secondary to brain tumours but it has not been shown to be effective in ALF with ICH.[25] Indomethacin causes cerebral vasoconstriction and rapidly reduces ICP. Data are scarce but an intravenous dose of 25mg intravenously over 1 minute can be considered when standard treatment fails.

Infection

Patients with ALF are at high risk of infection. The respiratory tract, urinary tract and blood are common routes of infection. Features to suggest active infection may not be obvious. Worsening encephalopathy and renal failure may be the only clues to an ongoing infection. Prophylactic use of antibiotics have not been shown to improve overall outcomes in ALF and therefore not advocated.[26] Instead, meticulous evaluation of signs and symptoms of infection coupled with periodic surveillance cultures are recommended. Antibiotics should only be started whenever active infection is suspected especially that of fungal infection.

Coagulopathy and bleeding

Coagulopathy is the hallmark of ALF due to decreased liver syntheses of coagulation factors. Thrombocytopenia is also common usually due to an ongoing infection. Spontaneous cerebral bleed and significant bleeding requiring blood transfusion however are rare.[27] The commonest site of bleeding is the gastrointestinal tract. All patients with ALF should be on stress ulcer prophylaxis with either H2 antagonist or proton pump inhibitor. Prophylactic use of fresh frozen plasma (FFP) has not been shown to be effective and may interfere with the monitoring of disease progression, causes fluid overload and is costly. FFP is only indicated in active bleeding or prior to invasive procedures such as ICP catheters insertion.[28] In extreme cases where coagulopathy cannot be corrected with FFP alone, the use of recombinant factor VIIa may improve or normalise coagulopathy and reduces the risk of bleeding.[29] Similarly, platelets transfusion is usually not necessary unless in the presence of an active bleed or severe thrombocytopenia. No actual level

of platelets counts have been documented as safe in patients with thrombocytopenia and coagulopathy but in general levels above 10-20,000/mm^3 are considered safe from spontaneous bleed. Levels above 50-70,000/mm^3 are considered adequate for invasive procedures.[30]

Renal failure

AKI occurs in 30% to 50% of patients with ALF.[3] The rate of AKI increases in ALF secondary to substance with nephrotoxic properties such trimethoprim-sulfamethaxazole. Mortality risk increases and the overall prognosis are poorer in the presence of AKI. As such, any further insult to the kidneys should be avoided. The use of nephrotoxic drugs particularly certain antibiotics and contrast for imaging should be avoided if possible. Maintaining renal perfusion pressure, ensuring adequate hydration and treating infections promptly are essential to preserve renal function. Continuous modes of renal replacement therapies are better tolerated than intermittent haemodialysis particularly with unstable haemodynamics and cerebral oedema.[31] The use of renal vessels vasodilators such as prostaglandins and NAC has very little evidence to suggest its effectiveness.[32]

Metabolic concern

Hypoglycaemia is common due to the impaired liver gluconeogenesis and depleted hepatic glycogen store. Blood sugar must be monitored closely and kept above 3.6 mmol/L with hypertonic glucose solution if necessary. Whenever possible enteral feeding is preferred but parenteral feeding should be considered if indicated. Severe protein restriction is not necessary. 1g/kg/day of protein is reasonable in most cases and should be initiated early.[33]

Hypokalemia, hyponatremia and hypophosphatemia are common and may require correction. Both alkalosis and acidosis occurs. Typically starting with alkalosis in the early phase and later acidosis as the disease progresses. Metabolic alkalosis promotes the conversion of ammonium (NH4+), a charged molecule to a non charged neurotoxic molecule ammonia (NH3). Blood brain barrier is penetrated thus, causing hepatic encephalopathy. As hepatocytes continue to die, lactic acidosis and AKI worsens. Patients may also start to hypoventilate with increasing level of encephalopathy contributing to the progression of acidosis.

SPECIFIC THERAPIES

Paracetamol induced ALF

Paracetamol toxicity is dose dependant. Most ALF occurs with level exceeding 10g/day although cases have been reported with levels as low as 4g/day.[15] A low or absent levels of paracetamol do not exclude hepatotoxicity as the time of ingestion may have lapsed for several days. Activated charcoal is useful for gastric decontamination if given within 1 hour of ingestion. NAC is the antidote for paracetamol poisoning. The standard paracetamol toxicity normogram may be useful in determining the likelihood of toxicity but is less sensitive with multiple dosing, altered metabolism and unknown time of ingestion. NAC has been shown to be safe and effective in paracetamol poisoning. These benefits appear to extend to the non paracetamol induced ALF.[34] In fact, many centres these days utilise NAC in almost all cases of ALF regardless of its aetiology. NAC prevents toxicity by limiting the formation and accumulation of N-acetyl-p-benzoquinone-imine and acts as a glutathione substitute and enhances nontoxic sulfate conjugation. Its anti-inflammatory, antioxidant, inotropic, and vasodilating effects improve microcirculatory blood flow and oxygen delivery to vital organs. NAC should be given as soon as possible but its therapeutic effect is still of value beyond 48 hours after paracetamol ingestion. NAC may be given orally (140mg/kg by mouth or nasogastric tube diluted to 5% dilution, followed by 70mg/kg by mouth every 4 hours for 17 doses). More commonly, intravenous NAC is given with a loading dose of 150mg/kg in 5% dextrose over 15 minutes, followed with 50mg/kg over 4 hours and 100mg/kg (6mg/kg/h) over the nexy 16 hours. Continuing NAC beyond the 72 hours mark is controversial.

Non paracetamol induced ALF

Unlike paracetamol, drug induced liver injury are not necessarily dose related. The onset of ALF too may vary from days to months after exposure to hepatotoxic drugs. There is no specific therapy for idiosyncratic drug reaction. Corticosteroids have not been found to be effective unless a hypersensitivity or allergic reaction is suspected. Viral hepatitis particularly hepatitis A and B are common cause of viral induced ALF. Hepatitis C on the other hand, appears not to cause ALF on its own. Nucleotide analogues lamivudine, widely used in chronic hepatitis B infection should be considered in hepatitis B induced ALF. Herpes virus including varicella zoster rarely causes ALF. Immunosupressed or pregnant ladies are at risk of contracting herpes. Skin lesion is only present in 50% of the time. Acyclovir 5-10mg/kg every 8 hours for at least 7 days should be given.

Wilson disease only accounts for 2-3% of ALF cases. However, it is important to diagnose Wilson disease as the cause of ALF early, as it has 0% hepatic regeneration ability. The only treatment is liver transplant. Steroids therapy is only indicated in autoimmune hepatitis. Prednisolone of 40-60mg/day is recommended for patients with coagulopathy and mild hepatic encephalopathy. Nonetheless, all patients with autoimmune hepatitis should be considered for liver transplant.

In acute fatty liver of pregnancy or the HELLP syndrome, delivery is the only treatment. Transplantation should be considered if ALF does not improve rapidly following delivery. Acute ischaemic liver injury or "shocked liver" often occur in the ICU following prolonged period of hypoperfusion or severe hepatic congestion. Aminotransferases and lactate levels improve as tissue perfusion restored. Successful management of tissue hypoperfusion or off loading a congested heart are usually adequate to ensure recovery and the need for transplant is rare. Budd-Chiari syndrome is confirmed with imaging. Prognosis is usually poor and transplantation may be necessary. It is important to rule out malignancy or thrombophiliacs in this group of patients. Malignancies are confirmed from imaging and biopsy. Treatments are mainly to that of the underlying malignancy. Transplantation has no role in such cases.

LIVER TRANSPLANT AND LIVER SUPPORT

Liver transplantation is the definitive treatment in liver failure. It is, however not suitable for everyone with ALF. Some patients have the ability to spontaneously recover while others have medical or psychosocial contraindications to transplantation such as severe cardiopulmonary disease and poor family support. Various prognostic models have been developed to objectively select suitable candidates for transplantation. Kings College Hospital (KCH) criteria are the most commonly used prognostic model. It incorporates both the aetiology of ALF and clinical parameters of the illness. Its sensitivity however is only 68% while its specificity is 82-92%.[35] Other prognostic models such as the Models for End Stage Liver Disease (MELDS), Sequential Organ Failure Assessment (SOFA) score, Clichy criteria and Acute Liver Failure Study Group (ALFSG) index are either methodologically flawed or too cumbersome for routine use.[36] Relying entirely on these models for transplant candidacy is not recommended.

As in renal failure, hepatic assist devices are available as an alternative artificial method of sustaining liver function. These machines are costly and not widely available. Furthermore, studies have not been able to show significant survival benefit in ALF.[37] These days, its usages are mainly limited to pre liver transplant bridging therapy and as a temporary measure while waiting for the liver to regenerate. The 2011 AALDS guideline does not recommend the use of hepatic assist devices outside of clinical trials.[1]

PROGNOSIS

The most important predictors of outcome in ALF are its aetiology, degree of encephalopathy and renal dysfuction. Paracetamol toxicity, ischaemic hepatitis and hepatitis A induced ALF carries transplant free survival rate of more than 50%. In contrast, Budd-Chiari syndrome, autoimmune and hepatitis B

induced ALF have less than 25% survival rate without transplantation. Grade I and II encephalopathy have 65-75% chance of spontaneous recovery. Grade III has a 40% while grade IV has less than 25% chance of spontaneous recovery. Age of the patients and length of time between the onset of illness and the onset of encephalopathy have not been shown to be contributors in determining the outcome in ALF.[38] The overall 1 year survival rate post transplantation is lower in ALF compared to CLF. However, beyond the first year, the survival rate reverses with ALF having a better long term survival rate as compared to transplanted CLF patients.[39]

CONCLUSION

ALF is a complicated and potentially fatal illness. Early diagnosis and identification of its aetiology is important for initiation of aetiology specific therapy, prognostication and selection of suitable candidates for transplantation. Prognosis varies according to its aetiology, degree of encephalopathy and renal dysfunction. Good intensive care maximises survival rate and is mandatory in advanced encephalopathy and multi organ involvement. Treatments are largely supportive while waiting for the liver to recover. The use of liver assist devices have yet to be proven effective. Should the hepatocytes fail to regenerate adequately or spontaneous recovery is unlikely, liver transplant is the only life saving treatment.

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Biomarkers of Acute Kidney Injury in the Intensive Care Unit

Azrina Md Ralib, MBChB (Manchester), MMed (Anaesthesiology) USM, PhD (Otago, NZ)
Consultant Anaesthesiologist, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

Acute Kidney Injury (AKI) is common in critical illness, and contributes to high mortality. Current consensus AKI definition is mainly based on functional biomarkers, plasma creatinine and urine output. Emerging studies showed the utility of structural biomarkers for earlier detection of AKI, and stratification of injury severity. A combination of these functional and structural biomarkers is of utility for risk stratification and prediction of outcome. This paper provides an overview of AKI with emphasis on critically ill patients. The major focus is on the early detection of AKI and prediction of outcome by functional and structural biomarkers. The future advances in the use of AKI biomarkers are explored.

INTRODUCTION

Acute Kidney Injury (AKI) is common and contributes to high mortality amongst hospitalised, and intensive care unit (ICU) patients.[1,2] Lack of early diagnosis of AKI has hindered the study of pathophysiological changes, and contributed to the failure to develop new therapies. Research into novel biomarkers for early detection of AKI has become a priority.[3] The nomenclature of AKI implies the occurrence of an acute onset of injury to the kidney and is a departure from the previous terminology, acute renal failure that denotes failure of function. AKI reflects the entire spectrum of severity from mild injury to full-blown failure of the system.[4] There is a considerable interest in this re-designation, which incorporates an earlier spectrum of disease that is potentially preventable and treatable.[3,5] The success of current efforts to identify new biomarkers has renewed interest in finding treatments for, or preventing AKI.[6-8]

Current diagnosis of AKI is mainly based on plasma creatinine, a surrogate marker of glomerular filtration rate (GFR). A small increase in creatinine within the 'normal' reference range reflects a large drop in GFR due to their inverse relationship. There is also a delay of about 10 to 48 hours in creatinine increase reaching the AKI threshold following a 33% drop in GFR.[9] Alternatively, a change in urine output is a more rapid indicator of change in kidney function. However, urine output is influenced by many extraneous factors such as fluid loading, urine obstruction and diuretic use. The current consensus definitions of AKI are based on creatinine or urine output changes, which are surrogates of kidney function.[4,10,11]

The discovery, and development of new biomarkers of injury has opened a new avenue in AKI research, which departs from identifying changes in function to identifying tubular injury. Biomarkers such as Alkaline Phosphatase (AP), γ-Glutamyl Transpeptidase (GGT), Neutrophil Gelatinase-Associated-Lipocalin (NGAL), Cystatin C (CysC), Interleukin-18 (IL-18), Kidney-injury Molecule-1 (KIM-1), L-Fatty Acid Binding Protein (L-FABP), α- and π- Glutathione S-Transferase (GST) have been demonstrated to be diagnostic of AKI and predictive of dialysis and mortality. However, the clinical use of these biomarkers in the critical care setting is complicated by the heterogeneity of the ICU population. Co-morbidities, baseline kidney function,[12] time of injury,[13] and cause of injury affect the performance of these biomarkers.[14,15] Consensus definitions of other disease states in the ICU such as acute respiratory distress syndrome,[16] and sepsis[17] encompass many different criteria. For example, sepsis is defined either by clinical criteria (body temperature, heart rate, respiratory rate. or signs of infection), or laboratory measurement (white cell count, or cultures).[18] Similarly, a consensus definition of AKI that incorporates both markers of injury and of function is needed to diagnose AKI, which takes into consideration clinical factors that modify risk of AKI.

DEFINITION AND SEVERITY CLASSIFICATION OF AKI

AKI is classically described as an abrupt or rapidly reversible reduction in the excretion of nitrogenous waste products, including urea, nitrogen and creatinine.[19-21] This definition emphasises on the filtration function of the kidney, a measure that is unique, and easily and routinely measured.[10,21] More than 35 definitions have been used in the literature, which has made comparing studies difficult.[21,22] Two consensus definitions were developed by the Acute Dialysis Quality Initiative (ADQI)[10] and Acute Kidney Injury Network (AKIN)[4] groups. Each of these uses criteria based on surrogates for change in filtration function (i.e. GFR), namely change in plasma creatinine and urine output (Table I).

The ADQI group proposed a consensus severity classification definition, called the RIFLE (Risk Injury Failure Loss and End Stage) criteria.[10] The RIFLE criteria use relative change in plasma creatinine concentration, estimated GFR loss and urine output to stratify cases into a five-stage classification. The original classification of GFR loss, however did not correspond to the increase in plasma creatinine.[24] The Acute Kidney Injury Network proposed a modification of the RIFLE criteria, the AKIN definition and classification.[4] Since a small increase in plasma creatinine was shown to be associated with increased mortality,[26,27] an absolute increment of > 0.3 mg/dl (or 26.5 μmol/l) in plasma creatinine was included in the definition of AKI and of AKIN stage 1. In addition, a window period of 48 hours was added, and those undergoing dialysis were categorised as stage 3 regardless of their plasma creatinine measurement. GFR loss *per se* was omitted from the AKIN classification. However, it has been suggested that GFR criterion should be maintained as a gold standard in the definition of AKI, especially with the future advent of continuous GFR monitoring and shorter serial creatinine clearance measurements.[28]

The consensus definitions and classifications have facilitated comparison between clinical and epidemiological studies. The RIFLE criteria have been used in many studies to predict kidney recovery, length of hospital or ICU stay, dialysis and mortality, e.g.[29-31] Incorporation of a smaller change of plasma creatinine in the AKIN criteria increased sensitivity for AKI detection, but did not improve prediction of mortality.[32,33] The categorical nature of these classifications does not reflect the continuous spectrum of plasma creatinine change. A 49% increase of plasma creatinine is categorised as stage 1, whereas a 50% increase is in stage 2. These differences may merely be due to variations in the laboratory measurements of plasma creatinine. Since plasma creatinine is a continuous variable, a continuous metric that reflects changes in creatinine better quantify the effect of changes in kidney function, and the effect of intervention in AKI clinical trials.[34] Pickering & Endre proposed the use of the integral of creatinine changes in relation to the baseline concentration; the average change in creatinine above baseline (AVC) and the AVC relative to baseline (RAVC) as continuous metrics.[34] The RAVC takes into consideration both extent and duration of creatinine changes from baseline, and hence RAVC or AVC may be a better outcome measure compared to the current categorical measures of AKI.

The presence of two different consensus AKI definitions[4,10] has led to a call for a standardised unified definition.[35] A collaborative network of nephrologists and intensivists, The Kidney Disease: Improving Global Outcomes (KDIGO) group,[11] has released an international clinical practice guideline for AKI. This defines and classifies AKI by combining both the RIFLE, and AKIN criteria (Table I). However, this guideline does not incorporate the RIFLE GFR criteria, nor does it incorporate novel AKI biomarkers of injury.

Urine output is a rapid estimates for kidney function and the 'oldest' known biomarker for AKI, historically described by Galen (119 - 200).[5] The use of urine output criteria in diagnosis and classification of AKI was initially described in the RIFLE, and later incorporated in the AKIN, and the recent KDIGO classifications.[4,10,11] However their use in the AKI definition has been less well validated

TABLE I: Consensus definition and severity classification of AKI

	GFR/Plasma creatinine definition RIFLE[23]	AKIN[4]	International KDIGO (2012)[11]	GFR/Plasma creatinine definition
AKI definition	≥ 1.5 fold increase in creatinine from baseline and sustained (≥ 24 h)* or Decrease in GFR by > 25% (corrected 33%)[24]	Increase in creatinine by ≥ 0.3 mg/dl (≥ 26.4 µmol/l) from baseline within 48 h or Increase in creatinine to ≥ 150 to 200% (1.5- to 2.0-fold) from baseline	≥ 1.5 fold increase in creatinine from baseline within 7 days or Increase in creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 h	< 0.5 ml/kg/h ≥ 6 h
Risk/Stage 1	≥ 1.5 fold increase in creatinine from baseline or Decrease in GFR by ≥ 25% (corrected ≥ 33%)[24]	Increase in creatinine by ≥ 0.3 mg/dl (≥ 26.4 µmol/l) or Increase in creatinine to 150 to 200% (1.5- to 2.0-fold) from baseline	1.5 to 1.9 fold increase in creatinine from baseline or Increase in creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l)	< 0.5 ml/kg/h ≥ 6 h
Injury/Stage 2	≥ 2 fold increase in creatinine from baseline or Decrease in GFR by ≥ 50%	Increase in creatinine to ≥ 200 to 300% (2.0- to 3.0-fold) from baseline	≥ 2 to 2.9 fold increase in creatinine from baseline	< 0.5 ml/kg/h ≥ 12 h
Failure/Stage 3	≥ 3 fold increase in creatinine from baseline or Creatinine of ≥ 4 mg/dl with an acute rise by ≥ 0.5 mg/dl or Decrease in GFR by ≥ 75% (corrected: ≥ 67%)[24]	Increase in creatinine to 300% (>3-fold) from baseline or Creatinine of ≥ 4 mg/dl (354 µmol/l) with an acute rise by ≥ 0.5 mg/dl (44 µmol/l)	≥ 3.0 fold increase in creatinine from baseline or Increase in creatinine to ≥ 4.0 mg/dl (353.6 µmol/l) or Initiation of renal replacement therapy (RRT) or In patients < 18 years: decrease in eGFR to < 35ml/min per 1.73 m^2	< 0.3 ml/kg/h ≥ 24 h or Anuria for ≥ 12 h

*Sustained (≥ 24 h) was not described in the original paper, but was included in the later reference.[25] Adapted from[4,11,23,24] Diagnosis based on urine output alone will require exclusion of urinary tract obstructions or of other easily reversible causes of reduced urine output, and following adequate fluid resuscitation.[4] GFR: Glomerular Filtration Rate. RIFLE: Risk, Injury, Failure, Loss of function, End-Stage Renal Disease. AKIN: Acute Kidney Injury Network. KDIGO: Kidney Disease: Improving Global Outcomes.

than the plasma creatinine criteria.[11] Urine output changes were shown to precede changes in plasma creatinine and to follow closely the pattern of GFR changes.[36] However, AKI can also occur without changes in urine output, such as in non-oliguric AKI, where tubular injury impairs maximal concentrating capacity of the tubules resulting in normal urine output.[37] Nevertheless, urine output is potentially the first indication of kidney dysfunction especially in critical care settings where hourly urine outputs are routinely measured. In the RIFLE criteria, a urine output threshold of 0.5 ml/kg/h was originally defined as AKI by consensus opinion amongst experts.[23] Utilising this definition, 35% of ICU patients identified as AKI based on urine output, did not have plasma creatinine changes quantifying as an AKI.[38] Other studies similarly reported a higher incidence of AKI by urine output compared to the creatinine criteria.[39-41] The current threshold of urine output maybe too liberally defined. A stricter definition of 6-hour urine output of less than 0.3 ml/kg/h has been shown to be associated with composite outcome of mortality or dialysis.[42]

STRUCTURAL INJURY BIOMARKERS IN ACUTE KIDNEY INJURY

The discovery of biomarkers of tubular cellular injury has opened an avenue in research that facilitates a new approach to AKI diagnosis by identifying tubular injury, in addition to identifying change in function. Injury to tubular cells results in impairment of proximal tubular reabsorption of filtered biomarkers (NGAL and CysC), sloughing of pre-formed tubular cells (AP, GGT, α-GST and π-GST), or activation of tubular expression (NGAL, KIM-1, IL-18, and L-FABP).[9] Structural biomarker of injury includes proximal tubular brush border enzymes, GGT, induced biomarkers such as NGAL, IL-18, KIM-1, or impaired absorption such as CysC and albumin (Figure 1).[9] Various studies have investigated the performance of these biomarkers in AKI across different population groups, and these are summarised in Table II. To date, plasma and urinary NGAL are the most promising and the most researched biomarkers in AKI. This is further explored in the next section.

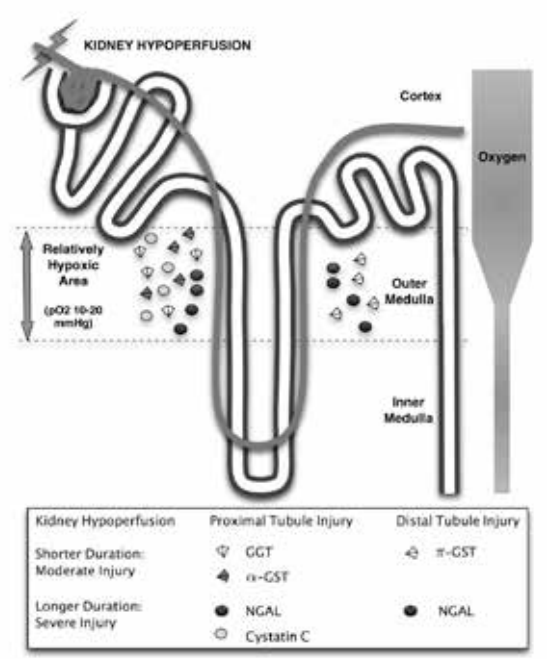

Figure 1: Tubular cellular injury following kidney hyoperfusion. From PhD Thesis by Azrina Md Ralib, University of Otago, New Zealand.[43]

TABLE II: Summary of urinary biomarkers of kidney tubular cell injury studies in critically ill patients

Biomarkers	Location/Role	Mechanism of increase	Diagnostic performance	Predictive performance
AP	Proximal tubule	Shedding from proximal tubule	*AKI* AUC 0.86 (0.68 to 0.97)[44] AUC 0.45 (0.40 to 0.65)[13]	*Dialysis*: AUC 0.63 (0.49 to 0.77)[13] *Mortality*: AUC 0.61 (0.53 to 0.70)[13]
GGT	Proximal tubule	Shedding from proximal tubule	*AKI* AUC 0.95 (0.79 to 1.00)[44] AUC 0.59 (0.54 to 0.65)[13] AUC 0.86 (0.78 to 0.95)[45]	*Dialysis*: AUC 0.60 (0.46 to 0.74)[13], AUC 0.64 (0.55 to 0.73)[46] *Mortality*: AUC of 0.65 (0.56 to 0.73)[13]
NAG	Glucosidase enzyme of (> 130 kDa), located in the lysosomes of the proximal tubular epithelial cell	Shedding from proximal tubule	*AKI* AUC 0.85 (0.64 to 0.96)[44]	*Dialysis*: AUC 0.81 (0.73 to 0.88)[46] *Composite outcome of dialysis & mortality* AUC of 0.71 (0.63 to 0.78) Adj OR of 5.4 (2.0 to 14.6)[47]
α-GST	52 kDa protein, located in the proximal tubule cells. Detoxification enzymes.[48,49]	Shedding from proximal tubule	*AKI*: AUC 0.89 (0.69 to 0.98)[44]	*Dialysis*: AUC 0.64 (0.55 to 0.72)[46]
π-GST	49 kDa protein, located in distal tubule cells. Detoxification enzymes.[48,49]	Shedding from distal tubule	*AKI*: AUC of 0.93 (0.74 to 0.99)[44]	
CysC	13 kDa protein released by all human nucleated cells.[50]	Impaired proximal tubular reabsorption or competition with albumin for reabsorption[51]	*AKI* AUC of 0.67 (0.62 to 0.73)[13] AUC 0.49[52]	*Dialysis*: AUC of 0.71 (0.57 to 0.84)[13], AUC 0.61[52] AUC 0.92 (0.86 to 0.96)[46] *Mortality*: AUC of 0.66 (0.58 to 0.75)[13]
α_1-microglobulin	31 kDa protein synthesised by the liver. Filtered through the glomerulus and reabsorbed by proximal tubular cells.[53]	Impaired proximal tubular reabsorption	NA	*Dialysis*: AUC 0.86 (0.78 to 0.92)[46]

TABLE II: Summary of urinary biomarkers of kidney tubular cell injury studies in critically ill patients

Biomarkers	Location/Role	Mechanism of increase	Diagnostic performance	Predictive performance
β_2-microglobulin	12 kDa protein presented at the membrane of nucleated cells. Filtered through the glomerulus and reabsorbed by proximal tubular cells.[53]	Impaired proximal tubular reabsorption	NA	*Dialysis* AUC 0.51 (0.42 to 0.60)[46]
IL-18	Pro-inflammatory cytokine. Mediator of inflammation and ischaemic tissue injury. In many organs	Up-regulated in proximal tubule epithelial cells and macrophages. Activated in apoptosis	*AKI* AUC 0.62 (0.56 to 0.67)[13] AUC 0.62 (0.54 to 0.69)[54], AUC 0.73, (>100 pg/ml) Adj OR 6.5 (2.1 to 20.4)[55] *Worsening AKI stage* AUC 0.68 (0.60 to 0.76) NRI 26.1% (7.3 to 44.8) IDI 5.7% (2.6 to 8.8)[56]	*Dialysis* AUC of 0.73 (0.59 to 0.86)[13] *Mortality* AUC of 0.68 (0.60 to 0.76)[13] (> 200 pg/ml) Adj OR 2.3 (1.2 to 4.4)[55] *Composite outcome of mortality or dialysis*: OR of 1.86 (1.31 to 2.64).[54]
L-FABP	15 kDa proteins, expressed in the proximal tubule.[57]	Upregulated in proximal tubules.[58]	*AKI* AUC 0.95[59] AUC 0.93 (0.88 to 0.97)[60]	*Mortality* AUC 0.99 (0.96 to 1.00) Adjusted OR 2.76, p=0.004[61]
KIM-1	90 kDa transmembrane glycoprotein in the apical membrane of proximal tubules[62,63]	Upregulated in proximal tubules, during regeneration of tubular cells, and scavenging of apoptotic cells.[64]	*AKI*: AUC 0.66 (0.61 to 0.72)[13] *Worsening AKI stage* AUC 0.64 (0.57 to 0.72) NRI 21.6% (2.7 to 40.6) IDI 6.0% (2.8 to 9.3)[56] *Worsening AKI stage/mortality* Adj AUC 0.69 (0.61 to 0.76) NRI 21.6% (2.7 to 40.6) IDI 6.0% (2.8 to 9.3)	*Dialysis*: AUC of 0.62 (0.48 to 0.76)[13] *Mortality*: AUC of 0.56 (0.47 to 0.64)[13] *Composite outcome of dialysis need and hospital mortality (ICU patients with AKI)* AUC of 0.61 (0.53 to 0.69) OR (adjusted for APACHE II; 4th to 1st quartile) of 2.8 (1.0 to 7.4)[47]

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is a small molecule of 25 kDa, which is covalently bound to gelatinase from neutrophils and expressed at low concentrations in several human tissues, including kidneys, lungs, stomach and colon. NGAL binds to iron via its siderophores; it can deplete bacterial iron, and plays an important role in immunity to bacterial infection. It also has a role kidney development, and may promote cellular repair.[65-67] NGAL expression is markedly induced by inflammation, such as in acute bacterial infections, severe sepsis and septic shock, asthma or chronic obstructive airway disease, or emphysematous lung.[68,69]

In the kidney, NGAL is expressed in the distal tubules and the collecting duct. In AKI, NGAL expression in the distal tubules is upregulated, and NGAL is excreted in the urine. Some is absorbed in the circulation and later filtered in the glomerulus.[65] Filtered NGAL is normally reabsorbed in the proximal tubule by megalin-cubilin mediated transport, and hence proximal tubular injury or competition with albumin may reduce reabsorption and increase excretion.[51] Increased urinary NGAL in AKI may result from an increase in NGAL synthesis in the distal tubules, and/or reduced reabsorption by the proximal tubules as a result of proximal tubular injury. Increased plasma NGAL in AKI may result from absorption of urinary NGAL into circulation, and/or increased NGAL production in distant organ, such as in lung and liver.[67] A decrease in GFR may reduce NGAL filtration, and result in accumulation of NGAL in the plasma. Hence, plasma NGAL may be represented both as a functional and structural biomarker of AKI.

To date, plasma and urinary NGAL are the most promising and the most researched biomarkers in AKI.[67,70] The first landmark study was in 71 paediatric cardiac surgery patients, which showed that urinary NGAL increased within 2 hours following surgery, and was highly and independently diagnostic of AKI.[71] This has prompted many studies, and two meta-analyses had been performed to investigate the utility of NGAL in AKI.[72] In a meta-analysis of 19 studies involving 2538 patients, both plasma and urinary NGAL were diagnostic of AKI, with an overall odds ratio of 18.6 (9.0 to 38.1), and AUC of 0.82 (0.73 to 0.89).[72,73] NGAL was also predictive of dialysis and mortality. In sub-group analysis of critically ill patients, NGAL had an odds ratio of 10.0 (3.0 to 33.1) and AUC of 0.72 (0.62 to 0.83) for prediction of dialysis or mortality. There was not much difference in performance of urinary and plasma NGAL.

A multicentre-pooled analysis was performed on ten studies of 2322 patients investigating AKI diagnosed by NGAL (NGAL-positive) compared to creatinine (creatinine-positive).[73] The cut-off points for NGAL were based on each individual study, and AKI by creatinine was defined by the RIFLE definition. There were 445 (19.2%) patients that were creatinine-negative and NGAL-positive, described as having "subclinical AKI". These patients had a higher dialysis need, mortality, and length of ICU and hospital stay, compared to those without AKI both based on both creatinine and NGAL. This study emphasises the role of NGAL in detecting those with tubular injury who would have been missed using creatinine alone.

NGAL studies in critically ill children[74,75] and adult,[76-80] and emergency department (ED) patients[81-83] are summarised in Table III. Most assessed biomarker performance solely by area under receiver operating characteristic (AUC of ROC) comparison. Of interest in the clinical setting is how do these biomarkers provide added value for AKI diagnosis or prediction of mortality or dialysis in the presence of the currently available clinical model. Several studies have assessed this by analysing the improvement in the AUC or by risk stratification (Integrated Discriminative Index (IDI) or Net Reclassification Index (NRI)) after addition of biomarker data to the reference model.[56,78,84,85] These indexes will be discussed in the later part of the paper.

TABLE III: Clinical studies of NGAL involving ED and ICU populations

Studies	NGAL	Population	n	AKI definition	Diagnosis of AKI	Prediction of mortality or dialysis
Zappitelli *et al.*(2007)[74]	uNGAL	Paediatric ICU	140	Modified paediatric RIFLE: eCrCl decrease by 25% from baseline	*AKI:* AUC 0.78 (0.62 to 0.95)	No difference in urinary NGAL between survivors and non-survivors
Nickolas *et al.*(2008)[81]	uNGAL	ED	635	RIFLE	*AKI*: AUC 0.95 (0.88 to 1.00)	*Mortality*: Adj OR: 24.7 (7.7 to 79)
Wheeler *et al.*(2008)[75]	pNGAL	Paediatric ICU	143	Urea > 100 mg/dl, or creatinine > 2 mg/dl or need of dialysis	*AKI*: AUC 0.68 (0.56 to 0.79)	NA
Bagshaw *et al.*(2009)[76]	pNGAL	Septic versus non-septic AKI	83	RIFLE	*Septic AKI*: pNGAL: AUC 0.77 (0.63 to 0.90) uNGAL: AUC 0.70 (0.59 to 0.82)	*Dialysis*: pNGAL: AUC 0.78 (0.61 to 0.95) uNGAL: AUC 0.70 (0.58 to 0.82) *Mortality*: pNGAL: AUC 0.69 (0.48 to 0.74) uNGAL: AUC 0.62 (0.49 to 0.76)
Cruz *et al.*(2009)[77]	pNGAL	ICU	301	> 50% baseline or urine output < 0.5 ml/kg/h for > 6 h	*AKI*: AUC 0.78 (0.65 to 0.90)	NA
Siew *et al.*(2009)[78]	uNGAL	ICU	451	0.3 mg/dl or > 50% from baseline creatinine	*AKI within 24 hours*: AUC 0.71 (0.63 to 0.78) Adj OR 1.7 (1.1 to 2.6) NRI (3 categories) -1.5%, p=0.78	*Mortality*: Adj HR: 2.6 (1.6 to 4.4)
Makris *et al.*(2009)[79]	uNGAL	Multi-trauma adult ICU	31	RIFLE	*AKI*: AUC 0.98 (0.82 to 0.98)	NA
Constantin *et al.*(2010)[80]	pNGAL	Adult ICU	88	> 50% from baseline creatinine	*AKI*: AUC 0.92 (0.85 to 0.97)	*Dialysis*: AUC 0.78 (0.69 to 0.87).
Shapiro *et al.*(2010)[83]	pNGAL	ED	661	Increase of > 0.5mg/dl within 72 h	*AKI*: AUC 0.82 (0.76 to 0.88)	*Hospital Mortality* AUC 0.75 (0.68 to 0.82)

TABLE III: Clinical studies of NGAL involving ED and ICU populations

Studies	NGAL	Population	n	AKI definition	Diagnosis of AKI	Prediction of mortality or dialysis
Martensson *et al*.(2010)[86]	pNGAL uNGAL	Adult ICU (septic shock)	65	AKIN or RIFLE	*AKI*: pNGAL: AUC 0.67 (0.39 to 0.94) uNGAL: AUC 0.86 (0.68 to 1.00)	NA
Endre *et al*.(2011)[13]	uNGAL	Adult ICU	529	AKIN	*AKI*: AUC 0.66 (0.60 to 0.72)	*Dialysis*: AUC 0.79 (0.65 to 0.94) *Mortality*: AUC 0.66 (0.57 to 0.74)
de Geus *et al*.(2011)[87]	uNGAL, pNGAL	Adult ICU	510	RIFLE	*Sustained AKI* (> 12 hours): uNGAL: AUC 0.80 (0.72 to 0.88) pNGAL: AUC 0.76 (0.67 to 0.85)	NA
Doi *et al*.(2011)	uNGAL	Adult ICU	339	RIFLE	*AKI*: AUC 0.70 (0.63 to 0.75)	*14-d mortality*: Adj OR 3.1 (1.1 to 8.9)
Kokkoris *et al*.(2012)[84]	pNGAL and uNGAL	Adult ICU	100	RIFLE	*AKI*: pNGAL: AUC 0.78 (0.68 to 0.85), adj AUC 0.85, difference p=0.03 cfNRI 78% (21), p=0.0002 IDI 0.16 (0.045), p=0.0004 uNGAL: AUC 0.74 (0.64 to 0.82), adj AUC 0.78, difference p=0.03 cfNRI 38% (21) p=0.07 IDI 0.032 (0.018), p=0.09	NA
de Geus *et al*.(2011)[85]	uNGAL pNGAL	Adult ICU	632	RIFLE	*AKI*: uNGAL: AUC 0.80 ± 0.04 pNGAL AUC 0.77 ± 0.05 *Severe AKI (RIFLE stage F)* uNGAL: Improvement in AUC, p=0.09 NRI (3 categories) 2.3% (p=0.37) pNGAL: Improvement in AUC,p=0.01 NRI (3 categories) 8.5% (p=0.09)	*Dialysis*: uNGAL: 0.89 ± 0.04 pNGAL: 0.88 ± 0.06 *Mortality*: uNGAL: 0.64 ± 0.06 pNGAL: 0.63 ± 0.06

uNGAL: Urinary NGAL, pNGAL: Plasma NGAL, eCrCl: estimated creatinine clearance

ASSESSMENT OF BIOMARKER PERFORMANCE

Area under receiver operating characteristic curve

The use of the area under curve (AUC) of the receiver operating characteristic (ROC) curve has became the most popular metric for assessment of new biomarkers against a gold-standard.[89] It is a measure of discrimination; that is how well a given test (e.g. a new biomarker) separates those with and without disease as determined by the gold standard (creatinine change).[90] The ROC curve is a graphical plot of sensitivity (true positive rate) against 1-specificity (false positive rate) across a series of cut-off points (e.g. biomarkers concentration).[91] The AUC ranges from 0.5 (no discrimination) to 1 (perfect discrimination).[90] Clinical validity is assumed at an AUC of more than 0.70.

The calculation of the AUC is based on rank, merely considering the comparative rank between those with and without the disease. It does not take into account the extent of change of the biomarker or its distribution. Any change of rank in those at low distribution will have the same impact in those at high distribution.[90] The additional value of a new biomarker to an available clinical diagnostic or predictor assessment (the reference model) may be assessed by the improvement in AUC after addition of the biomarker to the reference model. However, change in the AUC does not adequately reflect the incremental improvement of biomarker performance compared to established marker.[92,93] This limitation is addressed in new metrics for assessment of biomarkers using the risk stratification analysis.[94,95]

Risk stratification analysis

Due to the limitation of the AUC, there is a growing interest in new metrics using a more comprehensive risk stratification analyses to assess improvement of biomarker performance to the established marker. These include the integrated discrimination improvement (IDI) and net reclassification improvement (NRI).[54,95] These analyses take into account both the improvement in risk in prediction of an event, and also the reduction of risk in prediction of a non-event.

NRI was first described by Pencina *et al*. in 2008.[94] Limitation of NRI is the need for pre-determined risk cut-off points to allocate patients to risk groups. In contrast to the cardiovascular risk assessment, there is no consensus risk cut-off point for AKI. Pencina recognised issues arising when thresholds were not agreed upon, and therefore modified the NRI, creating the category-free NRI (cfNRI) that obviates the need to have cut-off points for different risk groups. NRI and cfNRI are calculated based on direction of change in risk for each individual from the reference test (positive or negative). However, they do not take into account the extent of change. The IDI was designed to address this issue.[96] The IDI measures the extent of change of increased risk for those who had an event (IDI_{event}) and decrease risk for those without the event ($IDI_{non\text{-}event}$).[95] Several studies in AKI biomarkers have integrated the use of IDI or NRI in the analysis of biomarker performance.[54,82,97-99]

Assessing structural biomarkers using a functional biomarker, plasma creatinine as the "gold standard"

Despite the known limitations of plasma creatinine in AKI diagnosis, it is still used in many studies as the reference or gold standard to assess biomarker performance. AKI based on creatinine reflects failure of kidney function, rather than tubular injury. The limitations of plasma creatinine may affect the assessment of new biomarkers, resulting in underestimates of biomarker performance even when they perfectly reflect tubular injury.[93,100] Consistent with this, a biomarker with good performance may merely reflect the same limitations as creatinine. Therefore, these comparisons must be interpreted cautiously, and be comprehensively evaluated. An assessment of the new biomarkers beyond creatinine, such as comparison with hard outcomes including mortality or dialysis may offer a more valid assessment.

The difference in measurement of function and injury may be evaluated more comprehensively by looking at the concordance and discordance between creatinine and biomarker of injury.[93] This may be achieved by determination of biomarker-negative or biomarker-positive patients based on pre-specified cut-off points and comparison with creatinine-negative or creatinine-positive patients utilising the RIFLE, AKIN or KDIGO definitions. Of special interest are those who are biomarker-positive and creatinine-negative, that is those who would not have been identified based on current consensus of AKI definitions, and regarded as 'subclinical' AKI. This was first analysed by Haase *et al*. in pooled analysis of more than 2000 critically ill patients with cardiorenal syndrome. Overall, 20 to 40% of patients were identified as NGAL-positive and creatinine-positive. These exhibited higher length of ICU and hospital stay, more dialysis, and greater in-hospital mortality compared to those without AKI by either creatinine or NGAL.[73] This study is revolutionary since it was the first study to identify biomarker-positive and creatinine-negative patients as a clinically relevant and at risk subgroup of AKI. In a multicentre biomarker study of 1,635 ED patients, 28% of patients were identified as intermediate risk (either creatinine-negative and urinary NGAL-positive, or creatinine-positive and urinary NGAL-negative).[82] This group of patients had a higher rate of dialysis or mortality compared to those at low risk (creatinine-negative and urinary NGAL/KIM-1-negative) (5.2% versus 2.1%, $p<0.01$).

These two studies clearly identify the additional value of new biomarkers over creatinine measurement, not only for early diagnosis of AKI, but also for identification of a group of patients who would not have been identified using the current consensus AKI definition.[101] The associated higher rates of adverse outcomes in these patients supports reassessment of the AKI definition to incorporate biomarkers of tubular cell injury.[102]

SUMMARY OF BIOMARKERS STUDIES

Increasing interest in novel AKI biomarkers has led to intensive discussion about how to utilise biomarker of tubular cell injury in the AKI definition. The AKIN group described AKI as "functional or structural abnormalities or markers of kidney damage including abnormalities in blood, urine, or tissue tests or imaging studies present for less than three months."[4] The current available AKI definitions are based on plasma creatinine or urine output, which reflect functional abnormalities, whereas novel AKI biomarkers of injury reflect structural abnormalities. Further advances in defining AKI and classifying its severity based on biomarker of tubular injury are needed. Most studies typically assessed the biomarkers in isolation. Combination of biomarker of injury in the AKI diagnosis has been proposed to be more reflective of the pathophysiological changes. Of interest is how the combination of these functional and structural biomarkers can be implemented in AKI definition and outcome prediction for risk stratification. The 10th Acute Dialysis Quality Initiative (ADQI) group has proposed the use of functional and structural biomarker framework to stratify patients with AKI.[103] This framework can be utilised to assess the aetiology, progression and sepctrum of AKI, and could provide the platform for assessment of biomarkers in future studies.

THE FUTURE OF ACUTE KIDNEY INJURY BIOMARKERS

In a research setting, AKI biomarkers could be utilised to triage for inclusion to AKI clinical trials, or as an outcome measure. Due to the known limitations of creatinine as a biomarker of AKI, it would be a step forward for the research community to utilise injury biomarkers in this setting. Biomarker measurement is already critical in drug development in assessing kidney toxicity.[104] In the clinical setting, it could be utilised to assist clinicians in detecting AKI, and monitoring its progress, response to therapy and recovery. Ultimately, AKI biomarkers could provide better decision support for clinicians treating the critically ill.

Triaging for AKI clinical trial

Most interventional trials in AKI therapy have been unsuccessful, partly due to lack of early

diagnosis of AKI. A promising avenue for AKI biomarker research should be translated into clinical trials. Biomarkers could be used to identify early injury in those who are at risk of AKI, enabling development of early interventional (or secondary preventional) therapies. The EARLYARF trial[105] is the only completed study to have utilised AKI injury biomarkers to triage patients to an intervention (high-dose EPO or placebo). Although this study used a proximal tubular brush border enzyme, which was subsequently shown to be a poor predictor of creatinine increase, it has opened a new frontier in how to utilise other more sensitive and specific new biomarker. This study has been described as a 'glimpse of the future'.[106] One on-going study is using a similar method to triage patients to inclusion based on an elevation of urinary NGAL.[107] The study aimed to compare the utility of intravenous hydration or volume expansion strategies for early intervention (or secondary prevention) in high-risk patients with elevated urinary NGAL following administration of intravenous contrast media.

Outcome measures

Biomarkers of injury may also be utilised as endpoints for clinical trials investigating AKI treatments. Early studies used urinary NAG, microalbumin or retinol binding protein as biomarkers of tubular cell injury in investigating the impact of specific interventions. More recent interventional studies in clinical trial registries are utilising biomarkers such as NGAL, IL-18, L-FABP or CysC as a primary or secondary outcome measures (examples in Table IV). Limitation to using this method is the determination of appropriate cut-off points and the time of measurement in relation to time of injury. In patients undergoing cardiac surgery and those receiving intravenous contrast agent, it is possible to determine the baseline concentration of the biomarkers before injury and to exactly time injury. However in critically ill patients, where the time and extent of injury are largely unknown, comparison is more difficult.

Translating research into clinical practice

Several factors hamper the translation of biomarkers to the clinical setting. Lack of consistent assessment of risk across different trials impedes the acceptance of biomarker assessment amongst clinicians. Most studies are observational studies, small and in a single-centre. To date, there is no randomised controlled trial comparing the use of biomarker data to standard clinical practice.[67] Lack of commercial assays for most biomarkers, and the high cost of available assays (e.g. NGAL or CysC) further limit their wide use. Nevertheless, their cost should be weighed against the cost associated with AKI (e.g. longer ICU or hospital stay, or need for dialysis). Despite these limitations, development of AKI biomarkers has regenerated interest and challenged the definition and assessment of AKI.

The most important question amongst the hype of finding an early biomarker for AKI is whether it would make a difference to patient outcomes. The added value of these biomarkers to the currently available measures, such as creatinine, urine output, urine microscopy or biopsy should be investigated in series of case studies and in population-based studies. A consensus definition of AKI is needed that incorporates both markers of injury and of function, and which takes into consideration of clinical factors (e.g. risk of AKI).

CONCLUSION

AKI is common in critical illness, and contributes to high mortality. The current functional biomarkers plasma creatinine and urine output are still useful in AKI detection. Structural biomarkers including induced biomarkers such as NGAL, filtered biomarker, CysC and tubular enzymes can be used for stratification of injury severity. A combination of these functional and structural biomarkers is of utility for risk stratifcation and outcome prediction. These could be utilised as outcome measures in clinical trial of novel AKI therapies. Ultimately this could provide better decision support for clinicians treating the critically ill.

TABLE IV: AKI biomarkers as outcome measures in AKI intervention trial

Registry Number/Published Reference	Title	Cohort	Biomarker as primary or secondary outcome
Yallop *et al*. (2008)[108]	The effect of mannitol on renal function following cardio-pulmonary bypass in patients with normal pre-operative creatinine.	Cardiac surgery	Urinary RBP, urinary microalbumin, α-GST (Primary outcome)
Mahmood *et al*. (2007)[109]	Randomised clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery	Abdominal aortic surgery	Urinary α1-microglobulin/Ucr, urinary Ig levels (Secondary outcome)
Hynninen *et al*. (2006)[110]	N-acetylcysteine for the prevention of kidney injury in abdominal aortic surgery: a randomised, double-blind, placebo-controlled trial	Abdominal aortic surgery	Urinary NAG/Ucr, urinary albumin/Ucr (Primary outcome)
Ristikankare *et al*.(2006)[111]	Lack of renoprotective effect of i.v. N-acetylcysteine in patients with chronic renal failure undergoing cardiac surgery	Cardiac surgery	Urinary NAG/Ucr > 30%, CysC > 1.4 mg/l (Primary outcome)
NCT00676234	Recombinant Human Erythropoietin Use in Intensive Care Unit (ICU) Patients: Does it Prevent Acute Renal Failure	Adult ICU	Urinary NGAL and plasma cystatin C (Primary outcome)
NCT01146925	Deferiprone for the Prevention of Contrast-Induced Acute Kidney Injury	Contrast-induced AKI in high-risk patients with CKD undergoing coronary angiography and PCI	Mean changes of AKI biomarkers from day 1 to peak of urinary NGAL, L-FABP, IL-18, KIM-1,α -GSTand π-GST, and urinary and plasma CysC (Primary outcome)
NCT00978354	Furosemide in Early Acute Kidney Injury (The SPARK Study)	Adult ICU	Urinary NGAL and IL-18 (Secondary outcome)
NCT01066351	Efficacy of Erythropoietin to Prevent Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Cardiac Surgery	Cardiac surgery	Urinary NGAL (Secondary outcome)
NCT00821522	The Influence of Remote Ischemic Preconditioning on Acute Kidney Injury After Cardiac Surgery	Cardiac surgery	AKI defined by elevation in NGAL (Secondary outcome)
NCT01690832	Fenoldopam for Prevention of Acute Kidney Injury (FANCY)	Contrast-induced AKI	NGAL (Secondary outcome)
NCT01098032	RenalGuard System and Contrast Media (REMEDIAL II)	CKD patients with contrast agent	Plasma and urinary NGAL (Secondary outcome)
ISRCTN85447324	Erythopoietin and delayed graft function in kidney allografts from extended criteria donors	Kidney transplant (from deceased donor)	Plasma and urinary NGAL, IL-18, HGF, L-FABP (Primary outcome)
ISRCTN52446152	Fluid restriction following open aortic aneurysm surgery	Abdominal aortic aneurysm surgery	Urinary IL-18, NGAL, RBP, albumin (Primary outcome)
ISRCTN11019960	The effect of the arm blood pressure cuff inflations during AAA surgery as a measure of protecting kidney and heart from injury	Emergency abdominal aneurysm surgery	Urinary NGAL (Primary outcome)

Source: Clinicaltrials.gov and ISRCTN Register.

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Haemodynamic Monitoring Using Echocardiography in the Critically Ill Patients

Wan Nasrudin bin Wan Ismail, MD (USM), M.Med (Anaesthesiology) UKM, EDIC
Consultant Intensivist, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia

Haemodynamic monitoring is very important in management of critically ill patients. Correct interpretation of the available data is vital to ensure appropriate intervention. The use of echocardiography in critically ill patients will allow accurate measurement of several haemodynamic variables noninvasively. By using echocardiography as a haemodynamic monitoring tool, clinicians can evaluate several aspects of shock states, such as cardiac output, fluid responsiveness, myocardial contractility and other medical emergencies such as cardiac tamponade and acute cor-pulmonale. In critically ill patient, focus echocardiography examination is useful for quick diagnosis and treatment.

INTRODUCTION

Haemodynamic monitoring is very important in managing critically ill patient. Assessing critically ill patients should start by quick history-taking followed by physical examination, however signs and symptoms often poorly correlate with measured haemodynamic variables.[1] Available modalities should be used for acquisition of additional haemodynamic parameters to guide therapy. Various techniques are available for haemodynamic monitoring. It varies from completely invasive to non-invasive, from intermittent to continuous, and differs in their basic principles, methods, parameters, and costs.[2-5]

The purpose of this paper is to provide an overview on how echocardiography can be incorporated as another modality for haemodynamic monitoring in critically ill patients. Echocardiography is very useful tool for haemodynamic monitoring because it is fast, easily available and noninvasive.[6] Transthoracic application is adequate in most of the time, however in selected patient, transoesophageal examination (TOE) is necessary. Both techniques could provide real-time imaging and dynamic imaging of the heart. The purpose of echocardiographic examinations are (1) to help in making correct diagnosis, (2) to guide in interventions and appropriate therapy, and (3) to monitor the progress of the patients.[7]

ECHOCARDIOGRAPHY IN CRITICALLY ILL - AN OVERVIEW

Performing echocardiography in critically ill patients can be challenging, especially if the patient is being mechanically ventilated, on high inotropic support and had underlying illness that can interfere with the sonographic examination. Image acquisition is one of the main limitations of echocardiography in the Intensive Care Unit (ICU). Various factors can reduce the quality of the images or interfere with sonographic examination such as hyperinflated lungs by positive pressure ventilation, postoperative subcutaneous emphysema, surgical incisions and drains, dressings, inadequate exposure or positioning. All of these factors contribute to a poor acoustic window.

Several factors could alter cardiovascular physiology of critically ill patients, such as positive pressure ventilation, sedation, variation in loading conditions, inotropic agents and carbon dioxide tensions.[8] All these factors must be considered when interpreting data from haemodynamic monitoring. Some of the examination such as assessment of fluid responsiveness must be done when there is no spontaneous breathing activity i.e. patient need to be adequately sedated or paralysed.

BASIC ECHOCARDIOGRAPHY

The type of probe used

The probe used for echocardiographic examination is phase array probe with smaller footprint. It emits and receives ultrasound in the range of 3.5 to 5 MHz.

Basic Mode of Echocardiography examination Techniques

2D Echocardiography

2D echocardiography is used to display anatomical examination in real time tomographic image. By aiming the ultrasound probe at the heart, precisely oriented anatomical 'slices' are obtained. It provides information regarding cardiac chamber size, global and regional systolic function, and valvular anatomy.

M-mode Echocardiography

M-mode or motion-mode images are a continuous 1D graphic display that can be derived by selecting any of the individual sector lines from which a 2D image is constructed. It is useful for quantification of myocardial wall and chamber sizes in estimating the left ventricular (LV) mass and chamber volume respectively. Since it has a high temporal resolution, M-mode is also helpful in assessing the motion of rapidly moving cardiac structures such as cardiac valves.

Doppler Echocardiograph

Doppler echocardiography is used to supplement 2D and M-mode echocardiography. There are four types of Doppler modality used; continuous wave (CW), pulsed-wave (PW), color flow mapping (CFM), and tissue Doppler. It can provide functional information regarding intra-cardiac haemodynamics: systolic and diastolic flow, blood velocity and volume, severity of valvular lesions, location and severity of intracardiac shunts, and assessment of diastolic function.[9]

PRACTICAL USE OF ECHOCARDIOGRAPHY IN THE ICU SETTING

To correlate echocardiographic findings with clinical examination

A significant proportion of patients admitted to an ICU with non-cardiac illness have underlying cardiac abnormalities, which can be detected with surveillance echocardiography at the time of admission. Bossone *et al*, found that 35% of medical ICU patients (169 of 500 patients) had occult cardiac abnormalities and of these 77% were unsuspected. They had longer duration of ICU stay, but no increase in mortality.[10]

In the ICU, echocardiography may also be used as a diagnostic tool for monitoring response to interventions or therapeutic maneuvers[11,12] as an extension to the clinical examination,[13-15] and as an adjunct to investigation and diagnosis in the peri-resuscitation period. Specific indications for echocardiography in acute care setting are for evaluation of hypotension or haemodynamic instability, myocardial ischaemia or infarction, respiratory failure and pulmonary embolism.[13]

Goal-directed examination

Echocardiographic examination in critically should be gold-directed. Detailed cardiac examination, including valvular function, congenital abnormalities, intracardiac shunt and estimation of pulmonary pressures, is best done by certified echocardiographer.[14]

Rapid Cardiac Assessment (RCA) is a goal directed examination to assess cardiac function in the compromised patient. The concept of critical care goal directed echocardiography by non-cardiologists has been gaining momentum. Several protocols have been proposed including Focused Assessment Diagnostic Echocardiography (FADE),[15] Rapid Assessment Cardiac ccardiography (RACE), Focused Cardiac UltraSound (FOCUS)[16] and focused assessed transthoracic echocardiography (FATE).[17] Novice operators with minimal training can perform these examinations. However, complex examinations should be done by trained echocardiographers with cardiologist consultation.

Rapid assessment by cardiac echocardiography or RACE is useful as the initial bedside echocardiographic evaluation of unstable critically ill patients. It provides fast and accurate measurement of patients' cardiac and haemodynamic status. The

examination is conducted systematically and the findings must be correlated with patients' clinical status. The examination uses two modes (M-modes and 2D dimensional imaging) and five views (parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber, and subcostal views) to answer four questions. At the end of examination we should be able to have ideas on these parameters, (1) What is the left heart function? (2) What is the right heart function? (3) Is there any evidence of pericardial effusion and cardiac tamponade? and (4) What is the volume status?

ECHOCARDIOGRAPHIC PARAMETERS FOR HAEMODYNAMIC MONITORING

ASSESSMENT OF VOLUME STATUS

A reliable assessment of volume status is very important especially in haemodynamically unstable patient. Fluid resuscitation is an important aspect in management of septic shock patient.[18,19] However, excessive positive fluid balance in critically ill patient has been shown to be associated with increased mortality.[20,21] In addition, positive fluid balance affects lung function, and has been associated with increase duration of mechanical ventilation.[22] We need to know whether patient will respond to a bolus of fluids by raising his cardiac output, blood pressure or both. Invasive pressure measurements to assess LV filling such as CVP and PA catheter are commonly used at the bedside to make inferences regarding LV preload. These pressure measurements, however, only weakly correlate with LV volume and fluid responsiveness.[23,24]

Echocardiographic evidence is quite obvious in patients with severe hypovolaemia. The triad of a "kissing" LV, small LV and RV size, together with a normal or small RA is strongly suggestive of severe hypovolaemia that will benefit from fluid resuscitation.[7] However, in less severe hypovolaemia, the evidence is not very obvious and is inaccurate, hence, need to depend on dynamic parameters.

Static parameters of intravascular volume

Apart from central venous pressure (CVP) and Pulmonary Artery Wedge Pressure (PAWP), echocardiography can measure additional parameters to reflect intravascular volume such as Left Ventricular Diastolic Area (LVEDA) and Inferior Vena Cava (IVC) diameter.

Left ventricular end-diastolic area

Cardiac ultrasound is also now increasingly used to assess volume status and fluid responsiveness in the ICU. Two-dimensional (2D) echocardiography can subjectively evaluate volume status. LVEDA correlates well with left ventricular end-diastolic volume and, as such, left ventricular preload.[25] Using two-dimensional echocardiography, systolic obliteration of the left ventricular cavity signifies underfilling of the heart, hypovolemia and fluid responsiveness.[25]

Inferior vena cava diameter

The diameter of the inferior vena cava (IVC) as it enters the right atrium can be measured by subcostal echocardiography. Several studies demonstrated that IVC diameter correlates with right atrial pressure.[26] However it is an indirect indicator of CVP and is associated with the limitations similar to CVP measurement.

Barbier *et al* demonstrated that in septic shock, evaluation of IVC 'distensibility' via transthoracic echocardiography could be an accurate predictor of fluid responsiveness in patients receiving controlled mechanical ventilation. In patients with circulatory failure such as severe sepsis, distensibility index is defined as percentage of [(IVC diameter at end-inspiration - IVC diameter at end-expiration) ÷ IVC diameter at end-expiration]. A value of more than 18% can predict the efficacy of volume expansion with 90% sensitivity and 90% specificity.[27]

Dynamic Parameters of Intravascular Volume

Cardiac output is dependent on interactions between preload, contractility and afterload, hence measurement of static parameters alone as described above are not enough to gauge adequacy of volume resuscitation. In view of this limitation, over the last

decade there is increasing interest in using dynamic parameters to assess intravascular volume based on the understanding of heart-lung interactions during mechanical ventilation. Examples of dynamic measurement include pulse pressure variation (PPV) derived from analysis of the arterial blood pressure waveform, stroke volume variation (SVV) derived from pulse-contour analysis (measured by LiDCO or PiCCO monitoring systems), and variation of the amplitude of the pulse oximeter plethysmographic waveform.

Dynamic changes in aortic flow velocity/stroke volume assessed by echocardiography

Assuming that the aortic annulus diameter is constant over the respiratory cycle, changes in aortic blood flow should reflect changes in LV stroke volume. Feissel *et al* demonstrated that the respiratory changes in aortic blood velocity assessed by echocardiography predicted fluid responsiveness in mechanically ventilated patients.[28]

Mandeville *et al* in a systemic review regarding the ability to use transthoracic echocardiography to predict fluid responsiveness has concluded that transthoracic echocardiographic techniques accurately predict fluid responsiveness in critically ill patients. Discriminative power is not affected by the technique selected.[29]

LEFT VENTRICULAR FUNCTION

Overall assessment of LV function (contractility) may be quickly obtained by "eyeballing" from the parasternal long- and short-axis, apical 2-chamber and 4-chamber and subcostal views.[17,18,30] However for detail assessment including ejection fraction (EF), combinations of ejection fraction or fractional shortening, Doppler patterns of ventricular filling, and tissue Doppler imaging can be used.[11] Visual estimation of LVF is the most commonly used and for experienced operators this is equal to formal method of assessment.[31,32] This is among the best technique used for haemodynamically unstable patients.[33]

Obtaining parasternal views in mechanically ventilated patients may be difficult. In that situation, the subcostal approach (view) is quite useful because it minimises signal attenuation from air in the lungs and rib cage.[7] For more comprehensive picture of contractility, several windows should be used.

RIGHT VENTRICULAR (RV) FUNCTION

Right ventricular dysfunction is common in the ICU. It can occur as part of biventricular dysfunction in sepsis[34] or precipitated by other factors such acute respiratory distress syndrome (ARDS), pulmonary embolism, heart transplantation, left ventricular assist device and mechanical ventilation[35] TTE is the modality of choice to evaluate the right ventricular systolic function. Usually 2D modalities of the right heart in parasternal, apical or subcostal views are used to estimate the size and the kinetics of the RV. Doppler is used to estimate the severity of the tricuspid regurgitation and systolic artery pulmonary pressure.[8]

RV function is assessed on various points that include its overall size, wall thickness and contractility. The American Society of Echocardiography has recently publish a comprehensive guidelines for this echocardiographic examination.[36]

Direct measurement of RV size by endocardial border tracing is difficult and not recommended. Instead, subjective assessment is used by comparing the right ventricular area to the left ventricular area in the apical 4-chamber view. The RV should be smaller than the LV, and a ratio of RV: LV end diastolic area of more than 0.6 indicates a dilated right ventricle, consistent with pressure or volume overload. Mechanical ventilation and pulmonary hypertension are common conditions causing RV dilatation in the critically ill patient. Normally the right ventricular wall is thin, hence thickened or hyperthrophied RV indicates prior disease such as chronic pulmonary hypertension. The contractility of RV can be assessed by eyeballing and as in LV function assessment. It should done

at various views such as parasternal long-axis, apical 4-chamber, and subcostal views to get better results.[7] The longitudinal motion of the tricuspid annulus correlates well with RV systolic function. Tricuspid annular plane excursion (TAPSE) records the tricuspid annular longitudinal displacement in the A4C view by means of M-mode. A TAPSE of 16 mm or less suggests RV systolic impairment.

MANAGEMENT OF HYPOTENSIVE PATIENT IN ICU, THE ROLE OF ECHOCARDIOGRAPHY

Hypotension is a common problem in ICU, and this requires rapid diagnosis. Together with clinical assessment, bedside echocardiography can help in getting an accurate diagnosis quickly. Preload, contractility, systolic function (global and focal), and assessment of diastolic dysfunction (common cause of congestive heart failure) can be performed quickly. Specific situations like pericardial tamponade, pulmonary embolism, left ventricular outflow tract obstruction, unexplained hypoxemia, and aortic dissection, among others, can all be reliably diagnosed using transesophageal echocardiography.[37]

In many occasions the cause for hypotension is obvious, which includes hypovolemic shock, cardiogenic shock, spinal shock or overuse of vasodilator. Understanding why the patient is actually hypotensive is crucial and should be addressed as soon as possible. This is where echocardiography is irreplaceable as a first-line diagnostic technique and should be able to pinpoint the mechanism of hypotension.[38]

By performing echocardiographic examination in hypotensive patient, we can get the relevant information which can help in acute management of the patient.[38,39]

- Evaluation of volume status/preload
- Assessment fluid responsiveness
- LV Systolic and diastolic function
- RV Systolic and diastolic function
- Pericardial space - to look for cardiac tamponade
- Valvular function and integrity

CONCLUSION

Continuous haemodynamic monitoring is of paramount importance to assess altered physiological parameters that requires therapeutic intervention. The trend is towards non-invasive monitoring that is easily available at the bedside. Echocardiography is widely used in the ICU. It can be used to solve unexplained haemodynamic disturbance, in evaluating volume status and diagnosing acute medical emergencies such as cardiac tamponade, acute cor-pulmonale and acute left ventricular dysfunction. Focus assessment using standard guidelines is used for quick diagnosis, but at the same time we must understand the technique. It is useful for the doctors taking care of critically ill patient to be familiar with the use of echocardiography.

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Clinical Use of Lactate Monitoring in Critically Ill Patients

Claudia Cheng Ai Yu, MBBS (Qld), FCICM, FANZCA, MRCP (UK), PDipID (HK)
Consultant Intensivist and Anaesthesiologist, Loh Guan Lye Specialist Centre, Penang, Malaysia

INTRODUCTION

Lactic acid ($C_3H_6O_3$) is a weak acid that was first discovered in sour milk by Karl Wilhelm Scheele in 1780 (Figure 1). It was subsequently demonstrated in human blood by Johann Joseph Scherer in 1843, from a patient who died from puerperal fever. Carl Flowarczny was the first to demonstrate lactic acid in the living patient in 1858.[1] Lactate ($C_3H_5O_3$-) is the conjugate base of lactic acid, but both terms are often used interchangeably in practice. In the hospital setting, hyperlactataemia is the commonest cause of high anion gap metabolic acidosis.

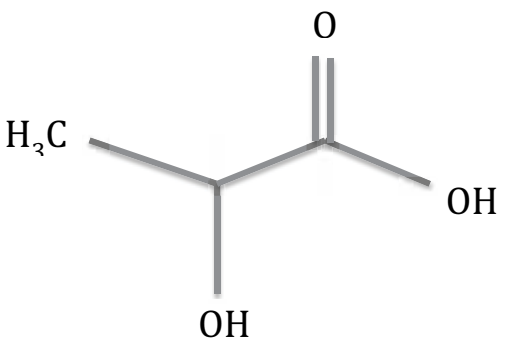

Figure 1: Lactic Acid Molecule

LACTATE PHYSIOLOGY

At physiological pH, lactic acid exists as lactate. 15-20 mmol/kg lactic acid is produced per day in all tissues including skeletal muscle, brain, red blood cells and kidneys. Lactate is utilized by the liver predominantly, and to a lesser degree in kidneys, heart and brain. The liver can metabolize lactate at a rate of up to 320 mmol/L/h. A continuous cycle of lactate production and metabolism occurs to maintain low levels of lactate in health.

In a normal physiological state, with normal oxygenation and perfusion, aerobic metabolism predominates and produces more energy. Pyruvate is converted to Acetyl CoA through oxidative decarboxylation to produce CO_2, H_2O and 36 ATPs (Figure 2). However this process requires oxygen. In circumstances of inadequate perfusion, the body undergoes anaerobic metabolism and pyruvate is converted to lactate and 2 ATPs (Figure 3). This process is catalyzed by lactate dehydrogenase which produces the L-lactate stereoisomer. D-lactate only occurs in certain situations such as short gut syndrome, requires a special assay to detect and will not be covered in this review.

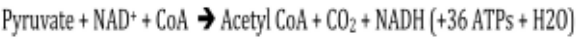

Figure 2: Aerobic metabolism - 36 ATP generated

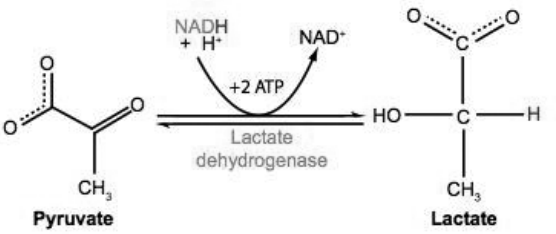

Figure 3: Aerobic metabolism - 36 ATP generated

PATHOPHYSIOLOGY

Elevated serum lactate or hyperlactataemia can be due to overproduction or underutilization of lactate. Causes of lactic acidosis are often divided into Type A lactic acidosis (presence of impaired tissue oxygenation) and Type B lactic acidosis (absence of overt systemic hypoperfusion). Type A may be caused by i) inadequate oxygen delivery e.g. various forms of shock (cardiogenic, hypovolaemia, dehydration, sepsis), cardiopulmonary arrest, profound anemia; ii) disproportionate oxygen demands e.g. status epilepticus, strenuous exercise,

hyperthermia, shivering. Type B usually result from toxin-induced impaired cellular metabolism e.g. metformin, salicylate overdose, cyanide toxicity, alcoholism, tumor-related, HIV.

THE MECHANISM OF HYPERLACTATAEMIA IN THE CRITICALLY ILL

In the critically ill patient, hyperlactataemia may result from a combination of anaerobic and aerobic mechanisms. From the anaerobic process, there is increased lactate production in hypoxic muscles. From the aerobic process, there is increased glycolysis and pyruvate production via cytokine-mediated cellular uptake of glucose or by catecholamine-stimulated Na-K pump hyperactivity. This results in increased pyruvate production that exceeds the capacity of the pyruvate dehydrogenase complex (PDH), with increased lactate levels by mass effect.[2] Secondly, in the critically ill septic patients, PDH dysfunction has been reported.[3] Thirdly, the lung is known to produce lactate, probably due to metabolic adaptations in response to inflammatory mediators rather than to lung tissue hypoxia per se. Finally, reduced clearance of lactate will result in increased levels even when lactate production is not increased. This can be seen in haemodynamically stable patients with sepsis with impaired lactate clearance as a result of septic liver dysfunction.

DEFINING HYPERLACTATAEMIA AND ITS IMPLICATIONS

Basal venous or arterial lactate of less than 1 mmol/L is regarded as a safe level. A range of 0.5-1.5 mmol/L is generally accepted to represent normal serum lactate in unstressed, healthy individuals. Values of < 2 mmol/L is still considered to be the normal range in critically ill patients. Levels of ≥ 4 mmol/L is widely accepted as high, and is considered to be the danger zone, with possible irreversible tissue hypoxia. The controversy arises as to the exact cut-off point that will define normolactataemia from absolute hyperlactataemia, and its clinical implication. Currently, values between 2 - 3.9 mmol/L are regarded as the intermediate zone of hyperlactataemia.

A study aiming to investigate the outcome of patients with relative hyperlactataemia recruited patients who have higher levels of lactate but still within the normal reference range of < 2mmol/L. Investigators prospectively looked at 7,155 critically ill patients in four ICUs, took more than 170,000 lactate measurements and divided them into admission lactate (LAC_{ADM}), maximum lactate (LAC_{MAX}) and time-weighted lactate (LAC_{TW}) levels. They found that LAC_{ADM} and LAC_{TW} of > 0.75 mmol/L were independently associated with increased hospital mortality. The investigators postulate that the transition from physiological to pathological lactataemia may occur well below 2 mmol/l.[4]

Fifty years ago, Broder and Weil published a landmark paper looking at lactate as an index of reversibility of shock in humans.[5] In a sample of 56 patients with a variety causes of shock, mortality rate was 89% with a single sample of lactate of > 4 mmol/L. The implication of a high serum lactate being associated with mortality has led many to believe that lactate may be useful as a "biomarker of death".

MEASUREMENT OF SERUM LACTATE - STATIC VERSUS DYNAMIC

Whilst previous research had been based on static measurements of elevated serum lactate, it is becoming apparent that an increasing serum lactate concentration may be more ominous than a single value. Dynamic lactate measurements can provide important information on the lactate trend and hence should better reflect the clinical status of the patient. One of the earliest works looking into the usefulness of dynamic measurements of lactate was on fluid resuscitation in non-cardiogenic circulatory shock patients.[6] It was found that survivors had decrease in lactate concentrations of > 10% during the first 60 minutes of therapy. There was no decrease in lactate levels in non-survivors. Investigators postulate that serial lactate levels were more reliable than a single value in the early phase of resuscitation as it can provide an early and objective evaluation of the patient's response to therapy. Initial lactate levels had less prognostic ability. Based on their findings,

the authors recommend monitoring lactate levels every 20 minutes in the first hour of resuscitation.

CLINICAL USES OF LACTATE MONITORING IN CRITICAL ILLNESS

Role in Resuscitation

Since its overproduction is mostly associated with a lack of oxygen delivery, lactate can be used as a surrogate to assess the adequacy of tissue or organ perfusion. It can help in optimizing the circulation and balance of oxygen supply to demand to tissues. In resuscitation efforts, lactate is an important clinical parameter of hemodynamic monitoring that can be used routinely together with pulse rate, blood pressure, cardiac output, mixed or central venous oxygen saturation and arterial blood gas. Lactate clearance is defined by the equation shown in Figure 4. The lactate clearance and interval change in lactate over the first 12 hours of resuscitation has been evaluated as a potential marker for effective resuscitation.[7]

$$\text{Lactate clearance} = \frac{(\text{Lactate}^{\text{ED Presentation}} - \text{Lactate}^{\text{Hour 6}}) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$

Figure 4: Lactate clearance. From reference 13

A multicentre randomized controlled trial investigated the role of early lactate-guided therapy in intensive care by aiming to reduce lactate levels as an initial goal of resuscitation. Approximately 350 patients with lactate levels of > 3mmol/L admitted into the ICU were recruited into the study. Investigators aimed for a 20% or more reduction every 2 hours for the first 8 hours of ICU stay for the intervention group. The lactate group were given more fluids and vasodilators, were weaned off inotropes earlier and had shorter ICU stays. The hospital mortality, which was the study's primary endpoint, was also lower but results did not reach statistical significance.[8]

Role in Sepsis

As a prognostic tool

Impaired microcirculatory perfusion is one of the hallmarks of severe sepsis. Hyperlactatemia is often the only indicator of the presence of severe sepsis and hence can be used as a surrogate of oxygen debt and oxygen deficit. Blood lactate levels, both initial and serial, have been shown to be superior to pulmonary artery catheter-derived data in predicting mortality in septic shock.[9] Serial blood lactate levels and *lac-time* (a term used to indicate the time during which lactate levels remain > 2 mmol/L) can predict the development of multiple organ failure following septic shock. Lac-time has been shown to be the best predictor of outcome in a multiple regression analysis. The longer the lac-time, the higher the risk of developing multiple organ failure.[10]

Early Goal Directed Therapy

In 2001, Rivers *et al* published a landmark paper looking at early goal-directed therapy (EGDT) in the treatment of severe sepsis.[11] The concept of EGDT strives to achieve 3 physiological targets by a set of interventions within a set time frame of 6 hours. They are: (i) using IV crystalloids to achieve a central venous pressure of 8-12 mmHg to optimize preload, (ii) using pressors either dopamine or noradrenaline to achieve a mean arterial pressure of ≥ 65 mmHg for perfusion pressure and, (iii) using dobutamine or red blood cell transfusion to achieve a central venous oxygen saturation ($ScvO_2$) of 70% or above to restore tissue oxygen delivery. Investigators in this single-centre trial were able to demonstrate a decrease in mortality from 46.5% to 30.5% by adhering to these quantitative resuscitation goals.

However, a central venous catheter is required to draw the central venous blood for measurement of $ScvO_2$. For continuous $ScvO_2$ monitoring, a specialized fibreoptic central venous catheter and monitor are required, which are not so readily available in every centre. It is known that a low $ScvO_2$ or a high lactate level is independently associated with increased morbidity and mortality.

Hence, lactate levels represent a more easily accessible parameter to monitor tissue oxygen delivery in EGDT compared to $ScvO_2$. The most recent Surviving Sepsis Campaign guidelines give a level 1C recommendation to monitor serum lactate and to begin resuscitation immediately in patients with hypotension or a serum lactate of > 4 mmol/l.[12]

Lactate clearance in sepsis

In 2004, the same investigators who introduced the concept of EGDT to the medical world also managed to show that successful clearance of lactate is associated with improved outcome in severe sepsis and septic shock. Goal-directed resuscitation in critically ill patients in the Emergency Department (ED) that resulted in a decrease in lactate of at least 10% in the first 6 hours of septic shock was associated with improved outcome. There was an 11% decrease in mortality with each 10% increase in lactate clearance.[13]

A non-inferiority study that compared lactate clearance and $ScvO_2$ randomly assigned 300 patients with severe sepsis or septic shock to undergo EGDT targeting either lactate clearance of ≥ 10% or $ScvO_2$ of ≥ 70%. There was no difference in hospital mortality (17% in lactate clearance-guided group vs 23% in $ScvO_2$ guided group), length of stay, ventilator-free days or incidence of multiorgan failure. Lactate clearance is a more accessible method to assess effective resuscitation and tissue oxygen delivery in most centres. This trial suggests that lactate clearance criteria may be a suitable alternative to $ScvO_2$ criteria in EGDT.[14]

It has been proposed that lactate clearance be included as an item into the current sepsis resuscitation bundle. Investigators looking at the outcome effectiveness of lactate clearance in severe sepsis added lactate clearance (any decrease in lactate within 12 hours) together with fluid bolus of 20 ml/kg and maintaining mean arterial pressure of > 65 mmHg by 6 hours in severe sepsis. Logistic regression showed that these 3 parameters were independently associated with decreased mortality (fluid bolus OR 0.47; MAP > 65mmHg achieved by 6 hours OR 0.20; lactate clearance OR 0.32).[15]

Lactate as a biomarker of sepsis

Biomarkers can be useful for identifying or ruling out sepsis, in identifying patients who may benefit from specific therapies or assessing the response to therapy. Often in the clinical setting, severe sepsis presents in an occult manner, and the diagnosis may be overlooked or missed. There has been many biomarkers that have been evaluated in clinical research for use in sepsis. Most have been tested clinically mainly as prognostic markers in sepsis, but few have been shown to be useful for diagnosing sepsis. The most commonly used are procalcitonin (PCT) and C-reactive protein (CRP), but they too, are limited in their ability to differentiate sepsis from other inflammatory conditions nor to predict outcome from sepsis. As a potential biomarker, lactate lacks the specificity and sensitivity to be utilized in routine clinical practice to diagnose or rule out sepsis.[16] However, it has been evaluated in clinical studies as a prognostic indicator.[13,17]

Role in Post Cardiac Arrest Management

Lactic acidosis is very common after cardiac arrest but should clear over time after adequate perfusion is restored. Effective lactate clearance correlate with survival in post cardiac arrest patients. In a retrospective study that looked at the outcome of post-cardiac arrest patients, lactate clearance at 6 hours and 12 hours was higher in early survivors (24 hours) and in-hospital survivors.[18]

In ICUs that offer post cardiac arrest therapeutic hypothermia, protocols invariably will include routine lactate monitoring. An example would be to measure lactate every 6 hours during cooling and rewarming. Lactate levels during hypothermia therapy should remain the same or decrease if patient is adequately resuscitated.

Role in Trauma

We were introduced to the "Golden Hour" in trauma resuscitation by Cowley in 1973 - the idea that trauma patients have significantly better survival rates if they receive appropriate and definitive care

within the first hour of injury to limit the extent of organ damage.[19] However, emergency physicians have queried the truth of this concept in the face of lack of evidence.[20] A study looking at critically ill multi-trauma patients found that patients who were able to normalize their lactate to ≤ 2 mmol/L in 24 hours all survived compared to those patients who only managed to normalize by 48 hours.[21] Another study looked at aggressive fluid resuscitation in trauma patients to correct occult hypoperfusion as reflected by the lactate levels. Patients who managed to achieve a lactate level of ≤ 2.5 mmol/L had a significantly higher chance of survival compared to those who took > 24 hours to achieve this lactate target (Figure 5). This has led to the lactate-driven adage of the "Silver Day" in trauma resuscitation, which is a reflection of the lactate clearance within 24 hours post trauma in determining survival.[22]

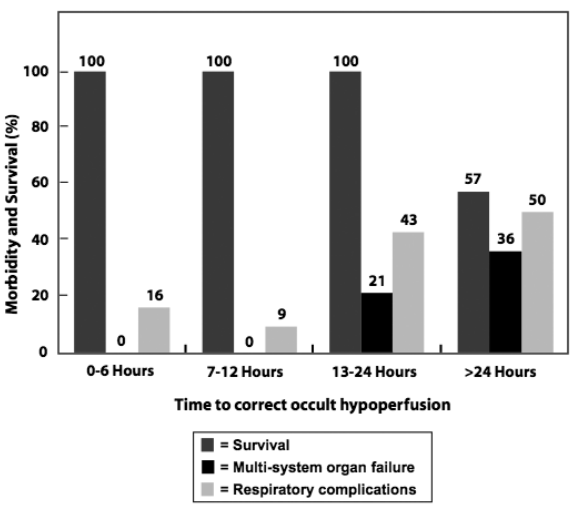

Figure 5: Morbidity and survival vs time to correct occult hypoperfusion. Reproduced with permission from reference 22.

Role as predictors of outcome in critically ill patients

Dynamic changes in lactate are more superior than static lactate in predicting outcome in critically ill patients (reference N = 6). Dynamic indices such as the time weighted average lactate (LAC_{TW24}) and the change in lactate over the first 24 hours ($LAC_{\Delta 24}$) have independent predictive value within 24 hours of ICU admission. These parameters (LAC_{TW24} and $LAC_{\Delta 24}$) when added into severity of illness score-based outcome prediction models, improve the performance and receiver operating curves (ROC) for ICU and hospital death.[23] A systematic review of the lactate literature also concluded that serial lactate monitoring looking at the trend is useful for risk assessment in patients admitted acutely to hospital, and in predicting in-hospital mortality.[24]

Miscellaneous uses of lactate

It has been proposed that routine lactate screening may be beneficial as a tool in aiding a myriad of clinical decisions in relatively stable patients who present to the ED. This include triage, decision for admission into hospital, need for continuous monitoring, need for aggressive intervention and resuscitation or ICU placement. A study looking at the role of lactate in screening and risk stratification obtained a single venous lactate sample from 1,278 normotensive, haemodynamically stable patients presenting to the ED with infection. They found that increasing lactate levels were associated with increased mortality. Levels of ≤ 2.5 mmol/L were associated with a much lower in-hospital mortality compared to patients with lactate levels of ≥ 4 mmol/L (Figure 6) .[25]

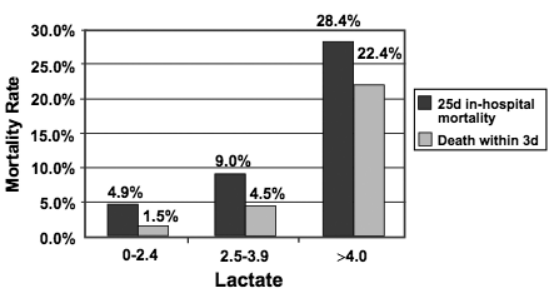

Figure 6: Lactate as a predictor of mortality. Reproduced with permission from reference 25.

Another use of lactate monitoring may be as a warning sign to suggest the presence of ongoing ischemia in a patient. It is not unusual for clinicians to encounter a persistently elevated serum lactate level despite appropriate resuscitation and no obvious source of hypoperfusion. The routine monitoring of lactate levels may increase awareness and spur clinicians to seek occult pathology especially in the abdomen or muscle compartment.

We know that early identification of hemodynamic derangement and shock is vital in improving survival. It has been suggested that extending lactate monitoring to the pre-hospital environment eg. in ambulance retrievals may potentially enable the early detection of occult shock. This will then allow pre-hospital resuscitation to commence, guided by lactate measurement.[26]

MEASUREMENT OF SERUM LACTATE - ARTERIAL VERSUS PERIPHERAL VENOUS SAMPLING

Mixed venous lactate from blood sampled via a pulmonary artery catheter reflects the balance between lactate production and clearance in the whole body. A study in 1987 has shown that there is good correlation between arterial lactate and lactate sampled either from a pulmonary artery or central venous catheter (central venous lactate).[17] However, mixed venous blood is not routinely available as pulmonary artery catheters are rarely used nowadays in clinical practice. Moreover, it was subsequently shown that there is significant lactate production from the lungs in acute lung injury/ARDS resulting in significant differences between mixed venous lactate and arterial lactate.[28] A more recent study has shown that central venous lactate collected within a 30 minute range are interchangeable for clinical practice.[29]

In routine practice, arterial blood sampling remains the gold standard to track changes in lactate levels during shock and resuscitation. Intensivists frequently placed arterial catheters in critically ill patients for haemodynamic monitoring and blood sampling. Arterial blood gas is the commonest laboratory test performed in the ICU and many blood gas machines have incorporated lactate measurement into the assay. Studies using arterial lactate had shown that it correlates with the development of multiple organ failure and death. Unfortunately, indwelling arterial catheters or frequent arterial punctures are not without complications and does require a certain level of experience and expertise. When comparing arterial lactate with peripheral venous lactate, there has been concerns of overestimation using a peripheral venous sample and the potential tourniquet effect resulting in a higher lactate value. Peripheral venous lactate has been investigated in various studies for correlation with arterial lactate and in general, the correlation has been found to be acceptable. Peripheral venous sampling should therefore be encouraged in the acute setting as sampling can be easily and rapidly obtained, with minimal risk and inconvenience for the patient.

CONTROVERSIES

Future research is warranted to determine the exact cut-off value for lactate. Most studies currently use 2.0 - 2.5 mmol/L as the transition from normolactataemia to hyperlactataemia. The higher the cut-off value, the likelihood of a positive predictive test, but will result in more false negatives. The significance of normal levels of lactate of < 2 mmol/L but > 0.75 mmol/L need to be looked into.

CONCLUSIONS

Since its discovery in humans in 1843, the measurement and monitoring of lactate has stood the test of time. Lactate levels are easily and inexpensively performed and results can be rapidly obtained from hand-held point-of-care testing devices or from arterial blood gas analyzers. The uses of serum lactate monitoring in the critically ill are extensive and varied, and adds value and clarity to the clinical information of the patient. Right from the beginning of patient contact, it can be used as a screening tool, as an aid in clinical decision making as a guide in resuscitation especially for sepsis and trauma and in monitoring the response to resuscitative efforts. An editorial in an intensive care

journal even went as far as to declare "don't take vitals, take a lactate".[30]

To date, lactate can also be considered as a biomarker for severity of illness and as a prognostic marker. Irrespective of the aetiology of lactate elevation in critically ill patients, a high lactate is associated with poor outcome. Dynamic measurements appear to be most predictive, whereby an adequate lactate clearance is an independent predictor for improved mortality.

It is worthy to note that clinical decisions should never depend solely on lactate levels. Instead as with any clinical test, it should be taken in concert with other clinical parameters and investigations. At the end of the day, lactate monitoring remains a tool; and as a tool, it can only be useful if used in a correct and appropriate manner.

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Coagulopathies in the Intensive Care Unit

Vineya Rai, MBBS (UM), MMed (Anaesthesiology) UM, EDIC
Consultant Intensivist, Department of Anaesthesiology and Intensive Care, University Malaya Medical Centre, Kuala Lumpur, Malaysia

INTRODUCTION

Coagulopathy is a potential problem for many critically ill patients, placing them at risk for haemorrhage. Critical illness activates both haemostasis and inflammatory-immune system, leading to physiological and potentially pathophysiological responses. Factors that induce coagulopathies include trauma, burns, sepsis, surgery and major blood losses. Identifying and anticipating patient at risk is a major challenge to the attending physician as the clinical manifestations of coagulopathy may be obvious or occult. Blood transfusion and its components has long been an important part of patient management, but is known to put patients at risk of transfusion-related complications. In current times, we should advocate blood conservation strategies and criteria to guide decisions on transfusion therapy.

HAEMOSTATIC RESPONSE TO AN INJURY

During an injury, damage to tissues and blood vessels will lead to activation of platelets and plasma coagulation factors. This is how haemostasis begins. In normal situation, platelets circulate freely and do not attach to the smooth endothelial lining of blood vessels. The procoagulants (e.g. prothrombin) and anticoagulants (e.g. antithrombin) exist in a delicate balance. Within an intact blood vessel, anticoagulants prevail over pro-coagulants and this ensures the blood remains in a fluid state.

Injury to the blood vessel will trigger process of primary haemostasis followed by secondary haemostasis. In primary haemostasis there will be platelet activation leading to aggregation of platelets which will form a platelet plug. The secondary haemostasis aims to prevent further blood loss from larger injured vessels. This phase results in fibrin clot formation.

THOMBOCYTOPENIA

Thrombocytopaenia is a common finding in the intensive care unit (ICU), with 25-38% of ICU patients with platelet counts below 100,000/uL and 2-3% with counts less than 10,000/uL.[1] It is absolutely essential to determine the presence of thrombocytopaenia. A platelet count of 35,000/uL may require immediate intervention, or be evaluated for life-threatening processes such as heparin-induced thrombocytopaenia (HIT) and thrombotic thrombocytopenic purpura (TTP).

Examination of the blood smear can quickly reveal whether pseudothrombocytopaenia (artefactual platelet clumping) is present or presence of fragmented red cells (schistocytes). Patients who presented only with severe thrombocytopaenia and no other systemic signs or symptoms (outside of bleeding) with a normal blood smear most often have either idiopathic or drug-induced immune thrombocytopaenia.

Sepsis

Sepsis is a clear risk factor for thrombocytopaenia in critically ill patients and the severity of sepsis correlates with the decrease of platelet count. In septic patients, impaired platelet production, increased consumption or destruction, or sequestration of platelets in the spleen can induce thrombocytopaenia.[2]

Drug Induced Thrombocytopaenia

Early heparin induced thrombocytopaenia (HIT) takes place within the first 5 days following heparin introduction and is usually mild. However, late HIT is a life threatening condition related to an immune mechanism.[3]

Table I: Common causes of thrombocytopaenia are as listed below:

First, rule out pseudothrombocytopaenia by asking the following question:
Is the blood sample clotted?
- Check for EDTA-dependent platelet antibodies by collecting the sample in an anticoagulant (e.g., citrate)

If pseudothrombocytopaenia has been ruled out, ask the following:
Is the patient taking drugs that could lower the platelet count?
- Check for receipt of:
  - Heparin, which may be associated with heparin-induced thrombocytopaenia
  - IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, tirofiban)
  - Adenosine diphosphate (ADP)-receptor antagonists (e.g., clopidogrel)
  - Acute alcohol toxicity

Does the patient have a hematinic deficiency (particularly, acute folate deficiency)?
Does the patient have any of the following:
Sepsis (especially consider)
- Human immunodeficiency virus (HIV) infection
- Disseminated intravascular coagulation

Major blood loss and haemodilution
Mechanical fragmentation
Post-cardiopulmonary bypass
Intraaortic balloon pump
Renal dialysis
Extracorporeal membrane oxygenation
Immune-mediated disorder
- Immune thrombocytopenic purpura
- Antiphospholipid syndrome
- Post-transfusion purpura

Microangiopathic haemolytic anemia
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Haemolytic-uremic syndrome

Hypersplenism
Other disorder
- Myelodysplastic syndrome
- Cancer
- Hereditary thrombocytopaenia

Adapted from Hunt BJ. N Engl J Med 2014; 370:847-859[13]

Thrombotic Microangiopathy

Thrombotic microangiopathy (TM) is a syndrome involving thrombotic thrombocytopenic purpura (TTP), haemolytic-uremic syndrome (HUS), malignant hypertension, HELLP syndrome and chemotherapy induced microangiopathy. This micro vascular occlusive disorder is characterized by a systemic or renal platelets aggregation, thrombocytopaenia and mechanical haemolysis. Despite these common characteristics, each disease has its proper pathophysiology. Although these two

disorders are linked to different pathophysiologic mechanisms, they are both managed similarly.[4] Plasma exchange is an effective therapy yielding superior remission and survival rates compared to plasma infusion alone.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. This condition typically originates in the microvasculature and can cause damage of such severity that it leads to organ dysfunction. Diagnosis can be established using a scoring system proposed by International Society on Thrombosis and Hemostasis (ISTH) as illustrated in Table II.

DIC usually presents as haemorrhage, with only 5 to 10% of cases presenting with micro thrombi (e.g., digital ischemia) alone. Sepsis is the most common cause of disseminated intravascular coagulation in critical care. The complex pathophysiology is mediated by pathogen-associated molecular patterns, which generate an inflammatory response in the host through signaling at specific receptors resulting in the synthesis of several proteins (including proinflammatory cytokines). These proteins trigger haemostatic changes, leading to the up-regulation of tissue factor[5] and impairment of physiologic anticoagulants and fibrinolysis.

Table II: Risk assessment for DIC

Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
If yes, proceed with this algorithm
If no, do not use this algorithm
Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)
Score the test results as follows:
Platelet count: 50,000 to 100,000 per mm^3, 1 point; <50,000 per mm^3, 2 points
Elevated fibrin-related marker (e.g., d-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points
Prolonged prothrombin time: <3 sec, 0 points; 3 sec but <6 sec, 1 point; 6 sec, 2 points
Fibrinogen level: 1 g per liter, 0 points; <1 g per liter, 1 point
Calculate the score as follows:
5 points: compatible with overt DIC; repeat scoring daily
<5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

Adapted from Hunt BJ. N Engl J Med 2014; 370:847-859 [14]

LIVER DISEASE

Thrombopoietin and most haemostatic proteins are synthesized in the liver. Thus, reduced hepatic synthetic function results in prolongation of the screening tests of coagulation (particularly the prothrombin time) and reduced platelet counts, although levels of factor VIII and von Willebrand factor are increased. In cholestatic liver disease, there is reduced absorption of lipid-soluble vitamins, so reduced amounts of the vitamin K-dependent coagulation factors II, VII, IX, and X are produced. Furthermore, in liver disease, the failure of the normal enzymatic removal of sialic acid from fibrinogen results in dysfibrinogenemia.

In a randomized, controlled trial published in 2013, investigators compared a liberal red-cell transfusion strategy (haemoglobin level, <9 g/dl) and a restrictive strategy (haemoglobin level, <7 g/dl) in patients with acute upper gastrointestinal bleeding. Patients who were treated with the restrictive strategy had longer survival (6 weeks) and a lower rate of rebleeding (10% compared to 16% in the liberal strategy group) than did those who were treated with the liberal strategy.[6] In this study, portal circulation pressures increased significantly among patients in the liberal-strategy group.

BLEEDING ASSOCIATED WITH ANTITHROMBIN DRUGS

It is difficult to treat a bleeding patient who is receiving an oral anticoagulant such as dabigatran and rivaroxaban, since there is no specific antidote. Studies that have evaluated the reversal of the new oral anticoagulants have been limited to reversal of drug effect with the use of recombinant activated factor VII and prothrombin complex concentrate. Current evidence suggests that prothrombin complex concentrate may be the best option and that it reverses the effects of rivaroxaban better than the effects of dabigatran.

With regards to prolonged prothrombin time (PT) or international normalized ratio (INR) in the setting of anticoagulation with vitamin K antagonists (ie, warfarin), there are numerous guidelines published.[7-9] In non-life threatening cases, vitamin K should be administered at doses between 3-5 mg.[8] Oral vitamin K is preferred when correction is not urgent (correction in about 24 hours). The slow intravenous route may be used when rapid correction is desirable (correction in 4-8 hours). Patients who are bleeding or who have high INR values do require the administration of fresh frozen plasma (FFP). In this case, the administration of 15-30 mL/kg of FFP will generally normalize the INR. Prothrombin complex concentrate may be used to correct the INR in patients who cannot tolerate volume infusion.

Another issue which is often encountered in the ICU is the correction of the PT or INR before invasive diagnostic procedures. This is an area of controversy as there is no definitive recommendation. However, data suggest that in the absence of other haemostatic abnormalities, most procedures can be performed with an INR not greater than 2. An exception however would be procedures involving central nervous system.

DYNAMICS OF THROMBOCYTOPAENIA

It is not uncommon to see acute and transient decrease of platelet count in critically ill patients during the first few days of ICU admission.[10-12] This phenomena is believed to be due to impairment of platelet production due to a depression of the bone marrow function caused by infection or toxic substances. It can also be due to increase platelets destruction (such as haemophagocytosis), excessive platelets consumption (such as in disseminated intravascular coagulopathy, sepsis, trauma) and haemodilution due to transfusion or fluid loading. Platelet counts is usually at its lowest on day-4 of admission and recovers in a week. A slow recovery may be associated with worse outcome to the patient.

MANAGEMENT OF THROMBOCYTOPAENIA

The risk for complications such as intracranial haemorrhage increases as the count decreases, such that transfusion is reasonable even in the stable, non-bleeding patient when the platelet count declines below 10,000 to 20,000/mL.[13] However, the transfusion threshold decreases for patients who are bleeding, require surgical interventions or who have platelets dysfunction. Despite that not all patients with thrombocytopaenia benefit from platelet transfusions. Patients with TTP and HIT should not receive platelets transfusions.

CONCLUSION

Coagulopathies are a common hematologic problem encountered in critically ill patients. Several conditions are particularly associated with these disorders (DIC, trauma, sepsis.). Transfusion decision should take into account the evaluation of bleeding risk, depth of disorder of coagulation, causes of coagulopathies and co-morbidities.

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Diagnosing and Treatment of Adrenocortical Insufficiency in the Intensive Care Unit

Mohd Basri Mat Nor, MBBCh.BAO (Ireland), MMed (Anaesthesiology) UM, EDIC, AM
Consultant Intensivist, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

INTRODUCTION

In critically ill patients, activation of the hypothalamus-pituitary-adrenal (HPA) axis with the production of cortisol is crucial for survival under conditions of physiologic stress. The increase in cortisol production results in several important effects on metabolic, cardiovascular and immune aimed at restoring homeostasis during stress. However, in critical illness, HPA axis undergoes complex changes and the optimum level of plasma cortisol is unclear. In addition to activation of the HPA axis, cortisol metabolism and function may be significantly altered by various aspects of critical illness. There are conditions in which cortisol concentration cannot increase appropriately to meet demand. Assessment of cortisol activity in this group of patients is also difficult because laboratory assays of total plasma cortisol concentration and response to adrenocorticotropic hormone (ACTH) stimulation do not consistently reflect corticosteroid deficient at cellular level. It has been suggested that during critical illness, plasma cortisol concentration poorly reflect the glucocorticoid activity at target tissues. Venkatesh *et al*. has postulated that the spectrum of adrenocortical dysfunction in sepsis (from plasma to tissue) should be grouped under 'sick euadrenal syndrome' rather than an adrenocortical insufficiency.[1]

Adrenocortical insufficiency (AI) may be considered as primary, secondary or relative. Despite numerous studies, definitions of relative adrenal insufficiency (RAI), critical illness related corticosteroid insufficiency (CIRCI) or functional adrenal insufficiency is still inconclusive. There is no consensus about the diagnostic criteria or indications for treatment of these syndromes. As the result, it is challenging to identify patients who have suboptimal cortisol production and therefore may benefit from administration of corticosteroids with the goal of improved outcomes such as mortality.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS PHYSIOLOGY

The adrenal glands, each weighing about 4 g are composed of centrally located medulla and a surrounding cortical zone. The adrenal medulla produces endogenous catecholamine vasopressors, adrenaline and noradrenaline. The adrenal cortex is divided into three regions; gromelulosa, fascicularis and reticularis, from outside to inside. These areas secrete steroid hormones, respectively aldosterone (mineralocorticoid effects), cortisol (glucocorticoid effects) and adrenal androgens. Glucocorticoids and mineralocorticoids have several important functions. Glucocorticoids preferentially regulate carbohydrate, protein and fat metabolism and indirectly lead to insulin secretion to counterbalance glucocorticoid induced hyperglycemia. Glucocorticoids also possess anti-inflammatory and immune-suppressive effects; they maintain cardiovascular integrity and blood glucose level. Mineralocorticoids regulate fluids and electrolytes such as sodium, potassium and hydrogen ions. The net effect is sodium conservation, potassium and hydrogen ion excretion and expansion of the vascular space. Aldosterone is the primary mineralocorticoid in humans, accounting for about 80% of all mineralocorticoid activity.

Three organs; hypothalamus, anterior pituitary and adrenal cortex collectively known as hypothalamic-pituitary-adrenal (HPA) axis, maintain appropriate levels of glucocorticoids. There are three distinct modes of regulation of the HPA-axis: diurnal rhythm in basal cortisol secretion, marked increases in steroidogenesis in response to stress and the negative feedback regulation by adrenal cortisol.

Production of glucocorticoids is stimulated by the adrenocorticotropic hormone (ACTH) which is mainly secreted by anterior pituitary gland. The corticotropin-releasing hormone (CRH) is secreted from paraventricular nucleus of hypothalamus in response to a normal circadian rhythm and various forms of stress. Examples of physiological stress stimuli are trauma, major surgery, severe infection, pain, hypoglycemia, hypovolemia, hypotension, hypoxemia, bleeding, and intense heat or cold. CRH triggers ACTH synthesis while glucocorticoids inhibit ACTH and CRH production through a feedback loop. Vasopressin, oxytocin, angiotensin II and beta-adrenergic agents also stimulate ACTH release. On the other hand, somatostatin, beta endorphin and encephalin reduce it. While ACTH is necessary for aldosterone secretion, it has a little effect in controlling the rate of secretion. Aldosterone secretion is not regulated by HPA-axis but primarily by the renin-angiotensin system in response to decrease in blood volume and elevated extracellular potassium. The daily output of aldosterone is about 100-150 µg/day.

The primary endogenous glucocorticoid in human is cortisol, accounting for about 95% of all glucocorticoid activity. Cortisol has only 1/400 the mineralocorticoid activity of aldosterone. However, it also provides a significant amount of mineralocorticoid activity because of its high plasma concentration which is nearly 1000 times that of aldosterone. Plasma cortisol levels are reported in both µg/dl and nanomoles/l: 1 µg/dl = 27.6 nmol/l. It is produced at a basal rate of 10mg/day which is equivalent to 20-30mg/day of hydrocortisone.[2] Cortisol is secreted in pulses and follows a circadian rhythm (refer Table I). The concentration reaches its peak in the morning at around 8-9 a.m. and nadir at midnight. Thus measurements of blood cortisol levels are meaningful when expressed in terms of the time of a person's sleep cycle at which they were measured. Normal serum cortisol levels range between 5 and 24 µg/dl. Diurnal rhythm is lost during physiological stress and enhanced secretion of ACTH results in increased cortisol level as high as 40-50 µg/dl, which is proportional to the severity of the illness.

Table I: Important physiological parameters

Important physiological parameters	
Total daily output of cortisol	5-30 mg/day (40-80 µmol/day)
Peak plasma concentration (8-9.00 a.m.)	5-20 µg/dl (150-550nmol/l)
Nadir plasma concentration (midnight)	4 µg/dl (110 nmol/l)
Plasma free cortisol concentration	0.2-1.4 µg/dl (5.5-38 nmol/l)
Plasma CBG concentration	26.0 mg/l
% of cortisol bound to CBG	80%
% of cortisol bound to albumin	12-15%
% free cortisol	5-8%

Approximately 90% of plasma cortisol is reversibly bound to cortisol-binding globulin (CBG) and up to 5% to albumin. CBG (also known as transcortin) has a high affinity for cortisol but relatively low binding capacity, while albumin has a low affinity but large binding capacity.[3] Therefore, only a fraction of cortisol that is unbound or free, however it is this free fraction that is biologically active. The high protein binding of cortisol is responsible for relatively long half-life of 60-90 minutes. Corticosteroids are metabolized by liver to form glucuronic acid and sulfates. They are primarily (75%) filtered by kidneys and excreted in the urine. The remaining 25% is eliminated by bile and feces. Therefore severe liver dysfunction decreases metabolism and renal dysfunction decreases the rate of elimination. Hepatic metabolism of cortisol can be increased by drugs such as rifampicin and phenytoin, and is decreased by certain drugs such as protease inhibitors. During acute illness, CBG levels fall by as much as 50%, resulting in a significant increase in fraction of free cortisol. CBG is a substrate for elastase (secreted by activated neutrophils) that cleaves CBG and reduces its affinity to cortisol.[4] This results in delivery of free cortisol to target cells at sites of inflammation.

Free cortisol passes through cell membranes to bind with glucocorticoid (GC) receptor.[5] Prior to binding with GC receptor, concentrations of cortisol are affected by the activity of the 11β-Hydrosteroid dehydrogenase 1 and 2 (11β-HSD 1&2) enzyme system. 11β-HSD1 acts in vivo as reductase, generating active cortisol from inactive cortisone. By contrast, 11β-HSD2 has dehydrogenase action, inactivating cortisol by conversion to cortisone. The system is able to regulate intracellular GC concentration irrespective of circulation concentration thus rendering plasma levels highly problematic as indicators of tissue GC action. Intracellularly, the resulting cortisol-receptor complex translocates into the nucleus and then modulates gene transcription. Here the GC receptor binds to specific DNA binding sites, termed glucocorticoid response elements (GREs) and influences gene transcription.[5] GREs can have positive or negative effects on transcription, affecting an estimated 2000 genes. Translocation occurs within 30 minutes of exposure of the cell to glucocorticoid.

Therefore, the following mechanisms are known to affect the glucocorticoid activity along the cortisol cascade from the plasma to the interstitium, cytoplasm and nucleus. The mechanisms are changes in plasma free cortisol concentration, interstitial cortisol concentration, 11β-hyroxysteroid dehydrogenase activity, alterations in the glucocorticoid receptor and glucocorticoid gene expression.

EFFECTS OF CRITICAL ILLNESS ON THE HPA-AXIS

In addition to activation of the HPA axis, cortisol activity may be altered in critical illness by the following factors: reduced cortisol metabolism may results in hypercortisolemia and corticotropin suppression, renal dysfunction may prolong the half-life of cortisol, reduction of plasma concentrations of both CBG and albumin and therefore increased in free cortisol.[6,7] There are conditions in which cortisol availability cannot be increased sufficiently in response to illness. Certain drugs e.g. ketoconazole and etomidate may impair cortisol synthesis.[8] Drugs such as rifampicin and phenytoin may induce hepatic cortisol metabolism. Etomidate is a selective inhibitor of adrenal 11β-hydroxylase, the enzyme that converts deoxycortisol to cortisol. Head injury, pituitary infarction, central nervous system depressants, adrenal haemorrhage, infections, malignancy and previous corticosteroid therapy can also impair HPA axis.

ADRENOCORTICAL INSUFFICIENCY IN CRITICAL ILLNESS

Primary adrenal insufficiency (AI) is a rare condition in intensive care unit (ICU), with incidence estimated to be less than 3%.[9] Relative adrenal insufficiency (RAI), also has been called 'critical illness-related corticosteroid insufficiency (CIRCI), is thought to be more common.

i) Primary adrenal insufficiency (Addison's disease)

The commonest cause in adult is autoimmune and the other causes are shown in Table II. These can be due to infections, haemorrhage, infiltration and drugs. Tuberculosis is the commonest infective cause worldwide. High levels of circulating cytokines have been reported to have a suppressive effect on ACTH release.[10] This condition is often unrecognized in its early stages as the manifestations are nonspecific (Table III). The presentation to the ICU is usually in the form of adrenal crisis that is refractory shock with a poor response to fluids, inotropes or vasopressors. This should be suspected in cases of undifferentiated shock not responding to standard management. Because it remains difficult to recognize adrenal insufficiency in the ICU, clinicians are encouraged to have a high index of suspicion. Patients with primary adrenal insufficiency present with more severe symptoms compared with those with secondary adrenal insufficiency. Hyperpigmentation on examination (e.g. in the palmar skin creases) is due to the hypersecretion of melatonin, a breakdown product of ACTH precursor pro-opiomelanocortin (POMC). Important laboratory findings are hyponatremia, hyperkalaemia, metabolic acidosis and peripheral blood eusonophilia. A random plasma cortisol concentration during crisis will be lower than 80 nmol/L. Treatment of primary AI should include intravenous hydrocortisone, 100 mg every six hours. At these doses, separate mineralocorticoid replacement is not necessary.[11]

Table II: Causes of primary adrenal insufficiency

Causes of primary adrenal insufficiency
1. Infections: Tuberculosis, Histoplasmosis, Cytomegalovirus,
2. Autoimmune mediated
3. Haemorrhagic: meningococcal infection, antiphospholipid syndrome, trauma, surgery, coagulation disorders.
4. Infiltrative: tumor, amyloid, sarcoidosis, haemochromatosis
5. Drug related: etomidate, fluconazole, ketoconazole, rifampicin, phenytoin,
6. Congenital: adrenal dysgenesis, impaired steroidogenesis, adrenoleucodystrophy
7. Cytokine mediated

Table III: Clinical manifestations of Addison disease

Symptoms	Signs
Muscular weakness, fatigue, abdominal pain, vomiting, diarrhea, arthralgia and myalgia, weight loss, salt craving, headache, sweating, syncope	Hyperpigmentation: skin creases, buccal mucosa, Postural hypotension, Vitiligo, decreased axillar and pubic hair, Vasodilated shock - in crisis

ii) Secondary adrenal insufficiency

Important causes of ACTH deficiency is abrupt cessation of exogenous glucocorticoid therapy. Patients at risk of adrenal suppression are who have been taking more than 30 mg/day of hydrocortisone or the equivalent for more than three weeks. Other causes are pituitary surgery, pituitary infarction and pituitary tumour. Specific signs of secondary adrenal insufficiency are pale skin, loss of axillary and pubic hair and decreased in libido. Hyperkalaemia is not a feature because of the intact secretion of mineralocorticoid. In primary AI, hyponatremia is mainly due to aldosterone deficiency and sodium

wasting, whereas in secondary AI it is due to low cortisol and free water retention mediated by secretion of vasopressin as a result of volume depletion.[12]

iii) Relative adrenal insufficiency

There has recently been a great deal of interest regarding the assessment of adrenal function and the indications for corticosteroid therapy in critically ill patients. Relative adrenal insufficiency (RAI) is referred to inadequate corticosteroid activity for the severity of the illness of a patient.[13] RAI is supposed to describe suboptimal cortisol production by adrenal gland to stress.[8] This condition has also been called "critical illness related corticosteroid insufficiency" (CIRCI). However, there is no consensus about the diagnostic criteria or indications for treatment of this syndrome. Controversies exists in the diagnosis of RAI in the critically ill patients with regards to what cortisol level is normal or appropriate in this population, what constitutes to adequate response to ACTH and what dose of synthetic ACTH should be used for simulation testing. The criteria for determining which patients have an adequate adrenal response to severe stress and which have an inadequate response are controversial.[13] Assays of the cellular activity of cortisol, cortisol glucocorticoid receptor binding and glucocorticoid receptor transcription activity are limited to experimental studies and their clinical relevance is still unknown.[14]

In a prospective study of 189 patients with septic shock, Annane et al identified three groups of patient prognoses by using ACTH stimulation test.[15] They found that patients with septic shock with a baseline cortisol level above 34 µg/dL (938 nmol/L) and response to ACTH of less than 9 µg/dL (248 nmol/L) were associated with the highest mortality, followed by those with baseline above 34 µg/dL with an increase of more than 9 µg/dL. The lowest mortality was found in those with baseline cortisol levels of less than 34 µg/dL and cortisol response greater than 9 µg/dL. Therefore, the higher the basal plasma cortisol level and the weaker the response to the ACTH stimulation test, the higher the mortality rate. This may represent a partially suppressed adrenal axis or may indicate overstressed axis, in which steroid therapy is debatable. Treatment of septic patients fulfilling RAI criteria with corticosteroid has been shown to improve outcome in only one study that is the French trial by Annane et al.[16] This trial was criticized for its high placebo-group mortality and the statistical methods used to describe outcomes.

It is uncertain whether RAI or CIRCI is a true diagnostic entity, since a clear definition is lacking. The uncertainty arises from the inability of the current tests to identify who is truly corticosteroid deficient at a cellular level and who requires supplemental corticosteroid administration. Venkatesh et al has put forward an alternative hypothesis to explain the HPA-axis changes in critical illness as 'sick euadrenal syndrome' analogous of the sick euthyroid state.[1,17] Changes in critically ill patients may affect any level of cortisol cascade i.e. in cortisol fraction, intracellular cortisol:cortisone interconversion, glucocorticoid receptor density and gene transcription.

INVESTIGATIONS OF ADRENAL INSUFFICIENCY

Measurement of cortisol levels with the ACTH stimulation test is the standard in stable adult patients to diagnose adrenal insufficiency. The test is based on the inability of a diseased adrenal gland to secrete adequate cortisol after injection of corticotropin. After drawing a baseline blood sample, synthetic ACTH molecule consisting of the first 24 amino acids: tetracosactrin (Synacthen) is given at a dose of 1 µg (low dose) or at supraphysiologic dose of 250 µg. Blood samples for the measurement of serum cortisol are drawn at 0 (baseline), 30 and 60 minutes. A normal response requires an incremental rise of at least 200 nmol/L and a final result must be over 525 nmol/L.[18] It is recommended to use local laboratory reference ranges since the current immunoassays exhibit a significant degree of variability.[19] The test is impossible to interpret once hydrocortisone has been started as this will cross react with the assays. If urgent treatment is required before test, dexamethasone is used as an alternative therapy.

Siraux et al compared low-dose and high-dose stimulation tests in 46 patients with septic shock.[20] They concluded that the low-dose test identified a subgroup of patients in septic shock with inadequate adrenal reserve who had poor outcomes and would have been missed by the high-dose test. Four studies have been published that compared the low-dose and high-dose tests in critically ill patients.[21-24] All four studies concluded that the low-dose test is more sensitive than the high-dose test. It seems reasonable that therapeutic decisions can be made by using the low-dose test. However, high-dose test is still preferred in the ICU setting because low-dose stimulation test has not been validated in critically ill patients and patients with septic shock.[8,25]

ASSESSMENT OF TISSUE CORTISOL ACTIVITY

Assessment of RAI in critically ill patients based on measuring plasma cortisol concentration has given rise to controversies. Alternative approach is to focus on the site of glucocorticoid activity within the tissues as this is likely to reflect adrenal function more accurately. The challenges in assessing adrenal insufficiency in critically ill patients are discussed below:

1. Limitations of random cortisol - Plasma free cortisol (PFC) provides a better assessment of adrenal function than total cortisol but PFC concentrations cannot be predicted from total cortisol because of the non-linear relationship. Studies have also shown that plasma cortisol levels are poorly correlated with interstitial cortisol concentration.[26,27] Fluctuation in plasma cortisol concentration also limits the utility of random cortisol.[28] The normal range of cortisol in critical illness is not defined and there is no consensus cut-off value below which adrenal insufficiency is present.

2. Limitations of total cortisol - There is large variation in total cortisol assay results when the same specimen is tested in different laboratories and using different assays. Using four commonly used immunoassays for the measurement of cortisol, Cohen et al reported a high degree of variability between cortisol assays which may potentially confound the diagnosis of RAI[29]

3. Limitations of the conventional Synacthen test - the high-dose short Synacthen test (HDSST) may results in plasma Synacthen concentrations that are supraphysiological. The low-dose test may be a better predictor of outcome but has not been validated in critically ill patients. Published data may have overestimated the incidence of AI as many studies have not excluded patients who received etomidate. In a recent meta-analysis of 7 studies, administration of etomidate for rapid sequence intubation is associated with higher rates of AI and mortality in patients with sepsis.[30]

STEROID THERAPY IN SEPTIC SHOCK

There are conflicting data on the role of glucocorticoid therapy in the management of septic shock. The results of the French trial by Annane et al which is the only prospective randomized trial of steroids with beneficial effect have not been widely accepted owing to problems of randomization, change of protocol and the use of etomidate in the study.[16] A second large randomized trial of steroid in septic shock (CORTICUS) failed to demonstrate a mortality difference between steroids and placebo. Both studies had inadequate statistical power to demonstrate a clinically significant in mortality.[31] The current recommendations while waiting for the results of adequately powered studies, intravenous corticosteroid therapy is to be administered to adult patients with severe septic shock (defined as SBP<90 mmHg for more than one hour despite adequate fluid resuscitation and vasopressor administration). Short Synacthen test should not be used to select patients for corticosteroid therapy. The dose of intravenous hydrocortisone is 200-300mg/day given as 50 mg every 6 hours or by continuous infusion. The treatment is for five to seven days and tapers the dose as guided by the clinical response. During treatment, close observation is recommended to monitor for superimposed infection, hyperglycemia and myopathy. There is no role of a separate fludrocortisone administration in septic shock since it has been argued that doses of cortisol above 50

mg a day provide sufficient mineralocorticoid cover. This is supported by a trial, the 'Corticosteroids and Intensive Insulin Therapy for Septic Shock' (COIITSS) comparing fludrocortisone plus hydrocortisone with hydrocortisone alone, failed to demonstrate a difference in clinical outcome.[32] There is considerable global uncertainty on the role of low dose corticosteroids in septic shock which translates into variation in prescribing practice. Currently a large multicenter randomized trial, 'Adjunctive Corticosteroid Treatment in Critically ill Patients with Septic Shock' (ADRENAL) trial is under way. The primary objective of this trial is to compare the effects of hydrocortisone and placebo on 90-day mortality. The trial should generate results that will inform and influence physicians prescribing of corticosteroids in septic shock patients.[33]

CONCLUSION

The concept of relative adrenal insufficiency in critically ill patients continues to be controversial. Standard methods of assessing adrenal activity based on plasma cortisol concentration are inaccurate. These methods are predisposed to numerous problems including limitation of a random cortisol, limitations of total cortisol and limitations of the conventional Synacthen test. The spectrum of adrenocortical dysfunction in sepsis can be grouped under the umbrella of a "sick euadrenal syndrome" rather than an adrenocortical insufficiency. The role of glucocorticoid treatment in the management of septic shock is still uncertain. We hope that a large multicenter randomized ADRENAL trial (clinical trials.gov NCT01448109) would be able to provide us with the answer.

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Anaesthetic Management of Pulmonary Hypertension in Obstetric Patients

Thohiroh binti Abdul Razak, MBBS (UM), MMed (Anaesthesiology) UKM, AM
Consultant Obstetric Anaesthesiologist, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Pulmonary Hypertension (PH) posts a big challenge for clinician to manage. The situation can be more risky when dealing with a pregnant patient. PH in pregnancy can cause high morbidity and mortality to both mother and baby. Risk of death is 30-50% if not managed properly. Thus PH patients must be managed by multidisciplinary team in a specialist centre. Changes in the cardiovascular system in parturients with PH are exaggerated due to inability of the heart to compensate for the increase in the cardiac output and blood volume. Pulmonary vessels in high risk patients undergo vascular changes which include thickening of smooth muscle, proliferation of cell wall, plexiform changes which lead to vasoconstriction and remodeling of the vessels and hence the rise in pulmonary vascular resistance and pressure. Three pathways are postulated to cause the vascular injury; Prostacyclin, nitric oxide and the endothelin pathways. Patients are at risk of developing thromboembolism, stroke, right heart failure, Eisenmenger's syndrome and death. Modern treatment with prostacycline analogue, nitric oxide and endothelin I antagonist are proven to provide better outcome for PH patients. Data are showing promising results for pregnancies with PH even in our developing country.

INTRODUCTION

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) higher than 25mmHg (normal 9-18mmHg) at rest, associated with a pulmonary capillary wedge pressure of less or equal to 15mmHg diagnosed by right heart catheterization. This is the latest definition agreed in the 4th World Symposium of Pulmonary Hypertension, in Dana Point, California, 2009. Previously, few definitions have been put forward since the first definition in 1973 in Geneva.[1] PH was first identified in 1970s when epidemics of PH were found in young people taking appetite suppressant aminorex. That has triggered clinical researches in this newfound cardiovascular illness then.

PH in pregnancy is rare, but is known to be associated with significantly high mortality rate of between 30% and 56%.[2,3] The physiological changes that occur during pregnancy and the peripartum period are poorly tolerated in these group of patients. Majority of maternal deaths occur during labour or within 1 month of postpartum.[2] Thus these mothers must be managed by a multidisciplinary team in a consultant-led centre.

PATHOPHYSIOLOGY

The pathogenesis of pulmonary hypertension is not fully understood but it is likely to be complex and involves an interaction of several external and internal stimuli which includes environmental and genetic factors (Figure 1 and 2). It is believed that in susceptible individuals, inciting stimuli cause an insult to the pulmonary vascular bed which then induce vascular injury. This can happen as early as in the embryonic and fetal life which might play a role in development of PH later in life.[2,4] This causes alteration in the normal balance between vasoconstrictors and vasodilators, growth inhibitors and mitogenic substances, and antithrombotic and prothrombotic determinants in the vascular wall leading to endothelial dysfunction that eventually results in the vascular remodeling. The vascular pathology of PH is characterized by smooth muscle intimal hyperplasia, medial hypertrophy, adventitial proliferation, in-situ thrombosis and plexiform lesions.

A strong association between mutations in the bone morphogenetic protein receptor type2 (BMPR2) gene and PH have been found in approximately 80% of families with pulmonary arterial hypertension (PAH) and 25% or less of families with idiophatic PAH.[2]

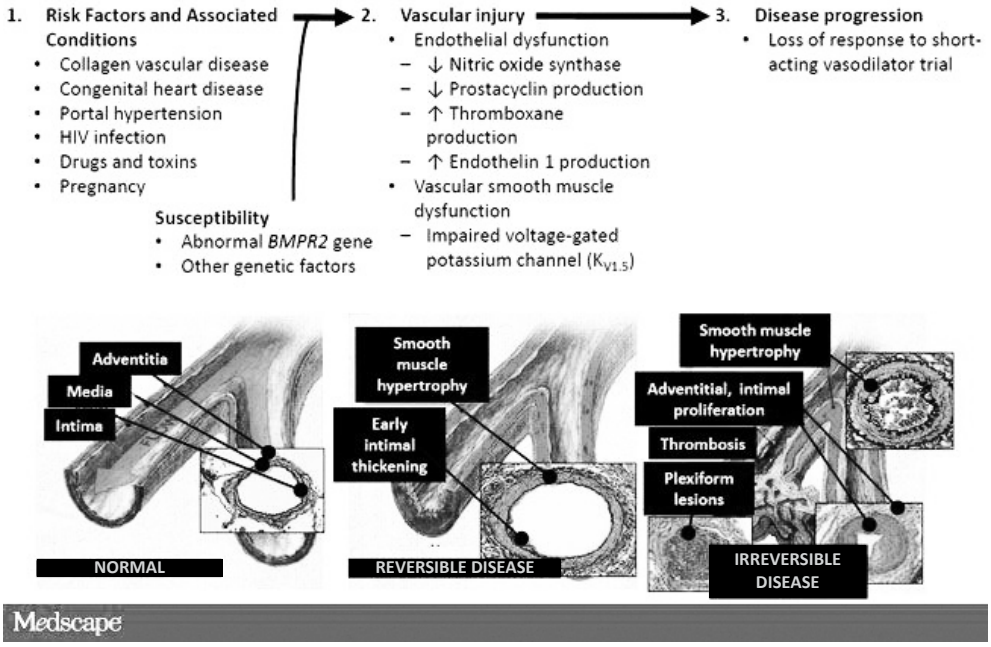

Figure 1: Pathogenesis of pulmonary hypertension.[4]

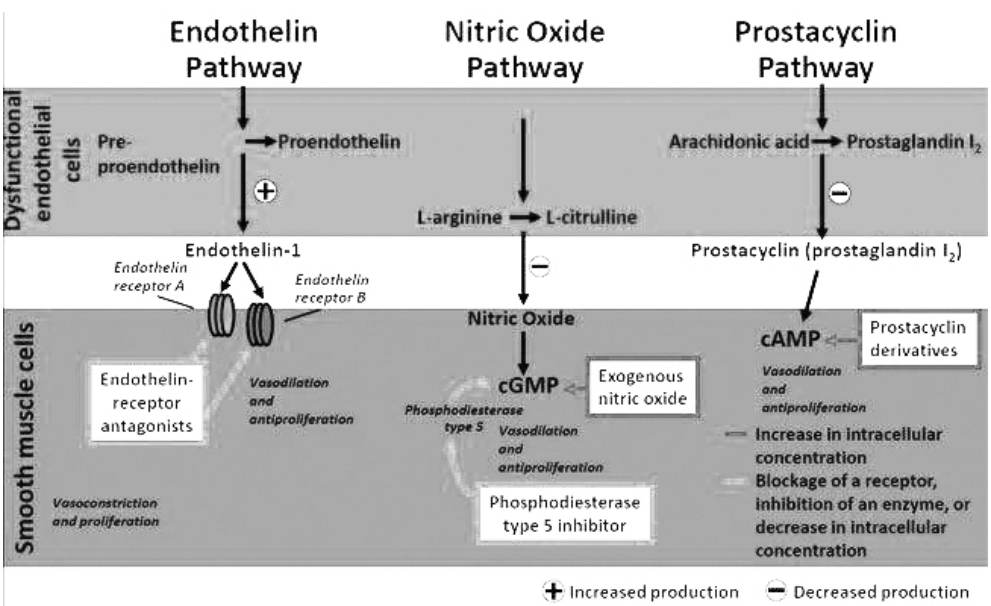

Figure 2: Pathways of development of pulmonary hypertension.[4]

Vascular remodeling of pulmonary circulation is believed to occur via 3 main pathways: the prostracyclin (PGI_2), the endothelin and the nitric oxide pathways. Figure 2.

The understanding of pathogenesis of PH, specifically the dysfunction and imbalance of the prostacyclin, endothelin and nitric oxide pathways, has led to the development of diseases-targeted therapies. Currently available classes of PH-specific agents thus target these 3 pathways. This will be discussed further in management of PH.

CAUSES OF PULMONARY HYPERTENSION

Causes of PAH Group 1 (Table I) are well described in most literature whom patients have a diverse spectrum of aetiologies of PAH. These include idiopathic PAH (IPAH), inheritable, drug and toxin induced collagen vascular disease and congenital heart diseases. Other groups include pulmonary hypertension secondary to left heart disease (Group 2), lung diseases and/or hypoxia (Group 3), chronic thromboembolic pulmonary hypertension (Group 4) and PAH associate with unclear multifactorial mechanisms (Group 5), such as glycogen storage disease or renal failure.[1,2,3]

Until this review, there is only a single report suggesting the cause of PH may be by pregnancy itself.[5] In PAH group there are diseases with very different pathophysiology and treatment approaches such as reversed shunting from congenital heart diseases (Eisenmenger's Syndrome) and IPAH. PH in pregnant parturient is poorly tolerated, thus termination of pregnancy is advised in most of literature.

Table I: Venice Clinical Classification of Pulmonary Hypertension[3]

Groups	Causes
Group 1 PAH	- Idiopathic (IPAH) - Familial (FPAH) - Collagen vascular disease (CVD) - Congenital L to R shunts - Portal Hypertension - HIV - Drugs toxins - Pregnancy
Group 2 Pulmonary Venous HPT	- Left heart disease
Group 3 PH associated with hypoxia (lung diseases)	- COPD - Interstitial lung disease (ILD) - Obstructive sleep apnoea (OSA) - High altitude
Group 4 Thromboembolic	
Group 5 Miscellaneous	

GRADING OF PH

Although PH has been defined by WHO decades ago, but there is still no single standardised clinical grading of PH as compared to systemic hypertension. The only grading available is based on histological changes as described above. A group of clinicians in India lead by Dr. S. Venkatesan MD has come out with a simple grading of PH based on their study of chronic rheumatic diseases patients with PH. The

grading was done via Doppler echochardiography analyzing tricuspid regurgitation (TR) and pulmonary regurgitation (PR) flow jets. TR jet provided the systolic PA pressure whilst PR jet provided mean as well as diastolic PA pressure. This is applicable mainly in rheumatic heart disease and primary pulmonary hypertension.[6] Grading for PH is outlined in Table II.[6]

Table II: Grading of pulmonary hypertension[6]

	Systolic (mmHg)	Diastolic (mmHg)	Mean (mmHg)
Grade 1 (mild)	30-50	20-25	>30
Grade 2 (moderate)	50-70	26-35	>40
Grade 3 (severe)	70-110	36-45	>50
Grade 4 (systemic or suprasystemic)	>110	46-55	>60

INCIDENCES AND OUTCOME

Incidence in pregnancy is estimated to be less than 1% - 8% depending on the selection of patient cohorts.[5] In a recent Dutch registry, the prevalence of PH (defined as a systolic pulmonary pressure > 40mmHg) in adults with congenital heart disease was ascertained. The prevalence of PH among all patients was 4.2% and 6.1% in those with septal defect. Of those with septal defects, 58% had Eisenmenger's syndrome. Female gender or PH were independently associated with decreased functional status.

Literature review from 1978 to 1996 showed that maternal mortality was 30% with IPAH (PAP=83mmHg),56% with secondary vascular PH (PAP=83mmHg) and 36% with Eisenmenger's syndrome (PAP=108mmHg). In these review, patients with secondary vascular PH were a heterogenous mixture of etiologies including drugs, congenital peripheral artery stenosis, thromboembolism, hepatitis, systemic connective tissue disease or vascular inflammatory disease, All deaths occurred antepartum or within 35 days of delivery, and maternal survival was better with early diagnosis and early hospital admission. Neonatal survival was 87-89%.[5]

A contemporary review (1997-2001) showed that 72% of patents were receiving advanced therapies (mainly nitric oxide, prostacyclin analogues and calcium channel blockers) and the overall mortality appeared to be significantly lower than a prior era (1978-1996). That is 25 versus 38%, P=0.047 and was 17% in IPAH, 28% in PH secondary to congenital heart disease, and 33% in PH of other etiologies. Importantly, 78% of deaths occurred in the first month after delivery (particularly due to refractory right heart failure) and patients who received general anaesthesia were at higher risk if death (odds ratio-3.70).[10]

Malaysian National Heart Institute, Kuala Lumpur had managed 330 pregnant parturient with heart conditions over 4 years (2009-2013)[7] , where 22 patients had PH. Patients would be sent to nearby tertiary hospitals for deliveries. 14 patients were successfully delivered at term or near term, 4 had termination of pregnancies due to severe PH and 4 defaulted. Hospital Kuala Lumpur had managed 77 of these heart cases whom 7 parturients had PH. All 7 patients were on sildenafil. One death recorded due to suprasystemic PH where patient had pulmonary hypertensive crisis while undergoing a repeat suction and curettage.

CARDIOVASCULAR CHANGES IN PREGNANCY

Progesterone plays a great influence in the physiological changes in a pregnant patient. Peripheral vasodilatation induced by the hormone which lead to a decrease in systemic vascular resistance (SVR) is thought to be the first cardiovascular change.[8, 11] Cardiac output increases in response to this, by 20% at 8weeks gestation and by up to 40-50% at 20-28 weeks gestation. (Figure 4). This is achieved predominantly by an increase in stroke volume (due to an increase in ventricular end-diastolic volume, wall muscle mass and contractility) and also by an increase in heart rate. Labour leads to further increases in cardiac output by 15% in the first stage and 50% in the second stage due to combination of auto-transfusion of 300-500 ml of blood back into the maternal circulation with each uterine contraction and sympathetic stimulation caused by pain and anxiety. Cardiac output increases again immediately after delivery due to auto-transfusion of blood via uterine contraction and relief of aorto-caval compression. This may increase cardiac output by as much as 60-80%, followed by a rapid decline to pre-labour values within 1 hour. Central venous pressure, pulmonary capillary wedge pressure and PAP remain constant throughout pregnancy.

The impact of these physiological changes to pregnant woman with cardiac disease will vary according to the type and severity of the disease. Women with the least ability to increase their cardiac output are at risk of decompensation earlier on in the pregnancy and may present before the 28 weeks of maximum 'pre-delivery' cardiac output is achieved. Those who tolerate the increase during pregnancy will be at further risk at the time of delivery and immediate post-partum due to the changes caused by sympathetic stimulation and auto-transfusion. These changes combined with the reduction in serum colloid osmotic pressure make women with cardiovascular compromise particularly susceptible to pulmonary oedema at the time of delivery and immediately during post-partum. The risk is increased if the woman is given excessive intravenous fluid (causing an increase in cardiac preload) or if she has also has pre-eclampsia (resulting in an increase in pulmonary capillary permeability).

HAEMODYNAMIC CHANGES IN PARTURIENT WITH PULMONARY HYPERTENSION

In normal pregnant women, the low resistance pulmonary vascular bed adapts easily to the large increase in circulatory volume and blood flow through vasodilation and recruitment of pulmonary capillaries. However pregnant ladies with significant PH have a pulmonary vasculature that is incapable of adequate compensatory vasodilation because of the obliteration and remodeling of the pulmonary vasculature which lead to hypertrophy and right ventricular failure. Increased right heart ventricular afterload is poorly tolerated, leading to increase maternal and neonatal morbidity and mortality. Risk of decompensation can occur between 20-28 weeks i.e during maximum pre-delivery cardiac output of gestation.

SYMPTOMS OF PULMONARY HYPERTENSION IN PREGNANCY

The symptoms of PH can overlap with pregnancy symptoms. However the symptoms of breathlessness and lethargy are particularly more severe and start early in the pregnancy in higher grade of PH. The symptoms can get worse at the peak of plateau at 24-28 weeks. Often, a person notices she can't perform the same activity as before without becoming winded. Other symptoms include chest pain, fatigue, passing out suddenly and swelling of legs.

DISTINGUISHING BETWEEN PAH AND EISENMENGER'S SYNDROME

The majority of the case reports in the field have "lumped together" patients with PAH and Eisenmenger's syndrome. Although the histopathologic pulmonary vasculature changes can be similar, their physiology during pregnancy is different and they have a different clinical course. Patients born with large, posttricuspid valve defects associated with Eisenmenger's syndrome, retain right ventricular function more like a typical fetal

heart and are able to relieve excess pressure by shunting blood from the right to the left across the defect, typically a large ventricular septal defect. These patients have a diminished quality of life despite better long-term survival than many patients with significant PAH.[5]

Patients with Eisenmenger's syndrome are known to suffer from chronic hypoxia and cyanosis. They are also at risk of developing associated complications such as erythrocytosis, hyperviscosity abnormal coagulation, heaemoptysis, cerebrovascular accidents and brain abscesses. These are seldom seen in patients with PAH.

Patients with congenital heart defects proximal to tricuspid valve (typically a large atrial septal defect) have the ability to decompress right-sided pressure via right-to-left atrial shunting. During pregnancy, patients with Eisenmenger's syndrome have the expected fall in systemic vascular resistance; however, because of their fixed, elevated pulmonary vascular resistance, they begin to shunt more from right to left with a resulting increase in hypoxia in both mother and fetus. These patients do not tolerate medications that can cause further systemic vasodilation and hypotension and worst still they tend to bleed more during labor and delivery.

MANAGEMENT

Approximately 60% of patients with PH are identified before pregnancy, thus focusing on pre-pregnancy counseling in the outpatient clinical setting is important.[3,5,12] First-line therapy is a tubal ligation or an intrauterine device. Contraceptive agents should be evaluated in view of their interactions with PAH therapies. Progesterone-only pills are probably the best option in these patients because they do not interact with warfarin (which many patients with PH take chronically) and their efficacy is not affected by bosentan (an endothelin receptor antagonist). Estrogen-containing pills have an increased thromboembolic profile and probably should not be used in these patients.[5]

TRADITIONAL AND PH-TARGETED TREATMENT

Guidelines by New York Heart Association of cardiac disease indicate the presence of PH makes a pregnancy a high risk (mortality 30-50%). Table III. A termination of pregnancy should be discussed and often advised. However some patients may decide to continue their pregnancy after considering the risks.[11,12]

When a heart disease particularly with PH conceives, a multidisciplinary team should be involved early in the pregnancy.[11,12] It should consist a cardiologist with expertise in heart disease in pregnancy, a feto-maternal expert, a neonatologist, cardiac anaesthesiologist or obstetric anaestesiologist. Pregnant patients with PH are advised to limit their physical activity, and a low-salt diet is encouraged. Although a partial pressure of oxygen greater than 70mmHg is optimal, oxygen therapy appears to have no impact on exercise capacity or survival. Medical treatment in Eisenmenger's syndrome include treatment of iron deficiency and the use of "air filters" or "bubble traps" with the intravenous line. Importantly, these patients are vulnerable with any type of surgery or anaesthesia and fluid loss or hypotension. The maintenance of these patients on anticoagulant throughout pregnancy is controversial. Options include using unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) until 13 weeks of pregnancy (to avoid teratogenic potential of warfarin early in gestation) switching to warfarin until week 35, and then finally treating the patients with UFH or LMWH until delivery. Patients with Eisenmenger's syndrome appear to have a higher risk of bleeding while on anticoagulant. Tight volume control at all stages of pregnancy is also essential. Diuretics such as frusemide can be used. Spironolactone should be avoided because it might cause inadequate virilization of a male fetus. There are several targeted therapies currently available for treatment of PH.[5, 22]

Table III: Risk of death or severe morbidity from certain cardiac lesions in pregnancy.[12]

Risk of death	Mortality	Cardiac lesions
Low risk	0.1 - 1%	- Most repaired lesions - Uncomplicated left-to-right shunts - Mitral valve prolapse; bicuspid aortic valve; aortic regurgitation; mitral rgurgitation; pulmonary stenosis; pulmonary regurgitation
Intermediate risk	1 - 5 %	- Metal valves - Single vetricles - Systemic right ventricle ; switch procedrae - Unrepaired cyanotic heart lesions - Mitral stenosis; mild/moderate aortic stenosis; severe pulmonary stenosis
High risk	5 - 30%	- NYHA III or IV - Severe systemic ventricular dysfunction - Severe aortic stenosis - Marfan's syndrome with aortic valve lesion or aortic dilatation - Pulmonary hypertension (Mortality 30-50%)

Prostacyclin Pathway

Prostacyclin (PGI2) is a potent, short-acting vasodilator and an inhibitor of platelet aggregation, produced by the vascular endothelium. In patients with primary pulmonary hypertension, PGI2 acutely decreases pulmonary vascular resistance, increases cardiac output and increases systemic oxygen delivery. Long term, continuous intravenous administration of PGI2 improves quality of life, hemodynamics and survival in patients with severe primary pulmonary hypertension. In patients with congenital diseases and PAH who failed conventional therapy, long term, continuous intravenous PGI2 reduced pulmonary artery pressure by 21%, improved cardiac index (69%), pulmonary vascular resistance (52%) ad New York Heart Association functional class, but not 6-minute walk distance. Use of PGI2 in secondary PAH (NYHA III and IV) similarly decreased mean pulmonary pressures and vascular resistance and improved both cardiac output and the duration of treadmill exercise.

The successful use of PGI2 during pregnancy with successful deliveries and good maternal and feta outcomes has been described in many articles.[21] PGI2 can be given either as nebulizer (as early as 8 weeks till 25-36/52) or intravenous.

Endothelin Inhibition

Endothelin-1 is produced by vascular endothelial cells and is a vasoconstrictor and mitogen for smooth muscle. In young patients with congenital heart disease and PAH, successful surgical repair decreases elevated levels of plasma endothelin-1. Bosentan is an orally active endothelin-1 receptor antagonist. It has been showed to be effective in treating IPAH and PAH secondary to connective tissue. However due to its potential teratogenic effect, it therefore should be discontinued in pregnancy.

Enhanced Nitric Oxide Production

The vasodilatory effects of nitiric oxide depend on its ability to augment and sustain cGMP content in vascular smooth muscles. Nitric oxide activates soluble guanylate cyclase that increase cGMP production, which then causes vasodilatation. Phosphodiesterases hydrolyze cAMP and cGMP,

limiting their intracellular signaling properties. Therapies such as inhaled nitric oxide and the phosphodiesterases-5 inhibitor sildenafil have been accompanied by favorable hemodynamic responses, improved symptoms and exercised capacity in patients with IPAH and in patients with Eisenmenger's syndrome. A study by Goland and colleagues have successfully treated a pregnant patient with PAH with both intravenous epoprostenol and sildenafil during peripartum period.[17,19]

Calcium-channel blocker

Calcium-channel blockers have been shown to improve and sometimes even normalize PAP in patient who responds to acute vasodilator testing at the time of right heart catheterization.[5,20]

MODE OF DELIVERY

In general, the mode and timing of delivery depends on the severity of maternal illness and the risk of continuing pregnancy versus the neonatal risk of preterm birth and other complications. This must be a conjoint decision by the multidisciplinary team involved. From National Heart Institute database, patients with high grade PH, symptoms of breathlessness and lethargy can present as early as 8-12 weeks and usually termination of pregnancy is performed to prevent worsening of the cardiac condition. However those who have passed their 28 to 30 weeks of gestation (at maximum pre-delivery cardiac output), they are normally able to tolerate the changes till at least 38 weeks of gestation.[7]

Vaginal delivery should be the preferred mode for most women with heart disease unless there are specific obstetric indications or deterioration in cardiac performance necessitating early delivery. This has been supported by many groups in the past because of lesser bleeding risk and greater haemodynamic stability.[5] Vaginal delivery should also be considered in a low risk patients with good effort tolerance, however those with worsening condition in moderate and high risk groups , vaginal delivery can be very stressful to them. A prolonged second stage needs to be shortened to limit or avoid maternal effort in 'pushing'. The second stage can be shortened by vacuum assisted or instrumental delivery. Some form of labour analgesia such as low dose epidural or patient controlled analgesia by short acting opiod like fentanyl or remifentanyl can be instituted to them. These can help to reduce the further increases in cardiac output and myocardial oxygen demand caused by pain and anxiety. Good regional analgesia will also facilitate instrumental delivery.

Caesarean section is increasingly in favour because the proper planning can be done when maximum resources are available. Those mothers in moderate to severe risk of mortality and in the presence of PH, caesarean will be a better choice. In case of fetal compromise, caesarean section will be the mode of delivery for an obvious reason. Furthermore caesarean section can be performed electively when the help of specialized team including cardiac anesthetist, obstetric anesthetist, the obstetrician and neonatal physician are available.

TYPE OF ANAESTHESIA

The goals of anaesthesia are to avoid pain, hypoxaemia, hypercapnia and acidosis all of which can lead to increase in pulmonary vascular resistance and thus pulmonary hypertension. Good anaesthesia may preserve patient's cardiac output, maintain normal heart rate and feto-placental circulation. This also helps to prevent pulmonary hypertensive crisis which can exhibit as vasospasm, hypoxia and even cardiopulmonary collapse.

Adequate analgesia and avoidance of systemic hypotension are important. Appropriate analgesia minimizes excessive sympathetic catecholamine release and can attenuate increases in PAP and pulmonary vascular resistance during labour.

Regional anesthesia comprises of spinal and epidural modalities have been reported to be successfully administered in patient with PH.[8,13,14] However a single shot spinal or epidural are contraindicated as they can cause profound hypotension. A low

dose spinal epidural approach or a slow titration of epidural anesthesia is preferred. The combined approach may provide a superior degree of anaesthesia while maintaining haemodynamic status of the patient.

A regime used for low-dose combined spinal epidural in HKL is 1.0ml of heavy bupivacaine mixed with 25mcg fentanyl (total of 1.5 ml) and for epidural is slow titration of 2% lignocaine in 1:200,000 adrenaline. Level of sensory block to pin prick is between T5 and T6 dermatome. Post operatively, epidural morphine 3mg in 5cc normal saline is instilled before the catheter is removed in recovery.[16]

For general anaesthesia, high dose opiod induction has been described in many case reports. In HKL, we use high dose fentanyl 10-15mcg/kg, midazolam titration, propofol or etomidate and intubation with high dose rocuronium. Maintenance is by O2, air and sevoflurane. Reversal is by neostigmine and glycopyrrolate or sugammadex.

If either the mother of the fetus rapidly decompensates, general anesthesia is necessary for a prompt and safe caesarian delivery, Potential hazards accompanying general anaesthesia include an increase in pulmonary pressure with laryngoscopy and tracheal intubation and the potential negative effects of positive end-expiratory pressure ventilation on venous return, and the negative inotropic effects of certain anesthetic drugs. Reports on worse outcome from general anaesthesia may reflect the higher risks of cases done under general anaesthesia.[9]

Monitoring during labour and intraoperative should involve invasive arterial line which allows beat to beat monitoring of blood pressure, continuous cardiac monitoring and a central line if vasopressor is needed. Dobutamine, Noradrenaline and phenylephrine have been used to maintain blood pressure, cardiac output and systemic vascular resistance. Most of literatures do not advocate using pulmonary artery catheter due to the risk of pulmonary artery rupture and thrombosis.[9] There is also no evidence that having pulmonary artery catheter improves outcome.[18]

Uterotonics can help to control haemostasis however drug such as oxytocin causes profound fall in systemic vascular resistance, hypotension, cardiac output and increases in pulmonary vascular resistance. It is recommended that if oxytocin is required post-delivery, it should only be administered by infusion without any bolus.[16] In HKL, oxytocin in heart patient is given via infusion of 5-10 units per hour for 4-5 hours.[16]

Ergometrine should be avoided in severe cardiac disease as it leads to vasoconstriction and hypertension and increases the risk of myocardial infarction and pulmonary odema. Carboprost which is synthetic PGF2, a potent smooth muscle constrictor can cause severe hypertension, bronchospasm, pulmonary vasoconstriction and thus increases pulmonary pressure.

POST PARTUM PERIOD

The postpartum period is the most critical period for acute decompensation of pulmonary hypertension. In the postpartum period, high level of maternal surveillance is required until the main haemodynamic changes have resolved. Post-operative analgesia can be achieved via epidural or intrathecal morphine or PCA opiod in addition to other multimodal modes of analgesia.

Therapy by nitric oxide inhalation and phosphodiesterase-5 inhibitor, sildenafil have shown favourable outcome in IPAH mothers. Monitoring in ICU or HDW is advisable for up to 2 weeks. This is because the worst cardiac compromise due to pulmonary hypertensive crisis can still be exacerbated by pain, hypoxia, anemia and infection during postpartum period

Anticoagulation is widely indicated with an activated partial thromboplastin time ratio between 1.5 and 2 within 12 - 24 h after delivery. Patients with history of thromboembolism or thrombophilia, the final target should have a higher targeted ratio

of 2-3.5.[5] It normally takes about 6 month for the cardiovascular parameters to normalize.

Heart transplantation is an option for patients whom their functional class does not improve or their projected 2-year survival is less than 50% despite normal therapy. After transplantation, patients with Eisenmenger;s syndrome have shown a better 10-year survival rates compared to IPAH.[5]

CONCLUSIONS

Pulmonary hypertension in pregnancy is a lethal combination. The physiological changes shown are worsening of cardiovascular parameters as early as in first trimester itself. It is when termination of pregnancy should be discussed to prevent worsening of cardiac condition. Parturients with pulmonary hypertension should be managed in a consultant-led center by a multidisciplinary expert to ensure a better outcome. Advanced medical therapies, particularly PGI2 analogues are being given earlier in pregnancy, and appear to improve symptoms and haemodynamic parameters without any obvious major risks to mother and fetus. There has been a major trend towards caesarean delivery with regional anaesthesia in these patients under controlled circumstances with an expert multidisciplinary team. Inhaled nitric oxide and sildenafil have been successfully instituted in IPAH mothers. The time of greatest risk to mother remains the first postpartum month. In general, outcome of parturient with PH is much better nowadays with the advancement of medicine in this modern era. Heart transplantation is the last option to those not responding to normal treatment.

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Strategies to Improve Hypoxaemia in Acute Respiratory Distress Syndrome Patients

Lim Chew Har, MD (UKM), MMed (Anaesthesiology) UKM, EDIC
Consultant Intensivist, Penang Hospital, Penang, Malaysia

Refractory hypoxaemia due to acute respiratory distress syndrome (ARDS) is one of the most challenging problems in intensive care. For years, mechanical ventilation (MV), using conventional mechanical ventilators, was the only supportive form of therapy providing adequate oxygenation and carbon dioxide elimination. The aim of this review is to summarize the current literature on a number of alternative strategies to improve oxygenation in ARDS patients with refractory hypoxemia. This will include the role of positive end expiratory pressure (PEEP) and lung-recruitment maneuvers, prone positioning, High Frequency Oscillatory Ventilation (HFOV), Extracorporeal Membrane Oxygenation (ECMO) and other adjuvant therapies.

INTRODUCTION

The acute respiratory distress syndrome (ARDS) was first defined in 1994 by the American-European Consensus Conference (AECC).[1] It was defined as severe hypoxemia (PaO2/FIO2 ≤ 200 mm Hg) of acute onset, with bilateral infiltrates on chest radiograph and excluding causes due to elevated left atrial pressure.

In 2011, a panel of experts convened (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) and developed the Berlin Definition. ARDS[2] is characterised by the following criteria:

i) lung injury of acute onset, within 1 week of an apparent clinical insult and with progression of respiratory symptoms
ii) bilateral opacities on chest imaging not explained by other pulmonary pathology
iii) respiratory failure not explained by heart failure or volume overload

The severity of ARDS is further classified into mild, moderate or severe based on the PaO2 / FiO2. Mild ARDS PF ratio 201 - 300, moderate ARDS PF ratio 101 - 200 and severe ARDS PF ratio ≤ 100. A minimum PEEP of 5 cmH2O is required; it may be delivered non-invasively with CPAP to diagnose mild ARDS.

The risk factors for development of ARDS are many and can be divided into direct or indirect causes of lung injury. Examples of direct causes include pneumonia, aspiration and trauma with pulmonary contusions. Examples of indirect causes include sepsis, massive blood transfusion and pancreatitis.

Persistent or refractory hypoxaemia is common in patients suffering from ARDS. Approximately 16% of deaths in patients with ARDS results from refractory hypoxemia, which is the inability to achieve adequate arterial oxygenation despite high levels of inspired oxygen or the development of barotrauma. Despite important advances, such as lung protective ventilation (LPV), the mortality rate of ARDS remains high. Rescue therapies, including recruitment maneuvers, inhaled nitric oxide, prone positioning, high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) are often needed, especially in the severe ARDS group.

LUNG PROTECTIVE VENTILATION (LPV) AND OPEN LUNG VENTILATION APPROACH

In ARDS, different parts of lung parenchyma are differentially affected. Areas of collapsed (unventilated) alveoli may be scattered among relatively normal lung areas. Traditionally, patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) requiring mechanical ventilation were subjected to higher tidal volumes (10-15 mL/kg) than a healthy individual, in an effort to maintain normal partial pressure of carbon

dioxide and arterial pH. However, ventilating patients using this traditional tidal volume can cause over-distension of the relatively normal (and more compliant) alveoli; and also this excessive transalveolar pressures can result in intense shearing forces at the junctions of the aerated lung units (mobile) and the consolidated lung units (immobile). A combination of these factors results in ventilator- induced lung injury (VILI), which may further worsen the pre-existing ALI /ARDS.

Ventilator management of ARDS has evolved significantly in the last few decades. The aims have shifted from optimal gas transfer without concern for iatrogenic risks to adequate gas transfer while minimizing lung injury. Lung protective ventilation (LPV) strategies should be used (e.g. ARDSNet protocol) to prevent worsening from ventilator-induced lung injury (VILI).

Lung Protective Ventilation (LPV) is often being defined as mechanical ventilation with low tidal volumes (VTs) and high PEEP. Lung protective ventilation is now the standard of care in ARDS. The open lung ventilation approach involves increasing the level of Positive End Expiratory Pressure (PEEP) in combination with protective ventilation. However, a universally accepted protocol for open lung ventilation does not exist and the use of PEEP, at what level and how to set it is controversial.

Low tidal volume ventilation

The rationale for low tidal volume ventilation is that smaller tidal volumes are less likely to generate alveolar overdistension, one of the principal causes of ventilator-associated lung injury. Since reducing mortality by a relative 22% in ARDSNet.[3] low tidal volume ventilation (4-8 ml/kg ideal body weight) has become the current standard of care for ventilating ARDS patients.

There is clear evidence from animal and human data that mechanical ventilation can induce and exacerbate lung injury.[4] Mechanical ventilation with conventional VTs was associated with a sustained increase in plasma IL-6 levels in one study.[5]

However, low tidal volume ventilation is associated with particular clinical challenges. When using low tidal volume ventilation, it is not uncommon to have elevated PACO2 (often termed permissive hypercapnia), which may be associated with a decrease in oxygenation. Some important adverse effects due to severe hypercarbia and acidosis include the negative effects on cardiovascular haemodynamics, pulmonary hypertension due to pulmonary arterial vasoconstriction, and elevation of intracranial pressure due to cerebral vasodilation. Though a pH values as low as 7.20 in very severe ARDS patients is commonly quoted as tolerable, the lower acceptable value is not clearly determined. The risks of permissive hypercarbia have to be balanced against the proven benefits of LPV.[3,6]

Role of PEEP and Lung Recruitment Maneuvers (RM)

Applying relatively high positive end expiratory pressure (PEEP) may prevent cyclic opening and collapsing alveoli in ARDS patients and therefore preventing atelectrauma and biotrauma . Ventilating patients with ARDS with PEEP levels below 5 cm H_2O has been shown to be harmful in a few observational studies.[7]

It has been suggested that PEEP should be of benefit in patients with higher lung recruitability and useless or harmful in patients with low lung recruitability. Actually two meta-analyses seem to confirm this hypothesis. The meta-analysis by Phoenix et al.[8] showed a trend towards improved survival in the high PEEP group with no evidence of increase in barotrauma. The other meta-analysis published in 2010 by Briel et al.[9] on the largest 3 trials (n=2229) reported no treatment effect on hospital survival between higher and lower PEEP groups while a significant improved survival was found in patients with more severe form of ARDS defined as $PaO_2/FiO_2 \leq 200$. In contrast, in patients with mild and moderate ARDS, higher PEEP seemed harmful. These results roughly account for what we know about the ARDS pathophysiology. In fact the putative beneficial effect of PEEP on survival should

be related to the prevention of excessive regional stress and strain by keeping open lung regions that would otherwise collapse.
Therefore a strategy employing higher PEEP along with low tidal volume ventilation should be considered for patients receiving mechanical ventilation for severe ARDS. Gattinoni et al hypothesised that patients with a higher percentage of recruitable lung probably had more atelectasis, given their greater underlying disease severity. Based on the available evidence, they recommend setting PEEP at the highest level compatible with a plateau pressure of 28-30 cm H_2O and a VT of 6 mL/kg predicted body weight.

Lung recruitment manoeuvre (RM) is a strategy aimed at re-expanding collapsed lung tissue, and then maintaining high PEEP to prevent subsequent 'de-recruitment'. The rationales to use RM in ARDS are that there is a massive loss of aerated lung and that once the end-inspiratory pressure surpasses the regional critical opening pressure of the lung units, those units are likely to reopen. The consequence of this should be the induction of lung recruitment. However, in order to recruit collapsed lung tissue, sufficient pressure must be imposed to exceed the critical opening pressure of the affected lung. This high pressure may over-distend and even injure the alveoli, predisposing them to VILI.

Multiple methods of lung recruitment maneuvers have been described. The most frequently investigated RM, due to its apparent simplicity, is the sustained inflation (SI), which consists of pressurizing the airways at a specific level and maintaining it for a given duration. A common combination is the application of 40 cmH2O airway pressure for 40 seconds.

Clinical trials have not found a survival benefit despite an improvement in oxygenation.[10-12] There is currently insufficient evidence for routine use of RMs. The effects of RM on extra-pulmonary ARDS may be more amenable to recruitment than pulmonary ARDS. However, the oxygenation benefits were found to be short lived and long term significance is uncertain. There was no study that has shown patient-orientated outcome benefits. The studies were also confounded by presence or absence of protective lung ventilation. Moreover, how to differentiate responders from non-responders is uncertain and there are still controversies regarding who, when, how often and for how long.

Whether recruitment manoeuvres that improve oxygenation reduce lung injury or impact patient outcome remains to be determined. They certainly may play a role in patients with refractory, life-threatening hypoxemia, but should be avoided in patients with hemodynamic instability and those at high risk for barotrauma.

PRONE POSITIONING

The clinical investigations of prone positioning illustrate many of the challenges in patient selection and study design for ARDS clinical trials. Prone positioning has been recognised to improve oxygenation in animal models of ALI and in a significant fraction of patients with ALI/ARDS. The proposed mechanisms include an increase in end-expiratory lung volume, improved ventilation-perfusion matching, more uniform distribution of lung stress and strain with tidal cycling, and regional improvement in lung and chest wall mechanics. Regardless of mechanism, an improvement in oxygenation occurs in a majority of patients when this intervention is applied. The potential risks of this intervention are primarily pressure related injury and tube dislodgement with turning manoeuvres.

Over the last 15 years, five major trials have been conducted to compare prone and supine position in ARDS regarding survival advantage. The sequence of trials enrolled patients who were progressively more hypoxemic, exposure to prone position was extended from 8 to 17 hours/day, and lung protective ventilation was more rigorously applied.

Single patient and meta-analyses drawing from the four major trials showed significant survival benefit in patients with PaO_2/FiO_2 lower than 100.[13] The latest PROSEVA trial[14] confirmed these benefits in a formal randomised study. The bulk of data

indicates that in severe and persistent ARDS (PaO_2/FiO_2 < 150 with $FiO_2 \geq 0.6$ and PEEP ≥ 5cmH2O),[15] carefully performed prone positioning offers an absolute survival advantage of 10-17%, making this intervention highly recommended in this specific population subset. In this group of patients, early application of prolonged prone-positioning sessions (at least 16h/d) significantly decreased 28-day and 90-day mortality.[14] In terms of complications, there were no significant differences between the groups, except for the incidence of cardiac arrests, which was higher in the supine group.

These results may be seen as sufficient evidence for a trial of prolonged prone positioning in patients with refractory hypoxemia or severe ARDS (PaO_2:FiO_2 ratio <150 mmHg with a FiO_2 ≥0.6 and PEEP ≥5 cm H_2O) despite use of lung protective ventilatory strategies, provided there is no contraindication.[15]

HIGH-FREQUENCY OSCILLATORY VENTILATION (HFOV)

Our understanding of the mechanisms and importance of ventilator-induced lung injury has advanced over the last three decades. High-frequency oscillatory ventilation (HFOV) should theoretically be an ideal mode to ventilate patients with severe lung damage. It achieves gas exchange by delivering very small tidal volumes (often less than the anatomic dead space) at frequencies ranging from 3 to 15 Hz (180-900 breaths/min) around a relatively constant mean airway pressure. Minimal variations in mean airway pressure as opposed to conventional ventilation may reduce the risk of ventilator-induced lung injury, by avoidance of both alveolar overdistension and cyclic alveolar collapse and re-expansion, as well as achieving and maintaining alveolar recruitment.

Animal models of ALI have suggested HFOV reduces the level of inflammatory mediators produced by the injured lung in comparison to conventional mechanical ventilation.

Prospective observational studies have reported that HFOV is a feasible and efficient method of ventilation that results in rapid and sustained improvement in oxygenation in patients with severe ARDS, though it has not been shown to reduce mortality. A recent systemic review and meta-analysis published in 2010 that included 8 randomised control trials found that HFOV improves oxygenation and reduces the risk of treatment failure (refractory hypoxaemia, hypercarbia, hypotension, or barotrauma) as well as hospital or 30 days mortality compared with conventional mechanical ventilation in patients with ARDS.[16]

However, the results of two trials published in 2013, the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE)[17] and Oscillation in ARDS (OSCAR)[18] trials that compared HFOV with LPV in patients with moderate to-severe ARDS, failed to prove that HFOV conferred treatment benefits.

Both OSCILLATE and OSCAR trials were set out to investigate the use of HFOV when used as an early ARDS strategy rather than a rescue therapy. These two long awaited trials showed no improvement in in-hospital death or 30 day mortality, respectively. The OSCILLATE trial, which enrolled almost 550 patients, showed a higher mortality rates for patients receiving HFOV [47%] compared to patients in the conventional ventilation group [35%]. The study was stopped early on the basis of a strong signal for increased mortality with HFOV (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; P=0.005).

Although the OSCILLATE trial showed increased in-hospital mortality with HFOV (47% vs 35 %), the Oscar trial saw no difference in mortality with either intervention. Mortality rates were approximately 41% in the nearly 800 patients in that study. However, these 2 trials had different designs. In the OSCILLATE trial, an arguably high mean airway pressures up to 38cmH2O was used in the HFOV group, compared to an effective LPV in the control group. This may have exaggerated the adverse outcomes of the HFOV. Similarly, there were significant issues with the OSCAR trial too. In the OSCAR trial, the LPV was not standardised and therefore may have led

to a higher mortality in the LPV group. Although these two important trials failed to demonstrate an outcome benefit with HFOV, and have weaken the promise of HFOV as a clinical breakthrough in ARDS, they did highlight the importance of LPV with a 6% mortality difference (35% vs 41%) between the LPV arms of either studies.[15]

Does this mean HFOV should never again be considered for treatment of ARDS? In an editorial[19] Atul Malhotra and Jeffrey Drazen suggest that it may be too strong a conclusion. Although the trials clearly show that HFOV treatment was not effective using these protocols, Malhotra and Drazen suggest that perhaps other HFOV protocols may allow for the theoretical benefits of this treatment to be realized. In addition, they suggest that more careful patient selection may be important. For example, in patients with homogenous and recruitable lungs, HFOV treatment, which increases mean airway pressure, may be beneficial. In patients with heterogeneous and nonrecruitable lungs, however, HFOV treatment may cause additional damage.[19] Further studies are needed to evaluate which, if any, patient populations may benefit from HFOV treatment. But for now, it's clear that this treatment is not as beneficial as it once seemed.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO has been used for over 44 years as a rescue therapy for severe acute respiratory failure that is refractory to mechanical ventilation. In the 1970s and 1980s, uncontrolled observational reports suggested clinical benefits with the use of extracorporeal support, but these were not realized in subsequent randomised controlled trials (RCTs).

The most recently published ECMO RCT is the CESAR (conventional ventilation or ECMO for severe adult respiratory failure) study.[20] This is a trial conducted outside the influenza pandemic, and is, to date, the largest prospective adult ECMO trial conducted, with 103 referring hospitals and 180 patients randomly assigned to either to be referred for consideration for ECMO or receive conventional mechanical respiratory support. ECMO was provided at a single highly ECMO-experienced centre while the standard care was conducted at less specialised centres. In this trial, the overall survival rate was 63% in the ECMO group compared with 47% in the control group (p=0.03). There was no increase in the risk of severe disability in the ECMO group.

However, the major limitation of the trial was that it was not designed to specifically test the clinical efficacy of ECMO alone for respiratory failure - rather it was an evaluation of a pathway for care of patients with severe respiratory failure, which often included ECMO as part of the package. Only 75% of patients in the treatment arm actually receive ECMO. Due to this inherent design limitations, the results of this trial have not been accepted unequivocally, but, at least in experienced centres, ECMO therapy may be considered as a valuable treatment option in severe cases.

Analysis of the highly variable global clinical data collected during the 2009 H1N1 pandemic shows that the overall reported mortality from ARDS during the pandemic was 14% to 41%. The mortality in patients treated with rescue ECMO was 0% to 39%. Interestingly, it was found that for the younger patients (mean [SD] age, 38 [13] years) who were more severely hypoxic and treated with ECMO, the mortality was much lower (22% vs 50%). However, the mortality rate for young patients (15-19 years of age) with ARDS who were managed conventionally is known to be lower (as low as 24%) from the previous reports. This may indicate that ECMO, as a rescue strategy, mainly benefit young patients who have failed LPV and other evidence-based adjuncts such as NMBAs and prone ventilation.

In another recently published French study, REVA Registry,[21] data of patients hospitalised in ICUs for H1N1 (2009-2011) associated ARDS was collected. Analysis of factors associated with death among 123 patients who received ECMO reported no differences in mortality when patients treated with LPV were compared with those treated with ECMO (40% vs 50%; P = .44). A recent systematic review and meta-analysis[22] of randomised controlled trials and

severity matched case-control studies comprising more than 300 patients also found the impact of ECMO on hospital mortality was unclear.
The goal of ECMO is to minimize ventilator-induced lung injury while allowing additional time to treat the underlying disease process and to permit recovery from acute injury. Based on current evidences, an ultra-protective ventilation strategy during VVECMO (venovenous ECMO) may be required to improve outcomes during VV ECMO.

The potential benefit of extracorporeal membrane oxygenation (ECMO) should be also weighed against the risk of complications e.g. bleeding, infection. ECMO is a complex technique and requires a dedicated team, appropriate equipment, institutional commitment and thorough preparation and these patients should be managed in a dedicated ECMO equipped centre. Potential complications are significant and its use is advocated only in patients who have substantial risk of death. Careful patient selection is important as not all patients with a potentially reversible cause of respiratory failure and severe gas exchange abnormalities while on LPV require ECMO.

ECMO is primarily reserved for circumstances in which patients are refractory to escalating conventional therapies and have a "high" predicted mortality. As per the Extracorporeal Life Support Organisation (ELSO),[22] indications for ECMO include PaO2/FiO2 less than 80 or FiO2 greater than 0.9 and Murray score 3 to 4. However, the French REVA Group proposed a more conservative criterion based on the current level of evidence. They recommend ECMO in patients with refractory and persistent hypoxemia defined by PaO2/FiO2 less than 50, despite high PEEP (10-20 cm H_2O) and high FiO2 (> 0.8) ventilation or a plateau pressure of 35 cm H2O or higher, despite VT reduction to 4 mL/kg.[21] Significant comorbidities and multiple-organ failure (Sequential Organ Failure Assessment Score >15) have been proposed as contraindications for ECMO. Mechanical ventilation for more than 7 days, major immunosuppression, and recent central nervous system haemorrhage have been shown to be associated with suboptimal outcomes.[23]

Prospective randomised controlled trials designed to evaluate the efficacy of ECMO for ARDS and to determine the group that may benefit most are still lacking. However, the current evidences demonstrated that referral to an experienced ECMO center significantly improves recovery and survival from severe ARDS.

ROLE OF OTHER ADJUVANT THERAPIES

Several adjuvant rescue therapies for refractory hypoxaemia are sometimes used. These include neuromuscular blockade, inhaled nitric oxide, inhaled prostacyclin, steroids and surfactant. All of them have shown some benefits in improving oxygenation but no clear mortality benefit.

Additionally, various management strategies can produce a more gradual improvement in oxygenation in ARDS, such as conservative fluid management, and nutritional modification. Although improvement in oxygenation has been reported with such strategies, demonstration of additional beneficial outcomes, such as reduced duration of mechanical ventilation or ICU length of stay, or improved survival in randomised controlled trials, as well as consideration of potential adverse effects should guide decisions on their use.

Neuromuscular Blocking Agents (NMBA)

In a multicentre trial involving 340 patients, treatment with the neuromuscular blocking agent (NMBA) cisatracurium for 48 hours early in the course of severe ARDS ($PaO_2/FiO_2 < 120$), improved the adjusted 90-day survival rate, increased the numbers of ventilator- free days and days outside the ICU, and decreased the incidence of barotrauma during the first 90 days.[24]

The mechanisms underlying the beneficial effect of neuromuscular blocking agents remain speculative. A brief period of paralysis early in the course of ARDS may facilitate lung protective ventilation by improving patient- ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels, thereby limiting the risk of both

asynchrony- related alveolar collapse and regional alveolar- pressure increases with over- distention. Another possible mechanism of the benefit involves a decrease in lung or systemic inflammation.

It's believed that these findings need to be replicated before neuromuscular blockade becomes part of the routine management of patients with early, severe ARDS. Until then, the body of evidence suggests that the administration of short-term (up to 48 hours) neuromuscular blockade to patients with ARDS who have severe gas exchange abnormalities (eg, $PaO_2/FiO_2 \leq 120$ mmHg) is probably safe and potentially beneficial.

Inhaled nitric oxide

Based on currently available data, the use of inhaled nitric oxide is safe in patients with ARDS to transiently improve oxygenation. However, no differences have been observed in survival, ventilator-free days, or attenuation in disease severity. Further studies with consistent end points using standard delivery devices and standard modes of mechanical ventilation are needed to determine the overall benefit with iNO.[25,26] It cannot be routinely recommended to be used as a rescue therapy in adults with ARDS.

Steroid

Given their effective anti-inflammatory properties, there has been extensive interest in the potential role of corticosteroids in both the prevention and treatment of ARDS. Different regimens have been investigated, varying from short courses of high-dose steroids to prolonged courses of lower doses.

High dose corticosteroids do not prevent ARDS in at risk subjects. Therapeutically, both high-dose and moderate-dose steroids have so far failed to demonstrate efficacy in ARDS. An ARDSnet randomised, double-blind trial in 180 patients with ARDS for more than seven days, showed no effect of prolonged treatment with moderate-dose methylprednisolone compared to placebo. In addition, initiation of treatment after 14 days of ARDS was associated with a harmful effect, with increased mortality at 60 and 180 days.[27]
Therefore, a definitive role of corticosteroids as a pharmacologic strategy to improve oxygenation in ARDS is not established. A possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS was suggested.[28,29]

Fluid management

Although increased vascular permeability is the primary cause of pulmonary oedema in early ARDS, the quantity of oedema formed depends directly upon hydrostatic pressure, since oncotic forces are less capable of retaining fluid within the capillaries. As a result, pulmonary oedema is more likely to develop in ARDS than in normal for any given pulmonary capillary hydrostatic pressure.

Thus, even in patients who are not volume overloaded, a strategy of conservative fluid management may help patients by reducing oedema formation. This was best illustrated by a trial in which 1000 patients with established ARDS were randomly assigned to either a conservative or a liberal strategy of fluid management for seven days.[30] Patients assigned to the conservative group were managed with a fluid strategy that targeted a CVP <4 mmHg or a pulmonary artery occlusion pressure (PAOP) <8 mmHg. Patients managed with the liberal strategy targeted a CVP of 10 to 14 mmHg or a PAOP of 14 to 18 mmHg. The mean cumulative fluid balance was -136 mL in the conservative strategy group and +6992 mL in the liberal strategy group. The conservative strategy improved the oxygenation index and lung injury score, while increasing ventilator-free days (15 versus 12 days) and ICU-free days (13 versus 11 days). The 60 day mortality rate was unaltered by the fluid management strategy. Despite clearly identified CVP and PAOP goals, mean CVP and PAOP remained well above the target goals in the conservative management group, suggesting that a CVP <4 mmHg or a PAOP <8 mmHg is difficult to achieve safely with the strategies outlined in this population.

Given the clinical benefits demonstrated in this trial, it's believed that a conservative strategy of fluid management is warranted in patients with ARDS, as long as hypotension and organ hypoperfusion can be avoided. It is reasonable to target a central venous pressure of <4 mmHg or a pulmonary artery occlusion pressure <8 mmHg; however, it should be recognised that such goals may be difficult to achieve. Preliminary data suggests that combination therapy with albumin solution and frusemide may improve fluid balance, oxygenation, and haemodynamics.

CONCLUSIONS

A variety of strategies are available to improve oxygenation in the setting of refractory hypoxemia in ARDS, which, if any, of these strategies should be used is often determined by the availability of equipment and clinician bias.

A number of rescue therapies that can be used when conventional mechanical ventilation does not achieve a specific target level of oxygenation are discussed. A literature search was conducted and narrative review written to summarize the use of high levels of positive end-expiratory pressure, recruitment manoeuvres, prone positioning, HFOV, ECMO and other adjuvant therapies. Each therapy reviewed has been reported to improve oxygenation in patients with ARDS. However, none of them have been shown to improve survival consistently when studied in heterogeneous populations of patients with ARDS. Moreover, none of the therapies has been reported to be superior to another for the goal of improving oxygenation. The goal of improving oxygenation must always be balanced against the risk of further lung injury. The optimal time to initiate rescue therapies, if needed, is within 96 h of the onset of ARDS, a time when alveolar recruitment potential is the greatest.

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Management of Acute Heart Failure in the Intensive Care Unit

Suneta binti Sulaiman, MBBS (Adelaide), MMed (Anaesthesiology) USM
Consultant Intensivist, Institute Jantung Negara, Kuala Lumpur, Malaysia

DEFINITION

Heart failure can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen suitable for the tissues metabolic demands. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to inadequate compensation for changes in preload or afterload. It can occur as the first manifestation of a failing heart (acute "*denovo*" heart failure) or on the background of chronic heart failure, termed acute decompensated heart failure.[11]

Severity of heart failure is shown by the New York Heart Association (NYHA) classification (Table I). However it does not correlate with left ventricular (LV) function. Killip classification maybe used to describe severity in acute myocardial infarction (MI).[12] This is useful when counseling family members regarding patient's prognosis.

Table I: New York Heart Association functional classification based on severity of symptoms and physical activity.[12]

Class	Description	1-year mortality (%)
1	No limitation on physical activity. Normal physical activity does not cause breathlessness	
2	Slight limitation on physical activity. Comfortable at rest but ordinary physical activity causes breathlessness, fatigure or palpitation	5 - 10
3	Marked limitation on physical activity. Comfortable at rest but less than ordinary physical activity causes breathlessness, fatigue or palpitation	10 -15
4	Unable to carry out any physical activity without discomfort. Symptomatic even at rest	30 - 40

There are different ways of classifying heart failure, one is by looking at the ejection fraction (EF). Heart failure with preserved EF (> 40%) are commonly found in older, female and obese patients.[5] They are less likely to have coronary artery disease and are more likely to have hypertension and atrial fibrillation. Patients with preserved EF have a better prognosis than those with heart failure with reduced EF.[5]

Acute heart failure (AHF) is not represented by a homogeneous group of patients but rather multiple types of patients who have heart failure with various forms of acute decompensation.[7] The most useful way of classifying AHF in ICU is by categorizing them into AHF with normal systolic blood pressure (SBP 90 to 140 mmHg), hypertension (SBP > 140 mmHg) or AHF with cardiogenic shock (SBP < 90 mmHg).

EPIDEMIOLOGY

Heart failure is the leading cause of hospital admission in patients above 65 years of age affecting 6 to 10% of patients in this age group. It is also one of the commonest diagnosis made worldwide accounting for 1 to 2% of disease prevalence in adult patients.[13] Heart failure is a predictor of readmission and death after discharge as high as 20%. Due to our aging population, the incidence of heart failure has tripled over the past 3 decades.[14] Approximately half of AHF admissions to ICU are female, and approximately half have a relatively preserved EF (> 40%).[5]

Despite significant reductions in cardiovascular morbidity and mortality over the last 10 years, post-discharge death and re-hospitalization from AHF remains high, affecting 45% of the discharged population within 90 days. On the other hand, inpatient mortality remains low, ranging from 4 to 9%, more than 10% at 1 month and 20% at 6 months. The re-hospitalization rate is very high around 30 to 40% at the first year.[16] Only 15 to 20% of AHF represents newly diagnosed heart failure. A history of coronary artery disease is present in 60% of patients, hypertension in 70%, diabetes in 40% and renal impairment in 25%.[2] At presentation patients are usually normotensive, 25 % are hypertensive and less than 10% are hypotensive.[2]

PATHOPHYSIOLOGY

Heart failure is unusual in an individual with no relevant medical history. Certain features especially previous MI, greatly increases the likelihood of heart failure in a patient with appropriate signs and symptoms.[12] This highlights the need to obtain objective evidence of a structural or functional cardiac abnormality that is thought to account for the diagnosis. Once the diagnosis of heart failure is made, it is important to establish the cause. Indeed, half of the patients have a precipitating factor for their acute decompensation.

AHF can be caused by intra and extra cardiac causes. Intracardiac causes include myocardial infarction, unstable angina and arrhythmias particularly atrial fibrillation. Extra cardiac causes such as infection, anemia, thyroid disease, renal dysfunction, noncompliance with medication, often resulting in suboptimal control of hypertension, exacerbation of COPD and side effects of chemotherapy (doxorubicin or trastuzumab).[5]

Table II: Causes of acute heart failure.[12]

Causes of acute heart failure
- Acute coronary syndrome
- Arrythmia
- Pulmonary embolism
- Hypertensive crisis
- Cardiac tamponade
- Acute dissection
- Surgery and perioperative problems
- Peripartum cardiomyopathy
- Infection
- Acute exercerbation of COAD
- Anaemia
- Kidney dysfunction
- Non adherence to diet or drug therapy
- Hypo or hyperthyroid
- Drug abuse
- Side effects of medication (NSAIDS, corticosteroid)

CARDIOGENIC SHOCK

Two to eight percent of patients who have AHF have severe LV systolic dysfunction with reduced SBP (< 90 mm Hg) and symptoms and signs of peripheral hypoperfusion and impaired renal function.[8] These patients exhibit a fourfold greater risk for adverse clinical outcomes in the next 6 months than those who have normal blood pressure and need emergent enhancement of cardiac contractility to achieve clinical stabilization.[8] The main targets of treatment in patients who have low output conditions are the attenuation of hypotension and improvement of peripheral tissue perfusion.

Patients presenting with hypotension are difficult to manage. The temptation to immediately raise the

blood pressure should be considered carefully on the background of the overall clinical picture combined with investigation of the patient's baseline state.[11] Patients with end-stage or advanced HF may have reduced systolic function to such a degree that low SBP may be normal. Inotropic agents are reserved for those patients with cardiogenic shock or evidence of hypoperfusion.[11]

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by MI or ischemia. The myocardial dysfunction resulting from ischemia worsens the ischemia, creating a downward spiral. When a critical mass of LV myocardium (usually about 40%) is ischemic or necrotic and fails to pump, stroke volume and cardiac output are decreased.[11] Compensatory mechanisms include sympathetic stimulation to increase heart rate and contractility and renal fluid retention to increase preload.[11] These mechanisms may become maladaptive and can actually worsen the situation.

Increased heart rate and contractility increase myocardial oxygen demand and exacerbate ischemia. Fluid retention and impaired diastolic filling caused by tachycardia and ischemia may result in pulmonary congestion and hypoxia. Vasoconstriction to maintain blood pressure increases myocardial afterload, further impairing cardiac performance and increasing myocardial oxygen demand. This increases demand, in the face of inadequate perfusion, worsens ischemia and begins a vicious circle that will end in death if it is uninterrupted. These maladaptive changes occurring in surviving myocyctes and extracellular matrix after myocardial injury lead to pathological "remodeling" of the ventricle with dilatation and impaired contractility with reduced EF.[11]

Recent data suggest that not all patients fit into this classic paradigm. In the SHOCK trial, the average systemic vascular resistance was not elevated and the range of values was wide, suggesting that compensatory vasoconstriction is not universal.[17] Some patients had fever and elevated white blood cell counts along with decreased systemic vascular resistance, suggesting a systemic inflammatory response syndrome (SIRS).[17]

Activation of inflammatory cascades, oxidative stress, and stretching of myocytes have been proposed as mechanisms that activate the apoptotic pathways. Another important concept is that dysfunctional ischemic myocardium may not be irretrievably lost. This reversible dysfunction can be described in two main categories: stunning and hibernation. Myocardial stunning represents post ischaemic dysfunction that persists despite restoration of normal blood flow; because normally perfused myocardium is viable, myocardial performance is expected to recover completely.[11]

Hibernating myocardium is a term originally coined to denote myocardial segments with persistently impaired function at rest due to severely reduced coronary blood flow when function can be normalized by improving blood flow.[13] Contractile function of hibernating myocardium improves with revascularization and stunned myocardium retains inotropic reserve and can respond to inotropic stimulation.[13] The idea that some myocardial tissue may recover function emphasizes the importance of measures to support hemodynamics and thus minimizing myocardial necrosis in patients with shock in the ICU.

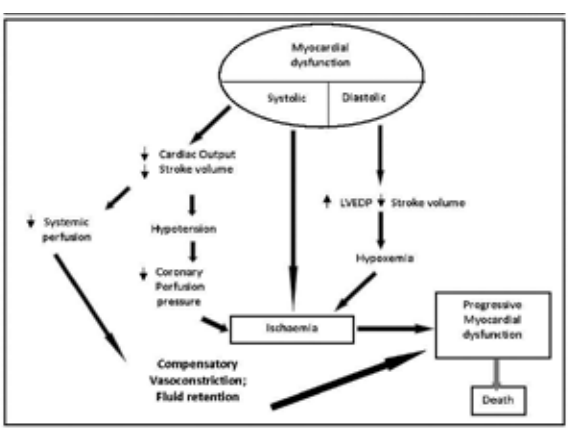

Figure 1: The downward spiral in cardiogenic shock. Adapted from Hollenberg, Parillo. Acute Heart Failure and Shock.[11]

INITIAL ASSESSMENT: HISTORY AND PHYSICAL EXAMINATION

Rapid diagnosis is needed to initiate appropriate treatment early to avoid risk of intubation.[9] It is essential to make a rapid initial evaluation on the basis of a limited history, physical examination and specific diagnostic procedures whilst initiating supportive therapy to maintain blood pressure, oxygenation and tissue perfusion. This is crucial to stabilize the patient and to allow time for instituting definitive interventions aimed at reversal of the underlying pathologic process.

Many signs and symptoms of heart failure are nonspecific. Symptoms that are more specific [i.e. orthopnea and paroxysmal nocturnal dyspnea (PND)] are less common. Symptoms of heart failure include shortness of bgureath, ankle swelling and fatigue. These patients would have signs of an elevated jugular venous pressure (JVP), pulmonary crepitations and a displaced apex beat.[14] Shortness of breath on exertion is the most sensitive whereas PND is the most specific symptom for AHF. On physical examination, increase JVP is the best indicator while on chest x-ray (CXR), the presence of pulmonary congestion and interstitial edema increases likelihood of AHF 12-fold.[16] However, CXR without evidence of volume overload does not rule out AHF because patients with underlying chronic heart failure adapt to a volume-overloaded state; thus radiographic features may be absent.[6]

Table III: Symptoms and signs of heart failure.[12]

SYMPTOMS **Typical**	**SIGNS** **Specific**
Breathlessness	Elevated jugular venous pressure
Orthopnoes	Hepatojugular reflux
PND	3rd heart sound (gallop rhythm)
Reduce exercise tolerance	Displaced apex beat
Fatigue, tiredness, increase time to recover after exercise	Cardiac murmur
Archive swelling	
Less typical	**Less specific**
Nocturnal cough	Breathlessness
Wheezing	Peripheral oedema
Weight gain	Lung crepitations
Weight loss (in advance heart failure)	Reduced air entry and dullness to percussion at lung base (pleural effusion)
Loss of apetitie	Tachycardia
Confusion	Irregular pulse
Depression	Tachypnoea
Palpitation	Hepatomegaly
Syncope	Ascites
	Wasting (cardiac cachexia)

Differentiation of low from high cardiac output (low from high filling pressures) dictates the level of urgency in which subsequent measures are taken. Patients with inadequate perfusion are usually ashen or cyanotic and can have cool skin and mottled extremities. Cerebral hypoperfusion may cloud their sensorium. Pulses are rapid and faint and may be irregular in the presence of arrhythmias.[5] Patients with hypovolemic shock and low filling pressures have flat neck veins, have no evidence of pulmonary congestion and generally lack cardiac gallops. Patients with elevated filling pressures have jugular venous distention or signs of hepatic or peripheral venous congestion. In contrast, normal or high-output shock is often characterized by a widened pulse pressure with a low diastolic pressure and warm extremities.[13]

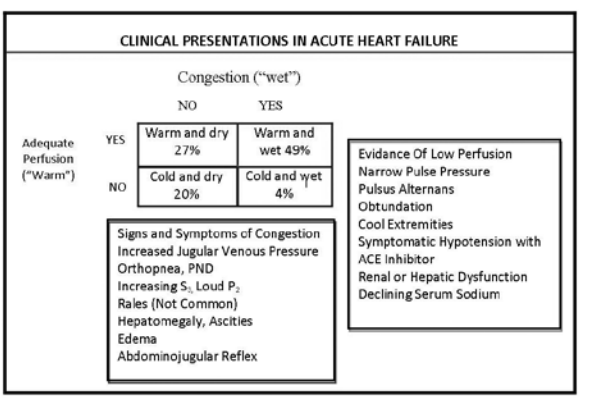

Figure 2: Clinical presentations in acute heart failure. Patients are classified on the basis of bedside assessment of congestion and the adequacy of perfusion. Adapted from Hollenberg, Parillo. Acute Heart Failure and Shock.[11]

DIAGNOSTIC TECHNIQUES

Laboratory Testing

Initial diagnostic tests should include measurement of arterial blood gases, electrolytes, blood urea nitrogen and creatinine concentrations, complete blood count, liver function studies, coagulation parameters and cardiac enzyme analysis. Serum calcium, phosphorus and magnesium concentrations should be checked as well. Increased lactic acid levels are commonly seen due to tissue hypoxia and anaerobic metabolism.

Measurement of enzymes released into the serum from necrotic myocardial cells after infarction aid in the diagnosis of MI.[5] The classic biochemical marker of acute MI is elevation of the creatine kinase MB isoenzyme. Troponin T and troponin I are constituents of the contractile protein apparatus of cardiac muscle. Both are more sensitive and specific for the detection of myocardial damage making troponin measurement better than creatine kinase MB isoenzyme analysis.[5]

B-type natriuretic peptide (BNP) is produced by ventricular myocytes in response to increased wall stress (i.e. increased filling pressures and stretch). Circulating concentrations of BNP and the amino-terminal fragment (NT-proBNP) of its prohormone (proBNP) are increased in congestive heart failure in proportion to the severity of symptoms, the degree of LV dysfunction and cardiac filling pressures.[11] Following the introduction of rapid, automated assays for determination of BNP, its measurement can be used to distinguish between heart failure and pulmonary causes of dyspnea in the ICU setting. Increased plasma levels of BNP and NT-proBNP, however, are not entirely specific for heart failure and may be influenced by a variety of cardiac and noncardiac conditions.[11] For patients presented with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 pg/Ml for NT-proBNP and 100 pg/mL for BNP.[12] A low BNP or NT-proBNP help rule out the diagnosis. But an elevated level maybe difficult to interpret in patients with stable, compensated cardiac dysfunction because their level maybe normally elevated.[12]

Chest Radiography (CXR)

CXR is most useful in identifying an alternative, pulmonary explanation for a patient's symptoms and signs (e.g. aortic dissection or sepsis due to pneumonia). It may, however, show pulmonary venous congestion or oedema in a patient with

HF. Cardiomegaly may result from ventricular failure or tamponade (in which case the heart may appear flask shaped).[12] Prominent pulmonary arteries may be seen with pulmonary emboli (loss of peripheral vasculature) as well as with pulmonary hypertension. Severe mitral or aortic valvular calcification suggests stenosis.[12]

Electrocardiography (ECG)

A 12-lead ECG should be performed immediately on presentation. This may reveal evidence of infarction or arrhythmias. ECG is important because it provides easy and immediate information regarding chamber volume, ventricle systolic and diastolic function, wall thickness and valve function. ECG also provides information on heart rhythm and electrical conduction i.e. whether there is SA node disease, AV block or abnormality of the intraventricular conduction.[11] Conversely, an entirely normal ECG makes it unlikely that myocardial ischemia is the cause of AHF. Low QRS voltage or electrical alternans support cardiac tamponade while an S1Q3T3 pattern is seen with pulmonary embolism (15%).[11]

Echocardiography

To the physician confronted with a critically ill patient, echocardiography will help to establish a diagnosis. This is particularly true in the evaluation of patients with AHF or suspected cardiogenic shock. Hence, early echocardiography should be a routine.[9] A quick evaluation of global and regional LV performance is crucial for management of congestive heart failure. Echocardiography is simple and safe. It allows view of the cardiac chamber size, left and right ventricular function, valvular structure and motion, atrial size and anatomy of the pericardial space.[11] Doppler studies can be used for noninvasive assessment of right and left ventricular filling pressures, pulmonary artery pressures, stroke volume and cardiac output.

Echocardiography can also reveal alternative diagnoses, such as valvular abnormalities, pericardial tamponade and hypertrophic cardiomyopathy.[16] Transthoracic echocardiographic images may be suboptimal because of poor acoustic windows in critically ill patients, particularly those who are obese, have chronic lung disease or are on positive-pressure ventilation.[11] Contrast and transesophageal echocardiography can be considered as better alternatives.

Intra-arterial line & CVP monitoring

Insertion of an intra-arterial line should be considered in all patients with AHF and a low systolic blood pressure despite treatment. Both intraarterial and CVP monitoring provides measures of filling pressures. However, neither has been shown to improve outcome.[12] Use of newer cardiac output monitoring devices also may also aid management of our pharmacological therapy.

Pulmonary Artery Catheterization

Pulmonary artery catheterization (PAC) provides simultaneous assessment of filling pressures and cardiac output and can be quite useful for initiation and monitoring of therapy.[11] The hemodynamic profile of cardiogenic shock includes a pulmonary capillary wedge pressure (PCWP) greater than 18 mm Hg and a cardiac index less than 2.2 L/min/m^2.[11] PAC can also be used to assess the adequacy of global perfusion. Mixed venous oxygen saturation is an indicator of the balance between oxygen delivery and consumption. In an otherwise stable patient, desaturation of hemoglobin in mixed venous blood can reflect a decreased cardiac output. Although prospective trials may never be able to demonstrate conclusively that acquisition of hemodynamic data leads to decreases in mortality, the benefits of more rapid diagnosis seem clear and optimization of supportive therapy is often best guided by hemodynamic assessment. Severe hypotension (SBP < 80 mm Hg), therapy with vasopressor or inotropic agents and cardiogenic shock represent class I indications for PAC hemodynamic monitoring in the latest American College of Cardiology/American Heart Association guidelines.[15]

Coronary angiography

Coronary angiography should be considered in patients with angina pectoris or a history of cardiac arrest if the patient is otherwise suitable for coronary revascularization.[15] Angiography should also be considered in patients with evidence of reversible myocardial ischaemia on non-invasive testing. Non-invasive assessment of myocardial viability should be considered prior to angiography because data show that coronary angiography contributes to an increased risk in the absence of myocardial viability.[12] Other indications include before an elective valve surgery, myocarditis, infiltrative diseases (e.g. amyloidosis) and patients for endomyocardial biopsy.[12]

Cardiac magnetic resonance (CMR)

CMR is a non-invasive technique that provides most of the anatomical and functional information available from echocardiography, including evaluation of ischaemia and viability.[12] It is the best alternative imaging modality in patients with non-diagnostic echocardiography. CMR is particularly valuable in identifying inflammatory and infiltrative conditions.[12] The disadvantage of this technique is the limited availability of the study.

INITIAL APPROACH TO PATIENTS WITH AHF: DIAGNOSIS

It is not always easy to make a diagnosis because signs and symptoms of AHF are also seen in other diseases. Given the heterogeneity of the patient suffering from AHF, dividing patients based on their presenting characteristics is recommended.[7] Patients can be divided into 3 categories: hypertensive (SBP >140 mm Hg), normal blood pressure (SBP 90-140 mm Hg) and hypotensive (SBP < 90 mm Hg). This allows for a more effective approach to immediate patient management. After achieving hemodynamic stabilization and symptomatic relief, all patients should be considered for further treatment involving neurohumoral strategies which include an ACE inhibitor [or angiotensin receptor blocker (ARB)], a beta blocker and a mineralocorticoid receptor antagonist. They are commonly used in conjunction with a diuretic to relieve the symptoms and signs of congestion and to prevent progressive worsening of HF.[5]

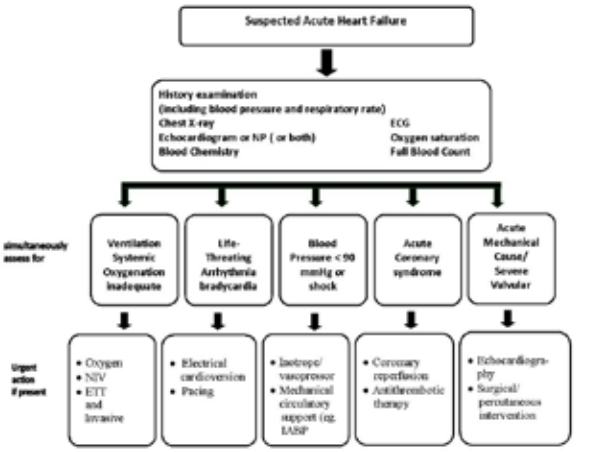

Figure 2: Initial assessment of patient suspected with acute heart failure. Adapted from[12]

THERAPEUTIC CONSIDERATIONS

Noninvasive Ventilation (NIV)

Noninvasive monitoring of blood pressure, respiratory rate, electrocardiogram and oxygen saturation is urgent. Symptomatic improvement is the focus of treatment. For patients with severe dyspnea or respiratory distress, noninvasive respiratory support can be very helpful. In our practice, we aim to start NIV as early as in the emergency department. NIV has a number of theoretical advantages. It augments cardiac output, decreases LV afterload, increases functional residual capacity and it can reduce the work of breathing.[5] The 3CPO trial (on the use of NIV in the treatment of AHF on presentation to the emergency department) showed earlier improvement in dyspnea with no difference in mortality between NIV and standard oxygen group.[1] Initial therapy consists of a positive pressure of 5 to 7.5 cm H^2O, with titration to clinical response. If patients do not manifest rapid clinical improvement with NIV, the strategy should be reconsidered.[1]

Diuretics

Loop diuretics are the most common first-line agent for the treatment of AHF although there is surprisingly little clinical trial evidence for their use. There is a paucity of large-scale randomized controlled trials evaluating loop diuretics in the management of AHF.[7] They remain a central component to AHF management because there are few alternatives and their use is endorsed by many guidelines. The lowest intravenous (IV) dose that achieves the desired level of diuretic effect should be administered. The European Society of Cardiology (ESC) recommends 20 to 100 mg of IV furosemide, depending on the severity of presentation.[12] DOSE-AHF trial showed no differences between continuous versus bolus diuretic dosing. However, their high-dose arm (equivalent to 2.5 times the oral dose divided over a 24-hour period), showed significantly greater urine output as well as greater dyspnea improvement.[19] Renal function and electrolytes should be closely monitored in these patients.

Vasodilators

Vasodilator therapy is recommended as first-line therapy in patients who have AHF associated with an elevated SBP at presentation. These patients represent more than 50% of patients with AHF presenting to the emergency department.[8] Vasodilators used in AHF are nitrates, nitroprusside and nesiritide.

Table IV: Vasodilators used in heart failure treatment.[5]

Vasodilator	Indication	Dosing	Main side effects	Other
Nitroglycerine	Pulmonary congestion/ edema	Start 10 - 20 µg/ min Increase to 200 µg/ min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	BP> 90 mmHg Pulmonary congestion/ edema BP> 90 mmHg	Start 1 mg/h Increase to 10 mg/h	Hypotension, headache	Tolerance on continuous use
Nitroprusside	Hypertensive AHF congestion/ edema BP> 90 mmHg	Start with 0.3 µg/ kg/min increase to 5 µg/kg/min	Hypotension, isocyanate toxicity	Light sensitive

Nitroglycerin

Nitroglycerin is a potent venodilator and a mild arterial vasodilator at higher doses. It mimics the effects of nitric oxide by stimulating guanylate cyclase leading to smooth muscle relaxation in the vascular wall. It reduces LV filling pressures, pulmonary congestion, wall stress and myocardial oxygen consumption without compromising cardiac output.[16] The initial recommended dose of IV nitroglycerin is 10 to 20 µg/min, increased in increments of 5 to 10 µg/min every 3 to 5 minutes as needed.[7] Common side effects are headache and hypotension.

Nitroprusside

Sodium nitroprusside is an arterial vasodilator that is mainly used in patients who have markedly increased afterload attributable to severe hypertension.[9] It reduces systemic vascular resistance, increases stroke volume and improve symptoms in AHF. Common side effects are reflex tachycardia and "coronary steal phenomenon," which may exacerbate myocardial ischemia.[7] Therefore, it is generally not used in patients who have acute MI.

Nesiritide

The ASCENDHF trial showed nesiritide did not affect mortality and rehospitalization rate. Nesiritide was not associated with worsened renal function, but it did improved dyspnea and congestion.[2] However, there are still no sufficient evidence to recommend its regular use.

Opiates

Opiates such as morphine reduce anxiety and relieve distress associated with dyspnoea.[3] Opiates causes mild venodilatation which in turn reduces preload. It also reduces sympathetic drive and produce anxiolysis.[4]

Inotropes

The ideal inotropic agent would improve LV systolic and diastolic function and reduce systemic and pulmonary vascular resistance, without increasing myocardial oxygen consumption. Traditional inotropes, such as beta-agonists and phosphodiesterase (PDE) inhibitors, improve hemodynamic but promote and accelerate detrimental biochemical pathways causing further myocardial injury.[7] Beyond their positive inotropic properties, PDE inhibitors also have vasodilatory effects, because of inhibition of vascular smooth muscle cells. Moreover, because they exert their inotropic action distal to the beta-adrenergic receptor, their effects are preserved even during concomitant administration of beta-blockers. Dopamine on the other hand, works in a dose-dependent manner. At doses less than 2 µg/kg/min dopamine exert some peripheral vasodilation effect predominantly on the renal, splanchnic and coronary vasculature. At 2 to 5 µg/kg/min it acts as a beta-adrenergic agonist, hence enhancing myocardial contractility. At doses higher than 5 µg/kg/min it acts as an alpha-adrenergic receptor agonist, having peripheral vasoconstrictive effects.[7] Levosimendan is a calcium sensitizer. It enhances myocardial contractility without increasing oxygen requirements and causes coronary and systemic vasodilation. Levosimendan has been shown to reduce the risk of death compared with dobutamine and placebo in patients with AHF. The recommended dose is 0.05-0.2 µg/kg/min for less than 24 hours.[10]

Vasopressors

Drugs with peripheral vasoconstrictor action such as norepinephrine and vasopressin, are sometimes given to severely ill patients with marked hypotension. These agents are given to raise blood pressure and redistribute cardiac output from the extremities to the vital organs.[7] However, this is at the expense of an increase in LV afterload. Their use should be restricted to patients with persistent hypoperfusion despite adequate cardiac filling pressures (cardiac output).[12]

Intra-aortic balloon pump (IABP) counterpulsation

IABP reduces systolic afterload and myocardial oxygen consumption and augments diastolic perfusion pressure whereby increasing cardiac output, coronary perfusion, and systemic blood pressure.[11] The effects of IABP, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. Moreover, decreased afterload is accomplished without lowering of blood pressure.[11] In patients with cardiogenic shock and compromised tissue perfusion, IABP can be an essential support mechanism to stabilize patients and to allow time for definitive therapeutic measures to be undertaken.

Chronic renal replacement therapy

Ultrafiltration or hemodialysis may be useful for AHF patients refractory to diuretic therapy. The largest randomized study evaluating ultrafiltration as a treatment for AHF showed greater fluid loss at 48 hours and less rehospitalization rate at 90 days.[20] However it is premature to suggest for the widespread use of ultrafiltration in the management of AHF.

CONCLUSIONS

In recent years, there have been major advances in the treatment of chronic heart failure, whereas the early mortality and morbidity for patients hospitalized for AHF have not changed substantially. Current therapies such as oxygen, noninvasive ventilation, loop diuretics, morphine and nitrates are the same therapies used 40 years ago. Most patients present with hypertensive episode of AHF. Less than 10% of patients present with heart failure and cardiogenic shock. However, this group has the greatest risk of mortality and usually represent the most challenging cases to manage in the ICU. Diligent monitoring and the fine balance of diuretics, vasodilators, inotropic and vasopressor therapy alongside careful fluid balance aids in the management of these patients. Unfortunately, there is no regime for AHF that succeeds in all cases. Hence, the management of AHF remains challenging, even for skilled clinicians.

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