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REVIEW

Current research priorities in perioperative intensive care medicine

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Abstract

Introduction: Surgical treatments are offered to more patients than ever before, and increasingly to older patients with chronic disease. High-risk patients frequently require critical care either in the immediate postoperative period or after developing complications. The purpose of this review was to identify and prioritise themes for future research in perioperative intensive care medicine.

Methods: We undertook a priority setting process (PSP). A panel was convened, drawn from experts representing a wide geographical area, plus a patient representative. The panel was asked to suggest and prioritise key uncertainties and future research questions in the field of perioperative intensive care through a modified Delphi process. Clinical trial registries were searched for on-going research. A proposed "Population, Intervention, Comparator, Outcome" (PICO) structure for each question was provided.

Results: Ten key uncertainties and future areas of research were identified as priorities and ranked. Appropriate intravenous fluid and blood component therapy, use of critical care resources, prevention of delirium and respiratory management featured prominently.

Conclusion: Admissions following surgery contribute a substantial proportion of critical care workload. Studies aimed at improving care in this group could have a large impact on patient-centred outcomes and optimum use of healthcare resources. In particular, the optimum use of critical care resources in this group is an area that requires urgent research.

Keywords: Intensive care, Surgery, Perioperative medicine

Introduction

Crude global estimates suggest that more than 300 million patients undergo surgery each year and this number continues to rise [1]. Mortality following uncomplicated surgery is low and recent international estimates put this figure at less than 1% [2, 3]. However, within this very large population there are high-risk patient groups. Major elective and emergency procedures are offered to an increasingly elderly and comorbid population [4]. Complications following surgery are associated with a five-fold increase in mortality [3] and contribute to long-term morbidity and cost [5]. Perioperative admission to critical care has long been regarded as an important standard of care for certain types of high-risk surgery, and recent data from the UK suggest that 40% of all critical care admissions follow surgery [6]. Unplanned admission to critical care following surgery is also associated with worse outcomes and increased need for organ

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Take-home message: Surgery is increasingly being offered to high-risk patients who require critical care; because the overall surgical population is very large, this represents a major challenge for healthcare providers. We identify some key uncertainties in perioperative critical care and suggest ten important areas to prioritise for clinical research.

support [7]. Thus, interventions aimed at identifying those in need of perioperative critical care admission and improving care of those admitted in the perioperative period are of great importance.

We set out to highlight recent advances, describe the key uncertainties and propose research priorities for perioperative critical care in the next 5 years.

Methods

This article was commissioned by the editorial board of *Intensive Care Medicine* journal. We undertook a priority setting process (PSP) using a modified Delphi technique, similar to previously published research PSPs for critical care and anaesthesia [8, 9]. A panel of experts in the field of perioperative intensive care, representing different geographical areas, were selected. A patient representative member was included in the panel (N.P.). The process consisted of three phases (Fig. 1).

Survey responses were collated and categorised by two experienced specialists in perioperative and intensive care medicine (M.A.G. and R.M.P.). Current standards (question 1) reflected usual care in the authors' regions of practice. Responses to the "recent advances" (question 2) were grouped into themes and organised into preoperative, intraoperative and postoperative sections. Key uncertainties and possible research priorities were sought (questions 3 and 4). Ten important uncertainties and ten potential research questions were identified by consensus. For each identified uncertainty a search for future or ongoing large clinical trials was undertaken (www.clinicaltrials.gov; www.isrctn.com). For each research question a study question using the "Participants, Intervention, Comparator, Outcome" (PICO) format was developed.

Results

Current standards of perioperative critical care

A summary of what was considered to be current standards of perioperative critical care in the geographic region of practice of working group members where resources were not a constraint is presented below.

Preoperative assessment

For many patients, the need for major surgery may accompany deterioration in other chronic diseases, so detailed preoperative assessment before high-risk surgery is essential to plan appropriate management. Medical complications following surgery, particularly nosocomial infections or cardiac complications, are important causes of adverse outcome after surgery [5, 10] and so the risk of these must be minimised. It is therefore important (and increasingly necessary) that other specialists beyond anaesthesia and surgery are involved in optimising patients for major surgery.

International guidelines recommend that functional assessment is carried out before high-risk surgery [11]. One method is cardiopulmonary exercise testing (CPET), which allows an objective assessment of exercise capacity providing a means of risk stratification, and triage for postoperative admission to critical care [12]. Plasma biomarkers such as NT pro-BNP may also be helpful in this context, although evidence for their use is less clear [13].

When patients present for emergency surgery, there is often insufficient time for a detailed preoperative assessment. Here, the use of preoperative risk scoring systems may allow an estimation of risk and help triage patients for postoperative admission to critical care. The American Society of Anesthesiologists Physical Status score, Portsmouth Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (P-POSSUM) and the Surgical Risk Scale have all been used for this purpose, although none of these scores is ideal [14].

Intraoperative care

For many years, the primary focus of perioperative care has been safety and over recent decades there has been a focus on team and human factors (e.g. WHO safety checklists). Thus anaesthetic-related and perioperative deaths have declined markedly in the last five decades [15]. The major development area for intraoperative care has now become the delivery of reliable high-quality care in order to prevent postoperative complications.

Current evidence suggests the intraoperative management of major elective gastrointestinal surgery should include consideration of cardiac output monitoring for haemodynamic management. Findings from a recent systematic review suggest a reduction in complication rates following this intervention [16]. Appropriate intravenous fluid therapy and avoiding intraoperative hypotension are also recommended to prevent acute kidney injury [17].

For patients undergoing major abdominal surgery who are at risk of pulmonary complications, a protective ventilation strategy is recommended, avoiding ventilation with excessive tidal volume, some level of positive end-expiratory pressure (PEEP) and recruitment manoeuvres [18]. Finally, although definitive evidence is lacking, most commentators agree that effective postoperative analgesia including epidural and other regional analgesic techniques are recommended following major surgery to minimise opiate use and reduce respiratory complications.

Postoperative care

Immediate postoperative care of high-risk patients should take place in a post-anaesthesia care unit or critical care unit; however, organisation and implementation of such care varies widely, particularly in settings where resources are limited. In most hospitals worldwide, low-risk patients are

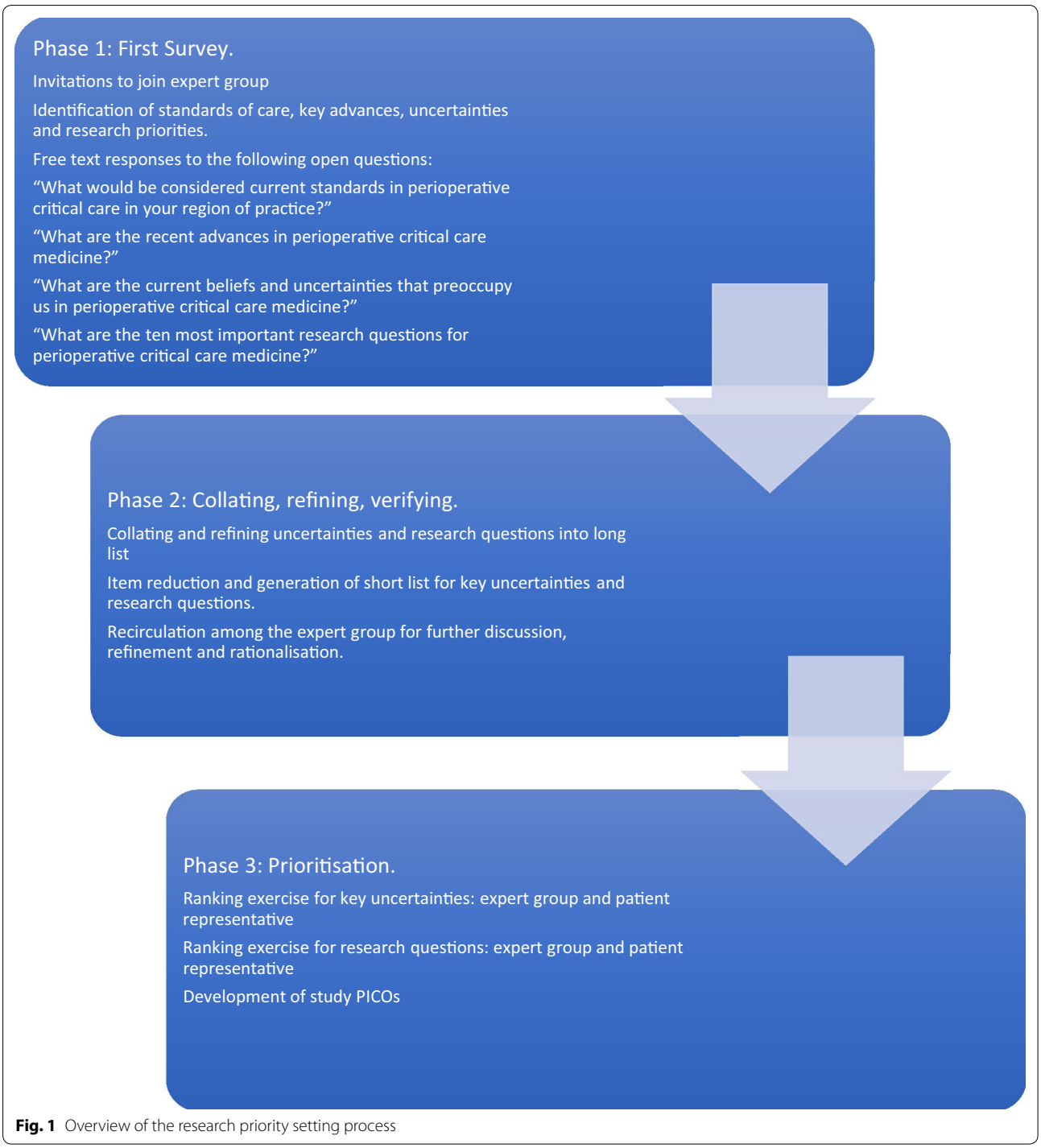

Fig. 1 Overview of the research priority setting process

admitted to a post-anaesthetic care unit or recovery ward for up to 4 h for basic observation immediately following surgery. These facilities represent the minimum standard of care and do not offer organ support on a routine basis.

Many hospitals provide extended post-anaesthetic care for high-risk patients, with many features of the traditional critical care unit, including short periods of invasive and non-invasive ventilation, and inotropic therapy. The key benefit of such facilities is the ability to provide early postoperative critical care interventions as routine to a larger number of patients. Later after surgery, the identification of patients at risk of deterioration,

with early intervention and organ support remains key to ensuring good postoperative outcomes for high-risk patients. Delivery of such care may be difficult in setting where resources are limited.

The Enhanced Recovery After Surgery (ERAS) approach is recommended following many types of surgery [19]. This is a group or 'bundle' of interventions aimed at encouraging early enteral nutrition and mobilisation, improving postoperative comfort, minimising nausea and vomiting, and optimising hydration. This approach may reduce duration of hospital admission, rate of complications and improve patient experience [20]. Regular review by an acute pain team should be mandatory for patients with complex analgesia needs. Acute pain teams also fulfil many other aspects of the perioperative medicine team role and undertake surveillance for complications and physiological deterioration. Elderly patients are at risk of postoperative cognitive dysfunction. Involvement of specialists in the medical care of the elderly patient is now commonplace, e.g. in emergency orthopaedic surgery [21].

What are the recent advances in perioperative critical care medicine?

A summary of what the expert group considered to be recent advances in perioperative medicine is presented in Table 1.

Organisational: perioperative medicine

The needs of high-risk surgical patients are best met through a specific care pathway covering all aspects of care from the moment of contemplation of surgery until full recovery: preoperative assessment, optimisation of co-existing disease, standardisation of intraoperative care, individualised postoperative care and discharge planning. This may be surgery specific, e.g. emergency laparotomy, fractured neck of femur, or colorectal resection, or focussed on specific high-risk patient groups, such as the diabetic patient. In recent years, the organisation of these many and varied care pathways has been brought under the single umbrella term of Perioperative Medicine to promote the delivery of high-quality perioperative care for all patients. In some types of surgery this has led to marked reductions in inpatient stay [22]. The intensive care physician has a key role to play in this development, in particular by improving access to a simplified form of perioperative critical care, and in the early prevention of physiological deterioration in the standard ward environment after surgery and avoidance of "failure to rescue" [23]. In future, remote monitoring of physiological variables using wireless technology may allow earlier detection of the deteriorating patient.

Table 1 Recent advances in perioperative critical care

Recent advances in perioperative critical care
Organisational
Perioperative care pathways
Alternatives to ICU care: PACU/HDU/23-h recovery
Perioperative medicine
Preoperative
Preoperative specialty-specific clinics
Patient education
Shared decision-making
Risk stratification and triage
CPET
Biomarkers
Scoring systems
Intraoperative
Goal-directed haemodynamic therapy
Lung protective ventilation
Point of care coagulation monitoring
Regional and neuraxial analgesia
Postoperative
Enhanced recovery after surgery programmes
Postoperative surveillance teams and critical care outreach
Specialist physician input into care of high-risk and elderly surgical patients

ICU intensive care unit, *PACU* post-anaesthesia care units, *HDU* high dependency units, *CPET* cardiopulmonary exercise testing

Preoperative assessment and risk reduction

Preoperative care should involve early contact with an anaesthetist or perioperative physician. This will facilitate individualised patient care, e.g. in the treatment of anaemia or cardiac disease. The use of physical training or 'prehabilitation' before surgery to improve physical fitness as well as to optimise nutritional and psychological status before surgery is currently being evaluated in various settings. Along with education packages to improve the expectation and understanding of postoperative care, these techniques may greatly improve how patients engage with perioperative care. Sophisticated preoperative assessment algorithms are now being developed which combine CPET data with medical history, clinical risk scores and epidemiological data. This may provide a more accurate risk of death or complications [24]. There may also be a role for plasma biomarkers such as estimated glomerular filtration rate, NT pro-BNP, and troponins for risk assessment in this context [13, 25]. In some circumstances, the risk of major surgery is very high and the planned operation may not be in the patient's best interests. Shared decision-making with the patient allows consideration of other options such as chemo/radiotherapy or palliation (for cancer surgery) or physical therapy (for joint replacement surgery), which best meet patients' hopes and expectations.

Intraoperative care

There is an increasing use of algorithms that incorporate physiological goals to direct intraoperative therapies. This is well established in haemodynamic management where invasive monitoring allows the titration of fluid, vasopressors and inotropic therapy to achieve prespecified blood pressure, cardiac output or other goals. Use of these algorithms may reduce complications and duration of hospital stay [16, 26]. A ventilator strategy targeting low tidal volume ventilation (6 ml kg^{-1}), use of PEEP and recruitment manoeuvres may reduce re-intubation rates and postoperative respiratory complications in high-risk patients undergoing abdominal surgery [18]. A recent meta-analysis suggests that driving pressure may be a key determinant of harm from intraoperative mechanical ventilation [27]. Electroencephalogram (EEG)-based monitors which determine depth of sedation and anaesthesia, e.g. bispectral index, are often used to prevent intraoperative awareness in situations where this is problematic using traditional means (e.g. cardiac surgery, during total intravenous anaesthesia). There is now increasing interest in the use of this monitoring approach to prevent excessive dosing of anaesthesia agents. The use of point of care coagulation testing to guide blood component therapy has become routine for some types of major surgery and trauma. Again, the use of algorithm-based coagulation management may reduce blood loss, transfusion and improve patient outcomes [28–30]. A recent meta-analysis investigating its use in trauma found insufficient evidence to make recommendations on its routine use in this setting [31].

Postoperative care

Ensuring patients at high risk of deterioration after surgery are monitored in an appropriate setting is an important standard of care. These patients are often managed in a critical care area in the early postoperative period, but remain at risk of developing complications following discharge to a standard ward. There has been an increase in the use of early warning scores in this setting, and also in the provision of intensive care outreach teams or physician-led perioperative medicine teams in an attempt to identify patients who are at risk [23]. The hospital level rate of death from postoperative complications, known as 'failure to rescue' is increasingly used as a metric of the safety and effectiveness of postoperative care [10]. Hospitals with a high-risk case-mix but very effective surveillance systems may use failure to rescue rates to demonstrate the quality of postoperative care.

Current beliefs and uncertainties in perioperative critical care

The process of identifying the key uncertainties is outlined in Fig. 2. The literature review process for these uncertainties is accessible in the Supplementary File. The key uncertainties are listed in order of importance as rated by the panel.

1. Fluid therapy

   Intravenous fluid therapy is a central component of perioperative care. In recent years, the traditional theories of fluid mechanics have been revised, and a new model involving the endothelial glycocalyx layer has been proposed [32]. The glycocalyx plays an important role in fluid ultrafiltration and maintenance of plasma oncotic pressure. These new concepts, along with a greater understanding of the potential harms caused by fluids, is driving a re-evaluation of the optimal approach to fluid therapy. There is limited consensus on the most effective type of fluid (e.g. crystalloid vs. colloid, balanced vs. conventional fluids), and dose (volume) [33] and this is reflected in on-going clinical trials (NCT02691676, NCT02721654, NCT01424150).
2. Postoperative critical care admission

   Postoperative admission to a critical care unit is commonly regarded as an important standard for complex major procedures [19]. Disparities exist in patient selection for intensive care; some high-risk patient groups, e.g. surgery for fractured neck of femur or emergency laparotomy, are not routinely admitted to critical care after surgery, whilst others are, e.g. cardiac surgery. This is especially true in settings where resources are limited.

   The use of postoperative critical care for low-risk major surgery may increase financial costs and duration of hospitalisation without improving patient outcomes [34]. Recent studies have failed to demonstrate any mortality benefit associated with postoperative critical care admission [3, 34, 35]. Many of the perceived benefits of critical care, such as high levels of nursing care and observation, could equally be provided in specialist wards. Hence the optimal use of critical care resources in the perioperative period remains unknown.

   Postoperative surveillance to ensure early identification of patients who are at risk of suffering major complications is also considered an area of great importance [23]. Shared decision-making about postoperative care, including critical care (with an advanced directive if appropriate) might better meet patient expectations of survival with acceptable quality of life [36]. Thus high-risk patients being offered major surgery should be fully counselled about the risks of, and the alternatives to, surgery.

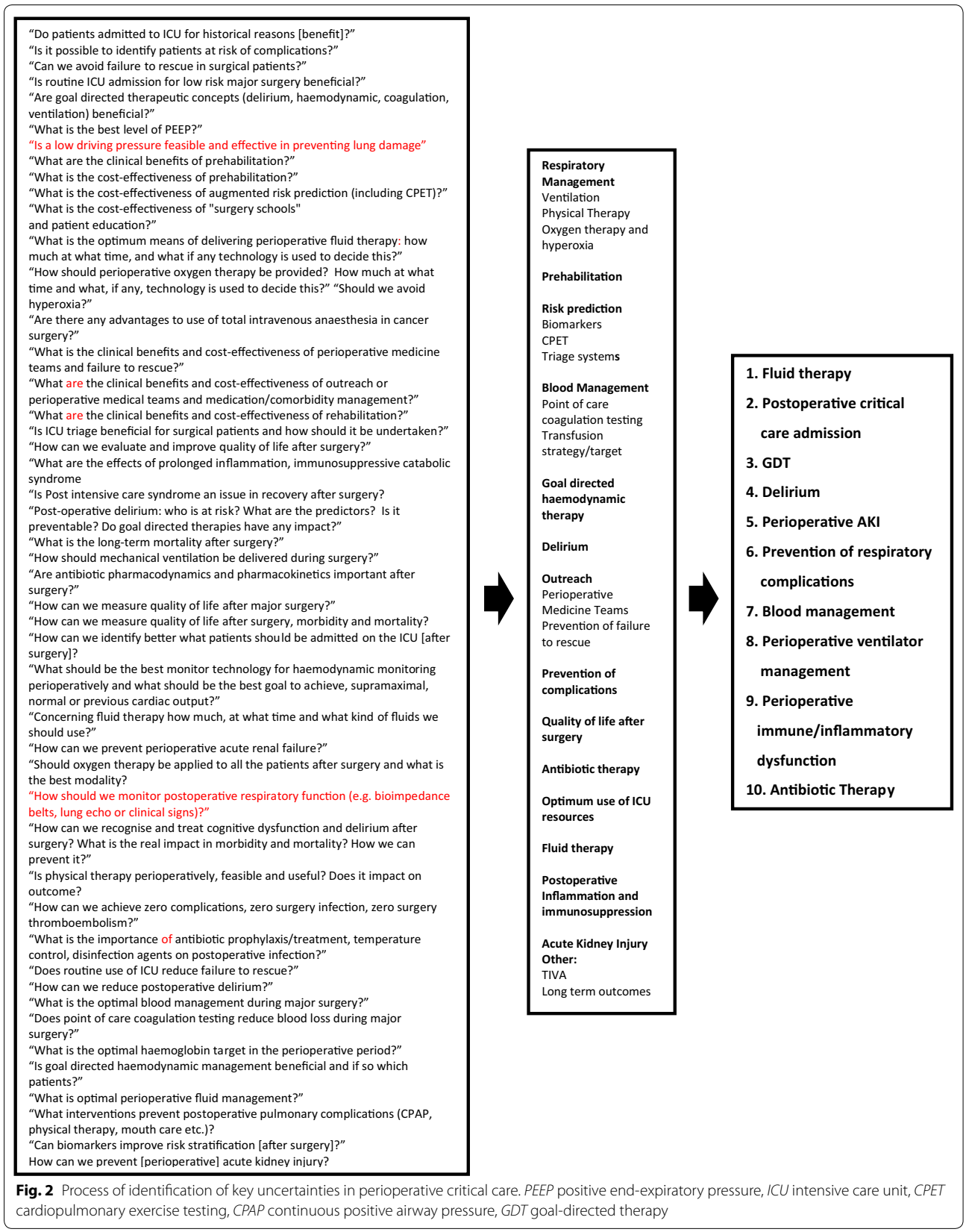

Fig. 2 Process of identification of key uncertainties in perioperative critical care. *PEEP* positive end-expiratory pressure, *ICU* intensive care unit, *CPET* cardiopulmonary exercise testing, *CPAP* continuous positive airway pressure, *GDT* goal-directed therapy

3. Cardiac output-guided haemodynamic therapy
   Perioperative heemodynamic therapy [also termed goal-directed therapy (GDT)] has been promoted as a method of reducing postoperative morbidity and mortality for high-risk surgical patients, and also the financial costs of surgery [37]. In early trials, this treatment was used to optimise tissue oxygen delivery for high-risk patients undergoing major surgery, with trial results suggesting that substantial mortality reductions could be achieved using a pulmonary artery catheter-guided treatment algorithm. However, few subsequent trials have demonstrated such impressive results. Differences between trials in terms of monitoring technology, treatment algorithms, patient cohorts, and timing of the intervention have resulted in a confused and controversial evidence base. Many clinicians believe this approach should be used as standard, whilst others are vocal about the risks of harm. Systematic reviews of efficacy trials suggest the treatment is safe and may be beneficial [16, 25, 26], but the findings of the largest trial to date were equivocal with regards to clinical effectiveness. A large trial of GDT in major abdominal surgery is underway (ISRCTN39653756).
4. Postoperative cognitive dysfunction (delirium)
   Delirium is common and often remains undiagnosed in surgical patients. It can be a serious complication, associated with prolonged duration of hospital stay, cognitive decline, risk of other major complications and death [38]. Clinicians caring for surgical patients should be trained to recognise delirium. Strategies which may prevent postoperative delirium include avoidance of drugs known to precipitate delirium (e.g. benzodiazepines), prolonged critical care admission and use of regional analgesic techniques to minimise systemic opioid administration [39]. Recently evidence has suggested that use of alpha-2 agonist drugs in the early postoperative period (e.g. dexmedetomidine) may reduce the incidence of postoperative delirium [40] and a large multinational multicentre trial is investigating the effect of depth of anaesthesia on postoperative cognitive dysfunction and mortality.
5. Perioperative acute kidney injury
   Sepsis and surgery are the two most common precipitants of postoperative acute kidney injury (AKI), which is associated with a considerable increase in mortality. Baseline preoperative renal dysfunction is also an important predictor of death after surgery [41, 42]. Although the pathophysiological mechanisms are incompletely understood, perioperative AKI may be preventable. Avoiding hypotension, hypovolaemia, fluid overload and nephrotoxic drugs is thought to reduce the incidence, severity and duration of postoperative AKI [43, 44] and there is research planned in investigating the impact of a postoperative AKI prevention bundle involving these elements (NCT02583945). Use of clinical risk prediction models [45, 46] and the measurement of biomarkers of kidney injury may enable earlier intervention and monitor the effectiveness of future treatments [47].
6. Prevention of postoperative respiratory complications
   Pulmonary complications are a major cause of morbidity and mortality after surgery, accounting for up to one in four deaths in the first week after surgery [48]. Identifying patients at high risk of postoperative pulmonary complications would allow modification of perioperative care to improve survival. Many advocate use of epidural analgesia for major thoracic and abdominal surgery, although evidence of reduced postoperative pulmonary complications has not been demonstrated.
   Although postoperative incentive spirometry has not been shown to be beneficial in reducing pulmonary complications after thoracic or abdominal surgery, there is some evidence to suggest that lung expansion using CPAP may be beneficial in higher-risk groups [49, 50]. Current evidence does not support routine use of high flow nasal oxygen after surgery [51]. Other potentially iatrogenic causes of postoperative respiratory failure include hyperoxia which may increase the incidence of wound infection and duration of ventilation [52, 53], and excessive maintenance fluid which may increase the incidence of respiratory failure after thoracic surgery [54]. Current areas of active research in this area include CPAP to prevent postoperative respiratory complications (e.g. ISRCTN56012545) and the effect of oxygen therapy on postoperative infectious complications.
7. Blood and coagulation management
   A restrictive transfusion strategy (i.e. haemoglobin target of 70–90 g L^{-1}) is considered appropriate in stable, hospitalised adults including critical care patients [55]. The situation in patients who have undergone major or high-risk surgery is less clear. Some commentators suggest that a restrictive transfusion strategy may not be safe in this context, particularly for patients with cardiac disease [56]. Use of intravenous iron has not been shown to benefit critically ill patients [57], and trials in surgical patients are ongoing (NCT01692418, NCT02972294).
   Point of care coagulation testing using thromboelastography and thromboelastometry are increasingly used to manage blood component therapy in trauma

and major surgery patients. Available data suggests that blood component therapy administered according to an algorithm using these tests may reduce blood transfusion rates, although the effect on patient outcomes is unknown [28–30]. A recent meta-analysis of use of point of care coagulation testing in adult trauma patients found insufficient evidence to make a firm recommendation on its use in this setting [31].

8. Perioperative ventilator management
   Modifiable ventilator parameters may influence pulmonary outcomes after surgery. Recent study data suggests [18, 58–60] that occurrence of pulmonary complications is influenced by three intraoperative ventilator settings: tidal volume, PEEP and the resulting driving pressure [59]. However, uncertainty remains over the role of each component in trial interventions. A recent trial demonstrated no benefit and the possibility of harm from high PEEP during intraoperative ventilation [61]. Thus benefit from the lung protective ventilation strategies might best explained by reductions in tidal volume size, and not the increase in levels of PEEP [59]. Current trials are focused on driving pressure and the optimum PEEP and their role in prevention of postoperative lung injury (e.g. NCT02851238, NCT02963025, NCT02148692).
9. Perioperative immune and inflammatory dysfunction
   Inflammation and activation of the immune system occurs normally following major surgery to promote tissue healing. The subsequent impairment of innate and adaptive immune responses results in immune compromise and a reduced bactericidal response to pathogens [62]. This phenotype of host immune compromise is further exacerbated by the effects of general anaesthesia. The consequence of postoperative immune compromise is increased susceptibility to nosocomial infections [63]. Although perioperative alterations in immune biomarkers such as IL-6, IL-10 and HLA-DR are associated with an enhanced susceptibility to postoperative infection, it remains unclear which biomarkers most accurately predict infection secondary to immune suppression. Whilst this immunological deficit is reversible using immune stimulants such as interferon gamma (IFNγ) and granulocyte–macrophage colony-stimulating factor (GM-CSF) the clinical consequences of these therapies in the perioperative setting remain unclear [64, 65]. A persistent immune suppression and catabolism has been identified following the tissue injury associated with major trauma but not as yet following elective or non-trauma emergency surgery [66].
10. Antibiotic therapy
    Antimicrobial resistance is perhaps the greatest single challenge facing modern healthcare and clinicians must balance need for antibiotic therapy with preserving their effectiveness. Prophylaxis is often recommended to reduce the risk of surgical site infection, and is the most frequent indication for antimicrobial use during the perioperative period. However, the evidence to support the use of antimicrobial prophylaxis is several decades old, preceding modern innovations which reduce surgical site infection e.g. modern antiseptic preparation, minimally invasive surgery, operating theatre airflow systems. There is widespread variation in practice of antimicrobial prophylaxis for surgical patients. When source control is secured with surgical or radiological drainage, antimicrobial therapy may be unnecessary in uncomplicated conditions e.g. appendicitis or cholecystitis [67].
    When antibiotics are given for life-threatening infections, timely administration and assurance of adequate tissue concentrations at the infection site are essential. Underdosing antimicrobials can result in resistance and treatment failure. Tissue concentrations of antibiotics may change during sepsis by hyperdynamic circulation, capillary leak, hypoalbuminaemia and need for large volumes of fluids during resuscitation. These may affect the volume of distribution, resulting in high antibiotic clearance and the possibility of inadequate dosing. These pharmacokinetic changes may result in failure to achieve pharmacodynamic targets, and hence the ability of antimicrobial agents to treat infection. Clinicians should consider these changes when prescribing antimicrobials as well as the interaction between the pathogen and antimicrobial agents at minimal inhibitory concentrations [68]. Changes to the dose and infusion regimen may be needed as well as more frequent plasma measurement of drug levels [69]. These enhanced dosing regimens require further investigation.

Ten priority research questions for perioperative critical care

The process for identifying and ordering the research priorities is presented in Table 2. The final ten research questions ranked in order of priority, with proposed PICO, are outlined in Table 3. Priorities marked with an asterisk were identified as the top five research questions by the patient representative member of the panel.

Table 2 Research priorities for perioperative intensive care medicine

Long list of research priorities	Top ten research priorities ranked in order
How is postoperative respiratory failure best prevented and treated?	1. What is the most appropriate use of fluid therapy in the surgical patient?
What is the most appropriate use of fluid therapy in the surgical patient?	2. What is the best use of intensive care resources in the perioperative period? *
Is cardiac output-guided haemodynamic therapy (goal-directed therapy) an effective way to improve postoperative patient outcomes?	3. How can postoperative cognitive dysfunction (delirium) be prevented and treated? *
What is optimal approach to oxygen therapy and invasive ventilation for patients undergoing major surgery?	4. Is cardiac output-guided haemodynamic therapy (goal-directed therapy) an effective way to improve postoperative patient outcomes?
What is the optimum PEEP for ventilating high-risk patients in the OR?	5. How can we prevent and treat postoperative acute kidney injury (AKI)?
Can reducing the driving pressure in perioperative ventilation reduce pulmonary complications?	6. How is postoperative respiratory failure best prevented and treated? *
How should patient blood management be adapted for the surgical patient?	7. How should patient blood management be adapted for the surgical patient?
What is the optimal indication and dosing of antibiotic therapy in the surgical patient?	8. What is optimal approach to oxygen therapy and invasive ventilation for patients undergoing major surgery? *
Can we modify the inflammatory response to surgery and improve immune function?	9. What is the optimal indication and dosing of antibiotic therapy in the surgical patient? *
How can postoperative cognitive dysfunction (delirium) be prevented and treated?	10. Can we modify the inflammatory response to surgery and improve immune function?
How can we prevent and treat postoperative acute kidney injury (AKI)?	
What is the best use of intensive care resources in the perioperative period?	
Which patient subgroups benefit most from enhanced recovery after surgery (ERAS)?	
What are the best risk stratification tools to use before surgery?	
What is the best mode of analgesia and sedation after surgery?	
How should we measure quality of life after surgery?	
How can we reduce perioperative gastrointestinal dysfunction?	

OR operating room, *PEEP* positive end-expiratory pressure

* Priorities marked with an asterisk were identified as the top five research questions by the patient representative member of the panel

1. What is the most appropriate use of fluid therapy in the surgical patient?
   Intravenous fluid therapy represents the cornerstone of perioperative management but unanswered questions remain. We need to confirm which formulation of fluid is best suited to surgical patients, and whether balanced crystalloid and colloid solutions offer any advantages over traditional fluid therapies such as normal saline. There is debate about the value of further trials to confirm the safety and efficacy of hydroxyethyl starch solutions for surgical patients who are not critically ill. Some argue that evidence from large trials of critically ill patients should influence this practice, whilst some believe that separate trials are needed [70]. What are the effects of fluid dose (volume) at different stages of the perioperative period, and does this vary between different procedures?
2. What is the best use of intensive care resources in the perioperative period? *
   Research is required to define the groups most likely to benefit from postoperative admission to critical care, and to identify patients in non-critical care areas at risk of deterioration. We need to investigate which preoperative biomarkers may best help to identify patients at greatest risk of postoperative morbidity and mortality, and hence need for postoperative critical care? What is the role of alternatives such as overnight or 23-h post-anaesthesia care units or specialist wards in delivering postoperative care following high-risk surgery, and are they more cost effective than traditional critical care? How can we identify patients at risk of developing postoperative complications in a ward setting? How can we improve the safety and quality of postoperative care using metrics such as failure to rescue?
3. How can postoperative cognitive dysfunction (delirium) be prevented and treated? *
   Postoperative cognitive dysfunction is common and associated with increased morbidity and mortality. Studies are needed to evaluate strategies to prevent cognitive dysfunction including optimum mode and depth of anaesthesia and ICU sedation, neuroprotective agents, and specific drug treatments for delirium.
4. Is cardiac output-guided haemodynamic therapy (goal-directed therapy) an effective way to improve postoperative patient outcomes?
   There have been many small efficacy trials of this treatment, utilising different monitoring technologies, different algorithms and different patient cohorts. Most suggest improved postoperative complication rates and hospital length of stay [16, 26], but definitive evidence of clinical effectiveness is

Table 3 Top ten most important research questions in perioperative critical care with "Population, Intervention, Comparator, Outcome (PICO)" structure

Research question	PICO
Fluid therapy: "Do balanced crystalloids offer advantages over conventional fluids in surgical patients?"	P: Patients undergoing major abdominal surgery I: Balanced crystalloid solution C: Normal saline O: Death, acute kidney injury
ICU resources: "Does ICU admission confer any benefit over specialist wards after high-risk elective surgery?"	P: Patients undergoing high-risk surgery I: Admission to intensive care unit C: Admission to specialist ward O: Death, complications
Postoperative delirium: "Does short-term postoperative infusion of dexmedetomidine reduce incidence of delirium?"	P: Patients over 65 years having major surgery I: Dexmedetomidine infusion C: Placebo O: Delirium, mortality
Goal-directed therapy: "Is cardiac output-guided haemodynamic therapy an effective way to improve postoperative patient outcomes?"	P: Patients undergoing major abdominal surgery I: Cardiac output-guided haemodynamic therapy algorithm C: Standard care O: Complications, length of stay
Acute kidney injury (AKI): "Does protocolised haemodynamic and fluid management reduce the incidence of postoperative AKI?"	P: Patients at risk of AKI undergoing major surgery I: Protocolised haemodynamic and fluid management C: Standard care O: AKI, new renal replacement requirement, death
Prevention of postoperative pulmonary complications: "Do preoperative conditioning and physical therapy prevent postoperative respiratory complications?"	P: Patients undergoing major abdominal surgery I: Preoperative conditioning, physical therapy C: Standard care O: Respiratory complications
Patient blood management: "What is the optimum transfusion threshold in patients at risk of cardiovascular complications having major surgery?"	P: Patients undergoing major surgery with CVS risk factors I: Restrictive transfusion threshold C: Liberal transfusion threshold O: Cardiovascular and infectious complications, death
Oxygen therapy and invasive ventilation: "What is the optimal ventilation strategy for patients undergoing major surgery?"	P: Patients undergoing major abdominal surgery I: Limited driving pressure, higher PEEP, higher FiO_2 C: Standard care O: Postoperative pulmonary complications, death
Antibiotic therapy: "Do rapid point of care diagnostic techniques for infection improve antibiotic therapy and outcome in surgical sepsis?"	P: Septic patients having surgical source control I: Rapid diagnostic PCR detection of infection C: Standard microbiological testing O: Infectious complications, duration of antibiotic therapy, progression to septic shock, death
Inflammatory response to surgery: "Does immune stimulation in patients with a genetic phenotype associated with increased incidence of postoperative infection reduce infectious complications?"	P: Patients with genetic predisposition to postoperative infection I: Immune system stimulation e.g. GCSF C: Standard care O: Infectious complications, progression to septic shock

CVS cardiovascular system, *PEEP* positive end-expiratory pressure, *PCR* polymerase chain reaction, *GSCF* granulocyte colony-simulating factor, FiO_2 fractional inspired oxygen

still lacking [16]. There remains a need for a large adequately powered randomised trial to confirm whether the benefits of this intervention are sufficient to justify routine use in all patients. Further questions include the incremental benefit of inotropic therapy as a component for such algorithms, and the role of 'dynamic' fluid responsiveness parameters such as stroke volume variation.

5. How can we prevent and treat postoperative acute kidney injury (AKI)?
   Future studies should focus on the prognostic significance of mild (i.e. KDIGO stage 1) AKI. Is this a suitable endpoint for studies aimed at reducing perioperative AKI? What is the clinical significance of preoperative chronic kidney disease, and can this be mitigated? Is there a role for biomarkers in the detection of subclinical AKI or risk stratification in surgical patients? Can protocolised fluid and blood pressure management in these patients reduce the incidence of postoperative AKI?
6. How is postoperative respiratory failure best prevented and treated? *
   The prevention and management of postoperative pulmonary complications may have a major impact on

patient outcomes and critical care admission. We need to establish whether specific interventions to improve pulmonary function will prevent pulmonary complications. Candidates include prehabilitation, incentive spirometry, inspiratory muscle training, continuous positive airways pressure, and high flow nasal oxygen therapy. There is also a need to confirm the effects of analgesia on postoperative pulmonary complications.

7. How should patient blood management be adapted for the surgical patient?
   Controversy still exists around the ideal transfusion thresholds in the surgical patient, particularly in the setting of cancer surgery, orthopaedic surgery, cardiac surgery, and patients with cardiac disease. Future studies should address the safety of liberal and restrictive transfusion strategies in these patients. The effect of algorithm-based blood component therapy using near-patient tests of coagulation on transfusion requirement, morbidity and mortality also requires further investigation.
8. What is optimal mode of oxygen therapy and invasive ventilation for patients undergoing high-risk surgery? *
   Inspired oxygen therapy is the single most frequently used treatment in the perioperative period, and yet we know very little about the optimal use of this treatment. There are conflicting reports about the benefits of oxygen therapy whilst potential harmful effects are now better understood [71]. Which monitoring targets should we employ for oxygen therapy, and which inspired oxygen concentration provides optimal benefit? What are the harmful sequelae of perioperative hyperoxia? What is the most effective approach to oxygen therapy in the perioperative period? It is now established that different approaches to mechanical ventilation may affect mortality amongst critically ill patients. We need to establish whether similar effects occur in the surgical population where the exposure period is much shorter, and patients are at much lower risk. Postoperative outcomes may be affected by ventilator driving pressure even in patients ventilated for short periods [72]. Future research should explore which components of an intraoperative ventilation intervention offer benefit and the optimal level of PEEP in different surgical groups (e.g. obese, trauma, laparoscopic surgery, etc.). We need to consider the feasibility of trials of low pulmonary driving pressure during mechanical ventilation for surgery.
9. What is the optimal indication and dosing of antibiotic therapy in the surgical patient with sepsis? *
   Infection is a leading cause of morbidity and mortality in surgical patients, but must be balanced against the need for antibiotic stewardship. Future research should establish the need for routine prophylactic antibiotic therapy in the surgical setting and optimum duration of antibiotic therapy, particularly where infection source control is achieved. The impact of perioperative changes in the pharmacokinetics of antimicrobials also warrants further investigation, as does the optimal dosing regimens in life-threatening infections associated with severe physiological disturbance. Availability of rapid near-patient microbiologic testing in the operating theatre may allow improved selection of antibiotic agent and warrant further investigation.
10. Can we modify the inflammatory response to surgery and improve immune function?
    Subclinical immune suppression following major surgery may increase susceptibility to infection, and possibly cancer recurrence. Important avenues of future research include identification of biomarkers that predict postoperative infection secondary to immune suppression, the benefit of perioperative immune stimulation, characterising a perioperative syndrome of persistent inflammation and immunosuppression and its consequences e.g. cancer recurrence and persistent infections.

Conclusion

The population undergoing major surgery is very large and conceals a significant number at much greater risk of complications and death. Improvements in their care could lead to benefit for greater numbers of patients. Although standards of care continue to improve for this patient group, clinicians are now much more likely to offer high-risk patients surgical treatments than 20 years ago.

While the focus of this review is on clinical trials which should be conducted in the next 10 years, it should be remembered that a great deal of research funding is awarded to basic and translational science. The importance of this must also be emphasised as this research sets the direction of the large clinical trials of the future.

It should be noted that this is a research priority setting exercise rather than a formal systematic review for each topic. Moreover, the PSP for this review considered research questions which were a priority in the developed world. Priorities in settings where resources are limited may well be different and many commentators predict a huge expansion in the volume of complex surgery carried out in this setting over the coming decades [73].

It remains a priority for critical care physicians to deliver better care for patients during the perioperative period in order to ensure that surgical treatments are as effective as possible. Many treatment approaches developed in the intensive care unit are increasingly applied to the operating

room or perioperative setting, to prevent and treat harm during this period. The findings of this review are that research priorities among clinicians remain focused on delivery of basic perioperative care i.e. fluid and oxygen therapy, ventilation, prevention of complications, whereas patients prioritise prevention of delirium, antibiotic resistance and availability of critical care for those who need it.

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Compliance with ethical standards

Conflicts of interest
RMP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, Glaxo Smithkline and Edwards Lifesciences, and is a member of the associate editorial board of the ***British Journal of Anaesthesia***.JM was the principal investigator of the CHEST trial; his institution, the George Institute for Global Health, has received unrestricted grant funding from Fresenius Kabi and Baxter Healthcare in relation to fluid resuscitation research; he is supported by a Practitioner Fellowship from the National Health and Medical Research Council of Australia.MPWG serves on the medical advisory board of Sphere Medical Ltd and has given lectures for Edwards Lifesciences, Fresenius Kabi and BOC Medical (Linde Group), Ely-Lilly Critical Care, Cortex GmBH. MPWG is the UK NIHR CRN National Specialty Lead for Anaesthesia, Perioperative Medicine and Pain. MPWG is also executive chair of the Xtreme Everest (XE) Oxygen Research Consortium and leads the Fit-4-Surgery research collaboration. MPWG is an associate editor of the journal ***Perioperative Medicine*** and editor-in-chief of the journal ***Extreme Physiology and Medicine***. AS is a consultant for Baxter, Astute, Edwards and FAST medical. All other authors declare they have no conflicts of interest.

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References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T et al (2015) Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet 385(Suppl 2):11
2. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C et al (2012) Mortality after surgery in Europe: a 7 day cohort study. Lancet 22(380):1059–1065
3. ISOS Study Group (2016) Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 117:601–609
4. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A et al (2006) Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care 10:R81
5. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ et al (2005) Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 242:323–326
6. Gillies MA, Power GS, Harrison DA, Fleming A, Cook B, Walsh TS et al (2015) Regional variation in critical care provision and outcome after high-risk surgery. Intensive Care Med 41:1809–1816
7. Gillies MA, Harrison EM, Pearse RM, Garrioch S, Haddow C, Smyth L et al (2017) Intensive care utilization and outcomes after high-risk surgery in Scotland: a population-based cohort study. Br J Anaesth 118:123–131
8. Boney O, Bell M, Bell N, Conquest A, Cumbers M, Drake S et al (2015) Identifying research priorities in anaesthesia and perioperative care: final report of the joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership. BMJ Open J5(12):e010006
9. Reay H, Arulkumaran N, Brett S (2014) Priorities for future intensive care research in the UK: results of a James Lind Alliance Priority Setting Partnership. J Intensive Care Soc 15(4):288–296
10. Ghaferi AA, Birkmeyer JD, Dimick JB (2009) Variation in hospital mortality associated with inpatient surgery. N Engl J Med 361:1368–1375
11. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B et al (2014) ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 130:e278–e333
12. Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J (2016) Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth 116:177–191
13. Rodseth RN, Lurati Buse GA, Bolliger D, Burkhart CS, Cuthbertson BH, Gibson SC et al (2011) The predictive ability of pre-operative B-type natriuretic peptide in vascular patients for major adverse cardiac events: an individual patient data meta-analysis. J Am Coll Cardiol 58:522–529
14. Moonesinghe SR, Mythen MG, Das P, Rowan KM, Grocott MPW (2013) Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review. Anesthesiology 119:959–981
15. Bainbridge D, Martin J, Arango M, Cheng D (2014) Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. Lancet 380:1075–1081
16. Pearse RM, Harrison DA, MacDonald N et al (2014) Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA 311:2181–2190
17. Sun LY, Wijeysundera DN, Tait GA, Beattie WS (2015) Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 123:515–523
18. Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A et al (2013) A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 369:428–437
19. Pearse RM, Holt PJE, Grocott MPW (2011) Managing perioperative risk in patients undergoing elective non-cardiac surgery. BMJ. 343:d5759
20. King AB, Alvis BD, McEvoy MD (2016) Enhanced recovery after surgery, perioperative medicine, and the perioperative surgical home. Curr Opin Anaesthesiol 29:727–732
21. Harari D, Hopper A, Dhesi J, Babic-Illman G, Lockwood L, Martin F (2007) Proactive care of older people undergoing surgery ('POPS'): designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. Age Ageing 36:190–196
22. Soffin EM, YaDeau JT (2016) Enhanced recovery after surgery for primary hip and knee arthroplasty: a review of the evidence. Br J Anaesth 117(S3):62–72
23. The Royal College of Anaesthetists Perioperative medicine: the pathway to better surgical care. https://www.rcoa.ac.uk/perioperativemedicine. Accessed 14 Dec 2016

24. Carlisle JB, Danjoux G, Kerr K, Snowden C, Swart M (2015) Validation of long-term survival prediction for scheduled abdominal aortic aneurysm repair with an independent calculator using only pre-operative variables. Anaesthesia 70:654–665
25. Gillies MA, Shah ASV, Mullenheim J, Tricklebank S, Owen T, Antonelli J et al (2015) Perioperative myocardial injury in patients receiving cardiac output-guided haemodynamic therapy: a substudy of the OPTIMISE Trial. Br J Anaesth 115:227–233
26. Grocott M, Hamilton M, Bennett D, Rowan K (2013) Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery. Br J Anaesth 111:535–548
27. Neto AS, Hemmes SNT, Barbas CSV, Beiderlinden M, Fernandez-Bustamante A, Futier E et al (2016) Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. Lancet Respir Med 4:272–280
28. Da Luz LT, Nascimento B, Shankarakutty AK, Rizoli S, Adhikari NK (2014) Effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma: descriptive systematic review. Crit Care 18:518
29. Weber CF, Klages M, Zacharowski K (2013) Perioperative coagulation management during cardiac surgery. Curr Opin Anaesthesiol 26:60–64
30. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP et al (2016) Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. Circulation 134:1152–1162
31. Hunt H, Stanworth S, Curry N, Woolley T, Cooper C, Ukoumunne O et al (2015) Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev (2):CD010438
32. Garrioch SS, Gillies MA (2015) Which intravenous fluid for the surgical patient? Curr Opin Crit Care. 21(4):358–363
33. Navarro LHC, Bloomstone JA, Auler JOC, Cannesson M, Della Rocca G, Gan TJ et al (2015) Perioperative fluid therapy: a statement from the International Fluid Optimization Group. Perioper Med 4(1):3
34. Wunsch H, Gershengorn H, Cooke CR, Guerra C, Angus DC, Rowe JW et al (2015) Use of intensive care services for medicare beneficiaries undergoing major surgical procedures. Anesthesiology 124:899–907
35. Gillies MA, Pearse RM (2015) Intensive care following high-risk surgery… What's in a name? Anesthesiology 124:761–762
36. Myburgh J, Abillama F, Chiumello D, Dobb G, Jacobe S, Kleinpell R et al (2016) End-of-life care in the intensive care unit: report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care 34:125–130
37. Sadique Z, Harrison DA, Grieve R, Rowan KM, Pearse RM (2015) Cost-effectiveness of a cardiac output-guided haemodynamic therapy algorithm in high-risk patients undergoing major gastrointestinal surgery. Perioper Med 4:13
38. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M (2009) Postoperative delirium in the elderly. Ann Surg 249:173–178
39. The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults (2015) Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. J Am Coll Surg 220:136–149
40. Su X, Meng Z-T, Wu X-H, Cui F, Li H-L, Wang D-X et al (2016) Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 6736(16):1–10
41. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR (2016) Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Med 42:521–530
42. Prowle JR, Kam EPY, Ahmad T, Smith NCE, Protopapa K, Pearse RM (2016) Preoperative renal dysfunction and mortality after non-cardiac surgery. Br J Surg 103:1316–1325
43. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. doi:10.1007/s00134-016-4670-3
44. Mårtensson J, Bellomo R (2014) Prevention of renal dysfunction in postoperative elderly patients. Curr Opin Crit Care 20:451–459
45. Kheterpal S, Tremper KK, Englesbe MJ, O'Reilly M, Shanks AM, Fetterman DM et al (2007) Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 107:892–902
46. Bell S, Dekker FW, Vadiveloo T, Marwick C, Deshmukh H, Donnan PT et al (2015) Risk of postoperative acute kidney injury in patients undergoing orthopaedic surgery-development and validation of a risk score and effect of acute kidney injury on survival: observational cohort study. BMJ 351:h5639
47. Martensson J, Martling C-R, Bell M (2012) Novel biomarkers of acute kidney injury and failure: clinical applicability. Br J Anaesth 109:843–850
48. Arozullah AM, Daley J, Henderson WG, Khuri SF, Program for the NVASQI (2000) Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Ann Surg 232(2):242–253
49. Chiumello D, Chevallard G, Gregoretti C (2011) Non-invasive ventilation in postoperative patients: a systematic review. Intensive Care Med 37(6):918–929
50. Pearse RM, Abbott TE, Haslop R (2016) Prevention of respiratory insufficiency after surgical management (PRISM) trial: report of the protocol for a pragmatic randomised controlled trial of continuous positive airway pressure (CPAP) to prevent respiratory complications and improve survival following major abdominal surgery. Miner Anestesiol 83(2):175–182
51. Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozencwajg S, Delay J-M et al (2016) Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). Intensive Care Med 42(12):1888–1898
52. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L et al (2009) Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery. JAMA 302:1543–1550
53. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G et al (2016) Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients a randomized clinical trial. JAMA 315:1354–1361
54. Mizuno Y, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K et al (2012) The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg 41:e161–e165
55. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J (2015) Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ 350:h1354
56. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst L et al (2016) Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. BMJ 352:i1351
57. Litton E, Baker S, Erber WN, Farmer S, Ferrier J, French C et al (2016) Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial. Intensive Care Med 42(11):1715–1722
58. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A et al (2013) Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology 118(6):1307–1321
59. Serpa Neto A, Hemmes SNT, Barbas CSV, Beiderlinden M, Biehl M, Binnekade JM et al (2015) Protective versus conventional ventilation for surgery. Anesthesiology 123(1):66–78
60. Hemmes SN, de Abreu MG, Pelosi P, Schultz MJ (2011) ESA Clinical Trials Network 2012: LAS VEGAS—Local assessment of ventilatory management during general anaesthesia for surgery and its effects on postoperative pulmonary complications: a prospective observational international multicentre cohort study. Eur J Anaesthesiol 30:205–207
61. Hemmes SNT, Gama de Abreu M, Pelosi P, Schultz MJ, PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology (2014) High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 384:495–503

62. O'Dwyer MJ, Owen HC, Torrance HDT (2015) The perioperative immune response. Curr Opin Crit Care 21:336–342
63. Torrance HDT, Pearse RM, O'Dwyer MJ (2016) Does major surgery induce immune suppression and increase the risk of postoperative infection? Curr Opin Anaesthesiol 29(3):376–383
64. Longbottom ER, Torrance HDT, Owen HC, Fragkou PC, Hinds CJ, Pearse RM et al (2016) Features of postoperative immune suppression are reversible with interferon gamma and independent of interleukin-6 pathways. Ann Surg 264:370–377
65. Spies C, Luetz A, Lachmann G, Renius M, von Haefen C, Wernecke K-D et al (2015) Influence of granulocyte-macrophage colony-stimulating factor or influenza vaccination on HLA-DR, infection and delirium days in immunosuppressed surgical patients: double blind, randomised controlled trial. PLoS One 10:e0144003
66. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA et al (2012) Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg 72:1491–1501
67. Andersen BR, Kallehave FL, Andersen HK (2005) Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. Cochrane Database Syst Rev (3):CD001439
68. Roberts JA, Taccone FS, Lipman J (2016) Understanding PK/PD. Intensive Care Med 42:1797–1800
69. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Lefrant J-Y et al (2016) Influence of renal replacement modalities on amikacin population pharmacokinetics in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother 60:4901–4909
70. Gillies MA, Habicher M, Jhanji S, Sander M, Mythen M, Hamilton M et al (2014) Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis. Br J Anaesth 112(1):25–34
71. Helmerhorst HJF, Schultz MJ, van der Voort PHJ, de Jonge E, van Westerloo DJ (2015) Bench-to-bedside review: the effects of hyperoxia during critical illness. Crit Care 19:284
72. Neto AS, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E et al (2014) Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. Lancet Respir Med 2(12):1007–1015
73. Molnar Z, Benes J, Reuter D (2017) Intensive care medicine in 2050: perioperative critical care. Intensive Care Med. doi:10.1007/s00134-017-4703-6