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The effects of major burn related pathophysiological changes on the pharmacokinetics and pharmacodynamics of drug use: An appraisal utilizing antibiotics

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ABSTRACT

Patients suffering major burn injury represent a unique population of critically ill patients. Widespread skin and tissue damage causes release of systemic inflammatory mediators that promote endothelial leak, extravascular fluid shifts, and cardiovascular derangement. This phase is characterized by relative intra-vascular hypovolaemia and poor peripheral perfusion. Large volume intravenous fluid resuscitation is generally required. The patients' clinical course is then typically complicated by ongoing inflammation, protein catabolism, and marked haemodynamic perturbation. At all times, drug distribution, metabolism, and elimination are grossly distorted. For hydrophilic agents, changes in volume of distribution and clearance are marked, resulting in potentially sub-optimal drug exposure. In the case of antibiotics, this may then promote treatment failure, or the development of bacterial drug resistance. As such, empirical dose selection and pharmaceutical development must consider these features, with the application of strategies that attempt to counter the unique pharmacokinetic changes encountered in this setting.

Contents

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1. Introduction

Burn injury represents a unique form of major trauma, characterized by severe skin and soft tissue damage, most frequently due to the application of heat energy. Separate categories include scalds, contact burns, fire, chemical, electrical, and radiation exposure. Liquids, steam or grease can cause scalds, while fire burns are often divided into flash and flame injuries [1]. Chemical, electrical, and radiation burns can result in deep tissue injury, with unique decontamination, safety, and therapeutic considerations. Depending on the depth and extent of the burn, profound systemic inflammatory changes can result in significant organ dysfunction, distant to the site of injury [2]. Major burn injury can have devastating effects on individuals and their families, not just in terms of crude mortality, but also long-term functional disability and psychosocial morbidity.

Prolonged hospitalization and intensive care unit (ICU) admission are frequently required in these scenarios, particularly where the extent of burns is significant (>20–30% total body surface area) or where there has been airway involvement [3]. Large volume intravenous (IV) fluid resuscitation, hemodynamic instability, respiratory support, repeated surgical intervention, end-organ dysfunction, metabolic derangement, and nutritional deficiency typically characterize the patients' course [4]. In addition to local wound management, numerous parenteral and enteral pharmacological therapies are provided. These routinely include sedatives, analgesics, anxiolytics, venous thromboembolism and gastric ulcer prophylaxis, aperients, multivitamins, trace elements, and antibiotics. Each has unique pharmacokinetic (PK) and pharmacodynamic (PD) characteristics, which are variably influenced by the significant pathophysiological changes encountered with major burn injury [5].

Antibiotic therapy is especially suited to a discussion of these considerations, as these agents do not have an easily measurable 'end of needle' pharmacological effect. In this fashion, the clinician is not immediately aware as to the adequacy of treatment, as is the case with other therapies, such as the relief of pain and discomfort with analgesics. In addition, adequate antibiotic therapy in the setting of severe infection has been repeatedly associated with improved patient outcomes [6–8], is now regarded as a quality of care indicator [9], and may significantly impact the development of future antimicrobial resistance [10]. However, confounding accurate dosing is the marked changes in PK encountered in this setting [11,12], such that prescriptions based on those used in an ambulatory setting, are likely to be grossly flawed.

This review article will highlight these issues by exploring the effects of major burn injury on antibiotic PK/PD, as a template for considering the use of any pharmacological therapy in this setting. Importantly, the diagnosis of infection itself is particularly challenging in this setting, as the profound systemic inflammatory response encountered in major burns results in clinical features often indistinguishable from that of sepsis. Clinicians therefore find it difficult to confidently diagnose infection in burns patients, although approaches to this clinical dilemma will not be reviewed in this paper.

2. Major burn injury

2.1. Epidemiology

Globally, an estimated 265,000 deaths occur every year due to major burns [13]. Importantly, incidence, severity, and outcomes demonstrate substantial geographic variability, with 90% of burns occurring in low to middle income countries [14]. In the European Union, the reported annual incidence of severe burns is between 0.2 and 2.9 per 10,000 inhabitants [15]. Approximately 60% were male, and mortality ranged from 1.4 to 18%. Flame injuries and scalds are the most common causes of burns worldwide [16,17], with the most vulnerable groups being children less than four years of age [18], women [19], and older adults (over the age of 60 years) [20]. In Australia and New Zealand, the median hospital length of stay following admission to a burns unit (between 2010 and 2014) was 5.6 days; 14.5% required ICU admission, and overall in-hospital mortality was 1.5% [3]. Importantly, key indicators of likely mortality are the extent of injury – e.g. total body surface area (TBSA) involved, the presence of an inhalational injury, and older age [21–23].

2.2. Pathophysiological changes

Major burn injury is defined as a surface area involving>20–30% TBSA, and classically is characterized by a bi-phasic systemic response. During the first 48 h, the severity and extent of local tissue injury results in inflammatory mediators being released into the systemic circulation. These induce specific haemodynamic alternations, including increased capillary permeability [24], peripheral and splanchnic vasoconstriction [25], and myocardial depression [26]. Large volumes of protein rich fluid is lost into the interstitial space[27,28], resulting in relative intravascular hypovolaemia, systemic hypotension and organ hypoperfusion. Modern burns resuscitation protocols therefore call for the delivery of large quantities of IV fluid, in order to restore circulating plasma volume, and ideally prevent further organ dysfunction [29]. The Parkland formula (based on the percentage TBSA burnt) [30], is commonly used to determine the estimated fluid deficit, although patients will often receive variable volumes of fluid, leading to over or under-resuscitation [31,32].

Other organ support modalities are often instituted during this period, including endotracheal intubation and mechanical ventilation, central venous access and vasopressor infusion, and renal replacement therapy [32]. Respiratory failure is often multifactorial, and may result from primary injury to the lungs and airways from direct thermal inhalation, or may be a secondary phenomenon due to widespread systemic inflammation [33]. Acute kidney injury (AKI) can occur in up to 25–30% of cases [34], with mortality increasing with worsening severity [35,36]. Initial surgical debridement (typically requiring significant blood product administration and complicated by coagulopathy) is often performed at this time.

The second phase of major burns injury is characterized by a hypermetabolic state, in part mediated by elevated concentrations of endogenous catecholamines, and oxidative stress [37]. Supraphysiologic thermogenesis, cardiac work, and resting energy expenditure are all hallmarks of this state [38]. Cardiac output and major organ blood flow are typically increased, systemic vascular resistance is low. Accelerated catabolism and reduced constitutive protein synthesis results in a negative nitrogen balance [39], necessitating strict attention to protein and energy delivery. Frequent surgical intervention is required, to ensure adequate debridement, change dressings, or complete skin grafting.

2.3. Antibiotic therapy in burns injury

Almost all major burns patients will manifest signs of profound systemic inflammation and/or organ dysfunction. Tachypnoea, tachycardia, fever, and plasma leukocytosis, are almost universally present in the critically ill [40]. Cardiovascular, respiratory, renal, and haematological dysfunction are common, such that distinguishing new onset organ impairment is challenging. Clinically diagnosing sepsis (host mediated organ dysfunction secondary to infection) is therefore difficult [41],

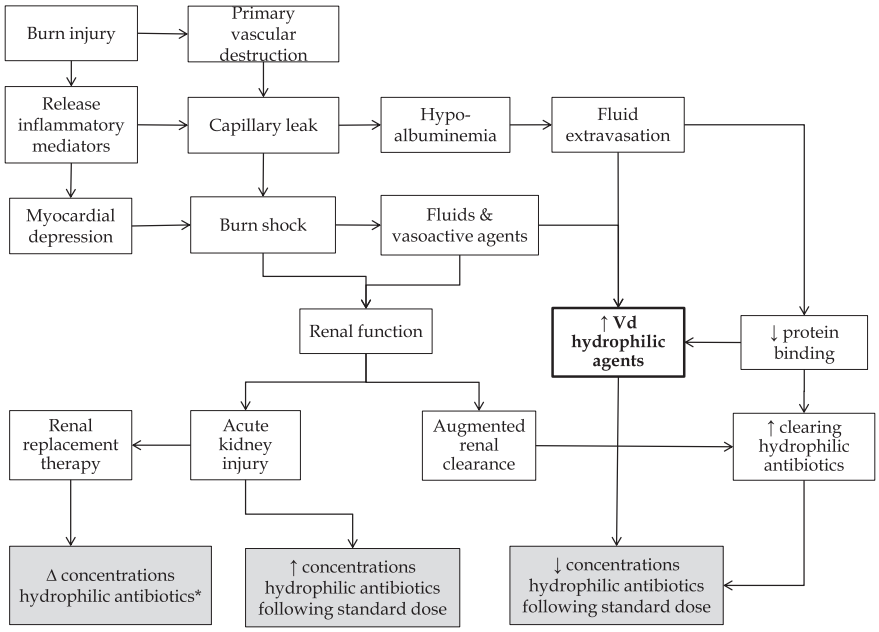

Fig. 1. Graphical illustration of the impact of major burns injury on the pharmacokinetics of hydrophilic antibiotics. * Δ depends on the sieving coefficient and saturation coefficient of the antibiotic (both depending on level of protein binding), mode of renal replacement therapy (either pre- or postdilution and either filtration or dialysis), the dose of renal replacement therapy and the actual dose delivered (taking into account interruptions, clotting of the filter, etc.). Vd – volume of distribution.

albeit early recognition and treatment are essential [9]. Indeed, burns patients are highly susceptible to nosocomial infection, due to loss of skin integrity, the requirement for long periods of invasive organ support, and a degree of functional immunosuppression [42]. In this fashion, although there is no role for prophylactic systemic antibiotic therapy in major burn injury [43], most patients will require a treatment course at some point during their in-hospital stay [44,45].

The choice of antibiotic agent should be guided by microbiological data [46], both local antibiogram and patient surveillance data, where available. Fungal colonization and infection often complicate large burns, and therefore adequate anti-fungal therapy must also be considered [47–49]. Importantly, multidrug resistant pathogens are an increasing problem in this setting [50], such that pharmacotherapy with less familiar agents, with significant potential side effects, are being increasingly employed [51]. Due to the profound physiological changes associated with major burns, the PK of these agents are significantly distorted [52], such that the application of'standard' doses are likely to result in sub-optimal concentrations (either sub- or supra-therapeutic), and clinical failure or drug toxicity.Fig. 1 graphically illustrates this paradigm.

3. PK/PD alterations in major burns – as exemplified by antibiotics

3.1. Basic antibiotic PK/PD

While an in depth review of antibiotic PK/PD is beyond the scope of this paper, a basic pharmacological framework is required to appreciate the impact of major burns on drug handling and efficacy. PK refers to the change in drug concentration (ideally at the effect site) over time, and is a reflection of the processes involved in absorption, distribution, metabolism, and excretion. For antibiotics, specific physicochemical properties (e.g. molecular weight, and lipid solubility), degree of protein binding, and the elimination pathways involved, are crucial in determining drug handling. PD involves measuring drug effect, typically illustrated by a concentration-effect relationship. In the case of antibiotics, this describes the ability to kill or inhibit the growth of a bacterial pathogen. Inherent susceptibility to any specific agent is quantified by the minimum inhibitory concentration (MIC), measured in vitro. PK/PD integrates all this information, and describes the optimal drug exposure required for maximal bacterial killing [53]. According to the PK/PD characteristic, antibiotics can exert concentration-dependent, time-dependent, and concentration/time-dependent killing.

Aminoglycosides (gentamicin, tobramycin, amikacin) represent the most extensively studied concentration-dependent group [54], whereby drug exposures defined by a maximum plasma concentration to MIC ratio (C_{max}:MIC) of at least 10, have been associated with greater efficacy [55,56]. Beta-lactams (penicillins, cephalosporins, carbapenems) are the most frequently prescribed time-dependent agents [57,58], with animal studies suggesting that the time above MIC ($fT_{>MIC}$) – e.g. that fraction of the dosing interval where unbound (free) concentrations remain above the MIC, is a key metric of drug exposure. Targets of at least 40–70% of the dosing interval are required to ensure adequate bacterial killing [59]. Indeed, a large multicenter pharmacokinetic point-prevalence study of critically ill patients receiving beta-lactams, demonstrated a three-fold greater risk of inferior treatment outcomes in those where 50% $fT_{>MIC}$ was not achieved [6]. Moreover, additional (albeit limited) data suggests that even higher drug exposures (4–5 × MIC for 90–100% of the dosing interval) may be required to ensure clinical success in some clinical scenarios [60,61].

Antibiotics displaying both time- and concentration-dependent characteristics include the glycopeptides [62] (vancomycin, teicoplanin), and fluoroquinolones [63] (ciprofloxacin, moxifloxacin, levofloxacin). In this case, achieving adequate area under the plasma concentration time curve to MIC ratios (AUC_{0-24}/MIC) is considered critical for efficacy. Specifically, values of at least 400 have been shown to improve outcomes in vancomycin treated methicillin-resistant *Staphylococcus aureus* (MRSA) lower respiratory tract infection [64]. Similarly, AUC_{0-24}/MIC ratios >125 for gram-negative [63], and >30 for gram-positive infections [65], are reported necessary for successful ciprofloxacin therapy. Importantly, ratios <100 may promote the emergence of bacterial resistance [66,67].

Although currently there are no large-scale clinical trial data quantifying the clinical effect of achieving antibiotic PK/PD targets, they do represent logical end-points for pharmacologically robust empirical dosing. For the clinician, the challenge exists in translating these largely animal in vivo data into clinical practice, in addition to tailoring therapy to major burns victims. Moreover, in a relatively unique fashion sub-optimal antibiotic exposure can not only lead to treatment failure, but can also have

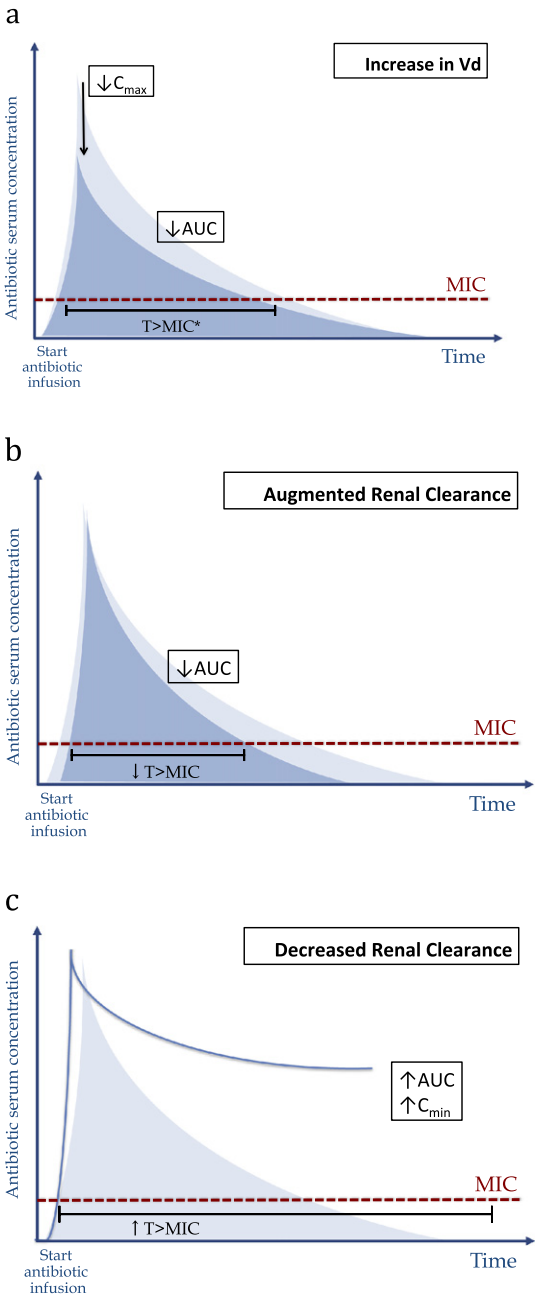

Fig. 2. Concentration-time curves illustrating the pharmacokinetics/pharmacodynamics of antimicrobial agents according to pathophysiological changes that might occur following severe burn injury[148].C_{max}, antibiotic peak concentration; AUC, area under the concentration-time curve; C_{min}, antibiotic trough concentration. *In case of increased V_d, the T > MIC can be increased following the first dose. At steady-state concentrations however, the T > MIC is prolonged because of increased half-life.
After J. Roberts et al. [148].

significant consequences at a macro level, the most concerning of which is the development of bacterial resistance and therapeutic redundancy.

3.2. Absorption

As the vast majority are administered intravenously, altered absorption via the gastrointestinal (GI) tract or subcutaneous tissues, has little bearing on antibiotic PK in major burn injury patients. However, multiple other medications used in burn management are routinely administered via non-intravenous routes, such as beta-blockers and gastric ulcer prophylaxis (GI tract), venous thromboembolism prophylaxis (subcutaneous), and nicotine replacement therapy (transdermal). During the immediate phase post-burn injury, peripheral and splanchnic vasoconstriction [25] is likely to significantly impair drug absorption via these routes, while conversely, during the hypermetabolic phase, perfusion and therefore absorption is plausibly increased. Indeed, local trauma and inflammation at the site of burn wounds may have variable effects on drug absorption, depending on underlying tissue viability. The use of vasopressor therapy will also influence this significantly. Moreover, separate to changes in perfusion, GI dysfunction is a common complication post-major burns [68], which will considerably impact the PK of any enterally administered drug.

3.3. Volume of distribution (V_d)

Key intrinsic properties that determine drug distribution include; molecular weight, degree of ionization, lipid solubility and protein binding. More lipophilic agents, such as the fluoroquinolones, have a larger V_d, and greater tissue distribution. In contrast, hydrophilic molecules (such as the aminoglycosides and beta-lactams) are principally restricted to the extracellular space, resulting in a relatively small (~0.2 L/kg) V_d[69]. However, in major burns injury this can be significantly increased, principally as a result of the widespread capillary leak, interstitial oedema formation, and aggressive large volume IV fluid resuscitation. Not unexpectedly, highly variable and unpredictable drug concentrations have been noted in this setting [70]. Fig. 2a illustrates the alterations in PK/PD in case of increased V_d.

Jeon and colleagues recently confirmed these assertions in their population PK analysis of piperacillin in fifty burn patients. Piperacillin V_d was estimated at 41.4 L at baseline, increasing to 56.2 L in those that were considered septic [71]. This represents a 4–5 fold increase in comparison to healthy volunteers [72], and a 1.5–2 fold increase compared with septic critically ill patients [73]. Similar changes in V_d have also been reported with other beta-lactams, such as meropenem [74], imipenem [75], and ceftazidime [76]. Of note, previous work exploring the subcutaneous distribution of cefalotin in major burns has demonstrated equivalent tissue exposures in both burn and non-burn sites [77], albeit this is likely to be influenced significantly by burn depth and tissue viability.

For concentration dependent antibiotics a larger V_d also represents a critical change in PK, as lower plasma concentrations are likely, if standard doses are employed. Indeed, data from nine burns patients has demonstrated a significant increase in daptomycin V_d, associated with a 44% reduction in C_{max}[78]. Similar findings have also been noted with amikacin, where higher daily doses were recommended [79].

3.4. Protein binding

The unbound (free) fraction of a drug (f_u) mediates its pharmacological effects and any potential toxicity, in addition to being available for elimination [11]. This reinforces the greater utility in measuring free (as opposed to total) drug concentrations [80]. Albumin is the predominant circulating plasma protein, and binds acidic antibiotics, such as ceftriaxone [81], flucloxacillin [82], teicoplanin [83], daptomycin [78], and ertapenem [84]. Of note, hypoabluminaemia (plasma albumin concentration < 25 g/L) is generally a common finding in the critically ill [85], as albumin concentrations fall as part of the acute phase reaction. With major burns injury, hypoalbuminaemia is even more pronounced [86]. This is principally related to the loss of protein-rich fluid via the burn wound, a decrease in constitutive hepatic protein synthesis, and an increase in catabolism. For highly bound drugs (>90%), this will significantly distort the PK profile, due to an increase in f_u. In contrast, alpha-1 acid glycoprotein synthesis increases post-burn injury, leading to a decrease in f_u for basic drugs which bind this carrier [87] (e.g. rifampicin).

Importantly, for those agents that principally distribute into the extracellular space, a greater f_u is associated with a larger V_d[88]. Similarly, for drugs that are renally cleared, a higher f_u also results in more rapid

elimination from the systemic circulation [78,81–84,89]. In such a scenario, the combination of a larger V_d, with more rapid clearance (CL), will predispose to sub-optimal concentrations for significant periods, particularly toward the end of the dosing interval [90].

3.5. Clearance (CL)

The principal mechanisms for drug elimination in major burns involves either renal clearance (CL_R), through a combination of glomerular filtration and/or renal tubular excretion, or non-renal clearance (CL_{NR}). CL_{NR} pathways include hepatic metabolism and/or biliary excretion, non-enzyme mediated degradation, and direct loss of substrate via ongoing wound exudate. Renal function following major burn injury is highly variable, and is best considered by examining the spectrum of kidney function encountered, namely; augmented renal clearance (ARC) and AKI requiring institution of renal replacement therapy. Fig. 2b and c illustrate the alterations in PK/PD in case of augmented renal clearance and impaired renal function, respectively.

3.5.1. Acute kidney injury requiring continuous renal replacement therapy

AKI can frequently complicate the course of many major burn patients [34]. Notwithstanding any kidney injury incurred during the initial phase (secondary to a reduction intravascular volume, cardiac output, and major organ blood flow), the utilization of nephrotoxic medications, radio-contrast media, and the subsequent nosocomial sepsis, can all contribute to a deterioration in renal function. As the kidney progressively fails, worsening azotaemia (typically identified by rising plasma creatinine concentrations), acid-base alterations, electrolyte abnormalities and fluid overload are all potential complications. As such, the V_d of hydrophilic antibiotics can increase [91–93]. However, as the majority of these agents are cleared via the kidneys, the major PK consequence is a reduction in CL_R. As such, clinicians often reduce dosing [69], in order to avoid drug accumulation and potential toxicity.

In the case of concentration-dependent agents (e.g. aminoglycosides), this is best achieved by extending the dosing interval, as compared to time-dependent antibiotics (beta-lactams), where the amount administered can be reduced, while maintaining a similar dosing frequency. Importantly, CL_{NR} can be substantially altered in these circumstances (see below) [94], and in combination with an increase in V_d, may not necessarily mandate any immediate dose reduction [95,96]. In this case, early aggressive antibiotic therapy is typically warranted with major burn injury, such that non-AKI dosing should be employed initially (typically for the first 24–48 h of treatment), regardless of renal function [97]. If using aminoglycosides and vancomycin, therapeutic drug monitoring (TDM) is particularly useful in guiding ongoing therapy [98], and may also be used to infer some information about the likely dosing requirements for other renally cleared drugs. TDM for other antimicrobials is being increasingly reported to show that it can increase the achievement of PK/PD targets [99]. Indeed TDM should be used where available for this reason, although clinical outcome data further supporting its role in burns patients is limited.

Significantly confounding this situation, is the application of extracorporeal support modalities, such as continuous renal replacement therapy (CRRT), intermittent haemodialysis (IHD), and slow low efficiency dialysis (SLED). Factors such as molecular weight, protein binding, mode of renal replacement therapy (dialysis versus filtration), filter porosity, blood flow rate, and total effluent rate, will all influence PK [100]. Clinical factors, including timing of CRRT, filter lifespan, and residual native renal function [101], will also impact drug exposure. Dosing decisions are therefore largely empirical, and based on data extracted from non-burn populations. Intra- and inter-patient variability is likely to be significant, potentially resulting in sub-therapeutic concentrations. Recent data from Jamal and colleagues exploring the impact of CRRT prescription, suggests that total effluent flow rate is an important predictor of extracorporeal beta-lactam clearance [102].

3.5.2. Augmented renal clearance (ARC)

ARC corresponds to the elevated renal elimination of circulating solute (such as waste products and drugs) [103], and is a phenomenon that has been repeatedly observed in burns victims [104,105]. As such, this cohort represents a major at-risk group. The biological mechanisms are thought to principally involve greater renal blood flow, and as a consequence, increased glomerular filtration (GFR) [106]. This is largely driven by the underlying hyperdynamic circulatory state [107,108], a reflection of ongoing systemic catabolism and inflammation. The infusion of large volumes of IV fluid and/or the application vasoactive medications, may further enhance renal solute excretion [109]. Moreover, the recruitment of 'renal reserve', whereby GFR increases in response to protein loading, may also be implicated [110].

ARC will significantly impact the PK of any agent that is primarily renally cleared, such as hydrophilic antibiotics (glycopeptides, aminoglycosides, and beta-lactams) and low-molecular weight heparins [111]. In such cases, more rapid renal elimination pre-disposes to sub-optimal drug concentrations [79], treatment failure [6], and drug resistance [112], particularly for time-dependent agents [113,114]. Unfortunately, facilities to evaluate drug clearance in daily practice are generally lacking. Where TDM is available, repeat plasma concentrations can be used to guide subsequent dosing [70], although in most circumstances this is not possible. Moreover, routinely available biochemical markers of renal function are not necessarily helpful, as they are typically reported within the 'normal' reference range [115]. As such, identifying ARC represents a significant challenge in this context [104].

Numerous mathematical estimates of GFR have been developed for clinical use. These include the Cockcroft-Gault formula [116], modification of diet in renal disease (MDRD) equation [117], and more recently the chronic kidney disease epidemiology (CKD-EPI) eGFR [118]. Each typically utilizes the plasma creatinine concentration, and a variety of demographic and/or anthropometric parameters, such as age, gender, height and weight. Albeit these measures have greater utility than static plasma biomarker concentrations, their application in major burns patients is inherently flawed [104,119]. This specifically relates to the derivation of these estimates, which primarily involve large cohorts of ambulatory non-critically ill patients. As such, they fail to account for the unique characteristics encountered in the burns population, and cannot be relied upon to accurately identify ARC [120].

In this fashion, a timed urinary creatinine clearance (CL_{CR}) has been employed as a more dynamic measure of GFR in critical illness [115]. Importantly, this approach suffers from all of the limitations associated with an endogenous filtration marker, in that creatinine production is unlikely to be at steady-state, and is intimately linked with baseline muscle mass [121]. Similarly, creatinine is also excreted in the proximal tubule, such that a measured CL_{CR} will over estimate true GFR in the setting of renal impairment [122]. Despite these caveats, CL_{CR} has been closely correlated with the renal clearance of exogenous filtration markers [106], and remains a widely available, minimally invasive, cost-efficient method for assessing renal function. Eight-hour collections appear to provide the best balance between feasibility and accuracy [123]. Moreover, CL_{CR} measures ≥130 mL/min/1.73 m^2 have been linked with sub-therapeutic beta-lactam [113], and glycopeptide concentrations [124], and in this manner, serves as a useful threshold above which alternative dosing strategies can be considered.

3.5.3. Non-renal clearance

Non-renal pathways for drug clearance include hepatic metabolism, biliary excretion, non-enzymatic breakdown, and elimination via tissue exudate and/or drain fluid. In major burn injury, all of these mechanisms may increase during the hypermetabolic phase, and have a significant effect on PK [106], although specific data for most drugs are lacking. Previous work investigating ethanol clearance post-major burn elegantly illustrates this potential effect, with elimination rates being double that of healthy individuals [125]. Notwithstanding this, emerging literature stresses the importance of the hepatic response to thermal burn injury

Table 1
Proposed dosing of antibiotics in burn injury patients.
After [147].

Antibiotic agent	Empirical dosage	PK/PD target	In case of moderate-severe renal impairment (without renal replacement therapy)
Amikacin	Loading dose 30 mg/kg Maintenance dose based on TDM, usually once daily	Cmax/MIC ≥8–10, AUC/MIC >70, Cmin <2 mg/L	Maintain high doses if possible; prolong dosing interval (36- to 48-h intervals are acceptable)
Gentamicin	Loading dose 7–10 mg/kg Maintenance dose based on TDM, usually once daily	Cmax/MIC ≥10, AUC/MIC >70, Cmin <0.5 mg/L	Maintain high doses if possible; prolong dosing interval (36- to 48-h intervals are acceptable)
Meropenem	1 g at 0, 4 and 8 h, thereafter 1 g every 8 h Consider prolonged infusion (1 g infused over 3 h)	*f*T > MIC 40%; fT > MIC 100% if immunocompromised	In case of intermittent dosing, dose can be reduced or dosing interval prolonged.
Piperacillin/tazobactam	4/0.5 g at 0, 3 and 6 h, thereafter 4/0.5 g every 6 h Consider continuous infusion	*f*T > MIC 50% (piperacillin); fT > MIC 100% if immunocompromised	In case of intermittent dosing, dose can be reduced or dosing interval prolonged.
Ciprofloxacin	400 mg/8 h or 600 mg every 12 h	AUC/MIC ≥125, Cmax/MIC ≥8	Maintain high dose if possible while prolonging dosing interval
Vancomycin	Loading dose 30 mg/kg, thereafter 1 g every 8 h, 1.5 g every 12 h or continuous infusion 30–40 mg/kg/day	Cmin 15–20 mg/L or steady state concentration 20–25 mg/L, AUC/MIC >400	Reduce total daily dose
Colistin	Loading dose 9 million international units (IU) colistimethate sodium (CMS), thereafter 9 million IU/day divided in 2–3 doses	Steady state concentration ≥ 2 mg/L, *f*AUC/MIC >25–35	Reduce dose or prolong dosing interval
Tigecycline	Loading dose 100 mg, thereafter 50 mg every 12 h or a 200 mg loading dose followed by 100 mg every 12 h	Varying AUC/MIC targets for different pathologies (e.g. pneumonia, intra-abdominal infection, soft tissue infections)	No adaptations required
Linezolid	600 mg every 12 h	AUC/MIC ≥85, T > MIC 85% Cmin >6 mg/L	In case of severe renal impairment: 600 mg once daily

TDM, therapeutic drug monitoring; Cmax, antibiotic peak concentration; Cmin, antibiotic trough concentration; AUC, area under the concentration-time curve; MIC, minimal inhibitory concentration; *f*T > MIC, time period in which the antibiotic concentration is higher than the MIC (expressed as % of the dosing interval).

as a key predictor of clinical outcomes [126]. Indeed, early transient liver dysfunction is a common finding, with persistent and advanced hepatic impairment being associated with greater mortality [127]. In such circumstances, the PK of agents that are extensively metabolised by the liver may be deranged.

Importantly, with major burns, loss of skin integrity and widespread capillary leak can potentially result in large quantities of hydrophilic drugs being lost in burn wound exudate [128–131]. Similarly, Adnan and colleagues have previously demonstrated that relatively large quantities of beta-lactams can be lost via high volume indwelling drain tubes [132]. Given the ongoing inflammatory process that characterizes major burn injury, such losses should be considered in empirical dose selection, particularly with a difficult to treat organism.

4. Alternative dosing strategies

Given the substantial variation in PK encountered in major burn victims, alternative dosing strategies are required. With the V_d being significantly increased (particularly for hydrophilic agents), an adequate loading dose is necessary [11]. In the case of antibiotics, this is essential, in order to rapidly achieve therapeutic concentrations, which in turn promotes fast, efficient bacterial killing. For concentration dependent agents, this is even more crucial, as adequate C_{max}:MIC ratios are required [133]. Suitably weight adjusted doses, which attempt to incorporate expansion of the extracellular space (e.g. ~30 mg/kg adjusted body weight amikacin or equivalent), are mandatory [79], while in the setting of ARC, more frequent dosing (e.g. 12–18-hourly) may also be considered. Recommendations concerning adequate loading doses have also been published for glycopeptides [134–136], beta-lactams [71,74], daptomycin [78], and tigecycline [137], and reinforce the importance of this strategy when initiating therapy.

Maintaining sufficient drug concentrations (above the MIC of the likely pathogen) over the entire duration of the dosing interval represents a biologically attractive approach when employing time-dependent antibiotics [57]. Intermittent dosing results in a substantial decline in drug concentrations post bolus administration, both as a consequence of drug distribution and clearance. In many cases, particularly in reference to the trough plasma concentration, this is intimately linked with CL_R[138].As such, in cases of ARC (which is highly prevalent following major burns), more frequent dosing should be employed.Similarly, continuous or extended infusions can be used, which offer a distinct PK advantage [139,140], albeit adequate loading doses are still mandatory. Whether this translates into improved clinical outcomes (greater clinical cure or a reduction in the development of resistance), is uncertain, as prior studies with beta-lactams [141–143] and glycopeptides [144,145] have generated conflicting results. Importantly, in the case of ARC, a higher daily dose is also likely to be required.

The marked PK derangement observed in major burns makes accurate dosing problematic. Adequate weight based loading doses, more frequent administration, or the use of continuous infusions represent empirical strategies that may increase the probability of achieving adequate drug concentrations. However, the lack of immediate clinical feedback makes subsequent dose adjustment challenging. In particular, burns patients will often continue to manifest features of systemic inflammation, irrespective of the adequacy of treatment. As such, titrating doses to achieve a desired plasma concentration, represents a pharmacologically robust approach, albeit is frequently unavailable, due to the technology required. In this fashion, prior observational data has reinforced the utility of TDM in optimizing beta-lactam concentrations [99]. Similar data have also been reported from a randomized clinical trial in the critically ill [146], while limited evidence appears to support the role of beta-lactam TDM is improving antibiotic prescribing in burns [70]. As such, particularly if point-of-care devices can be developed, TDM is likely to have a growing role in optimizing drug doses in burn patients, given the grossly distorted PK that is a hallmark of this population. Table 1 reports proposed empiric dosages and main PK/PD targets in burns patients either with or without renal impairment.

5. Conclusions

Patients suffering major burn injury represent a unique population of critically ill patients. Local skin and tissue damage results in systemic inflammation that is characterized by marked endothelial leak, fluid shifts, and cardiovascular derangement. Clinical management focuses on local decontamination, wound care, early debridement, and intravenous fluid resuscitation. The patients' clinical course from this point is

complicated by ongoing inflammation, protein catabolism, and marked haemodynamic perturbation. Tachycardia, thermogenesis, elevated cardiac output, increased major organ blood flow, hypoalbuminaemia, and leukocytosis are all common features. Regularly these patients develop nosocomial infection, necessitating the application of antibiotic therapy. Importantly, achieving adequate drug exposure in this context is crucial to successful treatment.

In this scenario, antibiotic PK is grossly distorted. The V_d, protein binding, and CL of many of these agents are significantly different from those observed in healthy volunteers. For hydrophilic agents (such as beta-lactams and aminoglycosides), these changes are marked, which particularly in the case of ARC, can lead to a reduction in drug exposure when 'standard' doses are employed. This in turn has been associated with inferior clinical outcomes. Moreover, this may also promote the development of bacterial drug resistance, and in turn, therapeutic redundancy. As such, empirical dose selection and pharmaceutical development must consider these features, with the application of strategies that attempt to counter the unique PK changes encountered in this setting. Use of adequate weight-based loading doses, more frequent dosing, and continuous infusions, represent pharmacologically sound approaches, which will hopefully counter some of this variability. Similarly, the use of TDM (where available) is highly recommended, in order to ensure adequate drug exposure, particularly where clinical feedback concerning dosing can be problematic.

These considerations highlight the complexity in drug delivery in major burns patients. The pathophysiological changes are extreme, and result in profound alteration in PK parameters, specifically drug absorption, distribution, metabolism and elimination. Importantly this is not unique to antibiotic therapy, and is highly relevant to the application of any pharmacological agent. As such, prescribers should be aware of these issues, and should make appropriate dose modifications as required.

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