

Antibiotic dosing in critical illness

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Early and effective antibiotic therapy is essential in the management of infection in critical illness. The loading dose is probably the most important dose and is a function of the volume of distribution of the drug and the desired plasma concentration but independent of renal function. Antibiotics are classified in a number of ways that have implications for dosing. Doses of hydrophilic agents such as β -lactams should be increased in the early stages of sepsis as the extravascular space increases. For lipophilic agents such as macrolides, the inflammatory process is less important, although factors such as obesity will affect dosing. Classification can also be based on pharmacodynamic properties. Concentration-dependent antibiotics such as aminoglycosides should be administered by extended interval regimens, which maximize bactericidal effect, minimize nephrotoxicity and allow time between doses for the post-antibiotic effect. The critical factor for time-dependent agents, such as β -lactams, is time above the MIC. Ideally administration of these agents should be continuous, although vascular access availability can restrict infusion time to between 4 and 6 h, which is probably adequate. As well as antibiotic factors, patient factors such as hepatic and renal failure will affect dosing. Hepatic failure will affect antibiotic metabolism, although it is most important in end-stage failure. Renal failure and support will affect drug elimination. Knowledge of these factors is essential. Patient safety and prevention of unnecessary harm is a weighty consideration in critical illness. To ensure effective treatment and minimize adverse effects, therapy should be reviewed daily and adjusted in the light of changes in patient organ function and underlying pathology.

Keywords: pharmacodynamics, aminoglycosides, β -lactams, glycopeptides, ICUs

Introduction

Serious infections are common in critically ill patients and require rapid treatment to limit mortality and morbidity. There are a number of different internationally recognized standards of care for treating infections in critical illness.¹ For sepsis and severe sepsis, this includes fluid resuscitation,² a degree of glycaemic control,³ corticosteroids (to reduce vasopressor requirements),⁴ oxygen delivery and consumption monitoring, drotrecogin alfa (activated human protein C) for severe sepsis⁵ and antimicrobial agents to treat the infection. In the Surviving Sepsis Campaign (SSC),¹ treatment strategies are split into different bundles depending upon how immediately the treatment is required. Fluid resuscitation, oxygen therapy and antibiotics are in the 1 h bundle.¹

The choice of antibiotic used for empirical treatment of bacterial infections in the intensive care unit (ICU) is based predominantly on the identity and susceptibility pattern of bacteria isolated commonly on that unit and is not discussed here. Furthermore, based on the information above, there appears to be common agreement on the timing of the first dose of antibiotics in the critically ill septic patient.⁶ What is less difficult to establish and often overlooked is the optimum dose of antibiotic, particularly the first, which is probably the most important and perhaps

most difficult to predetermine. This article reviews current practice and discusses a number of options that should be considered when choosing an antibiotic dose. It covers most aspects that the author considers essential, including the critical factors relevant to considering which class of antibiotic to use, and major patient factors that may significantly alter antibiotic dosing strategies.

Starting therapy

The SSC recommends that intravenous antibiotics are begun within the first hour after diagnosis of severe sepsis and septic shock.¹ This statement from the SSC is supported by the study by Kumar and colleagues⁶ who demonstrated that the most important factor affecting outcome after the onset of hypotension is the timing of the initial dose of antimicrobial agent. It cannot be assumed that this target is always met. A recently conducted audit on the Guy's and St Thomas' NHS Foundation Trust (GSTT) ICU demonstrated that as few as 25% of first doses of antibiotics were administered within 1 h of prescription (R. Wan and A. Jones, unpublished observations). Utilizing stat (immediate) dose prescription and improved multidisciplinary communication may help increase this rate.

Choosing a loading dose

Deciding on the first dose of antibiotic in a septic patient is probably equally important to the timing. The loading dose (LD) of any drug is calculated from the volume of distribution (V) and the required plasma concentration (C_p) using the formula $LD = V \times C_p$. Both V and C_p can be affected by critical illness. The V of hydrophilic agents (which disperse mainly in water) will be altered by changes in the permeability of the microvascular endothelium and consequent alterations in extracellular body water; a well-recognized phenomenon in the pathophysiology of sepsis.⁷ This will result in a larger predicted V and thus a larger required LD. In contrast, lipophilic agents have a greater affinity for adipose tissue, therefore an obese patient may require a higher than predicted dose of a lipophilic antibiotic to achieve the targeted plasma concentration.⁸

The second critical factor is the required C_p . The MICs of different antibiotics for susceptible bacteria vary greatly.⁹ With empirical therapy the causative pathogen is not identified beforehand; however, ICUs will usually know the types of bacteria commonly isolated from septic patients and their resistance patterns. For concentration-dependent antibiotics, a high initial dose is essential for maximum bactericidal effect, and for aminoglycosides, a high initial dose has been associated with a lower mortality.¹⁰ There is often little point in measuring this peak C_p as it can be easily predicted using pharmacokinetic principles. However, renal function plays no role in the calculation of the LD. For time-dependent antibiotics, where the critical factor is time above the MIC, the initial dose may not be crucial for pharmacokinetic effect; however, a large initial dose is often chosen to ensure good tissue penetration.

In summary, a high initial dose of antibiotic should be standard practice. However, account should be taken of the risk of adverse effects associated with excessively high doses of some antibiotics in a patient group that is already acutely unwell (e.g. seizures and CNS toxicity with high-dose penicillin, particularly when administered rapidly in renal failure).¹¹

Antibiotic classifications in critical illness

Where dosing is concerned in critical illness, classifying antibiotics in terms of their propensity to partition into either fat (lipophilic) or water (hydrophilic) or their pharmacodynamic mode of action can help guide dosing strategies.

Hydrophilic and lipophilic properties

Lipophilic antibiotics tend to have a much larger V , a greater degree of protein binding and are more likely to be metabolized in the liver.¹² Commonly used agents in critical care include linezolid and macrolides (Figure 1). Hydrophilic antibiotics will have a much smaller V , lower protein binding and are more likely to be excreted unchanged via the kidney (Figure 1).¹² These include β -lactams and aminoglycosides. When considering factors that are present in patients with sepsis and severe sepsis, it is important to bear in mind that the extravascular space expands as inflammatory mediators cause damage to the vascular endothelium and fluid leaks out into the extravascular space.¹³

The V of agents that are hydrophilic may expand during the acute inflammatory phase; this is when the volume of

extracellular water expands greatly. This expansion may be short lived as the vascular endothelium recovers.¹⁴ Thus a high starting dose may be optimal for hydrophilic antibiotics. For lipophilic antibiotics, diffusion into the extravascular space should be less pronounced because these agents penetrate deeper into fatty tissues. There are, however, other patient factors that may be important with lipophilic agents, including the effects of pre-morbid obesity where the lipid compartments will expand greatly.¹⁵ There is a paucity of evidence actually guiding dosing of antibiotics in this patient group. However, published evidence to date appears to support the concept of larger doses (up to 3-fold) of lipophilic agents in patients with a greater amount of adipose tissue.^{8,16}

Dosing strategies based on pharmacodynamic grouping

The dosing strategy for antibiotics will vary depending on the mode of action of the drug and also on individual patient factors that influence its pharmacokinetic and pharmacodynamic (PK/PD) interactions. A number of principles are described below that relate specifically to the mode of action of antibiotic groups that can govern and guide practice. This list is not exhaustive and includes only those agents used most commonly in critical care.

Concentration-dependent antibiotics

Aminoglycosides, fluoroquinolones and polymyxins are concentration-dependent antibiotics. With concentration dependence, a high initial concentration is required to ensure maximum bacterial kill. This high initial concentration may also aid tissue penetration.¹⁷

Aminoglycosides

There is good evidence for extended duration of aminoglycoside dosing in critically ill patients.^{18,19} A high initial peak concentration has been associated with an improved outcome in the acutely unwell patient.¹⁰ The post-antibiotic effect of aminoglycosides also means that an extended interval regimen that allows sufficient time between doses for the serum concentration to fall to undetectable levels will contribute to the pharmacodynamic effect. Lastly in terms of toxicity, the two widely recognized toxic effects of aminoglycosides are nephrotoxicity and ototoxicity. Nephrotoxicity is caused by a direct effect on the renal cortex.²⁰ Barclay and colleagues suggest that the uptake into the renal cortex is saturable.²¹ Thus a dosing strategy of extended duration will reduce the renal cortex exposure to aminoglycosides. As for vestibular and ototoxicity, the evidence is not as clear cut and factors such as peak area and genetic predisposition are critical.²²

Fluoroquinolones

The optimum way to maximize the therapeutic effect of fluoroquinolones is to ensure maximum peak concentration (C_{max}) above the MIC for a given pathogen.²³ The ratio of C_{max} to MIC, known as the inhibitory ratio (IR) is related to the clinical

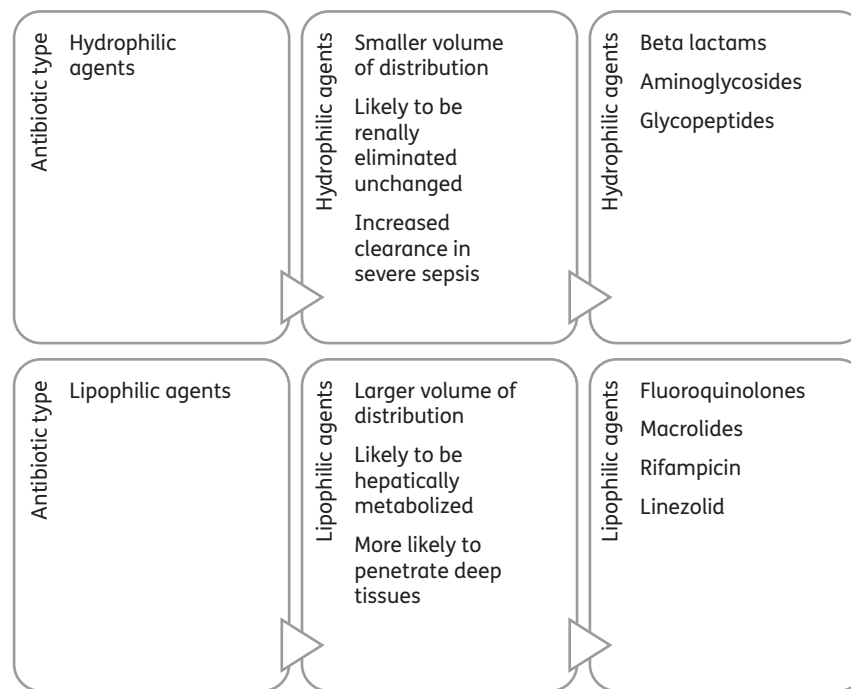


Figure 1. Classification of antibiotics in terms of their propensity to partition into fat or water.

effect and an IR of >8 is predictive of clinical success, although the pharmacokinetics of ciprofloxacin is complex in critical care, as there are multiple modes of non-renal clearance.^{24–26} Therapeutic drug monitoring would be ideal, but in its absence higher doses (e.g. 800 mg iv 8-hourly) may be necessary in the severely septic patient.²⁶

Polymyxins

Polymyxins are being used more frequently in critical care. Their mainstay of use is in the treatment of patients with multi-resistant Gram-negative bacteria, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.²⁷ Polymyxins are generally poorly absorbed from the gastrointestinal tract and thus are administered via the parenteral route or by inhalation (with a nebulizer). They exhibit concentration-dependent bactericidal activity and possess considerable post-antibiotic effect at high concentrations.²⁸ The agent used predominantly in the UK is colistin sulphate. Most of the literature on nebulized colistin has evolved from the treatment of cystic fibrosis where colistin is used commonly to treat resistant Gram-negative bacteria, particularly *P. aeruginosa*.²⁸ In the ICU nebulized colistin is commonly administered in doses of 1–2 mU 12-hourly. The parenteral route is used less frequently probably due to early reports of nephrotoxicity and neurotoxicity.^{29,30} However, colistin can be the sole agent active against multiresistant Gram-negative bacteria in critical care, and recent experience suggests that its toxicity may be overstated.²⁸

Time-dependent antibiotics

For time-dependent antibiotics, optimal bacterial kill is achieved by maximum amount of time over the MIC. The maximum effect

is achieved when a concentration above the MIC is achieved for 90%–100% of the dosing interval.³¹

β -Lactams

β -Lactams include penicillins, cephalosporins and carbapenems. The majority of these agents have a relatively short elimination half-life of between 1 and 3 h and are renally excreted. However, there are notable exceptions, including ceftriaxone, which has an elimination half-life of 7–8 h.²⁰ It follows that if the maximum time above the MIC is the critical factor for antibiotics with shorter elimination rate constants, then a strategy of short regular dosing should be best. This would include dosing regimens such as continuous infusion, where the antibiotic serum level is constantly above the MIC for the duration of treatment.

Extended or continuous infusions of β -lactams

A recent review by Roberts and co-workers,³¹ failed to show any improvement in outcome with extended or continuous infusion of time-dependent antibiotics compared with traditional dosing strategies. The authors concluded that there were insufficient clinical advantages to recommend a strategy of continuous infusion in all patient groups, but there may be specific groups, including critical care, where it may be advantageous.

There have been a number of clinical studies that have compared extended infusion with standard dosing of β -lactams in the acutely ill patient.^{32,33} The antibiotics studied include meropenem, piperacillin/tazobactam and the newer carbapenem, doripenem. The outcome of these studies has varied from no difference in clinical cure in the infusion group³⁴ to a clinically significant enhanced cure rate.³⁵ There have been

notable criticisms of a number of the studies, including the subjective nature of clinical cure.¹³ However, few comparative studies showed a poorer outcome using extended duration dosing in critical care, and in some studies there was clear suggestion of benefit. There are also patient safety benefits to a slower infusion rate that have to be taken into consideration, such as slower diffusion into the CNS. The rate of administration into the CNS contributes greatly to the development of CNS toxicity including seizures.²⁰

Given the equivocal nature of the evidence supporting a benefit for extended administration it is important that units implementing such a policy ensure that it does not compromise administration of other therapies. Continuous infusion over 24 h would constantly occupy intravenous access, whereas a duration of a few hours would allow a longer administration time, and at the same time not entirely block parenteral access. We have extended the administration time for piperacillin/tazobactam, co-amoxiclav and meropenem to 4 h on the GSTT ICUs, which has been acceptable to nursing teams managing the intravenous catheter access process.

Glycopeptides

The amount of time above the MIC is a critical factor in maximizing bactericidal activity for both vancomycin and teicoplanin. This is particularly pertinent when using vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates, for which the MIC can be variable within the susceptible range (0.25–2 mg/L). It is recommended that trough levels are maintained above 10–15 mg/L.³⁶ An AUC/MIC ratio of >400 has been advocated as a target to achieve clinical effectiveness with vancomycin.³⁶

Therapeutic drug monitoring (TDM) is still required as vancomycin is nephrotoxic, although less so than aminoglycosides, with serum peak concentrations rarely reaching the levels associated with toxicity.³⁷ One of the principal difficulties with TDM of vancomycin is predicting future doses from a trough level in ICU patients as their renal function continually fluctuates, altering elimination time and serum concentration, and potentially leading to a large variation in the dosing regimen.

As the pharmacodynamic activity of vancomycin is predominantly time dependent it is important to ensure maximum time above the MIC, which can be achieved using a continuous infusion protocol. Serum concentrations are taken once daily to predict the infusion rate for the next 24 h. There have been at least two publications on continuous vancomycin infusion in critical care.^{38,39} Neither showed a disadvantage to this type of administration and one study³⁹ demonstrated an improvement in clinical outcome.

A clinical audit of use at GSTT of 100 patients who received 100 courses demonstrated that the continuous infusion regimen achieved effective serum concentrations for the treatment of suspected MRSA infections in the majority of patients regardless of renal function.⁴⁰ Seventy-eight percent of patients had effective plateau concentrations (>15 mg/L) on Day 1 with minimal risk of toxicity (<35 mg/L). This increased to 85% of patients on Day 2 following infusion rate adjustments and was sustained for the course. The lowest concentration was 9.3 mg/L, which exceeds the MIC for most MRSA strains.

Patient factors

In addition to drug factors that will affect antibiotic dosing in critical care, there are also patient factors that will affect the way the drug is handled. Critical care patients do not present with homogeneous pathology. Therefore, in any given clinical situation where an antibiotic prescription is required, individual patient factors must be taken into account. Clearly one can have guidelines in place that will govern clinical practice and provide prescribing support for the majority of clinical situations. However, in the context of guidelines, individual patient factors should always be considered before any antibiotic is prescribed.

Liver failure

The major site of drug metabolism is the liver. Hepatic drug metabolism can be very broadly classified into phase 1 and phase 2 metabolism.⁴¹ Most of phase 1 metabolism takes place in the hepatic cytochromes and involves a number of transformations including oxidation and methylation, in order to make the parent drug more water soluble to facilitate renal excretion.⁴¹ In general, phase 1 metabolism is capacity limited. Antibiotics that are metabolized via this route include the fluoroquinolones and flucloxacillin.²⁰ The liver's capacity to metabolize drugs by phase 1 enzyme systems is compromised when in failure. However, the liver's metabolic capacity has to be reduced by >90% before drug metabolism is significantly affected.⁴¹

Phase 2 metabolism includes glucuronidation and glutathione conjugation. Phase 2 can occur after phase 1 or can occur in its own right. Broadly speaking, phase 2 metabolism is less capacity limited and can still occur even in end-stage liver failure.⁴²

Renal failure

The majority of hydrophilic antibiotics (including β -lactams and aminoglycosides) are excreted unchanged by the kidney. Elimination of such agents will be limited in renal failure, which is extremely common in the critically ill. In addition, aminoglycosides can exacerbate renal failure and halt the progress of recovery.⁴³ Therefore dosing regimens must be altered daily after assessment of renal function. The effects of this on patient management can be minimized by utilizing extended interval regimens and undertaking regular TDM.²¹ In addition, many lipophilic antibiotics produce metabolites that require renal elimination, such as flucloxacillin, which is metabolized by the cytochromes to its 5-hydroxymethyl derivative, which is then excreted renally, or a proportion of the parent antibiotic is renally excreted unchanged.²⁰

Renal support

Support for the failing kidney is an essential component of critical care medicine.⁷ Given the vital role the kidney plays in acid–base balance, electrolyte and fluid balance must be maintained even in the context of failure.

The major method for renal support in the critically ill patient is continuous venovenous haemofiltration (CVVH).⁴⁴ Knowledge of antibiotic clearance via this method of renal support is essential for effective prescribing in the filtered

Table 1. An example of a Critical Care Antibiotic Guideline, ICU, Guy's and St Thomas' NHS Foundation Trust. All doses are recommendations and specific regimens will depend on patient and pathology

Antibiotics: standard doses indicated (iv dosage regimens, please consider ng/po administration whenever possible)	CVVH doses ^a
Penicillins (check allergy status) benzylpenicillin (2.4 g q4h)—↓RF ^b amoxicillin (1 g q6h)—↓RF flucloxacillin (2 g q6h)—↓RF piperacillin/tazobactam (4.5 g q6h)—↓RF	↓ Always administer over 30 min in renal failure. Dosage reductions between 50% and 75% may be recommended. ↓ Consider reducing dose by approximately 50%. 1 g q6h when CR _{CL} <10 mL/min 4.5 g q8h
Cephalosporins cefuroxime (1.5 g/750 mg q8h)—↓RF ceftazidime (2 g/1 g q8h)—↓RF	1.5 g/750 mg q8h–q12h 2 g q12h
Other antibiotics ciprofloxacin (400 mg q8h)—↓RF clarithromycin (500 mg q12h)—↓RF meropenem (1 g q8h)—↓RF tigecycline iv initially 100 mg then 50 mg q12h metronidazole 500 mg iv q8h OR 400 mg po/ng q12h OR 1 g rectally q12h co-trimoxazole PCP treatment 120 mg/kg/day PCP prophylaxis 480 mg ng/po daily amikacin 20 mg/kg over 1 h gentamicin 5–7 mg/kg dose—over 1 h renal impairment (including CVVH) 5–7 mg/kg first dose (maximum dose 500 mg) then reduce to 3 mg/kg vancomycin (by continuous infusion) LD: <70 kg 1 g over 60 min >70 kg 1.25 g maintenance 0–104 mg/h 5 days for MRSA, severe sepsis, septic shock 14 days for MRSA bacteraemia	400 mg q12h (200 mg q8h recommended in the literature) consider early ng/po administration 750 mg ng/po q12h consider increasing in obese patients or severe sepsis to 800 mg iv q12h 250 mg q12h when CR _{CL} <10 mL/min 1 to 2 g q12/q8h consultant/microbiology approval only; hepatically metabolized; avoid in women of child bearing age; not active against pseudomonal species; see specific monograph metronidazole liquid is not activated if the stomach pH is increased e.g. co-administered with PPIs: crush and dissolve tablets ↓ Reduction recommended depending on CVVH rate in RF; administer by continuous infusion in RF; can be administered neat if central; check iv monograph for details of administration second-line aminoglycoside; use lean body weight; maximum dose 1500 mg; check levels 20 h post-dose; redose when level <5 mg/L. If >5 mg/L re-assay at 12–20 h aiming for high peaks and low troughs (<1 mg/L); first-line empirical Gram-negative cover; check levels 20 h post-dose (maximum dose 500 mg); if <1 mg/L re-dose at 7 mg/kg; if >1 mg/L check level in ≥12 h time daily levels at 0600 h aim for concentration of 20–25 mg/L prescribe as a range 0–104 mg/h so nurses can adjust dose within range dependent on level central administration: 500 mg in 50 mL of 0.9% NaCl peripheral administration: 250 mg in 50 mL of 0.9% NaCl

Abbreviations: q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; ng/po, nasogastric/oral; ↓RF, reduction in antibiotic dose recommended in renal failure; RF, renal failure; LD, loading dose; CR_{CL}, creatinine clearance; PPIs, proton pump inhibitors; PCP, *Pneumocystis carinii* pneumonia.

^aDepends on rate of CVVH, less adjustments in high flux. Consider omitting single doses in intermittent CVVH.

^bAmount of dose reduction will depend on combination of drug and patient factors. Clinical pharmacist will advise.

patients (Table 1). There are a number of publications on antibiotic removal via haemofiltration^{45,46} plus a number of excellent resources to guide practice, including the renal drug handbook that is produced by the UK renal pharmacists

group.⁴⁷ There are two main factors that govern how well an antibiotic is removed via CVVH. The first is the proportion of drug that is renally excreted. The more renal elimination, the more likely the drug is to be removed by CVVH. The

second critical factor is the extent to which the antibiotic is bound to plasma proteins (predominantly albumin). The higher the amount of albumin binding the less likely the antibiotic is to be removed by CVVH. Antibiotics such as rifampicin that are hepatically metabolized and are highly protein bound are poorly removed by CVVH.⁴⁸ Other factors that can affect drug removal by CVVH, such as binding of drug to the filter, have less bearing in day-to-day clinical practice.

Safety issues

The critically ill patient is often in a life-threatening situation and frequently lacks full mental capacity and particularly the ability to communicate. The decision to start any therapy therefore rests solely with the healthcare professional, which increases the weight of responsibility to protect the patient from unnecessary harm. In the context of antibiotics, one of the most important safety factors is allergy. Up to 30% of patients admitted to the ICU may have a documented record of allergy, and up to half of that will be to an antibiotic, of which β -lactams are the most prevalent.⁴⁹ At the same time the patient may have life-threatening infections for which these antibiotics are the first choice. It is therefore important to gain an accurate clinical history from relatives or other healthcare professionals prior to administration of the first antibiotic dose, particularly when allergy is suspected so that a risk-benefit assessment can be made during administration of antibiotic.

Conclusions

There are a variety of factors that influence the dosing of any individual antibiotic in critical care. The drugs, patient and environmental factors all play a role in the decision to prescribe or recommend an antibiotic dosing regimen in a specific patient. Importantly, in the critical care patient, there is day-by-day variation, and assessment of each regimen should be undertaken daily. For example, a large dose of flucloxacillin (often in combination with an aminoglycoside) is required for the treatment of methicillin-susceptible *S. aureus* endocarditis. This could typically be 2000 mg iv every 4 h in the patient with severe sepsis. However, if the patient develops acute kidney injury secondary to the endocarditis and cholestatic jaundice then the dose of flucloxacillin should be reduced. This is because flucloxacillin-induced cholestatic jaundice and ensuing liver failure is a reversible adverse effect secondary to accumulation of the methylated metabolite of flucloxacillin in renal failure.¹¹

It is thus critical that the antibiotic dose be reviewed daily in the ICU and that those involved in the review and recommended changes are familiar with pertinent drug, environmental and patient factors.

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