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Current Drug Treatment Strategies for Disseminated Intravascular Coagulation

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Summary

Disseminated intravascular coagulation (DIC) can be caused by a variety of diseases. Experimental models of DIC have provided substantial insight into the pathogenesis of this disorder, which may ultimately result in improved treatment. Disseminated coagulation is the result of a complex imbalance of coagulation and fibrinolysis. Simultaneously occurring tissue factor–dependent activation of coagulation, depression of natural anticoagulant pathways and shutdown of endogenous fibrinolysis all contribute to the clinical picture of widespread thrombotic deposition in the microvasculature and subsequent multiple organ failure.

Cornerstone for the treatment of DIC is the optimal management of the underlying disorder. At present, specific treatment of the coagulation disorders themselves is not based on firm evidence from controlled clinical trials. Plasma and platelet transfusion are used in patients with bleeding or at risk for bleeding and

low levels of coagulation factors or thrombocytopenia. The role of heparin and low molecular weight heparin is controversial, but their use may be justified in patients with active DIC and clinical signs of extensive fibrin deposition such as those with meningococcal sepsis. There is some evidence to indicate that low molecular weight heparin is as effective as unfractionated heparin but may be associated with a decreased bleeding risk.

Antithrombin III (AT III) replacement appears to be effective in decreasing the signs of DIC if high doses are administered, but effects on survival or other clinically significant parameters are at best uncertain. If AT III supplementation is used, the dosage should be selected to achieve normal or supranormal plasma levels of 100% or higher. Results of studies on protein C concentrate, thrombomodulin or inhibitors of tissue factor are promising, but the efficacy and safety of these novel strategies remains to be established in appropriate clinical trials.

Disseminated intravascular coagulation (DIC) is a frequent complication of a variety of disease states such as infection, trauma, malignancies and obstetric complications. Infection is the commonest cause,[1] and in patients with septic shock DIC is a strong predictor of death.[2] In patients with DIC, the systemic activation of blood coagulation results in the generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to the development of multiorgan failure. Depletion of coagulation proteins and platelets, due to the ongoing activation of the coagulation system, may induce severe bleeding complications.[3]

The management of DIC is primarily directed at treating the underlying disease, but supportive care may be important. This care may consist of supplementing the depleted coagulation factors and endogenous coagulation inhibitors, and of inhibiting coagulation by various anticoagulant strategies or by manipulating the fibrinolytic system. In this review we first briefly focus on the current insight into the pathogenesis of DIC, since currently available and future treatment strategies may be based on this knowledge. Subsequently, the various treatment strategies for DIC are discussed. We do not focus on the laboratory diagnosis of DIC, as an extensive review of this subject has been published recently by Bick.[4]

1. Pathogenesis of Disseminated Intravascular Coagulation

1.1 Activation of Coagulation

The initiation of the systemic activation of coagulation is dependent on the underlying cause of DIC. In most cases, however, the activation of coagulation appears to be mediated by cytokines, which are produced by the host in response to various pathogenetic insults. For example, in sepsis, the activation of coagulation is initiated by microorganisms and their products like endotoxins, and by cytokines, mainly produced by mononuclear cells in response to these endotoxins.

The derangement of the coagulation system comprises enhanced activation of coagulation, depression of inhibitory mechanisms of coagulation, and inhibition of the fibrinolytic system.[5] Most of the current insight into those pathogenetic pathways has been derived from experimental studies of bacteraemia or endotoxinaemia in humans or primates. The intravenous administration of endotoxin to human volunteers or primates resulted in the activation of coagulation as reflected by elevation in markers for thrombin generation like thrombin-antithrombin complexes and fragment F1+2.[6,7]

Although the intrinsic (contact system dependent) pathway of coagulation may be activated during sepsis, it seems not to be involved in the initi-

ation of DIC.[8,9] This system, however, may play an important role in the pathogenesis of systemic hypotension. It has been shown that thrombin generation is mediated by the (extrinsic) tissue factor/factor VIIa–dependent pathway. Indeed, tissue factor expression by endothelial cells and blood monocytes can be induced by endotoxin and by cytokines like tumour necrosis factor (TNF).[10,11] Furthermore, the importance of tissue factor in the pathogenesis of DIC was confirmed by observations that the coagulant response upon bacteraemia or endotoxaemia could be completely blocked by the simultaneous administration of monoclonal antibodies which are able to inhibit the activity of tissue factor or factor VIIa.[7,12,13]

It may be assumed that thrombin plays a pivotal role in the further activation of systemic coagulation. Not only may thrombin affect several positive feedback loops (for example by direct activation of factor XI, thereby resulting in the generation of even more factor IXa and subsequently factor Xa), but thrombin can also act as a potent agonist for platelet activation. Activation of platelets either by generated thrombin or as a direct effect of endotoxins or cytokines may then further facilitate coagulation activation. The mechanism of coagulation activation in DIC is summarised in figure 1.

The endotoxin-induced activation of the tissue-factor system and subsequent activation of coagulation seems to be mediated by proinflammatory cytokines like TNF-α, interleukin (IL)-1 and IL-6.

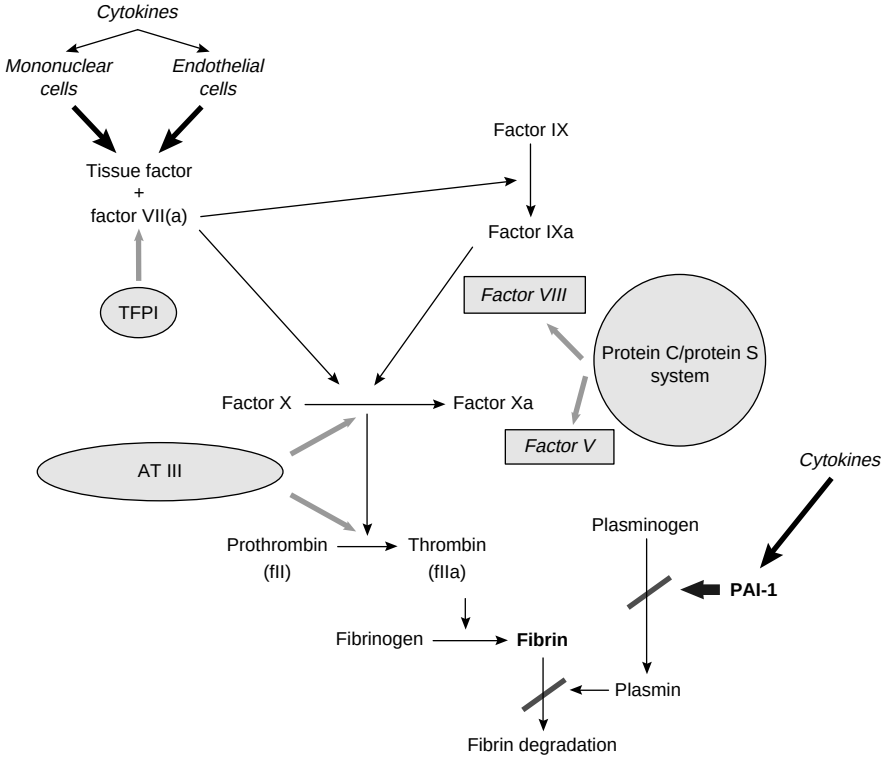

Fig. 1. Schematic representation of the coagulation and fibrinolytic system in disseminated intravascular coagulation. Tissue factor–dependent activation of coagulation occurs, ultimately leading to thrombin generation and subsequent conversion of fibrinogen to fibrin. The activation of coagulation is further promoted by depression of all 3 natural anticoagulant pathways [i.e. tissue factor pathway inhibitor (TFPI), the protein C/protein S system and antithrombin III (AT III)]. Simultaneously, fibrin degradation by activation of the endogenous fibrinolytic system is impaired, due to high concentrations of plasminogen activator inhibitor type 1 (PAI-1).

The administration of TNF-α to healthy volunteers elicited a rapid activation of coagulation, which was similar to that evoked by micro-organisms or endotoxin.[14] However, the role of TNF in endotoxin-induced activation of coagulation became less clear when subsequent studies showed that monoclonal antibodies directed against TNF activity were able to abolish the endotoxin-stimulated increase in TNF whereas thrombin generation was unchanged.[15]

In contrast to this observation, monoclonal antibodies directed against IL-6 were able to completely block the endotoxin-induced activation of coagulation in chimpanzees.[16] In addition, it was shown that IL-6 infusion in baboons and in human cancer patients induced thrombin generation.[17,18] Hence, these data suggest that IL-6, rather than TNF, is the primary mediator for the induction of coagulation in sepsis. The role of other cytokines, such as IL-1, is less clear. Treatment of septic patients with IL-1 receptor antagonist resulted in lower thrombin generation as reflected in decreased levels of thrombin-antithrombin complexes.[19] Also, administration of IL-1 to baboons resulted in the activation of systemic coagulation.[20] It is not clear, however, whether this effect of IL-1 is a direct effect or one mediated by other IL-1–induced cytokines.

1.2 Inhibitors of Coagulation

The thrombin generated by the activated coagulation promotes further activation of coagulation by a number of positive feedback loops. To balance this ongoing activation of coagulation, the human body uses various inhibitory systems. One of the major inhibitors of coagulation is antithrombin III (AT III). It rapidly binds and inactivates thrombin and factor Xa by forming thrombin-antithrombin and factor Xa–antithrombin complexes. Antithrombin III is decreased after endotoxin infusion in dogs[21] and during sepsis in humans due to increased consumption[22] and degradation by elastase released from activated neutrophils.[23] Low antithrombin III levels in DIC are associated with increased mortality.[2]

In addition to the decrease in antithrombin III, a significant downregulation of the protein C/protein S system may occur. Activated protein C (APC) proteolytically inactivates the cofactors factor Va and factor VIIIa, thereby rapidly and effectively impairing blood coagulation.[24] Protein C is activated by the complex of thrombin with the endothelial cell surface protein thrombomodulin and activated protein C is dependent on its cofactor protein S.

There are several explanations for an impairment of the protein C/protein S system in DIC. First, protein C and protein S levels are reduced in patients with DIC,[25] probably due to increased consumption. In addition, proinflammatory cytokines can induce downregulation of thrombomodulin on endothelial cells, resulting in a decreased activation of protein C.[26,27] Furthermore, the acute phase protein C4bBP, which can bind protein S, is increased during severe illness, leading to lower levels of the biologically active free protein S.

A third natural anticoagulant pathway consists of tissue factor pathway inhibitor (TFPI). Most of the TFPI in the body is bound to the endothelium and can be released into the blood, for example, following heparin administration. Much of the circulating TFPI is bound to lipoproteins.[28] TFPI is a direct factor Xa inhibitor and, in a factor Xa–dependent manner, produces feedback inhibition of the factor VIIa/tissue factor complex. In a primate model of sepsis TFPI levels increased 1.2-fold following sublethal and 2-fold following lethal *Escherichia coli* infusion.[29] Evidence for the importance of TFPI in sepsis was provided by a study in baboons that showed that its infusion after the start of a lethal intravenous *E. coli* infusion could prevent the activation of coagulation as well as death in all 5 animals studied.[30]

1.3 Fibrinolysis

In patients with DIC, deposition of fibrin in the (micro)vasculature is due not only to formation of intravascular fibrin, but also to inadequate removal. This inadequate removal is caused by an

impaired function of the fibrinolytic system. After endotoxin injection in healthy human subjects there is a rapid but short-lasting activation of fibrinolysis, due to an increase in tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA).

Following this initial activation a complete and sustained inhibition of fibrinolysis can be observed due to an increase in plasminogen activator inhibitor type 1 (PAI-1). Several experimental and clinical observations have shown that at the time of maximal thrombin generation fibrinolysis is markedly inhibited. Thus, a remarkable imbalance between coagulation and fibrinolysis exists, resulting in a net procoagulant state.[6,16] Antibodies to tissue factor or the specific thrombin inhibitor recombinant hirudin were able to completely block the endotoxin-induced thrombin generation in chimpanzees, but were without any effect on the activation of fibrinolysis. Hence, inhibition of coagulation did not affect the stimulation and subsequent inhibition of fibrinolysis, suggesting an independent regulation of these 2 processes. Experimental studies have shown that the dysregulation of fibrinolysis in DIC is completely mediated by TNF, whereas other cytokines, such as IL-6, have no effect.[31]

2. Treatment of DIC

The proper management of patients with DIC remains controversial. Unfortunately, adequate clinical trials on DIC treatment are scarce, probably due to the complexity of the syndrome and its variable and unpredictable course. The clinical picture of simultaneously occurring systemic thrombotic depositions and bleeding due to consumption does not directly indicate which specific therapy should be administered.

It is, however, well accepted that the cornerstone for the treatment of DIC is the management of the underlying disorder. In addition, therapeutic interventions based on our present knowledge of the pathogenesis of DIC may be appropriate. At present, these interventions may consist of plasma and platelet replacement therapy, anticoagulant strategies or administration of physiological coagulation inhibitors. Future therapies may include interference in the fibrinolytic system.

2.1 Plasma and Platelet Transfusion

Consumption of coagulation factors and platelets during DIC can increase the risk of bleeding. Treatment with plasma or platelet concentrates is guided by the clinical condition of the patient and should not be instituted on the basis of laboratory findings alone. Replacement may be indicated in patients with active bleeding and in those requiring an invasive procedure or otherwise at risk for bleeding complications. On the other hand, it has been suggested that transfusion of blood components may also be harmful by further stimulating the activated coagulation system. This in fact has rarely been proven to occur and simultaneous (low-dose) heparin might be useful to prevent these complications.[32]

The treatment with plasma is not based on evidence from controlled trials. The only randomised, controlled trial in neonates with DIC, comparing administration of fresh frozen plasma and platelets with whole blood exchange and no specific therapy, failed to show any change in outcome of DIC or survival.[33] Despite the lack of evidence most authors recommend treatment with fresh frozen plasma, at least when patients are bleeding or at increased risk for bleeding.[1,34,35]

To sufficiently correct the coagulation defect, large volumes of plasma may be needed. The use of coagulation factor concentrates may overcome this need; however, besides the fact that these concentrates usually contain only a selected number of the various clotting factors, they may be contaminated with traces of activated coagulation factors and may therefore be particularly harmful for patients with DIC. Cryoprecipitate, which contains fibrinogen as well as factor VIII, von Willebrand factor, factor XIII and fibronectin, is also used as replacement therapy in DIC. However, its use is not supported by controlled trials. Because it is not possible to produce cryoprecipitate without risk of

hepatitis C transmission, this product is not available in many countries.

2.2 Anticoagulant Strategies

2.2.1 Heparin

Heparin has been used as treatment for DIC since 1959.[36] Animal studies have shown that this drug can inhibit the activation of coagulation in experimental septicaemia but does not affect mortality.[37,38] Studies of heparin for the treatment of DIC in humans claimed to be successful, but were not controlled.[39,40] Although one of these uncontrolled studies concluded as long ago as 1970 that a controlled study giving heparin to patients with Gram-negative sepsis appeared to be indicated,[39] to date no such trial has been performed. A retrospective analysis of cases of DIC reported in the literature found similar survival for patients treated with heparin and those not so treated.[40] We can conclude that there is no sound evidence in favour of the use of heparin as routine therapy in patients with DIC. An exception may be made for patients with clinical signs of extensive fibrin deposition like purpura fulminans, acral ischaemia or venous thrombosis.[41] In such cases low-dose heparin 5 to 8 U/kg/h is advocated, potentially in combination with plasma and – if appropriate – platelet replacement.

2.2.2 Low Molecular Weight Heparin

Low molecular weight heparins (LMWH) are fractions of heparin with a molecular weight between 4000 and 8000 daltons. They differ from unfractionated heparins (UFH) in their higher anti–factor Xa to anti–factor IIa activity ratio. This ratio varies between 2 : 1 and 4 : 1 for LMWH, compared with 1 : 1 for UFH. It has been postulated that these LMWHs would have a decreased bleeding risk while having at least the same antithrombotic potential as UFH. Effective treatment of DIC with LMWH has been reported in rabbits.[42] In rats, LMWH was as effective as UFH in improving the symptoms of DIC after endotoxin or thromboplastin infusion.[43]

Successful treatment was also reported in 2 small uncontrolled studies in humans.[44,45] Furthermore, the effects of dalteparin sodium as anti-DIC treatment have been studied in a multicentre, double-blind, randomised trial.[46] The underlying cause of DIC in most of these patients was malignancy, and infectious disease was a causative factor in only 13% of the patients. Dalteparin sodium and heparin were given at daily dosages (U/kg) of 75 and 240, respectively. In this study, dalteparin sodium showed greater efficacy than UFH in improving bleeding symptoms and in improving a subjective organic symptoms score. The improvement in survival in the dalteparin sodium group was not significant. There was no difference in laboratory parameters for DIC between the 2 treatment groups. Hence, from this single study it may be postulated that LMWH offers the benefit of decreased bleeding complications compared to UFH in the treatment of DIC.

2.2.3 Hirudins

Recombinant hirudin is a potent and specific direct thrombin inhibitor. In contrast to heparin, its activity is not dependent on AT III[47] and it is therefore capable of inhibiting clot-bound thrombin. Recombinant hirudin appeared to be effective in treating DIC in animal studies,[48-50] and in one series of 5 patients with haematological malignancy and DIC.[51] However, to date, no randomised, controlled trials on the use of hirudin in patients with DIC are available. The high risk of bleeding with hirudin treatment, as shown for example in initial clinical trials, may potentially limit the use of hirudin in these patients.[52]

2.3 Coagulation Inhibitors

2.3.1 Antithrombin III Concentrate

AT III is an important physiological inhibitor of blood coagulation. Low AT III levels are associated with increased mortality.[2] Mortality due to Gram-negative sepsis could be prevented by AT III infusion in baboons, but only if adequate AT III concentrations were achieved early in the course of sepsis.[53]

In humans, 3 controlled clinical trials have been performed on the use of AT III concentrates in DIC. One trial compared AT III infusion with a synthetic

protease inhibitor (gabexate; FOY-007) in obstetric patients with DIC. A single infusion of AT III was significantly more effective in controlling the symptoms of DIC (improvement in 92 *vs* 60% of patients).[54]

Blauhut et al.[55] studied 51 patients with shock and DIC. They compared treatment with AT III concentrate alone against heparin treatment and the administration of AT III concentrate plus heparin. No difference in survival was observed between the groups, but the duration of symptoms of DIC was significantly shortened in the groups receiving AT III with or without heparin. Bleeding complications were increased in the group treated with AT III in combination with heparin.

The third study by Fourrier and others[56] compared the administration of supraphysiological doses of AT III with placebo in patients with septic shock. In the AT III–treated patients, recovery from DIC was earlier and blood transfusion requirement was less. A trend to decreased mortality was found, but statistical significance was not reached.

In a review of the trials on AT III concentrate for the treatment of DIC, Vinazzer,[57] one of the coauthors of the study by Blauhut et al.,[55] showed the results of a follow-up study in 170 patients with shock. In this follow-up study significantly fewer patients treated with AT III concentrate died compared with treatment with heparin. However, the information on a number of important methodological issues regarding this follow-up study remain unclear.[57] In all the abovementioned studies, AT III concentrate was given at dosages designed to reach normal or supranormal plasma levels and in the study by Fourrier et al.[56] even higher AT III concentrations, twice as high as usually found in the plasma, were attained. A recent publication suggested that much higher doses of AT III are needed to achieve maximal beneficial effect.[58]

The conclusion from the published studies is that AT III is able to improve DIC, but that the benefit in terms of clinical outcome is less certain. Since it cannot be inferred from the literature which patients will benefit in terms of increased survival or reduced morbidity, it seems reasonable to reserve this expensive treatment to cases were mortality attributable to DIC is expected to be high and to patients with very active DIC leading to substantial morbidity. An example of such is a patient suffering from meningococcal sepsis with purpura fulminans and acral ischaemia. In such cases, the aim of the treatment should be normal or supranormal antithrombin concentrations.[59] Future studies will probably indicate whether treatment with higher, supraphysiological, doses of AT III will result in more favourable clinical outcome in patients with DIC.

2.3.2 Protein C Concentrate and Thrombomodulin

As mentioned above, protein C levels are reduced during sepsis and clinical and experimental evidence indicate that depression of the protein C/protein S system may contribute to a fatal outcome.[25,60,61] On the basis of these observations, supplementation of protein C may be of advantage in patients with DIC. Indeed, in baboons, protein C prevented the coagulopathic and lethal effects of *E. coli* infusion.[62] APC also appeared to be effective in a thromboplastin-induced DIC model in rabbits.[63] There have been several reports of successful treatment with protein C in sepsis, both in children[64,65] and in adults.[66] However, no data from controlled clinical trials are available and routine treatment of DIC with protein C concentrate cannot yet be advocated. Clinical studies with activated protein C concentrate are ongoing and may yield promising results.

An alternative strategy to increase the activity of the protein C system is the infusion of thrombomodulin. In several animal models of DIC, treatment with soluble thrombomodulin not only showed a beneficial effect on coagulation, but also appeared to improve the pulmonary vascular injury and pulmonary accumulation of white blood cells.[43,67-69] These effects were not dependent on the thrombin-binding properties of thrombomodulin, but probably mediated by the increase in activated protein C.[69] To date, no studies on thrombomodulin treatment in humans with DIC have been reported.

2.3.3 Inhibitors of Tissue Factor

Since tissue factor plays a key role in the initiation of coagulation during DIC, inhibiting its action could be of value in the treatment of intravascular coagulation. In a rat model of DIC the infusion of recombinant TFPI immediately after endotoxin administration significantly inhibited the consumption of coagulation factors and platelets. Furthermore, a reduced number of fibrin thrombi was formed in liver, lungs, kidney and spleen.[70] Similar effects were found in a rabbit model of DIC.[71] Clinical trials on the use of TFPI in patients with DIC have recently been initiated, but results are not yet available. Also, other tissue factor–inhibiting agents may prove to be potentially useful treatment strategies in patients with DIC.

2.4 Interference in the Fibrinolytic System

Fibrinolytic inhibitors, such as aprotinin or tranexamic acid, are usually contraindicated in patients with DIC. Although generally useful in bleeding patients, in the case of DIC these agents are thought to further block the already depressed fibrinolytic system, thereby seriously promoting intravascular fibrin deposition. An exception may be made in patients with a rarely occurring type of coagulation disorder associated with acute promyelocytic leukaemia (AML-M3) or sometimes with prostate carcinoma. In fact, in these situations it is primary hyperfibrinolysis rather than DIC that is present, and here, fibrinolytic inhibitors may be very useful.[72]

Since the fibrinolytic shutdown in patients with DIC appears to be due to high circulating levels of PAI-1, strategies directed against this fibrinolytic inhibitor might be useful. Anti–PAI-1 strategies have been shown to be of benefit in initial experimental studies;[73] however, the effect of this treatment in clinical studies of DIC remains to be awaited. An alternative strategy to enhance fibrinolysis is the administration of t-PA. Some case reports have been published suggesting improvement of the clinical condition of patients with meningococcaemia and DIC after t-PA treatment,[74,75] but again, controlled clinical trials should be awaited before this treatment can be advocated.

3. Conclusions: Guidelines for Therapy

In the first instance, treatment of DIC should consist of optimal management of the underlying disease, e.g. antibiotic therapy and abscess drainage in bacteraemia. As mentioned above, there is a lack of firm evidence for any specific therapy directed at the coagulation system for a patient with DIC, and the following guidelines are based as much as possible on the data available in the literature.

In the case of bleeding or high risk for bleeding, we suggest plasma and platelet replacement therapy. Depending on the levels of coagulation factors and clotting times, 2 to 3 units of plasma can be given initially, followed by repeated transfusion depending on prothrombin time (PT) and activated partial thromboplastin time (aPTT) values.

When the decision is made to give platelet transfusion, the aim should be to achieve levels of 50 to 60 x 10^9/L. There is no evidence that treatment with heparin or LMWH is beneficial. We reserve heparin treatment for those cases with clinical signs of extensive fibrin deposition, such as patients with purpura fulminans. In these patients, heparin 300 to 500 U/h can be given intravenously. Finally, we start replacement therapy with AT III in patients with severe DIC and low levels of circulating AT III. In those circumstances, replacement therapy should be aimed at reaching at least normal AT III levels. The dose of AT III concentrate to reach normal levels can be calculated by the formula: dose (units) = (100 – measured AT III activity) × bodyweight (kg).[59]

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Erratum

Vol. 55, No. 1, page 41: In table VII, the alternative treatment for *Pseudomonas aeruginosa* should read 'ciprofloxacin *400mg q12h* IV'.

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