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Heart Transplantation

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Although the number of available donor hearts severely limits the epidemiologic impact of heart transplantation on patients with heart failure, patients with end-stage heart failure unresponsive to medical management currently have no other viable alternatives. Destination therapy with a ventricular assist device is the closest toward approaching clinical reality but has been plagued with problems of infection and stroke. The purpose of this review is to summarize recent developments in the field that may broaden the clinical impact of heart transplantation. For example, novel methods of cardiac preservation are being designed to safely evaluate and utilize “extended criteria” donors. Surgical techniques and medical management have reduced the incidence of postoperative right heart failure, and immunosuppressive regimens promise to limit chronic graft vascular disease.

Key words: heart transplantation, review, surgical technique, immunosuppression

The incidence of end stage heart failure is growing along with the population of the United States. Several novel therapies have been heavily investigated to address this problem: chronic mechanical assistance of the ventricle, myocyte transplantation to revive the failing heart, and xenotransplantation of a pig or primate heart. However, it is unlikely that any of these promising therapies will soon approach the impact on quality of life and survival that allogenic heart transplantation has made over the past 35 years (Figure 1). The purpose of this review is to highlight some of the challenges that persist in this field.

Recipient Listing

The process of cardiac transplantation begins with the acceptance of a donor organ that has been offered through the United Network of Organ Sharing (UNOS) matching system. A blood type-compatible donor heart is matched to a recipient based on characteristics such as height, weight, medical status, and time accrued on the waiting list. The thoracic organ waiting list is stratified by 3 levels: status 1a, 1b, and 2 (UNOS Policy 3.7.3). Status 1a is defined by the need for ICU care with high-dose inotropes or mechanical assistance including intra-aortic balloon pump. Although this status was initially granted for the first 30 days of mechanical assist, recent revision in policy has resulted in the selection of a 30-day window for listing as 1a at any point after implantation. This arose from the experience of early post-pump implants as a higher risk for transplant. Because infection and stroke are common with these devices, it is reasonable to afford these bridge patients a short period when they are prioritized prior to a complication but after recovery from the implant. The thoracic organ waiting list is stratified by 3 levels: status 1a, 1b, and 2 (UNOS Policy 3.7.3). Status 1a is defined by the need for ICU care with high-dose inotropes or mechanical assistance including intra-aortic balloon pump. Although this status was initially granted for the first 30 days of mechanical assist, recent revision in policy has resulted in the selection of a 30-day window for listing as 1a at any point after implantation. This arose from the experience of early post-pump implants as a higher risk for transplant. Because infection and stroke are common with these devices, it is reasonable to afford these bridge patients a short period when they are prioritized prior to a complication but after recovery from the implant. The 30-day window period, a complication due to a ventricular assist device (e.g., infection) is another, more controversial, method of being relisted as status 1a [1]. Heart transplant candidates who have a chronic mechanical assist device or who are inotrope dependent are granted status 1b. All other patients with compensated heart failure managed as outpatients are status 2.
The mortality of patients while on the waiting list is currently estimated at 10% per year [2]. This mortality can be minimized by a clear understanding of the “transplantation window,” meaning the patient is sick enough to require transplantation but does not have decompensated cardiogenic shock and irreversible multiorgan failure. While the ejection fraction is a useful screening test for heart failure, the peak oxygen consumption on exercise testing (peak VO₂) is widely regarded as the best way to quantify this “window.” Specifically, a peak VO₂ < 14 ml/min/kg is predictive of failure of medical management and the need for transplantation [3].

According to UNOS, there are 3894 heart transplant candidates as of January 31, 2003, which far exceeds the approximately 2200 transplants performed in the United States each year [4]. Therefore, all reasonable nontransplant options should be exhausted in candidates for transplantation. Optimal medical therapy includes agents such as ACEI and beta-blockers at the maximal tolerable doses. Further inhibition of the renin-angiotensin-aldosterone system by aldactone has been shown to improve mortality and therefore potentially avoid transplantation [5]. Biventricular pacing may be indicated in 50% of heart failure patients with interventricular conduction delay > 130 msec. This rather innocuous therapy has been shown to improve symptoms and decrease the need for hospitalization in the MIRACLE trial [6]. Automatic defibrillators have been recently shown to reduce mortality in ischemic cardiomyopathy in the MADIT I and II trials. Paradoxically, defibrillators may enhance the development of heart failure [7] simply as a byproduct of the effective prevention of sudden death or from an undefined effect of the defibrillator such as asynchronous pacing. Increasingly, coronary bypass grafting is being offered to cardiomyopathy patients with good coronary targets and reversible ischemia on viability studies [8]. The surprising and immediate improvement in ventricular function following mitral valve repair in those with a dilated annulus due to progressive ischemic and nonischemic cardiomyopathy is thought secondary to an acute reduction in wall tension from reduced ventricular preload (i.e., the Law of Laplace’s takes precedence over the Frank-Starling Law) [9]. Finally, “bridge to transplant” by a ventricular assist device (VAD) has proven to improve end-organ resuscitation and enhance physical therapy. Furthermore, the need for inotropes that may enhance heart failure and arrhythmias is eliminated. Although a VAD increases the technical challenge of heart transplantation, the posttransplant mortality is now similar to status 2 patients. Compared to similar patients on preoperative high-dose inotropes, the morbidity of heart transplantation for patients on a VAD is improved with significant reductions in perioperative renal (52.6% versus 16.7%) and right heart (31.6% versus 5.6%) failure [10]. Unfortunately, the onset of a blood-stream infection eliminates the benefit of a VAD [1]. Sepsis was the most common cause of mortality during the randomized destination VAD versus medical therapy (REMATCH) trial [11]. Rational efforts to minimize infection include tight perioperative glucose control [12] and nutritional support [13], elimination of nasal Staphylococcus aureus [14], and protocols for driveline care. Recently, data have suggested that the biomaterial-blood interface also reduces cell-mediated and antibody-dependent immunity [15].

Donor Selection

Due to inadequate supply of donor organs, heart transplantation has fallen well short of being a viable epidemiologic solution for end-stage heart disease. Recently, kidney transplantation has enjoyed a growth in the number of donations largely due to “extended criteria” and non-heart-beating donors. Application of these innovative measures in heart transplantation has been limited due to concerns of exacerbating the most common cause of 30-day mortality: primary graft nonfunction [16]. While a kidney transplant recipient with this complication may return back to dialysis, primary nonfunction invariably leads to mortality in heart transplant patients.

Hemodynamic collapse and cardiac arrest are the natural history of brain death [17]. Therefore, aggressive optimization of the donor must immediately follow the diagnosis of brain death. During their prior management by the neurosurgical team, donors are often given large doses of vasopressors with subsequent volume depletion for the purposes of optimizing brain perfusion. Pulmonary artery catheterization and echocardiography can provide guidance on appropriate fluid management. In addition, large doses of inotropes are often the result of hormonal deficiencies that develop after brain death. Donor infusions of glucose/insulin/potassium, triiodothyronine (T3), and cortisol have been shown to reduce donor inotropic requirements and improve recipient outcome following transplantation [18] and are recommended in a recent consensus statement [19].
The pathophysiological changes in the donor heart initiated by brain death are enhanced by subsequent events such as graft harvest, storage, and reperfusion. Graft ischemic time, while relatively less potent as an isolated risk factor, interacts with other risk factors present in the “extended criteria donor” to synergistically increase recipient mortality [16]. Therefore, expanding the cardiac donor pool may await the development of a clinically relevant graft preservation system that minimizes the effect of ischemia. The use of a continuous perfusion system during the ex vivo preservation period has been shown to neutralize the effect of the ischemic transport time on graft outcome, clinically in renal transplants [20] and experimentally in large animal heart transplant models [21]. Recirculation of oxygenated blood or asanguinous preservation solutions at warm or cold temperatures have been used for the purposes of preventing the anaerobic metabolism that occurs during the standard cold storage method.

Despite its increased complexity, this method of preservation provides many potential advantages for clinical heart transplantation. It would allow pretransplant, ex vivo evaluation of these extended criteria donor organs to minimize the recipient’s risk of developing primary graft nonfunction while maximizing use of the donor pool. Continuous perfusion has been shown to preserve the graft endothelium better than static cold storage and may provide time for a reversal of the activated coronary phenotype. A growing body of evidence points to the activation of the endothelium as a major factor in the development of reperfusion injury, primary graft dysfunction, and acute and chronic rejection [22,23]. Extension of the acceptable ex vivo preservation period using continuous perfusion would potentially allow for the implementation of an HLA matching system similar to kidney transplantation. Two large databases, the UNOS/ISHLT [24] and CTSG [25] Registries, have revealed a long-term benefit to HLA matching similar to that seen in renal transplantation.

Heart Transplantation

The issues surrounding the performance of heart transplantation remain similar to that originally outlined by Shumway, with a few notable exceptions. The morbidity of what are frequently redo operations with long cardiopulmonary bypass times has been reduced by the hemostatic agent aprotinin [26]. By inhibiting serine proteases, aprotinin has been shown to block plasminogen activators and therefore fibrinolysis while also inhibiting thrombin and therefore the CPB mediated “exhaustion” of platelets. The limitation of blood product usage has been shown to have a wide range of benefits in heart surgery, which are amplified in the transplant patient. Complementary to aprotinin is the use of a Thrombelastography™ (Haemoscope, Niles, IL) based transfusion algorithm, which more accurately predicts the risk for bleeding than conventional measures of the hemostatic system such as platelet count, PT/PTT, and fibrinogen [27]. This algorithm limits the number of empirically given, unnecessary transfusions, which likely increase the risk of hypercoagulability and, potentially, thrombotic events [28].

The most notable technical modification has been the substitution of the bicalve anastomoses for the earlier atrial-to-atrial cuff technique. The original heart transplantation involved 4 anastomoses: the aorta, pulmonary artery, and the 2 atrial cuffs. For the atrial cuffs, the donor’s atria are opened and sewn to a cuff of the respective atria of the recipient (Figure 2). While simple, several problems have been noted in the allograft that are thought to be related to this bi-atrial cuff technique: disyncriony between donor and recipient atria leading to AV valve regurgitation and reduced RV filling, increased trauma to the sinus node leading to a lowered rate of postoperative normal sinus rhythm, and technical difficulties with obtaining endomyocardial biopsies via right heart catheterization. These findings led to the modification in which anastomoses were performed between the superior and inferior cavae of the donor and recipient leaving the right atrium intact. Using the bicalve technique, several retrospective analyses have shown an improvement in allograft performance. A randomized trial comparing the bicalve versus the standard atrial cuff methods found an improvement in mortality using the bicalve technique [29].

Perioperative Management

The improved mortality following the bicalve technique is in large part due to improved right heart function. Difficulties with the right heart are the most common cause of primary graft dysfunction noted following weaning from cardiopulmonary bypass. Reasons for the problems noted with the right heart are not entirely clear but related to the acute changes in pulmonary vascular resistance that the heart is required to work against in the pre-
viously healthy donor versus the recipient with end-stage heart failure. In addition, the most common wall motion abnormality seen in donor hearts before and after transplantation is septal hypokinesia. In the donor, this pattern of hypokinesia is thought due to the enhanced sympathetic innervation of the septum over other areas and therefore greater potential for injury following the “autonomic storm” that follows brain death [30]. This initial damage predisposes the septum to the cumulative injuries that follow: graft harvest, ischemia, reperfusion, and reimplantation in an “activated” host. Right heart failure results in part due to the relatively greater role the septum plays in right versus left heart systolic function [31]. Additionally, diastolic dysfunction is induced by ischemia-reperfusion injury in both chambers but is less tolerated on the right side because of its predominant role as a compliance chamber [32]. Treatment of posttransplant right heart failure involves avoiding factors that increase right heart afterload (e.g., hypoxia, acidosis, excessive blood product transfusions) and using agents to reduce it (e.g., dobutamine, milrinone, inhaled nitric oxide). In addition, the intra-aortic balloon pump has also been shown to be of benefit in posttransplant right heart failure. Although it is often thought of only as a means of addressing left heart failure, the balloon pump augments coronary blood flow and therefore improves the function of the septum and right ventricular free wall [33]. Given their potential beneficial effect against donor heart reperfusion injury, aprotinin, leukocyte filters, and NO are strongly considered in recipients receiving a heart at increased risk for right-sided failure.

An elevated CVP in the setting of low cardiac output and reduced LV filling and septal dyskinesis by echocardiography establishes the diagnosis in most severe cases of RV dysfunction. However, part of the difficulty in managing right heart failure is making an accurate diagnosis and monitoring response to treatment of milder degrees of RV dysfunction. Echocardiography, which has been a major advance for monitoring left heart function, typically obtains images of the crescent-shaped right heart that are an insensitive measure of function. RV ejection fraction is a particularly poor predictor of true right ventricular function given its relatively greater dependence on loading conditions (i.e., pre/afterload). Tissue Doppler imaging has the potential to assess contractile function independent of ventricular shape. This method has been validated in a recent animal study against the “gold standard” of invasive pressure/volume relationships to measure the end systolic pressure/volume curve [34]. The use of commercially available conductance catheters, which measure RVEF and RVEDV, allows the derivation of this curve, providing a clinically relevant assessment of RV function.

![Fig. 2. Donor cardiectomy for biatrial cuff (A) and bicaval (B) anastomoses. Reprinted with permission from both Society of Thoracic Surgeons (Ann Thorac Surg. 1999;68:1242-1246) and Nizar A. Yonan, FRCS.](image-url)
function [35], but awaits further analysis in transplant patients.

An unusual cause of primary graft failure is hyperacute rejection (HAR), indicated by the gross anatomical findings of edema, hemorrhage, and thrombosis shortly following revascularization. This process involves preformed antibodies that immediately bind to and activate the endothelium, initiating the complement and coagulation cascades. These antibodies bind to oligosaccharide antigens of the ABO blood group that are similar to those found on numerous endemic bacteria, protozoa, and viruses. The cross-reactivity of antibodies directed against these endemic microbes is likely to be responsible for the preexisting natural antibodies that cause HAR after ABO-incompatible organs. Because the titer and avidity of preformed antibodies against the blood group antigens in newborn infants is low, ABO-incompatible cardiac allografts have shown greater success in these patients [36]. HAR also occurs from antibodies directed against human leukocyte antigen (HLA) Class I major histocompatibility complex (MHC) antigens that are constrictively expressed by allograft endothelium. The likelihood of anti-MHC Class I antibodies is increased in patients with a prior history of exposure to allogeneic HLA through prior blood transfusions, pregnancy, or recent mechanical support associated with blood product transfusions, especially platelets that express abundant MHC Class I antigen. If the transfusion of blood or platelets is required in a transplant candidate, the use of leukocyte-depleted transfusions can reduce the risk of HLA exposure [37]. CMV infection is known to increase the expression of HLA on platelets and contaminating leukocytes, and therefore CMV-negative blood should be used regardless of the CMV status of the recipient [37].

Candidates with preexisting HLA Class I antibodies have benefited by strategies designed to reduce circulating antibodies and B-cell antibody production [38]. Perioperative regimens of plasmapheresis and/or intravenous immunoglobulin (IVIG) and cytoxan continued posttransplantation have reduced HLA Class I antibodies and improved upon the likelihood of finding a negative donor. This use of aggressive posttransplant regimen has avoided HAR after transplantation despite a positive prospective cross-match [39]. IVIG may have its effect by anti-idiotypic antibodies; antibodies against membrane molecules, including CD4 and CD8; or soluble forms of HLA molecules. Recently, monthly cyclophosphamide (0.5-1.0 gm/M²) was shown to be effective against B-cell antibody production [40]. Antidonor HLA antibodies have developed in some after transplant despite a negative prospective cross-match. Titers may rise as early as 3-4 days after transplant, which implies a secondary antibody response with undetectable levels of preformed anti-HLA antibodies despite prior exposure. Although a process known as accelerated, acellular rejection occurs in a few, the induction of a protective phenotype (e.g., bcl-xL, bcl-2, and A20) inhibits endothelial activation and prevents vascular injury in the vast majority [41]. As T lymphocytes express MHC Class I antigens, the presence of preformed lymphocytotoxic antibodies, especially IgG isotype, detected on routine T-cell cross-match to donor blood is considered a contraindication to transplantation. Transplant candidates are routinely screened for these antibodies during the evaluation period. Candidate serum is tested against a panel of volunteers who contain the major HLA allotypes. The percentage of panels that demonstrate a reaction is referred to as measurement of panel-reactive antibodies (PRA). Patients with a high degree of “sensitization” to the donor panel (PRA > 10%-20%) are at risk of delayed transplantation because of the need for a negative prospective cross-match with a specific cardiac donor without which the risk of acute rejection is raised.

After primary graft dysfunction, the most common cause of mortality in the first month following transplantation is bacterial infection. The debilitated patient with cachexia due to end-stage heart failure who undergoes a major operation followed by aggressive immunosuppression is a setup for a perioperative infection. Thorough attention to measures that reduce this excessive risk is mandatory. Early extubation and removal of invasive lines and drains, aggressive pulmonary toilet, early physical therapy, and appropriate use of perioperative antibiotics are well-understood measures to reduce risk. In addition, preoperative nutritional support with specially designed dietary supplements has been shown to reduce the risk of wound infection in patients with cardiac cachexia [13]. Intensive insulin infusions to maintain a glucose level between 80 and 110 mg/dl has been shown to reduce septic mortality in a recent randomized trial of cardiothoracic ICU patients [12]. Other randomized trials support the use of high-perioperative FIO2 [42] and wound closure with skin staples (versus subcutaneous suture) [43] to reduce wound infection rates. The recent addition of rapamycin to the immunosuppressive regimen seems to be a great advance for reducing early cardiac allograft vasculopathy and renal toxicity. However, likely
due to its antifibrotic effects, the incidence of wound complications such as dehiscence and seromas seems to be increasing on this agent. Its overall effect on patient morbidity has not been defined.

It appears that acute and chronic rejection is primarily mediated by the indirect pathway of CD4 T-cell activation. This process is due to shedding of donor allo HLA peptides that are taken up and processed by recipient macrophages and B-cells (APC cells or antigen processing cells) that present the donor antigen to a TCR complex on a host T-cell. Acute rejection appears to be associated with anti-MHC class II (DR) antibodies and allopeptides. Recurrent and later rejection appears with intermolecular spreading and T-cell recognition of multiple donor HLA-DR alloantigens [44]. Acute rejection involving either cellular or humoral immunity is at risk for occurring within a week to a few months after transplantation. Although late acute episodes can occur, they often do so in the setting of a change in the balance of immunosuppression versus host immunity. A decrease in the blood level of immunosuppressant either by prescription or drug interaction or an up-regulation in alloreactivity owing to viral infection can cause a late allograft rejection.

Myocardial cytolysis on a protocol endomyocardial biopsy (grade ≥ 3) of an asymptomatic patient is the most common scenario that supports initiating a course of treatment. Noninvasive modalities, including radionuclide scanning for evidence of apoptosis [45], magnetic-resonance imaging [46], echocardiography [47], and intramyocardial EKG recordings [48] have shown good correlation with established high-grade rejections in some studies. However, none of these techniques have demonstrated sufficient predictive value to be included in routine clinical management. The treatment of acute rejection employs intravenous steroids as a first-line therapy for a grade ≥ 3 biopsy. Symptomatic patients (e.g., hemodynamic changes, arrhythmias, fever) are often treated despite lesser grade biopsy results. Thymoglobulin has proven highly effective for steroid-resistant episodes, with less toxicity and risk of malignancy seen with OKT3 [49].

**Immunosuppression**

Transplantation became established as the gold standard therapy for end-stage heart failure only following the development of a drug regimen that successfully inhibited the primary immune response. In addition to azathioprine (AZA) and cyclosporin (CsA), the regimen following heart transplantation has been based on steroids. Transplant physicians have recognized the benefits of corticosteroids from the very early days of clinical transplantation. These molecules have protein effects that are mediated through intracellular receptors that alter gene transcription [50]. Recent advances in the development of tolerance protocols have suggested that steroids block certain immune signaling pathways necessary to induce donor-specific anergy or suppressor cells [51]. There are suggestions of a decreased incidence of AV with steroid weaning protocols due possibly to the enhancement of tolerance in addition to a reduction in diabetes and dyslipidemia associated with steroids [52].

CsA inhibits the gene activation necessary for IL-2 production. It has recently been administered as a novel microemulsion, Neoral, which has significantly improved its bioavailability and reduced pharmacokinetic variability between patients. Approximately 30% of heart transplant recipients develop nephrotoxicity, the primary toxicity of CsA, which appears to be mediated by the inhibition of prostaglandin metabolites. In 2 recent series, calcineurin inhibition was the sole cause leading to metachronous kidney following heart transplantation [53,54].

Approximately 20% of heart transplant programs use the calcineurin inhibitor FK506 (tacrolimus), which has proven to be at least as effective as CsA in heart transplant recipients [55]. It has found particular success following a switch from CsA-based immunosuppression when faced with a refractory acute heart rejection. Given a similar mechanism of action to CsA, the reason for the improved effectiveness of tacrolimus in refractory rejection likely relates to more predictable pharmacokinetics. Compared to recipients receiving CsA, tacrolimus was found to be associated with less facial disfigurement, hirsutism, hypertension, and hyperlipidemia but equal nephrotoxicity and greater neurotoxic and diabetogenic effects.

The classic antimetabolite has been azathioprine (AZA), which inhibits purine synthesis and therefore DNA and RNA synthesis throughout all dividing cells. Mycophenolate mofetil (MMF) appears to be more selective for T and B cells than AZA [56] based on its ability to block the synthesis of purines in the de novo pathway; lymphocytes, unlike other cells, depend solely on the de novo pathway for purine synthesis. Acute rejection and antibody production are reduced with MMF com-
pared to AZA after heart transplantation [57]. In addition, neutropenia has not been a limiting factor as it has been with AZA.

Rapamycin (sirolimus, RPM) prevents the signaling between IL-2 receptor activation and cell cycle initiation and leads to a cell cycle arrest in B-cells and smooth muscle cells [58]. This antiproliferative effect leads to the arrest of AV in both small [59] and large [60] animal experimental models and the prevention of intracoronary restenosis after using RPM-coated stents [61]. In preliminary randomized studies, the use of RPM instead of AZA following heart transplantation has resulted in reduced AV by IVUS evaluation at 6 months [62] and 1 year [63]. Sirolimus is not nephroxic, but it may enhance the renal toxic effects of calcineurin inhibitors [64]; its main toxicity is hyperlipidemia and wound complications such as dehiscence and seromas.

Combinations of these drugs that act at the level of cytokine production, the proliferative response to cytokines, and/or the signaling between the two have demonstrated additive immunosuppressive effects [65]. This will not only effectively reduce the alloresponse but also potentially do so with lower doses of each.

Polyclonal anti-T cell preparations (ATG) and the murine anti-human CD3 monoclonal antibody (OKT3) recognize T-cell surface structures and kill by inducing Fc-receptor-mediated or complement-dependent cell lysis. Prior experience with ATG and OKT3 as induction agents in thoracic transplantation has demonstrated only a delay in the onset of acute rejection at the expense of a profound, uncontrolled immunosuppression that increases the risk for opportunistic infections and malignancy [66]. As a result, their current use is limited in most centers for the treatment of refractory acute rejection and as a calcineurin inhibitor sparing agent in those with perioperative renal dysfunction. However, the suggestion of clinical tolerance to abdominal transplants following ATG induction therapy deserves close attention in future protocols [67].

The “immunological synapse” between T cells and antigen-presenting cells includes the costimulatory molecules CD28, whose ligand is B7; CD154, which binds to CD40; CD2, the ligand for CD58 (LFA-3); and LFA-1, the ligand for ICAM-1. T cells that have been activated express CTLA-4, which may act as a competitive inhibitor of CD28, thereby blocking the generation of costimulatory signals [68]. Inhibition of costimulation using monoclonal antibodies against ICAM [69], CD40L [51], and CD28 [70] has generated donor-specific tolerance in preclinical transplantation models. Stimulation of alloresponsive T cells in the absence of costimulation seems to be a central feature in this form of tolerance as the addition of immunosuppressive medications such as FK506 or corticosteroids inhibits its development.

The development of a humanized monoclonal antibody (mAb) against the IL-2 receptor provided the clinical opportunity for a more selective targeting of activated T-cells. In a small (55 heart transplant recipients), randomized clinical trial, induction therapy using this mAb, dacluzimab, reduced the frequency and severity of acute rejection events over the study period with essentially no side effects and no increased risk of infections or malignancy [71]. Pilot studies using mAb against the cell adhesion molecules LFA-1 [72] or ICAM-1 [73] showed promise in preventing reperfusion injury but variable success against acute rejection. The combination of the two, which was synergistic against acute rejection in rodent models, has not been tried clinically. Also awaiting clinical trial is a strategy that inhibits T-cell costimulation such as the anti-CD154 mAb or CTLA-4 Ig, which has produced tolerance in the nonhuman primate model [51]. Given our understanding of this redundancy of costimulation, a combination of various mAb would likely be the best protocol to promote T-cell anergy. Unfortunately, no preclinical or clinical trials using a combination strategy have been performed in large part due to the financial conflicts between the different pharmaceutical companies that own the rights to these agents.

**Chronic Rejection**

Although chronic, persistent cell-mediated rejection causes progressive myocardial fibrosis and dysfunction, the term *chronic allograft vasculopathy* (AV) takes into consideration the role of multiple nonimmune factors in the etiology of this process. AV has a prevalence of at least 60% within 5 years of transplantation [74]. This obstructive process can progress to near-complete occlusion of the epicardial coronary arteries causing microinfarction and macroinfarction and is the leading cause of death after the first year following cardiac transplantation. The histologic findings differ from those seen in typical atherosclerosis, with a uniform pattern of near-luminal occlusion by neointimal proliferation, fewer early accumulations of extracellular lipid, and infiltrates of T cells that encircle the entire vessel [75]. The concentric nature of the lesion has led
to emergence of intravascular ultrasound (IVUS) as the optimal method for clinical detection of AV [76]. Endothelial cells generally remain intact but are known to be dysfunctional based on a paradoxical constrictive response to acetylcholine [77]. The determination of coronary flow reserve using an intracoronary doppler wire further complements IVUS in the evaluation of allograft vasculopathy. Because abnormalities in flow reserve most often reflect microvascular disease, this analysis is particularly important to detect early stage disease.

AV has been linked to multiple potential etiologies, but the most important clinical explanation has not emerged. The usual risk factors for atherosclerosis in the candidate prior to transplant such as hyperlipidemia, smoking, or diabetes are not predictors of AV. However, after transplantation, the development of metabolic markers of insulin resistance including hyperglycemia, hyperinsulinemia, and dyslipidemia predicted cardiac death [78]. Treatment of posttransplantation hyperlipidemia was shown in another randomized trial to reduce the incidence of AV [79]. Cytomegalovirus (CMV) infection might prompt the atherosclerotic process, but it has been clearly demonstrated that cytomegalic infection is not required for the process to occur [80]. Antidonor cellular and humoral immune responses are associated with clinical AV lesions, but these processes might equally well be a marker for high risk as opposed to a direct cause of chronic rejection. Events around the procurement process that result in early endothelial activation and dysfunction have demonstrated a convincing correlation with the development of AV [74]. Evidence that genetics plays a role in these events is supported by the finding that a specific TGF β genotype (i.e., proline at codon 10) was found to be associated not only with the development of AV [81] but also with the development of chronic nephrotoxicity from CSA [82]. Despite a significant improvement in the 1-year half-life of allografts in the modern CSA era of improved immunosuppression such as CSA [53], a finding that significantly limits clinical relevance. Clinical application of hypotheses generated from large animal models will be the most likely route of making an impact on this problem.

Our current limited pathophysiologic understanding of this relentless process is based largely on small animal models. By systematically isolating possible etiologic factors, these models have provided significant insight into the basic science of the vasculopathy process in cardiac allografts. However, out of logistical necessity, the surrogate pathologic lesion occurs much earlier than the typical changes of chronic rejection in clinical patients. Thus, the pathogenesis of the process being studied experimentally is almost certainly not the same as that occurring clinically. Indeed, many of the commonly used rodent models demonstrate suppression of AV lesion formation with standard immunosuppression such as CSA [53], a finding that significantly limits clinical relevance. Clinical application of hypotheses generated from large animal models will be the most likely route of making an impact on this problem.

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Fibroid disease is common and causes significant health problems in women of childbearing age. Over the past several years, uterine artery embolization (UAE) has emerged as a minimally invasive treatment for symptomatic uterine myomata. Embolotherapy is effective in relieving myoma-related symptoms in 80% to 90% of patients. It requires shorter hospitalizations than traditional surgical therapies for myoma disease and is associated with faster recovery and lower complication risks than surgery. Patient selection, the UAE procedure, and post-UAE management are reviewed.

Key words: uterus, fibroids, myoma, leiomyoma, embolization, uterine artery

Fibroids (myoma uteri, leiomyoma of the uterus) are the most common tumor of the female reproductive system and are the most common benign neoplasm in humans [1,2]. While their prevalence varies widely among various racial groups, fibroids occur in every population. In some populations, fibroids are present in as many as 80% of women in their reproductive years [1]. Fibroids are benign smooth muscle tumors that are similar to leiomyomata which arise anywhere else in the body [3].

Between 30% and 50% of women with fibroids will have symptoms [4,5]. The symptoms attributed to fibroids can be divided into 3 major groups. The most common symptom caused by fibroids is abnormal uterine bleeding. Fibroids typically cause menstrual bleeding to be heavier and/or prolonged (menorrhagia). Intermenstrual bleeding (metrorrhagia) is relatively rarely caused by fibroids, although some women can have their periods lengthened to the point where they describe bleeding that is virtually continuous throughout a typical month. In a typical fibroid population, 85% of patients complained of abnormally heavy bleeding, and this was the major fibroid-related symptom for 64% of patients [6].

Fibroids can also be associated with bulk or pressure-related symptoms, which actually includes a wide variety of complaints. The most common of these is daytime urinary frequency/urgency and nocturia. Other complaints such as pelvic or abdominal pressure, rectal pressure or constipation, dyspareunia, and low back pain can also be classified as bulk-related symptoms. In a typical fibroid population, 84% of patients complained of symptoms in this category, and this was the major fibroid-related symptom for 23% of patients [6]. Fibroids have also been implicated in subfertility in many women [7]. While most women with fibroids have normal fertility, fibroids can contribute to subfertility by a number of mechanisms. If the fibroids are positioned in a way that they occlude the fallopian tubes, they can prevent conception. More commonly, fibroids can distort the endometrial cavity. This can interfere with both implantation and progression of a pregnancy. As pregnancy progresses, the size and position of fibroids may limit fetal growth and/or interfere with delivery.

Symptomatic fibroids are a major health concern for women. An estimated 177,000 to 366,000 hysterectomies and approximately 35,000 myomectomies are performed each year in the United States for this problem [8,9]. In addition, many women receive medical treatment for fibroids, and many others suffer symptoms but never undergo treatment. Historically, the treatment of fibroids has been almost exclusively performed by obstetrician/gynecologists. Medical therapies are often tried as the first line of treatment [10,11]. Nonsteroidal anti-inflammatory medications are used to manage dysmenorrhea and may moderate menorrhagia in some women. Birth control preparations are often used to moderate abnormal bleeding. GnRH agonists such as leuprolrelin acetate (Lupron™) are also used to moderate both abnormal bleeding and bulk-related symptoms [12]. Surgical treatments for
fibroids have the goal of either removing the fibroids alone (myomectomy, myolysis), removing the entire uterus (hysterectomy), or moderating the abnormal bleeding without directly treating the fibroids (endometrial ablation) [13]. All surgical therapies except for hysterectomy carry a risk for recurrence of fibroids and their symptoms [14,15].

Embolization of the uterine arteries has been the standard of care for management of acute bleeding after childbirth or after gynecologic surgeries since the late 1970s [16,17]. Through the 1980s, apparently nobody in either the interventional radiology or gynecologic communities had thought of treating uterine fibroids by embolization. In the late 1980s, Jacques Ravina, a French gynecologist, became interested in the possible utility of embolization as a preemptive measure before gynecologic surgeries such as myomectomy. He was familiar with the utility of embolization for postoperative bleeding and decided to investigate preoperative embolization, hoping that this would decrease intraoperative bleeding as well as decrease the risk for postoperative hemorrhage. Preoperative embolization of the uterine arteries did indeed prove to be useful to decrease perioperative bleeding complications [18]. In some cases, there was a delay between the embolization and the planned surgery of at least a few days and in some cases a few weeks. Many of these patients experienced relief of their fibroid-related symptoms from the embolization alone and refused to go on with the planned surgery. Ravina and his colleagues published their initial experience in 1995 [19] and have since continued their study of uterine artery embolization (UAE, also referred to as “uterine fibroid embolization”) as a primary treatment for fibroids [20,21].

McLucas and Goodwin first reported UAE for fibroids in the United States from the UCLA Medical Center in 1996 [22]. Since then, there has been rapid spread of the procedure across the United States, Europe, and worldwide, with steadily increasing numbers of publications in both the radiologic and the gynecologic literature. At the time of writing, the authors estimate that the worldwide experience with UAE is approximately 35,000 to 50,000 cases, of which between one third and one half have been performed in the United States.

Patient Selection for UAE

Premenopausal or perimenopausal women with symptomatic fibroids are potential candidates for elective UAE. The diagnosis of fibroid disease has to be confirmed with imaging studies. While a high-quality ultrasound examination may be sufficient to establish the diagnosis, the overwhelming majority of physicians performing UAE (at least in the United States) routinely use MRI for diagnosis and follow-up. MRI has greater spatial and tissue sensitivity than ultrasound and allows for both more precise definition of the nature and extent of pelvic pathology and better assessment of the remainder of the pelvic contents than ultrasound [23]. MRI may also be helpful in predicting a patient’s response to uterine artery embolization; findings consistent with hemorrhagic degeneration may predict a poor response, while findings consistent with increased cellularity and/or vascularity may be predictive of a good response to UAE [24,25].

There are occasions when patients present to the hospital with severe or life-threatening hemorrhage from fibroid disease, or patients in the hospital for other reasons may develop such hemorrhage with the onset of their menses. Embolization of the uterine arteries, as mentioned previously, is also an option for women who have acute bleeding after childbirth or gynecologic surgery [16,17]. In these cases, UAE can also be offered as an alternative to urgent or emergent surgery, which would almost always be hysterectomy. The evaluation and management of these patients is obviously often more difficult than management of patients having elective procedures. In particular, in such an emergent or critical situation, MRI may not be available, and a high-quality ultrasound examination should be sufficient to establish the diagnosis of fibroid disease and allow for treatment.

While the imaging studies confirm the presence of fibroids and exclude other pathologies, the patient must also have symptoms that are clinically expected to result from the fibroids present. It should be noted that abnormal bleeding apparently does not require the presence of fibroids with a dominant submucosal component [26]. While bulk symptoms can occur with relatively modest increases in uterine volume, there is good correlation between the severity of bulk-related symptoms and overall uterine size [27].

Absolute contraindications to UAE include pregnancy, untreated infection (particularly in the pelvis), and life-threatening allergy to contrast. The presence of an undiagnosed adnexal mass is a contraindication to UAE until it has been adequately evaluated. Adenomyosis is a disease entity that can coexist with fibroid disease or be present alone.
The presentation of this process can mimic fibroid disease in many ways [28]. MRI is particularly valuable to identify adenomyosis when it is present with fibroid disease or to reveal that some patients with clinically diagnosed fibroid disease indeed have adenomyosis [23,29]. There has been significant debate in the interventional radiology community regarding embolotherapy as a treatment for adenomyosis [30,31]. This is an area of current research, and most interventional radiologists currently do not perform UAE in women whose only or dominant disease process is adenomyosis.

There are many women who have become pregnant after UAE [32-34]. In the authors’ experience, most of these women have had normal pregnancy outcomes with healthy children. However, there is not yet enough data available to predict fertility rates after UAE. The authors do not regard a desire to preserve fertility to be an absolute contraindication to UAE. However, there is insufficient data available to universally recommend UAE as the treatment of choice for patients whose only fibroid-related complaint is subfertility unless an experienced fertility surgeon feels that the patient is not a candidate for myomectomy.

Preprocedure Evaluation

Patient evaluation for UAE is a cooperative process between the interventional radiologist and the referring gynecologist. The first issue is to ensure that fibroids are indeed present and to exclude other significant pelvic pathology. As discussed above, this is done by a combination of the gynecologic examination and imaging studies. The gynecologist should exclude other processes such as endometriosis, pelvic inflammatory disease, and endometrial carcinoma. The authors specifically request an endometrial evaluation (by hysteroscopy, endometrial biopsy, or D&C) in all women with excessive bleeding older than age 40 and in all women with abnormal bleeding patterns regardless of age.

Patients must be seen in consultation by the interventional radiologist before the UAE. This gives the interventional radiologist an opportunity to establish a physician-patient relationship, to review the patient’s history, and to discuss fibroid disease, the alternatives for treatment, and the UAE procedure. An office-based consultation enables the interventional radiologist to review the gynecologic evaluation to date and arrange for any imaging, laboratory, or office-based testing that needs to be completed prior to UAE.

Procedure

The goal of the UAE procedure is to cause infarction of fibroids by significantly reducing flow in the uterine arteries. While differences in technique are seen among interventionalists performing UAE, most of the steps inherent to this procedure remain consistent. The arterial system is typically accessed via the right common femoral artery using standard angiographic technique. Once a sheath has been placed in the common femoral artery, a catheter is positioned into the left internal iliac artery under fluoroscopic guidance. An angiogram is then performed to localize the uterine artery prior to the selective catheterization of this vessel (Fig 1). The catheter is then advanced into the uterine artery, with contrast injected through the catheter to confirm the accurate positioning of the catheter. Once the catheter is positioned within the uterine artery, an embolization agent is injected through the catheter until flow is sufficiently reduced. At that time, the catheter is repositioned into the right uterine artery, and these steps are repeated until flow has been reduced in this vessel as well (Fig 2). Once both uterine arteries have been successfully embolized, a catheter is positioned in the abdominal aorta, and a final angiogram is performed to assess the adequacy of embolization and the presence or absence of significant collateral flow to the uterus and fibroids. The ovarian arteries represent the most common potential source of collateral

Fig 1. Mapping injection of the left internal iliac artery. The uterine artery (*) is enlarged and tortuous with many branches in the uterus.
flow to the uterus and fibroids (Fig 3). At this point, consideration can be given to embolizing collateral vessels if they are determined to provide a significant amount of blood flow to the uterus [35]. After the final angiogram, the sheath is removed from the femoral artery, and the arterial puncture site is compressed until hemostasis is achieved.

Recently, an increasing amount of attention has been paid to the agents used for embolization and the criteria used to determine when an adequate embolization has been performed. Much of the initial research supporting the use of uterine artery embolization as a treatment for uterine fibroids was performed using polyvinyl alcohol particles as the embolic agent. Since that time, a shift has occurred in the interventional radiology community toward the use of spherical embolization agents for this procedure. The most common spherical agents used during UAE include tris-acryl gelatin microspheres (Embospheres, Biosphere Medical, Rockland, MD) and polyvinyl alcohol microspheres (Contour SE Microspheres, Boston Scientific Corporation, Natick, MA). The primary appeal of spherical agents is that they are deformable and therefore easier to administer through angiographic catheters than irregular polyvinyl alcohol particles. In addition, traditional polyvinyl alcohol preparations tend to aggregate during intravascular administration, making their effective size larger than their actual size [36]. As a result, embolization with PVA particles would often lead to complete occlusion of the uterine artery due to the proximal aggregation of the agent. This tendency is not seen with spherical agents, allowing them to be directed by blood flow toward the more hypervascular regions of the uterus, which tends to be where the fibroids are located. As a result, embolization is now carried out until the hypervascular portions of the uterus are eliminated and flow in the main uterine artery is slowed [37]. This approach is being advocated as an attempt to minimize embolization of nonfibroid tissue within the uterus [38].

**Postprocedure Management**

Following the UAE procedure, most patients experience a constellation of signs and symptoms that constitute the postembolization syndrome. These include pelvic pain and cramping, nausea, vomiting, fever, leukocytosis, and malaise, most of which are consistently seen but often variable in severity. It has been shown that the degree of pain experienced after embolization does not correlate with the degree of symptomatic improvement [39,40]. Most patients experience little to no dis-
comfort during the procedure itself. Conscious sedation techniques are typically employed during UAE, with some centers utilizing spinal analgesia to improve patient comfort and reduce medication requirements [40].

It is the responsibility of the interventional radiologist to manage the symptoms experienced by these patients immediately after embolization. While medication regimens differ at different institutions, most use a combination of opioid analgesics and nonsteroidal anti-inflammatory drugs to address postembolization pain. These medications are often given in combination with antiemetics to address the nausea that is typically seen within the first 48 hours after embolization. Most centers utilize prophylactic antibiotics immediately before embolization is performed to reduce the risk of infection. At the present time, most centers performing UAE recommend an overnight admission for their patients to ensure that there is adequate control of these postembolization symptoms [40]. It has been demonstrated, however, that outpatient recovery is possible and safe for those patients experiencing symptomatic relief with oral medications prior to being discharged from the hospital [41,42]. In most patients, these symptoms gradually improve during the first 7 days after embolization, with most women resuming normal activities within 10 to 14 days after embolization [43].

Most UAE patients are otherwise well and are able to communicate their experience and need for adjustments in their medications for pain and other symptoms. However, occasionally patients may be treated who are not able to communicate as well about these issues. This is particularly true of women who may be treated on an urgent or emergent basis or have other medical conditions. In these situations, it is important for the patient care team to be aware of the potential for moderate to severe pain after UAE and provide effective pain management for those patients who may not be able to ask for it on their own. Similarly, patients with other medical problems or treated on an urgent or emergent basis may be at increased risk for postprocedure complications, including infection. In these situations, a more aggressive protocol of antibiotic prophylaxis may be warranted.

Outcomes

Several articles in peer-reviewed and non-peer-reviewed journals as well as abstracts from national specialty meetings have supported the conclusion that UAE improves the abnormal bleeding and bulk-related symptoms often associated with uterine fibroids. Several retrospective case series support the clinical success of UAE [37,41,44-48]. These studies found that 81% to 94% of patients reported improvement of menorrhagia and 64% to 96% of patients reported improvement of bulk-related symptoms (pelvic pain, abdominal distension, urinary frequency) after UAE.

Recently, the above findings have been confirmed by several additional case series. Ravina et al [49] published their experience with 286 patients and noted symptomatic improvement in 93.5% and a 60% reduction in size of the treated fibroids. Spies et al [50] reported on 200 consecutive patients with a mean follow-up of 21 months and found that menorrhagia improved in 90% and bulk-related symptoms improved in 91% at 1 year after treatment. A total of 10.5% of the patients in this series required an additional gynecologic intervention. McLucas et al [51] reported on 167 patients followed for a minimum of 6 months. Of these patients, 80% reported improvement or stabilization of symptoms. Uterine and fibroid volume reduction in this series was 52% and 37%, respectively, in the 46 patients followed for at least 12 months after embolization. Andersen et al [52] reported on 62 patients and found a 96% rate of improvement for abnormal bleeding and a 61% success rate for bulk-related symptoms. In their population, the mean fibroid volume was reduced 68% after 6-month follow-up. A large series by Walker and Pelage [32] described the results in 400 patients, finding that menstrual bleeding was improved in 84% of patients and menstrual pain was improved in 79% after a mean clinical follow up of 16.7 months.

With the recent introduction of these case series into the literature, the evidence supporting the clinical success of this procedure continues to mount. Even in a preliminary study comparing embolization with abdominal myomectomy, UAE was shown to result in better symptomatic improvement in association with fewer hospitalization days, less blood loss, quicker return to work, and fewer complications [53]. Despite the fact that markedly different methodologies have been used to assess results after embolization, the studies presented above are consistent in their conclusions that uterine artery embolization improves the symptoms associated with uterine fibroids and the health-related quality-of-life in this patient population [54].

The arterial occlusion induced within the uterine arteries by the administration of the embolic agents...
described above leads to interstitial edema followed by ischemic necrosis and hyaline degeneration within the fibroids [55,56]. Hyaline degeneration represents a permanent endpoint in the natural history of a uterine fibroid. The fact that embolization appears to initiate the cascade of events ultimately leading to hyaline degeneration bodes well for the long-term durability of embolization because pathologically, fibroids that have undergone hyaline degeneration are nonviable and do not cause the symptoms commonly associated with uterine fibroids. Ultimately, embolization can lead to the formation of dystrophic calcification, which is the end stage of hyaline degeneration [57].

Complications

The most common undesired outcome after uterine artery embolization is a failure of this procedure to address a patient’s presenting symptoms. Despite the excellent results presented above, there is still a 10% to 15% treatment failure rate after embolization. There have been several factors used to explain treatment failure after UAE. Technical failure, which occurs in 1% to 2% of cases, can be due to a failure to catheterize one or both uterine arteries; or to a small or absent uterine artery; small uterine arteries can be seen congenitally or due to a history of GnRH agonist therapy or myomectomy. The presence of a secondary source of blood supply to the fibroids is another potential cause for treatment failure. Ovarian arteries can potentially provide additional blood flow to fibroids, and if they supply fibroids or portions of fibroids not supplied by the uterine arteries, then a failure to embolize one or both of these vessels may lead to a UAE treatment failure [58]. Inadequate embolization caused by spasm or failure to reach an acceptable angiographic endpoint can lead to treatment failure as well. Finally, treatment failure has been attributed to adenomyosis [30], although as described earlier, favorable outcomes have also been described in this population as well [31].

The most common complications reported in association with the UAE procedure include infection, premature ovarian failure, and transcervical fibroid expulsion. Infections may involve the endometrium or myometrium or the infarcted fibroid itself. Fibroids located close to the endometrial cavity are at increased risk for infection after embolization due to the potential for bacterial seeding [59]. While most infections can be treated successfully with broad-spectrum antibiotics, gynecologic interventions such as dilatation and curettage, hysteroscopic myomectomy, and hysterectomy may be required to treat a complicated infection. One death has been attributed to sepsis resulting in diffuse intravascular coagulation [60].

Transcervical expulsion tends to occur most commonly in patients with submucosal fibroids or intramural fibroids with a submucosal component [61,62]. These patients often present with pelvic pain due to uterine contractions occurring to aid in the passage of the fibroid. These fibroids frequently pass on their own, although some require additional procedures such as a D&C or hysteroscopic resection to remove necrotic tissue from the endometrial cavity, due to the increased risk of secondary infection in these patients. Imaging is therefore recommended after expulsion to determine if tissue has been retained within the uterine cavity.

The occurrence of menopausal symptoms, including hot flashes, night sweats, mood swings, irritability, and vaginal dryness, have been demonstrated in association with UAE [63,64]. While these symptoms may be temporary, a 2% to 15% incidence of ovarian failure has been reported after UAE [64,65], with the incidence trending toward the upper end of this range in women older than 45 years of age. Potential causes of premature menopause after UAE include ovarian ischemia, interruption of the normal hormonal interaction between the uterus and ovaries, and radiation exposure to the ovaries [66]. The changes in endpoint described earlier may be helpful in reducing the incidence of both inadvertent ovarian embolization and premature menopause.

Less common complications associated with UAE include uterine ischemia and infarction (the incidence of which is limited due to the rich collaterals provided to the uterus from the ovarian arteries and other arteries arising from the internal iliac artery) [67], decreased sexual function (attributed to embolization of the cervicovaginal branch of the uterine artery that supplies the uterovaginal nerve plexus) [68], labial necrosis [69], and pulmonary embolism [70]; the source of the embolism may be from deep venous thrombosis (DVT) due to bed rest, uterine shrinkage relieving the compression of thrombosed pelvic veins, or thrombosis of the pelvic veins due to reduced arterial inflow [71]. Compression stockings may have a role in preventing DVT and pulmonary embolism in patients at increased risk for venous thrombosis, including patients who smoke and who are on oral contra-
Uterine Artery Embolization for Symptomatic Myoma

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Future Directions

As with all medical procedures, there remains a lot about UAE that needs to be defined [72]. Projects are ongoing that formally compare UAE to surgical therapies such as hysterectomy and myomectomy and to gather long-term outcomes data. To date, these have shown that UAE affords symptom relief similar to hysterectomy, with shorter hospitalizations, faster recovery, and lower rates of serious complications [53,73,74]. The Society of Interventional Radiology has created a prospective registry to evaluate UAE (http://www.fibroidregistry.org). The enrollment phase of the registry is complete, and the cohort of more than 3000 women is being followed. The FIBROID Registry is the largest prospective study done to date to evaluate any therapy for fibroid disease, and it is hoped that it can serve as a template for studies of other fibroid therapies. New embolization materials are being developed, and refinements to both the technique of embolization and patient management are evolving rapidly. Many questions about the place of UAE for younger women, particularly women who want to preserve fertility, remain and are a ripe field for further research.

Conclusion

UAE has been established as a valuable, minimally invasive therapy for the management of fibroid disease. Preliminary data from comparative studies have revealed that UAE is associated with a shorter hospitalization, lower complication risk, and faster recovery than the surgical therapy utilized for uterine fibroids. More important, UAE effectively reduces or eliminates the most common symptoms caused by uterine fibroids, with recent case series demonstrating the durable nature of this effect and significant improvement in quality of life. Given the increasing demand for minimally invasive therapy for uterine fibroids, it is clear that the safety and effectiveness of UAE will enable this procedure to continue gaining mainstream acceptance as a nonsurgical treatment option for this challenging patient population.
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Nerve Agents: A Comprehensive Review

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Nerve agents are perhaps the most feared of potential agents of chemical attack. The authors review the history, physical characteristics, pharmacology, clinical effects, and treatment of these agents.

Key words: nerve agent, organophosphate, poisoning, chemical weapons

The fear of chemical attack has never been greater both on battlefields abroad and in our cities at home. In the current climate of heightened alert, it behooves every physician to be well acquainted with the recognition and management of illness from chemical attack. Nerve agents, as some of the deadliest agents yet devised for use by man against man, are also felt to be among the most likely agents to be used as weapons. Indeed, these agents have already been employed on the battlefield and in terrorist attacks. We will review these agents, including their history, their physical and pharmacological characteristics, their clinical manifestations, and an approach to their management. We will also examine some of the long-term consequences of exposure to these agents, as well as some promising advances that might impact the future management of these exposures.

Historical and Contemporary Use

World War II

While the first organophosphate (OP) compounds were synthesized in 1854, the first nerve agents were not developed until 1936. A German chemist, Gerhard Schroeder, recognized that Tabun had potent effects on the nervous system. He had originally developed this compound as a pesticide for the chemical manufacturer IG Farbenindustrie. By the end of World War II, German scientists had developed several more of these agents, including Sarin and Soman, and had stockpiled large quantities that could be deployed as weapons. Fortunately, these agents were never used during the war, although the reasons for this are unclear. As Nazi resistance collapsed, Soviet forces captured the nerve agent production facilities in Duhernfort and Allied forces also recovered munitions containing these agents [1,2]. Both groups quickly recognized the military potential of these agents and set to work at developing and stockpiling their own supplies.

The Cold War

Both the United States and the Soviet Union developed large stockpiles of nerve agents in the 1950s [1]. In 1949, Dr. Ranajit Ghosh, a chemist working in England, was working on insecticide synthesis and discovered an extremely potent nerve agent that later came to be known as VX. This agent was refined and produced in quantity at Edgewood Arsenal in the United States [3]. The Russian military is believed to have produced similar, if not identical, agents including one known as VR55 [3].

Many countries signed the Geneva Convention in 1925 banning the use of chemical weapons. The United States had not yet ratified this agreement, but when President Nixon came into office, he pledged a “no first use” policy, reserving the right to retaliate in kind if nerve agents were used against Americans. Allegations have been made, however, that he broke this pledge in 1970, during the Vietnam War. Several members of an SOG (“Studies and Observation Group”) team have claimed that they were ordered to use Sarin in a “black operation” (known as Operation Tailwind) against a Laotian village reported to be harboring American defectors [4,5].
The Middle East

Several Middle-Eastern nations are believed to have developed and stockpiled nerve agents, notably Libya and Iraq. In 1984, it was confirmed that Iraq had used nerve agents (as well as other chemical weapons such as mustards) in its war against Iran. This was supported by an investigation by a U.N. fact-finding mission, as well as the examination of affected Iranis in Western Europe [1,2]. Iraq is believed to have continued stockpiling these agents despite a U.N. embargo on precursors of these weapons enacted after the First Gulf War in 1991, possibly having switched from Sarin to GF, which has more readily available precursors [6]. To date, however, evidence for this has been lacking.

Unintentional Military Exposures

There are periodic reports of unintentional exposures to nerve agents, generally involving mistakes in handling or testing [7,8]. Since the United States began decommissioning and destroying its nerve agent stockpiles in the 1990s [6], it is likely that these exposures will be uncommon in the future.

Chemical Terrorism

In 1994, almost 600 people in the Japanese city of Matsumoto became ill and 7 died after a local pond was contaminated with Sarin, in what is believed to be the first use of a nerve agent in a terrorist attack. Of note, 95 rescuers developed some symptoms of Sarin exposure, highlighting the need for greater awareness among prehospital personnel and care providers of the dangers posed by these agents [9,10].

The following year, Sarin was again used in Japan, this time in a terrorist attack on the Tokyo subway system by a religious cult [11,12]. When those reportedly responsible were arrested, they confessed to having used the agent VX in 3 attempted murders earlier that year. The veracity of this confession was supported by the clinical report of physicians who cared for one of these patients [13].

Chemical Weapons Ban

In 1997, the Chemical Weapons Convention went into effect. The treaty was signed by 148 nations, 123 of which have ratified it, including the United States. It is implemented by the Organization for the Prohibition of Chemical Weapons (OPCW) in The Hague and goes much further than the Geneva Convention, banning not only the use of these weapons, but also their development, production, acquisition, stockpiling, and retention [14].

 Agents and Their Physicochemical Characteristics

Nomenclature

Agents originally developed in Germany have been designated “G series” agents. These include GA (Tabun), GB (Sarin), GD (Soman), and GF, which has no common name. These agents are most hazardous when delivered through inhalation of vapors or aerosols. They may also be absorbed through exposure to the eyes or abraded skin, and they are toxic when ingested. They are less of a percutaneous threat than another group of agents known as “V series” agents (the “V” stands for venomous). These include VE, VG, VM, and the best known, VX. A newer group of agents known as “GV series” agents combine properties of the other 2 classes, posing a threat both through inhalation and through percutaneous absorption. In general, V series agents have greater persistency (a concept that will be discussed shortly) and potency than G series agents [15].

Binary Agents

A newer technology involves the separation of 2 nontoxic nerve agent precursors. This prevents unintentional toxicity to those handling or transporting these weapons. The components are combined in a projectile as the weapon is delivered, forming the fully active agent [16]. In 1996, the United States revealed the composition and location of its stockpiles in compliance with the Chemical Weapons Convention, including 680 tons of binary agent components [17]. Russia is also believed to have developed a binary agent known as “Novichuk”.

Physical Properties

Volatility and vapor pressure. The physical characteristics of the most common nerve agents are sum-
marized in Table 1. Of note, the volatility of these agents is low (the most volatile, Sarin, has a vapor pressure similar to water). Thus, the term “nerve gas” is a misnomer, as military nerve agents are predominantly liquids at room temperature. These agents pose an inhalation threat primarily when dispersed as an aerosol. This was demonstrated in the Sarin attack on the Tokyo subway. A plastic container containing the agent was placed under a seat, punctured, and subsequently allowed to evaporate. Because this method of dispersal relies on evaporation, there were very few fatalities (11 out of more than 5000 people requiring a medical evaluation) [11].

**Persistency**. The persistency of a nerve agent describes its ability to remain active in the environment after deployment [3,6]. Factors contributing to persistency include volatility, density, and stability with light and water exposure. Less volatile agents take longer to evaporate, while denser agents tend to remain in low-lying areas and are less likely to be dispersed by wind. In general, V series agents tend to have greater persistency than G series agents. Some G series agents, particularly Soman, may be mixed with viscous liquids to increase their persistency [15].

**Toxicodynamics**

**Acetylcholinesterase inhibition**. The primary mechanism of toxicity of all OPs is inhibition of acetylcholinesterase (AChE). AChE exists in the body to hydrolyze acetylcholine (ACh), reducing its concentration in the synapse or neuromuscular junction, and thus terminating cholinergic transmission at these sites. Two active sites, known as the **anionic site** and the **esteratic site**, are required for the function of this enzyme. The anionic site positions ACh in the active site through an electrostatic interaction with the quaternary nitrogen in choline. The hydroxyl group forms a serine residue in the esteratic site then covalently binds to the ester carbonyl group. This forms an unstable tetrahedral intermediate, which rapidly decomposes, liberating choline and leaving the enzyme covalently bound to acetate. A water molecule spontaneously hydrolyzes this bond, regenerating the free enzyme. OPs such as nerve agents interact with the serine hydroxyl residue in the esteratic site to block this process, as illustrated in Figure 1 [18-20]. Unlike acetate from acetylcholine, there is no spontaneous hydrolysis of OP intermediates. This causes accumulation of ACh in the synapse and neuromuscular junction, and the resultant clinical effects of these agents.

**Aging**. Over time, a functional group leaves the nerve agent, strengthening the bond and making it permanent. When this occurs, the enzyme-nerve agent complex is said to have **aged**. It appears that the glutamate-199 residue of the AChE plays a key role in the aging process; an in vitro study showed that a mutation replacing this residue with glutamine prevented aging after Soman poisoning [21]. Once aging occurs, the enzyme is permanently inactivated and no therapy can restore activity. Function does not return until a new enzyme is synthesized. The rapidity of this aging process varies greatly among different nerve agents (this

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will be discussed in greater detail under Toxicokinetics).

Carbamates, another group of compounds with anticholinesterase activity, bind reversibly to the active site and do not age [6,18,19]. This has important implications for prophylaxis.

Anatomic distribution of cholinergic neurons. The 2 basic types of ACh receptors are nicotinic and muscarinic. These were originally defined by their affinities for nicotine and muscarine, respectively. These receptor types are present in different anatomic locations, have different mechanisms of signal transduction, and also have different functions. Nicotinic receptors are present in the central nervous system (CNS), both sympathetic and parasympathetic autonomic ganglia, and at the neuromuscular junction. Binding of ACh to these receptors causes opening of sodium channels, leading to depolarization of the target tissue. Muscarinic receptors exert their effects through G-proteins and are found in the CNS, at postganglionic parasympathetic nerve endings, and in postganglionic sympathetic receptors for sweat glands. Activation of the G protein leads to different effects in the target cell depending on the target tissue and the subtype of muscarinic receptor.

Noncholinergic Effects

Nerve agents appear to have some effects that are mediated through noncholinergic mechanisms. Large doses of some anticholinesterases such as eserine (physostigmine) appear to block ACh and carbachol responses in isolated ganglion cells without depolarization or desensitization [26]. This suggests effects independent of elevated ACh concentration at the synapse. The contribution of these effects to clinical nerve agent intoxication is unknown. ACh has extremely complex effects in the CNS, including secondary effects on norepinephrine, dopamine, and serotonin. These effects have been implicated in the convulsant activity of OP anticholinesterases (in a rat model) [27,28].
Impairment of GABA receptor function has also been demonstrated in a rat model of Soman intoxication [29], which, if true in humans, is also likely to have a significant contribution to the convulsant effect of these agents. In addition, MK-801, an NMDA antagonist, suppresses seizures from convulsant doses of Soman in guinea pigs. This supports the hypothesis that nerve agents also affect NMDA glutamate receptors [30].

Finally, neuropathology of rats exposed to sublethal doses of Soman revealed diffuse axon and nerve terminal degradation sparing the cerebellum and the ascending pathways of dorsal root, intraspinal, and cranial nerve origin [31]. This pattern is distinct from patterns seen in fetal hypoxia (in an experimental model of a monkey asphyxiated at birth) or in delayed neurotoxicity from TOCP and is independent of convulsion, suggesting a direct neurotoxic mechanism [31].

**Toxicokinetics**

**Latency**

The latency of a nerve agent describes the delay between exposure and onset of clinical effects. This depends on the absorption and distribution characteristics of the agent, and the route and dose of exposure. Latency can range from 30 to 120 seconds for inhalation exposure of an aerosol or vapor [15]. It may be as little as 1 minute or as long as 18 hours after percutaneous exposure to a liquid agent, depending on the dose and the agent [15].

**Aging**

The aging time varies greatly between the different nerve agents, ranging from an aging half-time (time for half of involved cholinesterases to age) of 2 minutes for Soman to 5 hours for Sarin, to more than 40 hours for VX and Tabun [1,32,33]. This has grave implications for the treatment of Soman exposure, as will be discussed later.

**Effects of Ambient Temperature and Level of Physical Activity**

The effect of temperature on the absorption of VX was tested on U.S. Army recruits at the Edgewood Arsenal in Maryland. Higher ambient temperature was associated with greater penetration of VX into the skin, as measured by inhibition of cholinesterase activity [34]. Another group of military recruits was exposed to Sarin vapor and divided into 3 groups: mouth breathing at rest, mouth breathing with exercise, and nasal breathing at rest. While the exercising men retained a lower percentage of the vapor inhaled, their increased minute ventilation led to larger overall exposures, as reflected by inhibition of RBC-ChE. The route of breathing had no effect [35].

**Toxicity**

The degree of exposure necessary to produce toxicity from common nerve agents is summarized in Table 2.

**Clinical Manifestations**

The clinical manifestations of nerve agents can largely be predicted from their mechanisms of action, including muscarinic andnicotinic symptoms. There are also central effects that are much more complex and not fully understood.
Muscarinic Manifestations

The “SLUDGE” syndrome is familiar to many as a medical school mnemonic for muscarinic effects. These include salivation, lacrimation, urination, defecation, diaphoresis, and gastric emesis. While these features are helpful in recognition of the muscarinic toxidrome, they do not include its life-threatening effects. The “killer B’s” of bronchorrhea, bronchoconstriction, and bradycardia are the muscarinic manifestations that require immediate intervention. Bradycardia may not be seen because hypoxia from bronchoconstriction and bronchorrhea often causes a sympathetic response resulting in tachycardia and hypertension. Muscarinic effects may also be masked by cholinergic action at the nicotinic receptors in the sympathetic ganglia, causing tachycardia and mydriasis and making diagnosis more difficult.

The attack on a Tokyo subway in 1995 provided data on the incidence of these clinical manifestations after exposure to Sarin. Of 640 patients who presented to 1 hospital, 83% had only mild symptoms (defined as the presence of eye findings only, including miosis, eye pain, dim vision, or decreased visual acuity). Moderate poisoning was defined as the presence of systemic signs and symptoms without the need for intubation, while severe poisoning was defined as requiring intubation and mechanical ventilation. Of the 111 (17%) patients with moderate or severe poisoning, miosis was the most common sign, seen in 99% of patients. Rhinorrhea was seen in 25%, lacrimation in 9%, nausea in 60%, vomiting in 37%, and diarrhea in 5% of patients. Dyspnea, the most common concerning symptom, was reported in 63% of moderately or severely poisoned patients. Bradycardia was only reported in 3.6% of these patients [11]. It should again be noted that most of these patients had minimal exposures and that a much higher prevalence of severe symptoms would be expected if the agent were delivered more efficiently.

Nicotinic Manifestations

Nicotinic manifestations are what give “nerve” agents their name. Elevated ACh at the motor end plate causes fasciculations, weakness, and ultimately, flaccid paralysis. Paralysis of the diaphragm and muscles of the chest wall is the potentially lethal result. Experience from the Tokyo subway attack has confirmed the predominance of nicotinic findings after nerve agent exposure when compared to OP insecticides. In the case series above, 23% of moderately or severely poisoned patients had fasciculations, while 37% had muscle weakness [11]. Another report of 58 patients in that attack found that among severely poisoned patients requiring hospital admission (who had symptoms such as fasciculations and flaccid paralysis), none had bradycardia or excess secretions [12]. Tachycardia, however, was seen commonly [12]. Another severely poisoned patient was reported to have a heart rate of 155/min [36].

Central Manifestations

Some of the manifestations of nerve agent poisoning are not easily explainable by peripheral cholinergic mechanisms and do not respond to treatment targeting these mechanisms.

Seizures. Seizures may be seen in patients with severe nerve agent poisoning. In the Tokyo subway attack, 3% of moderate to severely poisoned patients had convulsions [11]. As discussed earlier, the mechanism of convulsant activity is unclear but may involve effects on GABAergic, glutamatergic, noradrenergic, dopaminergic, and serotonergic systems [27-30]. In military research, monkeys exposed to Soman will have severe and prolonged convulsions even if pretreated with pyridostigmine and treated with atropine and pralidoxime (2-PAM) [37] immediately after exposure (the rationale for this therapy will be discussed later). Hypoxia may also contribute to seizures in severely poisoned patients who are untreated. Another model suggests that seizures may result from overstimulation of central muscarinic acetylcholine receptors. This is supported by recent work showing that antimuscarinic agents with greater CNS effects, such as diphenhydramine, provide greater protection from convulsant activity from an OP pesticide than more peripherally acting agents such as atropine [38].

Respiratory depression. Nerve agent poisoning appears to cause respiratory depression independent of its effects on the respiratory muscles and secretions. A study of Sarin poisoning in a rabbit model demonstrated decreased phrenic nerve activity (in addition to neuromuscular blockade and increased airway resistance) in association with respiratory failure [39]. A later study using a cat model of intravenous Sarin, Soman, Tabun, and VX poisoning suggested that it resulted from suppression of medullary respiratory-related neurons. In this study, it was found that when the medullary neurons were suppressed to the point of respirato-
ry arrest, electrical stimulation of the phrenic nerve still caused contraction of the diaphragm [40]. Administration of Sarin by injection directly into the medulla of rabbits also produced respiratory arrest, further supporting the idea of a central mechanism [41]. A more recent study demonstrated that anticholinergic agents with the ability to cross the blood-brain barrier prevent respiratory arrest from dichlorvos (an OP insecticide) poisoning in rats, while agents with only peripheral effects do not [42]. While the relevance of studies on OP pesticides to discussions about nerve agents is debatable, this finding is consistent with other data supporting a central cholinergic mechanism for respiratory depression.

Neuropsychiatric effects. Victims of nerve agent exposure may suffer a variety of neuropsychiatric effects. One study in which military recruits were exposed percutaneously to EA-1701 (a classified experimental nerve agent similar to Sarin) described increasing depression and “jittery”-ness with increasing RBC-AChE inhibition. Increasing anxiety, psychomotor depression, intellectual impairment, and unusual dreams were also reported [43]. Severe persistent amnesia was reported in 1 victim of the Tokyo subway attack, although it may be difficult to separate the effects of hypoxic brain injury from direct nerve agent toxicity [44]. It may also be difficult to separate direct neuropsychiatric effects from posttraumatic stress disorder after exposure to nerve agents on the battlefield or in a terrorist attack.

Diagnosis

Physical Examination

Recognition of the cholinergic toxidrome and the cluster of symptoms described above is the most important means of diagnosis after a nerve agent exposure. When these symptoms are recognized, physicians must promptly move on to treatment of severely ill patients, rather than waiting for ancillary testing.

POP Scale. Physicians in developing countries have more experience than most Americans in recognizing OP poisoning, likely due to more agrarian societies and the prevalence of these agents as insecticides. A Sri Lankan group has used this experience to develop and validate a scoring system to assess the severity of OP poisoning [45]. The Peradeniya Organophosphorous Poisoning (POP) Scale scores several objective parameters (miosis, fasciculation, respiratory rate, heart rate, and level of consciousness) from 0 to 2, with 1 additional point if convulsions are present (Table 3). These scores correlate with death, need for intubation, and atropine dose required for therapy. No patients in the study with scores of 3 or less died [45]. The scale corroborates the idea that victims with ocular findings alone are unlikely to be severely poisoned, as was observed after the attack on the Tokyo subway [11]. Obviously, a scoring system such as this cannot substitute for good clinical judgment. Furthermore, the system, developed for patients with OP pesticide poisoning, has not been validated for nerve agent OP exposure. However, it may help in estimations of prognosis, and standardization of documentation may help in gathering epidemiological data after a mass exposure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Miosis</td>
<td>Pupil size &gt; 2mm</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pupil size = 2mm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pupils pinpoint</td>
<td>2</td>
</tr>
<tr>
<td>Fasciculation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present, not generalized or continuous</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Generalized and continuous</td>
<td>2</td>
</tr>
<tr>
<td>Respiration</td>
<td>Respiratory rate (RR) = 20 min⁻¹</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>RR &gt; 20 min⁻¹</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>RR &gt; 20 min⁻¹ with central cyanosis</td>
<td>2</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Heart rate (HR) &gt; 60 min⁻¹</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>HR 41-60 min⁻¹</td>
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<td></td>
<td>HR = 40 min⁻¹</td>
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<tr>
<td>Level of</td>
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</tr>
<tr>
<td>Consciousness</td>
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</tr>
<tr>
<td></td>
<td>Impaired, no response to verbal commands</td>
<td>2</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

Laboratory Findings

Admission screening tests. There are no reliable findings on typical laboratory screening examina-
tions (complete blood count, serum electrolytes, liver enzymes, urinalysis) after exposure to nerve agents. However, physicians treating patients after the Matsumoto attack did note some common laboratory abnormalities. Of 311 people treated, 33 (11%) had elevated serum creatine kinase (CK) (the most common abnormal finding), 25 (8%) had leukocytosis, 17 (5%) had hypokalemia, and 10 (3%) had hypolipidemia. In severely poisoned patients (not defined in the report), hyperglycemia, ketonuria, and decreased serum triglycerides were seen [10]. A report of laboratory findings in 166 patients after the Tokyo attack contradicts these findings; 15% of patients had elevated CK, but none of the other findings described above were seen [46]. Obviously, none of these findings is likely to be very helpful in caring for individual patients.

Pancreatitis has been reported after OP exposure [47], but review of larger series has revealed that more commonly, hyperamylasemia may be seen without lipase elevation or clinical evidence of pancreatitis [48]. Amylase elevation may be seen in as many as 62% of patients and tends to resolve quickly [49]. This finding is neither sensitive nor specific enough to be clinically useful.

QTc interval prolongation on ECG has also been reported but is a rare finding [50].

**Cholinesterase levels.** Measurement of AChE activity has the potential to provide an objective marker of the degree of poisoning, or to confirm that an exposure has occurred. The problem is determining which ChE to measure. Ideally, neuronal AChE would provide the most accurate information, but neuronal biopsy is unjustifiably invasive in these patients. It would also be slow and difficult to obtain in a critically ill patient. Furthermore, there are wide variations in baseline levels of enzyme activity in the general population, as well as from day to day in an individual, making interpretation difficult. Blood cholinesterases are reasonable to measure, although problems remain in determining a baseline in any individual patient. RBC-AChE, as a true AChE, is thought to correlate better with neuronal AChE poisoning than BuChE [18,51], although there is no evidence that this is true of nerve agent exposure. As always, therapy should be guided by the clinical picture.

**Cholinesterase reactivation.** Since baseline levels of ChE activity are rarely known, another approach is to measure ChE activity, add an agent to restore activity to inhibited enzyme in vitro, and then measure activity again. A study in rats poisoned with Sarin, Soman, VX, and GV suggested that reactivation of blood AChE activity after the addition of trimedoxime may be a better marker of clinical toxicity than measurement of blood AChE activity alone [52]. Another technique was studied on serum samples from victims of the Tokyo subway attack. Fluoride added to the samples covalently binds to the OP, displacing it from the ChE, regenerating ChE activity and allowing the nerve agent itself to be measured as well [53]. Although this method appeared to work well in confirming exposure to Sarin in humans, it is unclear whether it will be equally effective in detecting exposure to other nerve agents.

**Nerve agents and their metabolites.** Sometimes detection of the nerve agents themselves, or their metabolites, may be possible. Gas chromatography with mass spectrometry (GC-MS) was successfully used to identify Sarin metabolites in blood samples from 4 patients who were killed in the Tokyo subway attack [54] and to identify VX metabolites in a victim of a 1994 VX incident [55]. This method was also used to identify Sarin in a pond at the Matsumoto poisoning site [56]. Unfortunately, these methods are more useful for forensic purposes than for clinical use.

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### Treatment

#### Decontamination

Removal of the victim’s clothes and accessories is the most important part of decontamination. This should be followed by irrigation of the entire body with copious quantities of water (showering). Military sources recommend irrigation with a dilute bleach solution with soap and water [6,57]. This may be preferable, but only if the solution is premixed and ready for use. Decontamination should never be delayed by a search for the ideal cleaning solution.

Specialized decontamination materials have been studied in animal models but were not compared to copious amounts of water. When decontamination with alcohohate and clay were compared in rats and pigs pretreated with an oxime ointment, there was no difference in outcome [58].

It should be noted that there are unlikely to be significant amounts of retained nerve agent on the patient after an inhalational exposure. Ambulatory patients who arrive at the hospital are also unlike-
ly to be significantly contaminated (or ill). While decontamination should still be performed and there may be some benefit in very ill patients exposed to liquid agents, the alleviation of health care providers’ fears in treating these patients may be an equally important effect of the decontamination process. It is important that health care providers involved in the decontamination process have appropriate personal protective equipment (PPE). This will be discussed below in the PPE section.

ABCs

Nerve agents compromise a victim’s airway and breathing through multiple mechanisms, as already discussed. Intubation and ventilation of patients with apnea or respiratory compromise should be performed prior to antidotal therapy. A bag-valve mask may be used until the airway is established. Mouth-to-mouth rescue breathing is potentially hazardous to the provider and should not be performed [59]. Once the airway is established, bronchoconstriction and copious secretions may cause difficulty in ventilating the patient, and high pressures may be needed [8]. Antidotal therapy should be instituted at this point to counter these effects.

Atropine

The role of atropine, a pure antimuscarinic agent, was recognized soon after the development of these agents [60]. Atropine works through competitive antagonism of ACh at the muscarinic receptor. Any substance with antimuscarinic properties is an effective antidote, and substances with greater CNS penetration, such as scopolamine or 3-quinuclidinyl benzilate (BZ), actually offer theoretical advantages for the reversal of CNS effects. However, the inherent toxicity of these “antidotes” when nerve agents are not present led to their rejection in favor of atropine [6]. A recent study supported the importance of atropine’s CNS activity, showing greater survival benefit after dichlorvos (an OP insecticide) exposure in rodents from diphenhydramine and atropine, drugs with potent CNS effects, than from glycopyrrolate, an agent that does not cross the blood-brain barrier [42]. Patients with anything more than ocular findings should get atropine therapy. Although it has not been well studied, nebulized ipratropium bromide is a reasonable adjunct for treatment of bronchoconstriction and bronchorrhea, as nebulized atropine has been reported as effective after a case of malathion poisoning [61].

Route. If intravenous (IV) access is available, then that is the preferred route of administration. Atropine is also available as an autoinjector as part of the military Mark I kit, and this is the preferred method of administration in the field. These autoinjectors can inject through clothing and should be administered to the lateral thigh. The pharmacokinetics of atropine delivered intramuscularly (IM) by autoinjector are superior to IM administration with a conventional syringe and needle and are comparable to IV administration in terms of speed and effectiveness [62-64].

Atropine eyedrops have also been used effectively in the treatment of patients with ocular findings alone, although many subsequently complained of photophobia and blurry vision [12]. There is currently insufficient evidence for a recommendation for or against this therapy.

Dosing. The initial adult dose of atropine recommended by the U.S. military is 2 mg (the amount contained in 1 autoinjector). In a severely poisoned patient (one unable to treat himself or herself with an autoinjector), 6 mg may be given initially. Further dosing should be guided by the response to therapy. If required, atropine may be administered every 5-10 minutes. The endpoint for titration should be the drying of secretions, not normalization of pupils or heart rate [6,65]. One study supported the measurement of peripheral vascular resistance as an endpoint for adequate atropinization [66]. However, this study was based on OP insecticide poisoning, in which muscarinic effects are much more prominent, and caution is advised in applying these results to nerve agents. In general, victims of nerve agent poisoning require less atropine than those poisoned by OP insecticides [1,6]. In one series from Tokyo, only 21 of 107 patients who required atropine needed more than 2 mg, and none needed more than 9 mg, although very few of these patients had significant exposure because of the means of dispersal [11].

Pralidoxime and Other “Oximes”

Pralidoxime (2-PAM) is one of several oximes studied as “reversal agents” for the treatment of OP poisoning, including obidoxime and the bispyridium Hagedorn oximes (H oximes) such as HI-6 and
Nerve Agents

Hlö-7. The mechanism of action of these agents is illustrated in Figure 2. Oximes are positioned in the active site of AChE through interaction of the positively charged quaternary nitrogen with the anionic site. The phosphate moiety of the nerve agent then undergoes a nucleophilic attack by the oxime, displacing the nerve agent from the esteratic site of the enzyme [18,19,67]. Once a nerve agent-AChE complex has aged, it should not be susceptible to reactivation by an oxime. There are some data in animal models, however, that suggest that the H oximes may be able to reactivate AChE even after aging and that 2-PAM may also have this effect in extremely high doses [68,69].

There is far more experience worldwide in using these agents for the treatment of poisoning from OP insecticides than from nerve agents. However, 2-PAM has been tested in military recruits and found to be effective for the treatment of VX and Sarin poisoning [33]. Animal studies suggest that pralidoxime may be less effective than obidoxime, Hi-6, and Hlö-7 in Tabun, Soman, and GF poisoning [69,70]. These other oximes are less effective for OP insecticides, and their safety profile is not as well defined as that of 2-PAM [67].

There are much conflicting data on the efficacy of different oximes in the treatment of different nerve agents in various animal models. While it appears that Hi-6 and Hlö-7 may be more efficacious in treating a broader range of nerve agents, 2-PAM (the only oxime approved by the FDA for use in the U.S.) has a long record of safe use and is likely to be effective in most nerve agent exposures if dosed promptly and in appropriate doses. Furthermore, it is impossible to determine at the bedside which nerve agent is responsible for a given exposure. There would therefore be little basis for choosing one oxime over another in an unknown exposure.

**Route.** If IV access is available, this is the preferred route of administration. As with atropine, IM administration with an autoinjector is the route of choice in the field. The pharmacokinetics of 2-PAM by this route are similar to those seen in IV administration [62,64].

In one study, oral administration of pralidoxime was effective as prophylaxis against Sarin in rats [71]. While these rat data might suggest that oral treatment may be an effective alternative if parenteral treatment is not possible, it should be considered that rodents do not vomit and that emesis is part of the cholinergic toxidrome in humans, which would preclude oral administration after nerve agent exposure.

**Dosing.** There is currently great controversy over the appropriate dosing of pralidoxime. Most sources recommend an initial adult dose of 1 to 2 grams of 2-PAM (three 600 mg autoinjectors in the field). This should be diluted in 100 mL of 0.9% NaCl and infused over no less than 20-30 minutes [1,6,67]. This dose results in a serum concentration of 2-PAM of at least 4 mg/L, a level that has been shown to provide protection from a Sarin analogue in a cat model [72]. Some have argued that this has never been replicated with other nerve agents, other oximes, or other species [73]. Others have made the point that this does not take into account the dose and route of exposure of the nerve agent [74]. There is anecdotal experience that nerve agent–intoxicated patients may require much higher doses for effective treatment [74]. Further controversy arises from whether to continue treatment

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**Fig 2.** Mechanism of action of 2-PAM. 2-PAM is positioned by interaction between its quaternary nitrogen and the anionic site of AChE. It then effects a nucleophilic attack on the phosphate, displacing it from the esteratic site [67].

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Serine

Anionic site

Esteratic site

Reactivated AChE

Fig 2. Mechanism of action of 2-PAM. 2-PAM is positioned by interaction between its quaternary nitrogen and the anionic site of AChE. It then effects a nucleophilic attack on the phosphate, displacing it from the esteratic site [67].
with intermittent bolus dosing or continuous infusion. A pharmacokinetic model based on the half-life of 2-PAM in human patients showed that serum levels fall below 4 mg/L within 90-120 minutes after intermittent bolus dosing, while levels remain above 13 mg/L with a continuous infusion of 500 mg/h [75]. This has since been confirmed in a study on human volunteers, which demonstrated almost exactly the predicted kinetics [76]. Continuous infusion therapy was reported to be effective in a case series of OP insecticide poisonings in India [77], but there has been no head-to-head randomized controlled comparison of intermittent bolus and continuous infusion therapy for nerve agent intoxication.

Based on our interpretation of the available data, we recommend an initial dose of 1-2 gm followed by a continuous infusion at 500 mg/h. Some patients may require higher doses for the reasons discussed above. The duration of therapy is controversial, and there are not good data supporting any one approach. However, a reasonable approach is to continue oxime therapy until at least 24 hours after symptoms resolve.

Benzodiazepines

For reasons discussed above, seizures due to OP intoxication do not respond well to atropine and oxime therapy alone. Benzodiazepines are recommended as adjunctive treatment in these patients. There is some evidence supporting this approach. In one study, addition of diazepam to atropine and oximes greatly improved survival time in Soman-poisoned rats [78]. In another study, diazepam improved performance scores and survival after Soman exposure in rhesus monkeys [79]. A review of numerous animal studies suggested that differences in effectiveness of different oximes disappeared with the addition of diazepam (and pretreatment with pyridostigmine, which will be discussed below) to atropine and oxime therapy [80]. Based on this type of evidence, soldiers in the U.S. military are equipped with autoinjectors containing diazepam, to be used in addition to Mark I kits in cases of severe nerve agent poisoning. Unfortunately, diazepam is poorly absorbed when administered IM, and the IV route is therefore preferred in the hospital setting. Standard dosing should be used.

An alternate agent under investigation for treatment in the field is midazolam. A recent study found intranasal midazolam effective at treating seizures due to OP insecticide poisoning in a rat model as long as 30 minutes after exposure [81].

Special Populations

Children

There are minimal data about nerve agent intoxication in children. Recommendations for therapy are based on scaling down an adult dose by weight. Generally 0.05 mg/kg of atropine (to be repeated every 2-5 minutes as needed) and 20-40 mg/kg of pralidoxime (repeated every 3-8 hours or followed by an infusion of 10-20 mg/kg/h) are suggested doses [67,82]. In June 2003, the FDA approved 2 pediatric atropine autoinjectors for treatment in the field. The 0.5 mg injector is recommended for children weighing between 15 and 40 pounds (7-18 kg) and would also be preferable to withholding therapy after a significant exposure in children weighing less than 15 pounds. The 1 mg injector should be used for those weighing 40-90 pounds (18-41 kg). Adult injectors should be used for those weighing more than 90 pounds (41 kg). If these injectors are unavailable, an adult autoinjector may be discharged into a sterile vial and subsequently drawn up in the appropriate dose by weight. Another possibility is to administer one adult autoinjector each of atropine and 2-PAM. This amounts to an appropriate initial dose of 2-PAM if the child is 15 kg or more. While the atropine dose thus administered is somewhat high for infants and small children, it is probably preferable to withholding treatment from a child who is clinically ill from nerve agent poisoning.

The Elderly

In general, the elderly should be treated as other adults after nerve agent exposure. One caution, however, is that the elderly are known to be particularly sensitive to the central effects of anticholinergic toxicity [83]. Care should therefore be taken to avoid overtreatment with atropine in this group.

Pregnant Women

There are limited data regarding nerve agent exposure in pregnancy. After the Tokyo subway attack, 5 pregnant women were mildly poisoned and were admitted for observation. All had normal babies without complications, the first of which was born 3 weeks after the attack. 2-PAM was withheld in the
treatment of these patients [11,84]. For severely poisoned pregnant patients, however, we would not recommend withholding oxime therapy.

Complications and Persistent Sequelae

Organophosphate-Induced Delayed Neurotoxicity

From 1930 to 1931, during Prohibition, an epidemic of neuropathic disease affecting more than 50,000 people swept through the southern and midwestern United States. The unfortunate victims developed upper and lower extremity weakness and an abnormal gait. It was later determined that this neuropathy was caused by “Ginger Jake,” a ginger extract purportedly sold as a medical supplement, but widely used because of its ethanol content. The product was found to be contaminated with triorthocresylphosphate (TOCP), an organophosphorous compound [85]. The syndrome, known as OP-induced delayed neuropathy (OPIDN), has since been demonstrated to occur in animal models with many other OP compounds. It typically presents 9-14 days after an OP exposure. The pathogenesis of this polyneuropathy is not fully understood but is believed to involve NTE [86-89]. OPIDN has not yet occurred in humans after nerve agent exposure, although Sarin produces it in a hen model. Extrapolation based on their potency of action on NTE in the same model seems to indicate that Soman and Tabun might cause OPIDN in doses of 100-150 times the LD50 [88]. It seems unlikely that anyone would survive such an exposure, so the clinical relevance of this finding is questionable.

Intermediate Syndrome

A neurotoxic syndrome that presents 24-96 hours after exposure to OP insecticides is also described. This syndrome, known as intermediate syndrome, typically involves proximal extremity and neck flexor weakness and appears to be distinct from OPIDN [90]. The etiology is controversial. Some believe the syndrome is due to inadequate oxime therapy and/or to redistribution of OP from fat stores. While it is described in association with several different OP pesticides and the prevalence is estimated to be as high as 42% after these exposures [91-94], it has never been described after a nerve agent OP exposure.

Long-Term Electroencephalogram (EEG) Changes

There appears to be EEG changes that persist long after the acute effects of OP poisoning resolve. While the diagnosis of past OP exposure by EEG was not possible in one study, there were significant between-group differences between EEGs of Sarin-exposed individuals and controls. The clinical significance of these changes is unknown, but they may be related to the long-term neuropsychiatric effects of Sarin exposure [95].

Complications of Therapy

Overatropinization. Anticholinergic toxicity is always a risk of aggressive atropine therapy. A possible danger is that physicians’ inexperience with OP insecticide poisoning may cause them to be much more aggressive with atropine therapy than nerve agent poisoning would warrant. As long as the dose is titrated to the patient’s symptoms (drying of secretions), however, this should not be a problem.

Unintentional autoinjector discharge. In communities where autoinjectors were distributed (e.g., Israel, military personnel), there have been problems with unintentional self-administration of atropine and 2-PAM in the absence of nerve agent exposure. These injuries typically involve children, and most injuries are to the hand. One boy sustained a high-pressure injection injury to his finger from a 2-PAM autoinjector. He did not require operative therapy, and his symptoms resolved spontaneously [96]. In fact, this has been the general course of these exposures. One series of 268 children with similar exposures in Israel (where autoinjectors were distributed to the population in anticipation of a nerve agent attack during the first Persian Gulf War) demonstrated that while many children became clinically anticholinergic, there were no deaths or life-threatening complications (seizures, dysrhythmias) [97].
Prevention

Personal Protective Equipment (PPE)

It is absolutely imperative that first responders at the scene of a chemical attack are provided with adequate PPE before entering potentially contaminated areas. This is particularly important for persistent agents like VX. In the field, chemical protective masks with activated charcoal canisters provide protection from inhalation of nerve agents present as vapor or gas. Self-contained breathing apparatus (SCBA) or suits with supplied air are another alternative. Chemical protective overgarments with butyl rubber chemical protective gloves and boots provide protection from dermal exposure [98].

Patients arriving at the hospital on their own (not transported by emergency medical systems) are unlikely to be significantly contaminated. Patients who are ill enough to require therapy, however, should be decontaminated by personnel wearing PPE similar to that provided to first responders. Inside the hospital, no specific PPE is necessary for health care providers because patients should already have been decontaminated. In the unlikely event of an oral exposure, however, these patients may continue to pose a risk to providers [99].

Pyridostigmine Pretreatment

Military forces have used pretreatment with pyridostigmine bromide, a carbamate AChE inhibitor, as prophylaxis for nerve agent exposure when troops are in areas felt to be at high risk. While it may seem counterintuitive to treat anticholinesterase poisoning with another anticholinesterase, it improves outcome in several animal models when followed by treatment with atropine and oxime therapy [100,101]. The rationale for this therapy is that AChE is protected from the nerve agent by the carbamate, which competes for the binding site. Because carbamate AChE inhibition is reversible, as discussed above, this preserves some AChE activity once the carbamate dissociates from the enzyme (at which point, the exposure has presumably terminated and the patient has been treated with atropine and oxime therapy) [60]. This approach would theoretically be particularly useful in Soman poisoning because of its rapid aging.

There is some human experience with this therapy from the first Persian Gulf War. A review of the effects of more than 40,000 soldiers treated with pyridostigmine prophylaxis has been reported. About 1% of soldiers had cholinergic effects significant enough to seek medical attention, and 0.1% had effects severe enough to warrant discontinuation of the drug [102]. There is as yet no published evidence of its effectiveness for nerve agent prophylaxis in humans.

Some authors have advocated the use of physostigmine instead of pyridostigmine for prophylaxis because of its ability to cross the blood-brain barrier, providing protection against the central incapacitating effects of nerve agents [103]. The problem with this approach is that treatment with physostigmine in the absence of nerve agent exposure is itself too incapacitating, whereas pyridostigmine is better tolerated [1,60].

In civilian life, there is unlikely to be any warning before a terrorist nerve agent attack, and there is clearly no role for treatment with pyridostigmine after exposure. There is therefore little utility to this approach for nonmilitary use. First responders in the field should have PPE, obviating the need for prophylaxis in this group.

Dosing. Pyridostigmine has been used in doses of 30 mg orally every 8 hours for prophylaxis [60,102]. The goal at the molecular level is inhibition (and protection) of 30% of AChE [1].

Challenges and Future Advances

Hospital and Community Preparedness

The experience after the Sarin attack in Tokyo and the subsequent attack on September 11, 2001, have highlighted the need for better hospital and community preparedness to address the terrorist threat. Some specific areas to be addressed include disaster drills in areas at risk, improved communication between responders at the scene and hospitals and law enforcement, PPE for first responders and decontamination personnel at hospitals, and mobile decontamination units to allow rapid decontamination of patients at the scene [104-107]. Regional Poison Control Centers will be instrumental in coordinating the appropriate response to a chemical attack, so continued support of these centers is also critical.
Antidote stockpiles. In the past, it was feared that a terrorist attack with a nerve agent would quickly deplete hospital supplies of atropine. With the heightened state of alert that has come in the wake of September 11, 2001, however, most hospitals in urban areas have begun to stockpile atropine and pralidoxime. In addition, prehospital units in some large cities have begun to stock Mark-I kits. Strategies for therapy if parenteral atropine supplies are depleted have included the use of expired atropine, or the use of diphenhydramine or ophthalmologic atropine, although none of these approaches have been studied in humans [38]. The large supply of available atropine should obviate the need for such therapy. The limited supply of oximes is currently a much greater problem.

Novel Therapies

There are many approaches to prophylaxis and therapy that are currently being investigated. Some of these therapies have included pretreatment with exogenous cholinesterase [108,109] (an approach that might be particularly useful if combined with mutation of the Glu-199 residue required for aging), monoclonal or catalytic antibody therapy [108,110], and prophylactic gene therapy [111]. All of these approaches are still in the experimental stage.

Summary

While much progress has been made in recent years, nerve agents continue to pose one of the greatest threats to our cities and troops. The combination of aggressive prosecution of suspected terrorists, preparedness in our communities, PPE for first responders, decontamination of exposed individuals, and atropine, oxime, and benzodiazepine therapy offer the best strategy currently available to address this threat. Hopefully, future advances in therapy will further improve our ability to treat poisoned patients, while political advances will decrease the likelihood of attack.

References


Blood Transfusion Policy Among European Pediatric Intensive Care Physicians

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The objective of this study was to define current blood transfusion practices among European pediatric intensive care physicians treating critically ill children. A questionnaire of case scenarios was administered to members of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Of the 258 members of the ESPNIC, 134 (51.9%) pediatric intensive care physicians completed the questionnaire. The suggested blood transfusion thresholds for case scenario 1 (post–orthopedic surgery child) ranged from <7.0 g/dl to 11 g/dl. A total of 57.3% suggested 7 g/dl, 33.6% suggested 8 g/dl, and 6.9% suggested 9 g/dl as a hemoglobin threshold for transfusion (mean, 7.54 ± 0.75). For case scenarios 2 to 4, the suggested hemoglobin thresholds were 7 g/dl to 12 g/dl. For case scenario 2 (a child with acute respiratory distress syndrome), 22.4% suggested 8 g/dl, 15.7% suggested 9 g/dl, and 41% suggested 10 g/dl as a hemoglobin threshold for transfusion (mean, 9.40 ± 1.27 g/dl). For case scenario 3 (a post–cardiac surgery infant), 20.1% suggested 7 g/dl, 24.6% suggested 8 g/dl, 21.6% suggested 9 g/dl, and 25.9% suggested 10 g/dl as a hemoglobin threshold for transfusion (mean, 8.72 ± 1.24 g/dl). For case scenario 4 (a child with septic shock), 23.1% suggested 8 g/dl, 16.4% suggested 9 g/dl, and 41% suggested 10 g/dl as a hemoglobin threshold for transfusion (mean, 9.45 ± 1.24 g/dl). The threshold for transfusion was not statistically different (P > .05) between the physicians according to their subspecialty, years of experience, or country of origin. The suggested volume of transfused blood was 10 to 15 ml/kg in 427 responses (82.6%) and 20 ml/kg in 89 responses (17.2%). Most physicians, 78/128 (60.9%), did not consider the age of the transfused blood an important factor in their decision to transfuse. Of the 106 (79.1%) physicians who detailed their considerations for elevating the threshold for transfusion, 82 (77.3%) gave a general nonspecific indication, 47 (44.3%) stated hemodynamic instability and shock, and 40 (37.7%) an ongoing bleeding. The hemoglobin threshold for blood transfusion and transfusion volume varies among European pediatric intensive care physicians, for the same patient.

Key words: red blood cells, transfusion, children, anemia, hemoglobin, pediatric intensive care

The need to decrease the complications associated with blood transfusion, such as infections, transfusion-associated acute lung injury [1,2], and transfusion effect on the recipient immune system [3], has led to a worldwide decrease in the number of units of transfused packed red blood cells (PRBC). Recently, Hebert et al [4] found an increased survival rate of critically ill patients, younger than 55 years of age with APACHE scores of 22 or less, who were managed with a restrictive blood transfusion policy, that is, hemoglobin maintained within a range of 7 to 9 g/dl. The American College of Physicians [5], the Canadian Medical Association [6], and the American Society of Anesthesiologists [7] have published recommendations and guidelines regarding PRBC transfusion. Apparently, however, they have not gained adequate acknowledgment among practicing physicians. Several studies have reported that up to 66% of transfused PRBC were not justified [8,9]. In a Canadian survey, Hebert et al [10] found that physicians tended to be liberal regarding blood transfusion, with 40% of them using hemoglobin of 10 g/dl as the threshold trigger for transfusion and automatically transfusing two units of PRBC.

Only one [6] of the above studies was conducted in the pediatric population and recommended general transfusion guidelines in children. Yet there are no existing recommendations regarding blood transfusion among critically ill children, and there is no information regarding PRBC transfusion policy of pediatric intensive care physicians. The aim...
of the present survey was to define PRBC transfusion practices of European pediatric intensivists during treatment of critically ill children.

Methods

Instrument

A two-part questionnaire was formulated with the assistance of statistical analysts experienced in the field of questionnaires. The first part was designed to collect data on the physician's background (specialty, years of pediatric intensive care practice, academic rank) and characteristics of the pediatric intensive care unit (PICU) (unit type, number of beds, etc). The second part described four scenarios of common, clinical situations in the PICU. Each scenario isolated one important variable. The scenarios were (1) a child, after orthopedic surgery, with stable respiratory and hemodynamic status; (2) a hemodynamically stable, hypoxic, ventilated child with acute respiratory distress syndrome (ARDS); (3) a child with stable respiratory status after cardiac surgery with inotropic support; and (4) a septic, hemodynamically unstable child. The scenarios are listed in the appendix.

For each case, the physicians were asked to state the hemoglobin level at which they would prescribe a transfusion and the volume of the blood transfusion. They were also asked to explain their considerations for applying a liberal blood transfusion policy (more than one consideration was allowed).

Procedure

The questionnaire was mailed to all members of the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) (pediatric and neonatal intensive care physicians). Stamped, self-addressed envelopes were included. Physicians were asked to answer the questionnaire only if they work in a pediatric intensive care unit on a regular basis. Questionnaires returned by neonatologists were excluded.

A second mailing was done 3 weeks after the first to all physicians who failed to respond. Since the physician's phone number was not available, a third mailing to nonresponders was done as well.

Statistical Analysis

Descriptive statistical tables and bar diagrams were used. For each scenario, mean ± SD threshold for transfusion was calculated. For testing the difference between the means of hemoglobin for transfusion threshold between the different subspecialties, we used the one-way ANOVA test (a P value < .05 was considered as statistically significant).

Results

Of the 258 registered ESPNIC members, 134 (51.9%) pediatric intensive care physicians returned the questionnaire. One hundred (74.6%) of them were pediatric intensivists in their training, and more than half of the responders, 78 (58.2%), had 11 years or more of experience in the field of pediatric intensive care. Their background and academic characteristics are listed in Table 1.

The suggested hemoglobin threshold for transfusion for scenario 1 (stable child after orthopedic surgery) ranged from less than 7 g/dl to 11 g/dl (mean, 7.54 ± 0.75). The suggested hemoglobin thresholds were 7 g/dl by 57.3%, 8 g/dl by 33.6%, and 9 g/dl by 9% of the responders.

For case scenarios 2 to 4, the suggested hemoglobin thresholds were 7 g/dl to 12 g/dl. For scenario 2 (hypoxic, ventilated child with ARDS), 22.4% suggested 8 g/dl, 15.7% suggested 9 g/dl, and 41% suggested 10 g/dl as a hemoglobin threshold for transfusion, (mean, 9.40 ± 1.27). For scenario 3 (stable child after cardiac surgery), 20.1% suggested 7 g/dl, 24.6 suggested 8 g/dl, 21.6% suggested 9 g/dl, and 23.9% suggested 10 g/dl as a hemoglobin threshold for transfusion (mean, 8.72 ± 1.24). For scenario 4 (a septic hemodynamically unstable child), 23.1% suggested 8 g/dl, and 41% suggested 10 g/dl (mean, 9.45 ± 1.24). The detailed number of replies for each threshold in the different scenarios is shown in Table 2.

Except for one responder, for all the scenarios, the suggested volume of red blood cell transfusion ranged from 10 ml/kg to 20 ml/kg. For case scenario 1 (stable child after orthopedic surgery), 52/125 (41.6%) suggested a transfusion volume of 10 ml/kg, 43/125 (34.4%) suggested 15 ml/kg, and 30/125 (24%) suggested 20 ml/kg. Detailed suggested red blood cell transfusion volumes in the 4 pediatric scenarios are shown in Figure 1. The one responder who differed suggested 5 ml/kg transfusion volume in one of the scenarios.
The mean threshold for transfusion was not statistically different ($P > .05$) between the physicians analyzed to their background (subspecialty, number of years of experience in the ICU, and country of origin).

Most of the physicians (78/128, 60.9%) did not regard the age of the transfused blood as a criterion for deciding whether to transfuse.

A total of 106 physicians (79.1%) detailed their consideration for applying an elevated threshold for transfusion. Most (82, 77.3%) gave a nonspecific reason, such as "need to improve oxygen delivery," "underlying disease," "high oxygen consumption," and "cardiac output"; other reasons were hemodynamic instability and shock (47, 44.3%), ongoing bleeding (40, 37.7%), and hypoxemia and cyanosis (29, 27.4%). Only 25 (23.6%) of the responders considered the patient’s age, specifically, neonatal age group, as a consideration for liberal blood transfusion (see Table 3).

**DISCUSSION**

The present study demonstrates that the threshold for blood transfusions among European pediatric intensive care physicians vary, with a range span of up to 5 g/dl for the same case scenario. This means that some pediatric intensivists would be satisfied with their patient having a hemoglobin level of 7.1 g/dl, while others will transfuse the same patient to maintain his or her hemoglobin at 11.9 g/dl. Thus, the same patient might be at risk of undertransfusion (eg, tissue hypoxia) or overttransfusion (eg, unnecessary exposure to blood) by different treating physicians.

The response rate to the questionnaire was 51.9%, which is not uncommon in mailed questionnaire surveys, yet the survey represents a sig-
significant number, 134, of European pediatric intensive care physicians.

The aim of PRBC transfusion is to improve oxygen delivery to the tissues and to avoid tissue hypoxia. Basically, in critically ill children, oxygen delivery exceeds oxygen consumption by 2- or 3-fold [11,12]. When oxygen delivery decreases, due to a decrease in hemoglobin level, for example, a few compensatory mechanisms, such as tachycardia, increased myocardial contractility, increased production of 2,3 diphosphoglycerate, and increased oxygen extraction, are activated [13]. However, they are effective only to the point of “oxygen delivery and consumption dependency” [14]; thereafter, the tissue becomes hypoxic. At present, pediatric physicians lack a bedside tool that will help them to recognize this dependency in a critically ill child, and thereby, the decision of when to transfuse a critically ill child is arbitrary. Since a true mixed venous saturation is not available in the vast majority of critically ill patients, and hemodynamic studies are rarely done routinely, oxygen delivery and consumption cannot be measured accurately and can be evaluated only clinically. This may explain the wide threshold range noted in our study. Furthermore, there is no clear consensus regarding early, readily available parameters for tissue hypoxia [15,16]. Lactate may be a late indicator, and it may also be influenced by many other parameters such as hepatic function, pyruvate dehydrogenase activity, and various metabolic disturbances [17]. Base deficit is also a nonspecific late parameter of tissue perfusion. Gastric mucosal pH is often unavailable and may also not be reliable since it is influenced not only by CO₂ production but also by CO₂ removal, regional blood flow, and lactate metabolism [18]. Finally, some general recommendations for PRBC transfusion in pediatric patients have been published by the American Association of Blood Banks [19] and the Canadian Medical Association [6]. However, there are no specific guidelines for PRBC transfusion in children nor in the specific subgroup of critically ill children [20-22]. This lack of recommendations is reflected in the wide range of hemoglobin thresholds for blood transfusion in our study.

It is noteworthy that 60.9% of the respondents do not consider age of PRBC as an important factor. However, it has been shown that after 15 days of blood storage, the level of 2,3 diphosphoglycerate decreases to 0 and, as a consequence, its deformability is low [23]. Poorly deformable red blood cells may become entrapped in the microcirculation [24,25], causing low oxygen availability to the tissue and even tissue ischemia [26,27]. Therefore, transfusion of old blood may not lead to the expected increase of oxygen delivery to the tissues.

The recommended volume of PRBC transfusion is 10 to 15 ml/kg [11,12]. In our survey, 427 (82.7%) of the PRBC transfusions would be within this volume, but 89 (17.2%) would not. Indeed, 8 (6%) physicians recommended a volume greater than 20 ml/kg regardless of the clinical status. We assume that the large volumes are intended to decrease the exposure of the child to donated blood. The effect of large-volume PRBC transfusion on the intravascular volume and its consequences has not yet been studied in critically ill children.

Most of the considerations given for liberal blood transfusion policy were relatively nonspecific and were led by the rationale of improving tissue oxygenation. However, the level from which there is a need to transfuse a critically ill child, to supply the tissue oxygen demands, is still unclear.

At this time, it is very difficult to recommend a hemoglobin threshold for transfusion to a critically ill child. Pediatric intensive care physicians may extrapolate from the studies done among adult patients to target, in general, a lower hemoglobin threshold for PRBC transfusion. Yet we should remember that pediatric physiology is not the same as adult or elder patients’ physiology, including the effect of decreased oxygen delivery on organ function, especially the heart. We should also notice that the spectrum of disease in a PICU is different from that seen in the adult intensive care unit. To try to answer this difficult issue, there is a need for a large, multicenter study that will investigate the effect of two different blood transfusion policies, restrictive and liberal, on the morbidity and mortality of critically ill children hospitalized in the PICU.

In their survey of Canadian physicians, Hebert et al [10] changed one parameter in each scenario to identify the considerations that influence physi-
cians’ decisions regarding blood transfusion threshold. By contrast, we asked the physicians, after completion of the questionnaire, to freely describe situations in which they would elevate the threshold for transfusion. We believe our technique harbors less physician bias than that of Herbert et al [10].

In conclusion, European pediatric physicians vary in their range of hemoglobin thresholds and volumes for transfusion, and they place their decision on different considerations. We believe the problem derives from the lack of readily available bedside tools, which help the clinician recognize the point at which the tissue becomes hypoxic due to low oxygen delivery, and the lack of practical clinical guidelines for transfusion in critically ill children.

**Appendix**

### Clinical Case Scenarios

**Scenario 1:** A 6-year-old child admitted to the pediatric intensive care unit after fixation of femoral fracture. He is well oxygenated on room air and stable hemodynamically.

**Scenario 2:** A 2-year-old child with acute respiratory distress syndrome due to aspiration. He is on a ventilator; parameters are as follows: PIP = 29 cmH2O, PEEP = 12 cmH2O, FiO2 = 80%, RR = 28/min; ABG: PO2 = 59 mm Hg, PCO2 = 43 mm Hg, pH = 7.39. He is stable hemodynamically and metabolically.

**Scenario 3:** A 10-month-old infant, 3 hours after complete operative correction of atrioventricular septal defect. He is normovolemic and not bleeding. He receives dopamine, 7.5 mcg/kg/min. Ventilation parameters are in the usual range, with good blood gas levels. He is otherwise stable.

**Scenario 4:** A 4-year-old child with gram-negative septic shock treated with boluses of fluids, dopamine 10 mcg/kg/min, dobutamine 7.5 mcg/kg/min, and antibiotics. With this treatment, blood pressure is 70/40 mm Hg, capillary filling time is 5 seconds, and urine output is 0.4 c/kg/h. Ventilation parameters are as follows: PIP = 26 cmH2O, PEEP = 4 cm H2O, FiO2 = 35%, RR = 20/min; ABG: PO2 = 95 mm Hg, PCO2 = 42 mm Hg, pH = 7.30. He is otherwise stable.

### References

Tissue Plasminogen Activator as an Adjuvant Therapy for Pleural Empyema in Pediatric Patients

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Pierantonio Russo, MD
Joseph D. Tobias, MD

The authors retrospectively review the clinical course and outcome of 6 pediatric patients, ranging in age from 2 to 13 years, who were treated with TPA for complex empyema. Efficacy was assessed by evaluating pleural fluid drainage for 6 hours prior to and subsequent to each dose of TPA, as well as by resolution of fever and length of hospital stay. The average volume drained for 6 hours before infusion of TPA was 22.5 mL ± 18.4 mL, and the average volume 6 hours after TPA therapy was 141.7 mL ± 28.3 mL, P < .0001. After initiation of TPA therapy, 5 out of 6 patients became afebrile within 48 hours. The median length of stay after initiation of TPA therapy was 6 days, with a range from 4 days to 12 days. A discussion of other current therapies for empyema, along with a comparison of these therapies to TPA regarding the costs of therapies and risk-benefit ratios, is also included.

Key words: tissue plasminogen activator, streptokinase, urokinase, empyema, pleural effusion

Empyema is the accumulation of purulent material in the pleural cavity secondary to a viral or bacterial infection [1,2]. Complex empyema or complicated parapneumonic effusions have been known to develop in as many as 27% of patients with parapneumonic effusions [3]. Mortality from empyema was at one time as high as 74% in some populations, and although this figure has significantly decreased since the advent of better therapies, complex empyema still remains a noteworthy source of morbidity in the population [1]. There are 3 stages of pleural effusions due to infection [4-6]. The first is the exudative phase, which is characterized by thin communicating pleural fluid and is most often treated by closed tube drainage combined with intravenous antibiotic therapy. The second stage is the fibrinopurulent phase, characterized by gelatinous fluid, fibrin loculations, and adhesions. The first stage may become loculated, thereby advancing into the second stage, in a matter of hours [7]. The best treatment for the second stage is a matter of debate and includes thoracoscopy, instillation of fibrinolytic agents, and/or other surgical approaches such as thoracotomy or video-assisted thoracic surgery (VATS). The third stage of pleural effusions is the organization phase, characterized by cross-linking of the fibrin to form a thick encasing pleural peel, which may restrict the lung leaving it immobile. The third stage often requires surgical treatment to remove the pleural peel, thereby restoring lung expansion.

In the second stage of empyema, an imbalance of the coagulation cascade allows fibrinous debris to be deposited on the pleural surface, creating loculations that prevent tube drainage of the fluid [8]. The loculations wall off the pleural fluid, making it inaccessible to drainage, and the debris obstructs the drainage tube, thereby complicating the drainage process. These complications often result in the need for surgical intervention such as thoracoscopy or thoracotomy [9]. It is in these cases that the use of tissue plasminogen activator (TPA) is potentially beneficial. The fibrinolytic action of TPA breaks up the fibrinous debris, thereby allowing drainage of the fluid.

Other fibrinolytic agents, which have previously been used in this condition, include streptokinase...
and urokinase. Because of the reservations regarding the use of streptokinase in children because of the potential for allergic phenomena and the period of unavailability of urokinase (see below), TPA has been used as adjunctive therapy in cases of complex empyema in children. This retrospective chart review examines the use of TPA in 6 children, ranging in age from 2 to 13 years.

Methods

This retrospective chart review was approved by the Institutional Review Board of the University of Missouri. The need for written consent was waived. The pharmacy and Pediatric ICU records were reviewed and patients identified who had received TPA for the treatment of empyema or loculated pleural effusions. Demographic data included age, weight, and gender. Information regarding the pleural effusions from the initial drainage procedure (thoracentesis or catheter placement) included cell count, protein, glucose, culture, and volume collected. Pleural fluid was drained by either a chest tube or an 8.5 French pigtail catheter (Cook Catheter, Bloomington, IN). If chest tube drainage decreased and residual fluid was demonstrable on chest x-ray (CXR), then TPA therapy was initiated.

The TPA (2-5 mg) was reconstituted by the pharmacy in saline. The solution was then infused through a stopcock on the pigtail catheters or via a catheter tip syringe through the chest tubes. The solution was left in the pleural space for 4 to 6 hours and the fluid drained at the end of this period. During this period, the patient was repositioned every 30 minutes in 4 different positions: Trendelenburg, reverse Trendelenburg, left lateral decubitus, and right lateral decubitus. The treatment was repeated as needed every 12 to 24 hours until either a CXR demonstrated disappearance of the effusion or the therapy was no longer beneficial (volume of fluid coming out equaled the volume of the fluid going in). The chest tube was removed when there was less than 10 to 20 mL of drainage in 24 hours. Any adverse effects seen during therapy were noted. The volumes of fluid that drained before and after TPA were compared by a paired, 2-tailed \( t \) test.

Results

We identified 6 patients who received TPA for treatment of empyema or loculated pleural effusions. The patients ranged in age from 2 to 13 years. Patient demographics are outlined in Table 1. A bacterial etiology was identified in 2 of the 6 cases as \textit{Streptococcus pneumoniae}, whereas no etiology was identified in the other 4 patients. Reasons for initiating TPA included a positive chest x-ray despite placement of a drainage device, fever, decreasing chest tube output, and residual fluid after placing drainage systems. Laboratory analysis was performed on the fluid from the initial drainage procedure and included a cell count, protein, glucose, LDH, and pH. In addition to this, a Gram stain and culture were also performed on each sample. Results of the laboratory evaluation are summarized in Table 2.

Once TPA therapy was initiated, fluid output was measured for 6 hours before and 6 hours after TPA administration. These data, plus the drainage systems and dosages of TPA used, are summarized in Table 3. The volume of the TPA solution infused was subtracted from the volume drained for the 6 hours after administration. Therefore, the volume reported is the additional fluid drained. For 6 hours before TPA, there was a total of 22.5 mL ± 18.4 mL that drained from the chest tube and an average volume for 6 hours after TPA of 141.7 mL ± 28.3 mL, \( P < .0001 \).
### Table 2. Laboratory Evaluation of Fluid From Initial Tap

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Volume (mL)</th>
<th>WBC Count</th>
<th>% Neut</th>
<th>% Lymph</th>
<th>% Mono</th>
<th>% Eos</th>
<th>RBC Count</th>
<th>Protein (g/dl)</th>
<th>Glucose (mg/dl)</th>
<th>pH</th>
<th>LDH</th>
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<tbody>
<tr>
<td>1</td>
<td>300</td>
<td>4200</td>
<td>97</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>2700</td>
<td>3.9</td>
<td>45</td>
<td>7.40</td>
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<tr>
<td>2</td>
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<td>8500</td>
<td>42</td>
<td>46</td>
<td>4</td>
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<td>28965</td>
<td>4.8</td>
<td>74</td>
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<td>NP</td>
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<tr>
<td>3</td>
<td>330</td>
<td>3900</td>
<td>99</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>1600</td>
<td>3.3</td>
<td>18</td>
<td>7.28</td>
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</tr>
<tr>
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<td>430</td>
<td>47500</td>
<td>97</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>18500</td>
<td>4.2</td>
<td>41</td>
<td>7.00</td>
<td>10251</td>
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<tr>
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<td>50</td>
<td>11</td>
<td>4</td>
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<td>—</td>
<td>115109</td>
<td>2.5</td>
<td>109</td>
<td>7.20</td>
<td>1625</td>
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</tbody>
</table>

**NP = Test not performed.**

**Pleural fluid from all patients was culture and Gram stain negative.**

### Table 3. Effects of TPA

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Drainage System Used</th>
<th>Dosage (mg TPA/mL saline)</th>
<th>Volume Drained 6 Hours before TPA (mL)</th>
<th>Volume Drained 6 Hours after TPA (mL)</th>
<th>Hospital Stay after Initiation of TPA Therapy (days)</th>
<th>Adverse Effects Observed during TPA Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.5 FR pigtail catheter</td>
<td>3/20</td>
<td>20</td>
<td>165</td>
<td>8</td>
<td>Sanguinous drainage; No ↓ in HCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/50</td>
<td>5</td>
<td>170</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/50</td>
<td>25</td>
<td>180</td>
<td>8</td>
<td>Day 4—serum albumin 1.2 gm/dl→ edema, ascites—probably due to the large amount of pleural fluid drained and not TPA itself.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/50</td>
<td>25</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/50</td>
<td>25</td>
<td>140</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>3/50</td>
<td>29</td>
<td>145</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>8.5 FR pigtail catheter</td>
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<td>605</td>
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</tr>
<tr>
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<td>220</td>
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<tr>
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<td>390</td>
<td>5</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>5/50</td>
<td>30</td>
<td>410</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/50</td>
<td>25</td>
<td>190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>20 FR chest tube</td>
<td>5/100</td>
<td>0</td>
<td>170</td>
<td>4</td>
<td>Sanguinous drainage; No ↓ in HCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/100</td>
<td>10</td>
<td>150</td>
<td>4</td>
<td>Sanguinous drainage; No ↓ in HCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5/100</td>
<td>5</td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8.5 FR pigtail catheter</td>
<td>5/250</td>
<td>15</td>
<td>420</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>25</td>
<td>395</td>
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<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>35</td>
<td>185</td>
<td>7</td>
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<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>25</td>
<td>115</td>
<td>7</td>
<td>Sanguinous drainage; No ↓ in HCT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>20</td>
<td>25</td>
<td>7</td>
<td>Sanguinous drainage; No ↓ in HCT</td>
</tr>
<tr>
<td>6</td>
<td>8.5 FR pigtail catheter initially used on L, 24 FR chest tubes were later inserted on both L &amp; R sides.</td>
<td>5/50</td>
<td>0</td>
<td>337</td>
<td>12</td>
<td>None</td>
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<tr>
<td></td>
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<td>240</td>
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<td>5/250</td>
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<td>410</td>
<td>12</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>15</td>
<td>L = 250</td>
<td>12</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>5/250</td>
<td>20</td>
<td>R = 150</td>
<td>12</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Totals &amp; Averages</th>
<th>25 doses total</th>
<th>3-6 doses/patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.5 ± 18.4</td>
<td>141.7 ± 28.3</td>
</tr>
</tbody>
</table>
Discussion

We noted that TPA effectively aided in the clearance of residual pleural fluid. Average volume drained before infusion of TPA was 22.5 mL ± 18.4 mL, whereas the average volume 6 hours after TPA therapy was 141.7 mL ± 28.3 mL, \(P < .0001\). The use of TPA improved average fluid output by a factor of 6 to 7. After initiation of TPA, 5 out of 6 patients became afebrile within 48 hours. The sixth patient had a more complicated course of illness (see below). The median length of stay was 6 days, with a range from 4 days to 12 days. Patients were discharged from the hospital when they were afebrile for 24 to 48 hours, required no supplemental oxygen, and had radiographic evidence demonstrating clearing of infiltrates and the absence of residual fluid.

Therapy with TPA was found to be effective in 5 out of 6 patients (see Table 4). Patient 6 had a more complicated course of therapy, requiring additional chest tubes to be placed. This patient presented to our hospital after a 2- to 3-week course of illness and may have already advanced to phase 3 (the phase involving the formation of an organized pleural peel). As previously mentioned, this stage is thought to require surgical intervention. This patient developed loculated effusions bilaterally, requiring the placement of additional chest tubes. This patient's length of stay was considerably longer than the other patients; however, after placement of chest tubes, thrombolytic therapy was sufficient and surgical intervention was not necessary.

Three of the 6 patients receiving TPA therapy demonstrated a change in the color of the pleural drainage after initiation of TPA. The pleural fluid was not grossly bloody, but rather tinged with blood. We propose that this resulted from bleeding from the initial insertion site of the catheter or alternatively from the inflamed pleural surface. These patients' hematocrits were followed and no change was noted. Patient 1 also developed a low albumin (1.2 gm/dL), and consequently edema and ascites. This patient was 2 years old and weighed 11.6 kg. We would postulate that the loss of albumin was from the large amount of pleural fluid drained.

Table 4. Comparison of Various Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Success Rate</th>
<th>Average Hospital Stay after Initiating Treatment (days)</th>
<th>Cost at MU</th>
<th>Adverse Effects/Risks</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracostomy</td>
<td>6%-75%</td>
<td>16</td>
<td>$200</td>
<td>Often not effective when used alone, pain, hemorrhage, pneumothorax, subcutaneous emphysema</td>
<td>Good for stage 1 effusions without loculations</td>
</tr>
<tr>
<td>Intrapleural streptokinase</td>
<td>40-100%</td>
<td>11</td>
<td>$96 for 250,000 U</td>
<td>Bleeding, allergic reaction</td>
<td>Avoidance of surgery</td>
</tr>
<tr>
<td>Intrapleural urokinase</td>
<td>63%-100%</td>
<td>10</td>
<td>$152 for 100,000 U</td>
<td>Bleeding, period of unavailability, more expensive than streptokinase</td>
<td>Avoidance of surgery, not immunogenic, usually no adverse effects seen</td>
</tr>
<tr>
<td>Intrapleural TPA</td>
<td>100%</td>
<td>6</td>
<td>$101 for 5 mg</td>
<td>Bleeding</td>
<td>Avoidance of surgery, not immunogenic, usually no adverse effects seen</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>87%-100%</td>
<td>12</td>
<td>$2800-$3200</td>
<td>Cosmesis, sometimes requires additional procedures, drainage, etc</td>
<td>Usually results in complete resolution of empyema</td>
</tr>
<tr>
<td>VATS</td>
<td>&lt; 50% for chronic PPE 70%-100% otherwise</td>
<td>5-7</td>
<td>$2400-$3200</td>
<td>10%-30% need to convert to formal thoracotomy once begun. Not good for chronic parapneumonic effusions (low success rate)</td>
<td>↓↓ scarring, faster recovery, lower relapse rate than thoracotomy</td>
</tr>
</tbody>
</table>

**The above data were compiled from our data, in addition to data from references 4,5,14,18,19.
rather than an effect of TPA therapy. No other adverse effects were observed.

Other thrombolytic agents used in the past to treat complex empyema include urokinase and streptokinase. Due to the commonness of *Streptococcal* infections in children, the possibility of allergic reaction from antistreptokinase antibodies relatively contraindicates the use of streptokinase in the pediatric population. Therefore, an alternative thrombolytic agent was needed in children. For a while, urokinase filled this void; however, because of its isolation from fetal renal cell, the safety of urokinase was questioned and it was consequently removed from the market until it could be formulated in a safer manner. Urokinase has recently become available again; however, it is still not on the formulary of our hospital pharmacy. An alternative agent was needed for our pediatric population during this period of inaccessibility to urokinase. TPA has been employed as an alternative agent and, given our experience, has become our standard of therapy.

To date, there are 3 previous reports in the literature regarding the use of TPA as adjunctive therapy for empyema in children [10-12]. The first is a web-based article by Castaneda that discusses the use of urokinase in 27 patients and TPA in 3 patients [10]. The patients’ ages ranged from 2 to 84 years old, and 1 to 4 chest tubes were utilized in each. For the 3 patients treated with TPA, therapy consisted of infusing 5 mg TPA reconstituted in 20 to 30 mL saline into the pleural space and allowing it to remain there for 2 hours before draining. Twenty-nine of the 30 patients were successfully treated, meaning that they experienced complete drainage of their pleural fluid or a decrease in the amount of fluid with resolution of clinical symptoms. It was not stated in the article which type of therapy, urokinase or TPA, was being used in the patient in whom therapy was unsuccessful.

We have previously reported our experience with the use of TPA for complex empyema in 1 patient, a 6-year-old boy [11]. The child was treated with 2 doses of TPA (5 mg/50 mL) separated by an 8-hour interval. The solutions were allowed to remain in the pleural space for 1 to 2 hours each and resulted in 960 mL of drainage over the next 24 hours, which was significantly greater than the 240 mL of drainage collected in the 24 hours preceding TPA therapy. This patient is not included in the current series of 6 additional patients.

The third report found in the literature is another case report regarding the use of TPA in a single patient, a 16-month-old girl with complete consolidation of the right lung [12]. When drainage through the intrapleural catheter decreased to less than 10 mL/d, the tube was checked for patency and a 2 mg solution of TPA was infused and left in place for 4 hours. There was greater than 200 mL of drainage over the next 24 hours. This therapy was repeated 4 times over the next 6 days with nearly complete resolution of the effusion. To our knowledge, our current series of 6 patients is the largest experience in the literature, to date, regarding the use of TPA therapy for parapneumonic effusions in the pediatric population.

The alternative to using simple drainage procedures in conjunction with thrombolytics is the utilization of surgical procedures such as formal thoracotomy or VATS. However, surgical intervention and general anesthesia may be difficult in patients with acute infectious processes, empyema, and respiratory compromise. Formal thoracotomy involves making a large incision into the chest wall and manually breaking away the adhesions and fibrinous loculations from the pleural surface. The negative aspects of this procedure are the cosmetics of the scar left after surgery and the postoperative morbidity of pain. Patients commonly experience severe postthoracotomy pain, and up to 50% of patients may develop chronic pain symptoms lasting up to 2 years after the procedure [13]. The mini-thoracotomy is a variation on this procedure involving a smaller incision into the chest wall, but otherwise following the same process. VATS involves making several small incisions and, under the guidance of thoracoscopy, removal of the fibrinous coating. VATS leaves less scarring and seems to be associated with a faster recovery rate and less postoperative morbidity [5,14]. Other, less common, risks of these surgeries include bleeding, infection, bronchopleural fistula, carbon dioxide embolism (with VATS), and damage of the diaphragm and/or mediastinal structures [4].

Wait et al compared VATS to therapy with streptokinase [15]. The authors noted that treatment with VATS resulted in a shorter hospital stay; an average of 6.7 days for patients treated with VATS versus an average of 11.6 days for patients treated with streptokinase therapy. The VATS procedure was also seen to have a higher treatment success of 100% versus the treatment success of streptokinase therapy of 88%. There was a 10% conversion rate during the VATS procedure to formal thoracotomy [15]. This study was performed in adults older than 18 years of age and, therefore, may not necessarily be applicable to the pediatric population. Also, streptokinase has been found to be the least effective of
the thrombolytic agents (see below for a comparison of the efficacy of the 3 thrombolytic agents in the treatment of empyema) [6]. The treatment protocol and criteria for treatment failure with streptokinase were very strict and different from our practice. In the study, only one dose of streptokinase (250,000 U/100 mL saline) was used every 24 hours, and if at the end of 3 doses there was not a reduction in fluid on CXR by greater than 50%, the treatment was considered a failure and the patient sent to surgery.

Another retrospective study compares thoracotomy to therapy with urokinase in patients with stage 3 pleural effusions [16]. The 43 patients receiving surgical intervention all received posterolateral thoracotomy and had a mean postoperative stay of 8.7 days. Although all of the patients receiving thoracotomy recovered, postoperative complications included incisional infection, atelectasis, and hemorrhage. The 28 patients receiving fibrinolytic therapy received 20,000 IU of intrapleural urokinase, which remained in the pleural space for 2 hours. Six of these 28 patients (21%) did not respond sufficiently to fibrinolytic therapy and consequently underwent surgical decortication. One patient receiving urokinase died of sepsis following an allergic reaction and pleural hemorrhage. Patients receiving fibrinolytic therapy had a postinterventional hospital stay of 9.5 days. The conclusions of the authors were that for this stage of empyema (phase 3), thoracotomy is the preferred intervention and that fibrinolytic therapy may be more useful in stage 2 pleural effusions before an organized pleural peel is formed.

Many of those in favor of the surgical approach would perform surgery as soon as the patient is diagnosed with loculated empyema [5,9,17]. Characteristics common to loculated empyema include positive Gram stain or culture, pleural fluid with a pH < 7.0, glucose < 40, LDH > 1000, and/or evidence of loculations on imaging studies (ultrasound, CT, etc) [5,14]. Loculated empyema was evident in all of our patients by either evidence of fluid on CT imaging or by decreasing chest tube output with residual fluid on CXR. Therefore, all of our patients would have been candidates for surgery in some centers. However, by utilizing TPA in their treatment, complete recovery was attained with avoidance of surgery for all patients.

Although urokinase is twice as expensive as streptokinase, it has been shown that for most patients, using half the normal dose of urokinase (50,000 U) results in the same effect [6]. This makes it roughly the same price as streptokinase. In the paper previously mentioned comparing thoracotomy to urokinase therapy, the dosage of urokinase used was only 20,000 U/20 mL saline, suggesting that even a smaller dose may be as effective thereby decreasing the cost even further [16]. Since it has been shown to be more effective and have fewer adverse effects than streptokinase, urokinase appears to be the better thrombolytic agent when compared with streptokinase [6].

Many of the patients in our current series received 5 mg of TPA. However, the optimal dose is not known and a dose of less than 5 mg may be equally effective. A future study comparing a lower dosage, 2 mg, for example, to 5 mg would be worthwhile in an effort to further decrease the cost. At our hospital, a 50 mg vial of TPA is currently $1014. The pharmacy can split the 50 mg vial into 5 mg aliquots, thereby decreasing the price of TPA to $101/5 mg dose.

In addition to the costs of the therapies themselves, one must consider the costs of a hospital stay, which range from $600 to $800 a day. In addition to this, there are the costs associated with the necessary lab tests used to monitor the patients while they are in the hospital. By shortening the patient’s length of stay, one decreases the total cost of therapy. In a trial comparing streptokinase to urokinase, average length of stay was 10 to 11 days [6]. The median length of stay for the patient’s receiving treatment with TPA in our experience was 6 days, with a mean stay of 6.8 days. The average length of stay in a trial examining VATS was 5 to 7 days, a comparable time period to our patients receiving TPA therapy [5,14]. Due to the potential efficacy, low-cost, and limited adverse effect profile, we use TPA therapy as our first-line approach for children with stage 2 pleural effusions.

Summary

We found that TPA was successful in the treatment of complex empyema in 5 out of 6 patients and may have benefited the sixth patient. On average, treatment with TPA therapy increased pleural fluid output by a factor of 6 to 7. One patient required the placement of additional chest tubes, as she developed loculated bilateral effusions. That did not totally resolve with TPA therapy. Based on the presence of a loculated effusion, all of the patients in our current series would have been considered surgical candidates in some centers; however, with the use of TPA, surgery was avoided in all cases [5,9,17]. The existence of loculated effusion was...
determined in these patients by residual fluid on CXR or CT imaging after placement of a drainage system. When each patient was determined to have a loculated effusion, 2 to 5 mg of TPA reconstituted in saline was infused directly into the pleural cavity through the drainage system already in place. The solution was left in for 4 to 6 hours and the resultant fluid collected. Therapy was repeated every 12 to 24 hours until the volume of fluid going in equaled the volume of fluid coming out. An additional benefit of TPA may be the ability to drain complicated pleural effusions through a smaller drainage catheter. Five of the 6 patients in the current series were effectively drained using an 8.5 French drainage catheter, which can be placed using the Seldinger technique. A prospective clinical trial comparing TPA therapy to other thrombolytic agents and/or surgical approaches would be worthwhile.

References

Drotrecogin Alfa (Activated) in an Infant With Gram-Negative Septic Shock

Imran Sajan, MD*
Shonola S. Da-Silva, MD*
R. Phillip Dellinger, MD, FCCM†

The authors observed the effect of drotrecogin alfa (activated) in a case of pediatric severe sepsis. A 4-month-old male infant with Serratia marcescens septic shock, multiple organ dysfunction syndrome (MODS), and consumptive coagulopathy was admitted. The safety and efficacy of drotrecogin alfa (activated) has not yet been established for patients younger than 18 years of age. This is the first published report of the use of drotrecogin alfa (activated) in an infant with severe sepsis. Within 6 hours of starting therapy, there was a significant improvement in hemodynamics, which was not maintained after the drotrecogin alfa (activated) infusion was temporarily discontinued. No significant bleeding complications occurred during the infusion. A brain MRI on day 22 after drotrecogin alfa (activated) infusion showed bilateral small occipital hemorrhages. Drotrecogin alfa (activated) in this infant was temporally related to significant improvement. It is unknown whether the MRI brain lesions are related to severe sepsis with disseminated intravascular coagulation or drotrecogin alfa (activated) infusion. The authors believe that drotrecogin alfa (activated) should be considered in select children with life-threatening severe sepsis.

Key words: severe sepsis, drotrecogin alfa (activated), recombinant human activated protein C, multiple organ dysfunction syndrome, intracranial hemorrhage, disseminated intravascular coagulation

Outcomes in neonatal and pediatric sepsis have improved with a reduction in mortality from 97% to 9% [1-3]. This is markedly better than the 28% mortality reported for adults [3,4]. However, sepsis still continues to be an important cause of mortality in the pediatric population. It is the 13th leading cause of death in patients older than 1 year of age and the 9th leading cause of death in patients 1 to 4 years old. The incidence of sepsis is higher in infants, especially those born prematurely [5,6].

Over the past several years, a new understanding of sepsis pathophysiology has emerged focusing on the interplay and coupling of inflammation, microvascular coagulation, and endothelial cell dysfunction.

In line with the recognition of the importance of microvascular coagulopathy, the use of the recombinant form of the natural antithrombotic factor, recombinant human activated protein C, drotrecogin alfa (activated) was explored, and phase II studies suggested a treatment benefit [7,8]. This prompted the initiation of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, which demonstrated that drotrecogin alfa (activated) significantly reduced mortality in adult patients with severe sepsis [9]. The following case study demonstrates the use of drotrecogin alfa (activated) in a 4-month-old infant with septic shock.

Case Report

A 4-month-old 3.5-kg male infant was admitted to the general pediatric service of a university teaching hospital with presumed viral bronchiolitis. He was the product of a 36-week gestation pregnancy. The infant had a significant past medical history and at 3 months of age was placed on a mechanical ventilator secondary to respiratory failure from nontypeable Hemophilus influenza pneumonia. He was also failing to thrive, with height, weight, and head circumference below the third percentile. With this admission, he proceeded to have a complicated course requiring several transfers to the pediatric intensive care unit (PICU) secondary to increased work of breathing and oxygen requirements. A respiratory syncytial virus and per-
Tussis cultures were negative. An echocardiogram was normal. The infant was given a 10-day course of erythromycin ethyl succinate and was placed on methylprednisolone.

On the 15th day of hospitalization, he was again transferred to the PICU because of progressively worsening respiratory distress and increasing oxygen requirements. He underwent a diagnostic bronchoscopy, which revealed moderate laryngomalacia and severe tracheomalacia. He was then electively intubated to facilitate sedated imaging studies of his chest. The intubation was complicated by a left main stem bronchus intubation with subsequent hypoxia and bradycardia, requiring brief cardiopulmonary resuscitation. Because of the left endobronchial intubation, no breath sounds were heard on the right hemithorax leading to an emergent right needle thoracentesis with presumption of a pneumothorax. This led to a right pneumothorax, which was subsequently evacuated by a Fuhrman pigtail catheter. During the first few days of conventional mechanical ventilation, his respiratory status steadily worsened and he progressed to acute respiratory distress syndrome with refractory hypoxemia. His oxygenation index was 17 with a PaO2/FiO2 ratio of 64, and he was started on inhaled nitric oxide at 20 ppm. High-frequency oscillatory ventilation was instituted on day 6 of mechanical ventilation.

On day 12 of mechanical ventilation, he showed manifestations of systemic inflammatory response syndrome, disseminated intravascular coagulation (DIC), and profound thrombocytopenia (Table 1). He was administered platelets, coagulation factors, and crystalloids. Despite preload augmentation and inotropic/vasopressor support, he remained severely hypotensive (mean arterial pressure [MAP] 48 ± 14.6 mm Hg) with lactic acidosis and capillary leak. Blood cultures obtained at the onset of hemodynamic instability grew gram-negative rods from multiple sites within 24 hours. This was subsequently identified as *Serratia marcescens* sensitive to the initial empiric antibiotic coverage. Within 24 hours of the onset of septic shock, we began infusion of drotrecogin alfa (activated) at 24 µg/kg/h.

Hemodynamic data and serial serum lactate are depicted in Table 2. Invasive blood pressure monitoring was performed with a standard arterial catheter inserted in the dorsalis pedis artery. At the onset of drotrecogin alfa (activated) infusion, norepinephrine, dobutamine, and dopamine infusions were being administered at 0.5, 6, and 10 mcg/kg/min, respectively. This adrenergic therapy had been in place at same or lower doses for 12 hours. Within 6 hours of starting drotrecogin alfa (activated) infusion, there was an improvement in hemodynamics, with the MAP increasing from 48 ± 14.6 mm Hg to 68 ± 3.7 mm Hg. Within 24 hours after starting drotrecogin alfa (activated) infusion, the inotropic/vasopressor infusions were weaned to dopamine at only 5 µg/kg/min. Approximately 7 hours after onset of drotrecogin alfa (activated) infusion, oozing was noted from the invasive lines and skin puncture sites. There was also a question of increased head circumference. The drotrecogin alfa (activated) infusion was held. A head ultrasound was performed and showed no evidence of intracranial hemorrhage (ICH). Platelets and coagulation factors were being concomitantly administered for continuing thrombocytopenia and prolonged coagulation. The MAP quickly decreased from 73.6 ± 4.6 mm Hg to 53 ± 3.09 mm Hg, requiring reinstitution of inotropic/vasopressor support. Drotrecogin alfa (activated) infusion was restarted after 4 hours and continued for a total of 76 hours with stabilization of hemodynamics. The infusion time was shortened from the recommended 96 hours for adults based on a lack of pharmacody-

<table>
<thead>
<tr>
<th>Table 1. Coagulation Profile and Platelet Count at Baseline, Prior to, and During Drotrecogin Alfa (Activated) Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to Onset of Septic Shock (baseline)</td>
</tr>
<tr>
<td>PT</td>
</tr>
<tr>
<td>PTT</td>
</tr>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>FDP</td>
</tr>
<tr>
<td>D-Dimer</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
</tbody>
</table>

PT = prothrombin time (normal value = 10.5-13.2 seconds); PTT = activated partial thromboplastin time (normal value = 25.0–37.0 seconds); fibrinogen normal value = 200-410 mg/dl; FDP = fibrin degradation product (normal value = <5 µg/ml); D-Dimer normal value = 0.5 µg/ml; platelets normal value = 150-400 K/µl.
namic and pharmacokinetic information for pediatric dosing. The infusion was tolerated well, with one episode of decompensation associated with bronchospasm and hypoxemia felt to be unrelated to drotrecogin alfa (activated). No overt bleeding episodes were noted during the infusion. Daily head ultrasounds were performed while on drotrecogin alfa (activated) and did not demonstrate any ICH. A brain MRI obtained on day 14 after drotrecogin alfa (activated) infusion also did not show any ICH. However, a follow-up brain MRI obtained on day 22 showed small bilateral occipital hemorrhages. The infant subsequently developed systemic hypertension controlled by sodium nitroprusside infusion. He was weaned to labetolol and hydralazine. His systemic hypertension was controlled, and he was weaned off hydralazine within 2 weeks.

Discussion

Severe sepsis is associated with an uncontrolled cascade of inflammation, coagulation, and endothelial cell dysfunction [10-12]. Ongoing consumption of the coagulation regulators (antithrombin, protein S, and protein C) cause uninhibited coagulopathy [10,11]. To maintain homeostasis and prevent vascular thrombosis, the body relies on the natural anticoagulant activity of the protein C pathway, together with that of antithrombin and tissue factor pathway inhibitor. Protein C is a vitamin K–dependent glycoprotein synthesized in the liver that circulates in the blood as a zymogen. It is activated by endothelial and platelet thrombin-thrombomodulin complexes and requires protein S as a cofactor for its full anticoagulant function. Activated protein C (APC) has antithrombotic and anti-inflammatory properties. APC has also been found to inhibit plasminogen activator inhibitor–1 and thus facilitate fibrinolysis, which is suppressed in severe sepsis [13,14]. APC inhibits thrombin formation through the inactivation of clotting factors VIIIa and Va, thus blocking the extrinsic pathway of coagulation. By inhibiting the formation of thrombin, APC also acts as an indirect anti-inflammatory agent. It blocks the inflammatory response to thrombin expression, including platelet activation, neutrophil adhesion, and endothelial cell surface activation. However, because of the systemic inflammatory response in sepsis, protein C is consumed and endothelial damage impairs its activation via thrombin/thrombomodulin complexes and the endothelial protein C receptor [15-18].

During sepsis and systemic inflammation, protein C levels fall [19-26]. In both children and adults, acquired deficiencies in protein C (due to consumptive coagulopathy) and deficits in protein C activation (due to thrombomodulin downregulation) are directly correlated with morbidity and mortality in septic shock from all observed etiologies [19-22]. Profound deficiencies in protein C have been documented in pediatric sepsis and particularly in purpura fulminans. In children with meningococcal sepsis, levels of activated protein C are low or undetectable and fail to rise after administration of unactivated protein C [19-21]. Other studies have confirmed acquired protein C deficiency in critically ill patients. Boldt et al [22] found that patients with sepsis had lower protein C values at baseline in comparison to other critically ill patients. In addition, Yan et al [23] demonstrated that >85% of patients with severe sepsis had acquired protein C deficiency and that this also cor-

Table 2. Hemodynamic Data and Serial Serum Lactate at Baseline, Prior to, and During Drotrecogin Alfa (Activated) Infusion

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart rate (M ± SD)</th>
<th>Mean arterial pressure (M ± SD)</th>
<th>Arterial serum lactic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Hours Prior to Onset of Septic Shock (baseline)</td>
<td>129 ± 15.2</td>
<td>70 ± 2.62</td>
<td>—</td>
</tr>
<tr>
<td>24 Hours Prior to Starting Drotrecogin Alfa (Activated) Infusion</td>
<td>177 ± 9</td>
<td>47 ± 14.6</td>
<td>4 mmol/L</td>
</tr>
<tr>
<td>24 Hours After Starting Drotrecogin Alfa (Activated) Infusion</td>
<td>123 ± 2.05</td>
<td>68 ± 3.7</td>
<td>1.3 mmol/L</td>
</tr>
<tr>
<td>6 Hours After 12 Hours of Drotrecogin Alfa Infusion</td>
<td>109 ± 1.8</td>
<td>107 ± 5.2</td>
<td>1.7 mmol/L</td>
</tr>
<tr>
<td>24 Hours After 6 Hours of Drotrecogin Alfa Infusion</td>
<td>116 ± 13.2</td>
<td>82 ± 21.04</td>
<td>1.3 mmol/L</td>
</tr>
<tr>
<td>48 Hours After 24 Hours of Drotrecogin Alfa Infusion</td>
<td>83 ± 1.24</td>
<td>116 ± 1.41</td>
<td>0.8 mmol/L</td>
</tr>
</tbody>
</table>

Serum lactic acid normal = 0.5–2.2 mmol/L.

a. Norepinephrine, dobutamine, dopamine at 0.5, 6, and 10 mcg/kg/min, respectively.
b. 24 µg/kg/h, inotropic/vasopressor unchanged.
c. Norepinephrine, dobutamine, and dopamine weaned.
d. Dopamine 5 mcg/kg/min.
related with severity of sepsis and outcome. Decreased protein C levels in severe sepsis have been shown to correlate with mortality [24-26].

Drotrecogin alfa (activated) is the first agent shown to be effective in ameliorating the sepsis cascade. The PROWESS trial [9] demonstrated protein C deficiency in 87.6% of 1574 septic study patients at baseline. Twenty-eight-day mortality was 24.7% in patients receiving drotrecogin alfa (activated), compared with 30.8% in the placebo group ($P = .005$), with a reduction in the relative risk of death of 19.4%. All patients included in this study were older than 18 years.

Bleeding is the only recognized serious adverse effect associated with drotrecogin alfa (activated) therapy. The incidence of ICH in open-label studies of drotrecogin alfa (activated) is approximately 1% during the infusion period. This risk increases in patients with risk factors for bleeding such as severe coagulopathy and thrombocytopenia. In the PROWESS trial, 2 cases of ICH occurred during the infusion period for drotrecogin alfa (activated)–treated patients, and no cases were reported in the placebo patients. The incidence of ICH during the 28-day study period was 0.2% for drotrecogin alfa (activated)–treated patients and 0.1% for placebo-treated patients.

The incidence of intracerebral hemorrhage in a pediatric intensive care population with severe sepsis and DIC is not known. Central nervous system lesions have, however, been described in adult patients dying with septic encephalopathy. These include multiple microabscesses, multiple small ischemic lesions or ischemic neurons in the hippocampus or watershed infarcts, a proliferation of astrocytes and microglia, brain purpura, multiple small white matter hemorrhages, and central pontine myelinolysis [27-30]. Thrombocytopenia is frequently seen in sepsis, and it may result in multifocal white matter hemorrhages seen in septic patients with DIC [31]. The infant described in this report developed thrombocytopenia preceding the drotrecogin alfa (activated) infusion. Multiple ultrasound brain-imaging studies during the infusion did not show ICH. Bilateral occipital hemorrhages were seen on a follow-up MRI performed on day 22 after infusion. Clinically significant thrombocytopenia continued for approximately 3 weeks, requiring multiple platelet transfusions. Whether the hemorrhages were related to or exacerbated by drotrecogin alfa (activated) therapy is not known.

The infant required a protracted antibiotic course to clear the $S$. marcescens blood stream infection. There is a possibility that the anti-inflammatory properties of drotrecogin alfa (activated) could have contributed to the prolonged bacteremia. However, this patient had one previous episode of severe sepsis and could also have an inborn or acquired immunologic defect.

There are no published data on the use of drotrecogin alfa (activated) in pediatric patients ≤18 years of age and specifically in young infants. The pediatric data available so far include data from the EVAO pediatric trial, which was an open-label, nonrandomized, sequential, 2-part study conducted in the United States and the United Kingdom. In this study, 83 pediatric patients with severe sepsis, aged term newborn to less than 18 years, were enrolled to investigate safety and pharmacokinetic properties of drotrecogin alfa (activated). There is currently a multicenter, multinational, randomized, placebo-controlled trial under way since the fall of 2002, and it is expected to continue for approximately 3 years.

Drotrecogin alfa (activated) has not yet been approved by the Food and Drug Administration for use in patients ≤18 years. Off-label use (use that is not included in the approved label) of drugs approved only for adults remains common in the practice of pediatrics. Our patient was thought to have a high chance at mortality, with the mortality due to pathophysiology potentially affected in a positive manner by drotrecogin alfa (activated).

The hemodynamic characteristics of adult (≤18 years) and pediatric septic shock are unique. Unlike adult septic shock, in which vasomotor paralysis is a predominant cause of mortality [32], pediatric septic shock manifests as a hypodynamic, low cardiac output state [33-35]. Despite these differences, the underlying sepsis pathophysiology is very similar. Hence, a pediatric intensivist when faced with a child with life-threatening illness from severe sepsis should weigh the risk-benefit ratio and consider the off-label use of drotrecogin alfa (activated) based on sound scientific evidence and expert medical judgment.

References


In this issue of the *Journal of Intensive Care Medicine*, Dr Sajan and colleagues present a Case Report detailing the treatment of an infant with gram negative septic shock with the new drug Drotrecogin Alpha (Activated) (rhAPC, Xigris®). The report deserves careful attention because published pediatric experience with this drug is scarce [1], and it represents an early description of the use of this drug outside of its current FDA-approved indication [2].

Recombinant human-activated protein C (rhAPC) has been demonstrated to reduce mortality in adult patients with sepsis (PROWESS study [3]) and is currently FDA approved for the treatment of sepsis in adults. Although there may be similarities between adult and pediatric sepsis, important differences exist with respect to mortality rates, types of organisms, site of infection, end-organ dysfunction, and the potentially greater risk for intracranial bleeding in the very young. We outline some of the important currently available data with regard to the use of rhAPC in children below.

Based on the Food and Drug Administration (FDA) response to the Biologics License Application (BLA) submission for rhAPC, complete or partial data are available for only 182 pediatric patients receiving treatment. Eighty-three patients have been treated in an open-label pharmacology/safety study in pediatric sepsis (EVAO). The 14-day mortality rate in this trial was 9.6%, and the incidence of serious adverse bleeding events reported during the 14-day study period was 4.8%. Another 14 pediatric patients were treated during an open-label compassionate-use trial in purpura fulminans (EVAS). In this trial, one pediatric patient died (7%) and 1 serious adverse bleeding event was reported at 24 days posttreatment (7%). Eighty-five patients have been treated with rhAPC in open-label studies. There have been no data submitted to the FDA on these patients. Based on these results, the incidence of serious adverse bleeding events in the pediatric population appears comparable to that in the adult population (3.5% in the PROWESS study [3], 4.8% in the EVAO study). However, the mortality benefit of treatment with rhAPC in children was not comparable to that in adults [4,5].

The FDA BLA submission for this drug contains pharmacokinetic and pharmacodynamic information that may be useful in determining the optimal dose of rhAPC for use in children. Based on the preliminary sequential dose escalation study using 6-hour infusions of 6, 12, 24, and 36 mcg/kg/h conducted in 21 pediatric patients during phase I of the EVAO trial, a dose of 24 mcg/kg/h was well tolerated and found to achieve steady-state activated protein C levels approximating those achieved in the adult phase III studies. Additional pharmacokinetic studies conducted during this trial using 24 mcg/kg/h in patients ranging in age from 38 weeks to 18 years of age determined that mean steady-state plasma concentrations and weight-normalized plasma clearance of activated protein C were similar to that of adults. In addition, the time needed to reach undetectable plasma concentrations (< 10 ng/ml) increased with age but ranged up to 1.5 hours versus 2 hours in adults [4,6].

It has been well documented that sepsis-related protein C deficiency is associated with an increased risk of mortality in both adults and children [5,7,8]. The Pediatric EVAO data demonstrate that biomarkers of sepsis such as protein C are positively affected in pediatric patients treated with rhAPC. The effects of rhAPC noted in children in this trial
are similar to the effects noted in the Adult PROWESS study. However, despite evidence to indicate the efficacy of this drug in adult severe sepsis and a positive effect on biomarkers for sepsis in children, there remain to date no conclusive randomized placebo-controlled data to guide us in our off-label use of this drug in pediatric sepsis.

Given the similar rates of complications related to the use of this drug in the pediatric and adult populations with sepsis and the markedly lower mortality rate among children with sepsis [9], the current evidence does not support the routine use of rhAPC in pediatric sepsis. However, the currently available data likely favor its use in pediatric patients who have a high risk of sepsis-related mortality. At present, the use of rhAPC in pediatric sepsis calls for careful individual analysis of mortality-associated risk factors [10] and the potential benefits and risks associated with the therapy. Additional caution should be exercised in extrapolating the currently available safety and efficacy data to infants less than 38 weeks gestation who may have an increased baseline risk for intracranial hemorrhage.

There is a clear need for additional research to define the safety and efficacy of rhAPC in pediatric patients with sepsis. Although the overall mortality risk with sepsis is lower in the pediatric patient population, the benefits of further lowering mortality are likely to be considerable. As a result, the manufacturer has recently initiated a large multicenter, multinational randomized placebo-controlled trial of rhAPC in pediatric sepsis. The trial is expected to include approximately 600 patients over the course of about 3 years.

Additional study is also needed to:

- Identify subcategories of pediatric patients with severe sepsis who have the highest mortality risks and the potential to benefit most from therapy.
- Determine the impact of this treatment on severe sepsis-related morbidity and intensive resource utilization.
- Demonstrate the ability of this treatment to reduce exposure to blood-products and other potentially high-risk interventions sometimes required for the management of severe sepsis in children.
- Define y-site compatibility of rhAPC with vasoactive drugs, antimicrobial agents, and other drugs commonly used in the management of severe sepsis. Because maintaining multiple venous accesses in critically ill children is often challenging, compatibility data for this drug will be essential to its widespread pediatric use.

The case reported by Dr. Sajan and colleagues in this issue helps to point out the frequent need for extrapolation from available adult data in the treatment of children. This serves to underscore the vital importance of pediatric drug trials in proving the safety and efficacy of new adult drug treatments in the pediatric population. Without the data resultant from the inclusion of pediatric patients in the clinical trials of this drug to date, we would have been completely unaware of the possible differences in risk and benefit presented by the use of this drug in the pediatric population. The partial data currently available for the use of rhAPC in children will help to guide the way for clinical care while a larger placebo-controlled study takes place.

Acknowledgement

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References

In 1927 Warner Brothers released a film entitled *The Jazz Singer* starring Al Jolson, May McAvoy, and Warner Oland. The film featured a revolutionary process called Vita phone, which allowed for synchronized sound and film. The movie was a hit earning more than $3.5 million at the box office (approximately $7 cojillion in today’s money) and vaulting Warner Brothers to the top of the Hollywood food chain. Although the film was only about 25% “talkie” (The first full-length “talkie” *Lights of New York* would not be released until 1928), it marked a departure from which there could be no going back.

Well, if you’ve been to enough Powerpoint presentations using blurry graphics, busy charts, and indecipherable tables in order to demonstrate a dynamic process (don’t even start me on The Far Side cartoons . . .), then you probably agree that we are in need of evolutionary change. In addition, demonstrating to your colleagues during sign-out what a patient looked like, or looks like during an event, using hand gestures and weird body contortions may not only be less than adequate for patient care, it may also result in difficult-to-explain muscle strains.

ICU video can ameliorate both problems. Adding video to your presentations can make them easier to follow and understand (in addition to helping keep your audience awake for such thrilling ICU talks as “Borborigmy, The Thunder from Down Under?” or “Inaccurate ICU Urine Charting: More Than Just Water under the Bridge?”). Video can bring immediacy to presentations that allow your audience to see exactly what you saw and creates a mutual experience that can facilitate education. The addition of video to a presentation allows for dynamic activity to be present dynamically. In addition, by keeping videos of patient exam points, patient care can be enhanced, as all parties have the same baseline examination from which to proceed. Has the seizure activity changed? Have the unusual movements become more or less pronounced? Has the breathing pattern altered substantially aside from rate? For these answers and more, let’s go to the video tape. Video also allows for improved follow-up by following findings over time, and some diagnostic tests are best transmitted in motion; consider echocardiography, and bronchoscopy looking at dynamic obstruction.

In the previous article, we discussed how to obtain video in the ICU, now let us take a look at how to incorporate video into your education and practice.

Now that you have your shiny new DV camera, and have shot some video, we need to get it into a computer. One of the wonders of the DV (or most likely mini DV) format is the ability to transmit video to the computer via means of a very fast connection, called IEEE394, or alternately Firewire (Mac) or I-Link (Sony, others). Using this connection, video and audio can be brought directly into a computer synchronously.

Once in the computer, we need to manipulate the video in several different ways. The first thing we need to do is edit the video. Just as no one but your mother can stand to sit through hours of video of you and the kids at Happy Peach Log Place (note, not a real place, just made up for this example), the same is true of your clinical video. Brevity may be the soul of wit, but it is even more important in clinical video.

There are 2 reasons for this. The first is that video takes up an enormous amount of space on your hard disk. The more footage, the more memory usage. It makes sense to use as little video as makes your point. The second reason is that even excellent video can become repetitive and boring; using short clips to make your points keeps your audience interested and attentive.

The program where you edit video is called a nonlinear editor (NLE). These range from the very simple and inexpensive such as Apple’s iMovie, which comes free as part of the software bundle with each new Macintosh, to very complex and expensive such as Avid’s Express Pro and assorted hardware that can run thousands of dollars. There are excellent low-end products on both the PC and the Mac, and excellent information can be found on the Internet (http://www.macdevcenter.com/pub/a/mac/2003/06/13/dv_tips.html). An entry-level NLE will allow you to edit your video, and even add titles, labels, and do basic audio editing. When you have created your final video segment, it is time to move to compression.
Just as in still graphics, where compression allowed us to display large images with a minimum amount of storage, compression plays an even larger role in video display. First, let’s do a little math. When you watch your television, you are getting an amazing amount of data. Television flies by your eyes at 29.97 frames per second. It is this rapid change of pictures that simulates motion. Moreover, within each frame are 2 separate fields, which contain basically the same information but which are scanned to increase clarity. Digital video contains 720 horizontal pixels and 480 vertical pixels. Some quick math shows us that for each frame of digital video, we show 345,600 pixels multiplied by 29.97 frames per second to give us 10,357,632 pixels per second, and multiplied by 2 (the number of fields) gives us 20,715,264 pixels, each of which can vary in terms of color and luminosity (brightness). As you can see, that’s a lot of data for each second of video. (In terms of bytes of computer memory needed, it’s about 7 cojillion bytes.) To allow display, as well as storage, we need to compress this video.

What video compression does is take like elements and make them even more similar, thus giving the computer less to “remember.” The process is similar to compressing data for a still graphic but much more data intensive and processor dependant. It is for this reason that it is best to obtain the fastest computer your budget allows if you plan on working with a lot of video.

Although most NLE’s will also compress video, there are excellent programs that just handle this task. Once again, if you plan on working with a lot of video, an investment in one of these compression programs can save a considerable amount of time and improve the quality of your video as well.

Finally we need a way to display our video. Many NLE’s will allow a user to export the edited video back to a camera or video deck. Using cables and a projector, or a video monitor, the edited video can then be displayed. This allows the highest level of display quality, as it eliminates the compression stage. However, it is difficult to archive your video in this manner, as DV tape is cumbersome and expensive. A much better solution is to compress the video, and then display it on a computer, either from a DVD one can create or within Powerpoint. To display video from within Powerpoint, create a new slide, go to the insert menu, scroll to Insert>Movie from file, locate your movie, and click on it. Powerpoint has options for optimal size and automatic playback.

Well, I hope this has whetted your appetite to get started in the world of video. For examples of some of these concepts, surf over to http://www.ohsu.edu/doernbecher-picu/medialab/, and feel free to e-mail me with questions.

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BOOK REVIEWS

*Beating Heart Coronary Artery Surgery*

Edited by Thomas A. Salerno, Marco Ricci, Hratch L. Karamanoukian, Giuseppe D’Ancona, and Jacob Bergsland

Futura, 2001

This monograph, published in 2001, is one of the first bound publications to summarize the state of the art in this growing and developing field of cardiac surgery. It is edited by renowned experts in the field, with chapters authored by 36 surgeons from 7 different countries. For both the novice and the experienced off-pump surgeon, it is a true experts’ statement.

The book is organized into 4 sections: The first is a brief, single-chapter historical overview of the field, pointing out quite interestingly that the first attempts at any coronary revascularization were indeed “off-pump” and that only after experience with the detrimental effects of cardiopulmonary bypass became concerning was attention turned back to off-pump (“OPCAB”) surgery.

The subsequent 3 sections constitute the bulk of the book, concentrating in turn on the technical aspects of the procedure, the various surgical approaches to the heart, and finally a review of special topics and outcomes. Each chapter is short, well organized, and consistently edited for a smooth and easy-to-read product.

The section on technical aspects discusses and instructs the reader in each of the skills required to successfully perform OPCAB: LIMA harvesting, exposing the coronary arteries, stabilizing the target vessel, verifying graft patency, maintaining hemodynamic stability, converting to cardiopulmonary bypass when necessary, and using blood products appropriately. There is also a very important chapter on forming a treatment “team” with the interventional cardiologist for hybrid surgical-PCI approaches, something that is often overlooked. Each discussion is short and to the point, with a balance of opinion and literature references. My only criticism of this section is the paucity of figures, which unfortunately are reproduced in monochrome, are of rather poor quality, and are sometimes mislabeled and/or have almost useless captions. More attention paid here would certainly have benefited the reader.

The section on surgical approaches concentrates on alternatives to the straightforward, first-time median sternotomy. It is quite interesting as it provides examples of situations where OPCAB technology is far simpler and safer than the more traditional on-pump approaches. Examples here include the small left anterior thoracotomy approach, re-operation, use of the right gastroepiploic artery, and alternatives to use in the face of a calcified ascending aorta. Many surgeons will find that they may have actually stumbled on these approaches in their own patients, and be actually relieved that others are using the same clever solutions to difficult problems. Many of the figures in this section are line drawings, which although less realistic, are still easier to understand than the low-quality monochrome photographs.

The section on complications and outcome data is, in this reviewer’s opinion, the most important of the entire work. It is heavy on outcomes data, which is generally lacking in this nascent field, and therefore fills an important void. Although there are not much data yet available comparing important outcome measures between on- and off-pump surgeries, what was available at the time of this publication has been included and is discussed nicely. The sensitive topics of neurological, renal, and bypass graft function are covered, as is the success rate of OPCAB in the high-risk and elderly patient (although the latter 2 topics are largely from single-center nonrandomized experiences).

In summary, *Beating Heart Coronary Artery Surgery* is a timely work. It is a small and easy-to-read text that fills an important void in this field at this time. The easily digested, distinct chapters provide the reader with very useful information and data, and better equip him or her to learn this field. It is certainly a worthy addition to the bookshelf of any cardiac surgeon or surgeon-in-training.

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*Pain in Infants, Children and Adolescents, 2nd Edition*


Lippincott Williams & Wilkins, 2003

This is a major and important text detailing pain assessment and treatment in children. Well on its way to becoming a classic, this, the second edition, is a revision of the initial text created by these editors nearly 10 years ago. It contains much updated material, which will be of use to both trainees and practitioners in all manner of treatment settings for children.

The book is divided into 3 sections: first the physiology and sociology of pain; then pain as it specifically applies to children, with a review of therapeutic interventions; and finally, perhaps the most valuable part of the text, its third section, which addresses specific pain problems and covers the most common treatment consultations encountered in managing the child with pain. The editors, recognized experts in the treatment of pediatric patients with pain, have again assembled a group of international authors spanning the North American Continent from coast to coast while also including authors from Western Europe, Scandinavia, and the United Kingdom.

In the first section, the chapter on identifying and classifying pain intensity in children deals specifically with different ages. The chapter on pain assessment in infants and toddlers is up to date and an excellent authority for
practitioners in the critical care setting. The chapter on the ethics of pain control in infants and children is valuable for treatment encounters in seriously ill children.

The second section includes an excellent chapter on unconventional analgesics, alternative modalities for pain management, psychological and behavioral treatments, hypothermia therapy, and imaging.

Section 3, the management of specific pain problems in children, includes excellent chapters on treating pain associated with sickle cell disease as well as management of pain in childhood cancer. There is a separate section on sedation and analgesia in the emergency department. Practical advice is given in the chapter on classification and management of headaches in children.

The book’s penultimate chapter includes a detailed and updated outline of considerations for pain management of critically ill children in the pediatric intensive care unit, with clinically relevant recommendations for drug substitutions and how to cope with patients’ increasing requirements over time for larger doses of drugs.

In summary, this book should find its way into the hands of anyone taking care of acute and chronic pain in children. It is an invaluable resource, which should be readily available to those practitioners who must confront children with pain in the critical care setting.

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Conference Announcement

The Ninth International Conference on Continuous Renal Replacement Therapies will be held at the Hotel del Coronado in Coronado, (San Diego), California on February 26-28, 2004.

For further information please contact Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, CA 92108; telephone (619) 299-6673; fax (619) 299-6675; e-mail: c-c-m@worldnet.att.net.