Aspirin Sensitivity
Implications for Patients With Coronary Artery Disease

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For primary and secondary prevention of coronary artery disease (CAD) events, treatment with antiplatelet agents including acetylsalicylic acid forms a cornerstone of therapy and can lead to a 33% event reduction rate.1 However, some patients are unable to tolerate acetylsalicylic acid (aspirin) due to sensitivity or to sensitivity to other nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Aspirin sensitivity can be manifested by aspirin-exacerbated respiratory tract disease, urticaria/angioedema, or anaphylaxis.2

The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10% and for aspirin-induced urticaria the prevalence varies from 0.07% to 0.2% in the general population.3,4 Similarly, one third of patients with chronic idiopathic urticaria will have flare-ups of hives after taking acetylsalicylic acid or NSAIDs.3

Given the prevalence of CAD and sensitivity to acetylsalicylic acid or NSAIDs, practitioners are frequently asked to determine the best antiplatelet regimen for this small, but significant, number of patients. Guidelines from the American College of Cardiology and the American Heart Association for CAD and myocardial infarction indicate a class I indication for acetylsalicylic acid therapy unless a true sensitivity to acetylsalicylic acid or NSAIDs exists in which case thienopyridine (clopidogrel bisulfate, ticlopidine hydrochloride) therapy is indicated.6,7 However, monotherapy for CAD with a thienopyridine is not as cost-effective and sometimes can lead to life-threatening hematologic derangements including thrombotic thrombocytopenic purpura and neutropenia.8

Furthermore, combination therapy with acetylsalicylic acid and a thienopyridine is increasingly indicated for some patients with CAD. In patients with unstable angina/non–Q-wave myocardial infarction, the recently reported Clopidogrel in Unstable Angina

Context Although acetylsalicylic acid (aspirin) is commonly used for patients with chronic cardiovascular disease, a minority of patients have a sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs.

Objective To provide a diagnostic strategy for evaluating and treating patients with aspirin sensitivity, with additional consideration for issues specific to patients with coronary artery disease (CAD).

Evidence Acquisition Published articles were identified through a search of MEDLINE and the Cochrane databases using the dates 1966 to June 2004 and the search terms aspirin allergy, coronary artery disease, aspirin desensitization, and aspirin sensitivity. References of retrieved articles were also reviewed for pertinent studies. Articles were included in this review if they were controlled studies, published in the English language, and appeared in a peer-reviewed journal.

Evidence Synthesis The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10% and for aspirin-induced urticaria the prevalence varies from 0.07% to 0.2% of the general population. Aspirin sensitivity is most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase 1. The primary mechanism of sensitivity is less often related to drug-specific IgE antibody production leading to urticaria/angioedema and rarely to anaphylaxis. Most patients with acetylsalicylic acid sensitivity are able to undergo desensitization therapy safely and successfully except in cases of chronic idiopathic urticaria. However, there have not been any randomized trials that specifically focus on the efficacy of aspirin desensitization. Furthermore, experience with acetylsalicylic acid desensitization in patients with CAD is very limited. After successful desensitization, acetylsalicylic acid therapy must be indefinitely continued to prevent resensitization.

Conclusions Acetylsalicylic acid sensitivity is common and desensitization can be performed safely in many patients. Large-scale trials are warranted to determine the safety and efficacy of acetylsalicylic acid desensitization therapy in patients with concomitant CAD because data are currently limited to small case series.
gina to Prevent Recurrent Events (CURE) trial and Clopidogrel for Reduction of Events During Observation (CREDO) trial\textsuperscript{10} suggest that combination therapy with acetylsalicylic acid and clopidogrel reduce long-term coronary events. Because of the results of these trials, guidelines from the American College of Cardiology and American Heart Association added a class I indication for combination antiplatelet therapy for patients with unstable angina/non–Q-wave myocardial infarction.\textsuperscript{7} Similarly, antiplatelet regimens after drug-eluting stent insertion consistently use combination therapy with acetylsalicylic acid and a thienopyridine to reduce the risk of acute and subacute stent thrombosis.\textsuperscript{11,12} Therefore, treatment with acetylsalicylic acid in combination with a thienopyridine is warranted in an increasing proportion of patients with CAD.

Given the efficacy of acetylsalicylic acid, what should a clinician do when a patient says that he/she is allergic to acetylsalicylic acid? Many patients who think they are allergic to acetylsalicylic acid are not at risk for any reaction\textsuperscript{13}; for those who truly do react to acetylsalicylic acid, options such as acetylsalicylic acid desensitization therapy are available.\textsuperscript{13} Acetylsalicylic acid desensitization therapy refers to slowly increasing the exposure to oral acetylsalicylic acid to reduce and/or eliminate pharmacological and presumed immunologic reactions. Despite the safety and availability of acetylsalicylic acid desensitization therapy, physicians rarely refer patients and thus acetylsalicylic acid may be underused in patients with sensitivity to acetylsalicylic acid or NSAIDs and CAD.\textsuperscript{14} We reviewed the pathophysiological characteristics of sensitivity to acetylsalicylic acid or NSAIDs to create a treatment algorithm that practitioners can use to evaluate and treat patients with sensitivity to acetylsalicylic acid or NSAIDs.

**METHODS**

Published articles were identified through a search of MEDLINE and the Cochrane databases using the dates 1966 to June 2004 and the search terms aspirin allergy, coronary artery disease, aspirin desensitization, and aspirin sensitivity. References of retrieved articles were reviewed for pertinent studies. Data presented at national allergy and cardiology meetings were reviewed for abstracts pertaining to sensitivity to acetylsalicylic acid or NSAIDs and CAD. Criteria for inclusion in this review were articles reporting on controlled studies and of clinical relevance and published in the English language. Data quality was determined by relevance to patient care and publication in a peer-reviewed journal. In specific reference to sensitivity to acetylsalicylic acid or NSAIDs and CAD, no randomized trials exist, thus data from small case series and treatment guidelines from national societies are presented herein.

**Acetylsalicylic Acid as an Antiplatelet Agent**

Aspirin’s mechanism of action involves inhibition of platelet activation and aggregation (FIGURE 1). Acetylsalicylic acid irreversibly inhibits cyclooxygenase 1 (COX-1), thereby limiting production of thromboxane A\textsubscript{2}, which is a potent stimulator of platelet aggregation.\textsuperscript{15} Because platelet activation and aggregation are the nidus
for thrombus formation, inhibition of platelet activity in atheromatous disease is critically important. Furthermore, potential actions of acetylsalicylic acid include stimulation of nitric oxide production, protection of low-density lipoproteins against oxidation, scavenging of free radicals, and protection from endothelial dysfunction. Other potent and clinically useful inhibitors of platelet stimulation and aggregation include glycoprotein IIb/IIIa inhibitors and thienopyridines.

**Pathophysiological Characteristics of Sensitivity to Acetylsalicylic Acid or NSAIDs**

Adverse effects of acetylsalicylic acid and other NSAIDs include a wide variety of pharmacological and presumed immunologic reactions that are categorized by their clinical presentation (Table 1). Pharmacological reactions induced by NSAIDs are dependent on inhibition of the COX-1 pathway and presumed immunologic-mediated reactions are dependent on drug-specific IgE production against an NSAID (Table 2). Of note, cyclooxygenase 2 inhibitors are rarely implicated in NSAID sensitivity because they do not inhibit the COX-1 enzyme except at high concentrations and generally do not act as a hapten for IgE-mediated reactions. Patients may not always present with only one category of reaction, but rather have “blended” reactions such as a predominant urticarial response with a less prominent respiratory tract reaction. Similarly, the same NSAID can induce a pharmacological reaction at one time and presumed IgE-mediated reaction at another time in the same patient.

**Type I: Rhinitis and Asthma Induced by NSAIDs.** Respiratory tract reactions to NSAIDs typically consist of rhinorrhea, bronchospasm, and laryngospasm. Patients will usually have a past history of asthma, nasal polyps, and/or rhinosinusitis. These reactions to NSAIDs are termed aspirin-induced asthma, aspirin sensitivity, aspirin intolerance, or more appropriately aspirin-exacerbated respiratory tract disease (AERD). During NSAID-induced respiratory tract reactions, levels of prostaglandin E2 are rapidly depleted due to COX-1 inhibition. In the absence of the braking effect of prostaglandin E2 on 5-lipoxygenase activating protein and 5-lipoxygenase, there is unrestrained synthesis of new leukotrienes and release of histamine from mast cells (Figure 1). Patients with AERD are particularly susceptible to the effects of leukotrienes that are manifested by excessive nasocutaneous and asthmatic reactions. This airway hyperreactivity may become severe enough to require intubation. Furthermore, patients will cross-react with most other NSAIDs because they also inhibit the COX-1 enzyme (Box). Prior studies have demonstrated that most (or the vast majority of) patients with AERD can successfully undergo acetylsalicylic acid desensitization therapy.

**Type II: Urticaria/Angioedema Induced by NSAIDs.** Patients with a history of chronic idiopathic urticaria (CIU) will frequently experience an exacerbation of their urticaria/angioidema when challenged with acetylsalicylic acid or other NSAIDs. The prevalence of NSAID-induced urticaria in patients with CIU is between 20% and 30%. The pathogenesis of NSAID-induced urticaria is unknown, but similar to AERD, it appears that pa-

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**Table 1. Types of Reactions to Acetylsalicylic Acid and Other NSAIDs and Clinical Risk Factors**

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Underlying Risk Factor</th>
<th>Cross-Reactions to Other NSAIDs</th>
<th>First Exposure Reaction</th>
<th>Mechanism of Sensitivity</th>
<th>Able to Undergo Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NSAID-induced rhinitis and asthma</td>
<td>Asthma, nasal polyps, sinusitis</td>
<td>Yes</td>
<td>Yes</td>
<td>COX-1 inhibition</td>
<td>Yes</td>
</tr>
<tr>
<td>II</td>
<td>NSAID-induced urticaria/angioidema</td>
<td>Chronic idiopathic urticaria</td>
<td>Yes</td>
<td>Yes</td>
<td>COX-1 inhibition</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>NSAID-induced urticaria/angioidema</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>COX-1 inhibition</td>
<td>Yes</td>
</tr>
<tr>
<td>IV</td>
<td>NSAID-induced urticaria/angioidema</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Immunologic*</td>
<td>Yes</td>
</tr>
<tr>
<td>V</td>
<td>NSAID-induced anaphylaxis</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>Immunologic*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: COX-1, cyclooxygenase 1 enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Presumed to be mediated by drug-specific IgE antibody production.

**Table 2. Oral Challenges to Detect Reactions Induced by Acetylsalicylic Acid and Other NSAIDs**

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Response Reaction</th>
<th>Start Dose for Acetylsalicylic Acid, mg†</th>
<th>Interval Between Challenges</th>
<th>Range of Reaction, mg</th>
<th>Usual Time to Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NSAID-induced (cross-reacting)</td>
<td>Rhinitis/bronchospasm</td>
<td>20</td>
<td>3 h</td>
<td>30-100</td>
<td>1-2 h</td>
</tr>
<tr>
<td>III</td>
<td>NSAID-induced (cross-reacting)</td>
<td>Urticaria/angioidema</td>
<td>150</td>
<td>4 h</td>
<td>150-650</td>
<td>2-4 h</td>
</tr>
<tr>
<td>IV</td>
<td>Urticaria§§</td>
<td>Urticaria/angioidema</td>
<td>40</td>
<td>30 min</td>
<td>15-60</td>
<td>15-30 min</td>
</tr>
<tr>
<td>V</td>
<td>Anaphylaxis§§</td>
<td>Anaphylaxis</td>
<td>10</td>
<td>30 min</td>
<td>15-60</td>
<td>15-30 min</td>
</tr>
</tbody>
</table>

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

*Type II reactions are unable to undergo effective acetylsalicylic acid desensitization therapy.

†Patients with type I, II, III, IV, and V reactions receive a double dose on the advance dosing schedule.

‡Avoid the suspected NSAID and challenge with another NSAID or acetylsalicylic acid to prove drug tolerance.

§§Recent recommendations have argued against attempting desensitization therapy in patients with concomitant coronary artery disease and type V reactions.
patients with CIU are sensitive to COX-1 inhibition by NSAIDs. Thus, these patients will cross-react with all NSAIDs that inhibit COX-1. It is believed that excessive leukotriene production by 5-lipoxygenase causes increased vascular permeability and subsequent urticaria.22 Patients in acetylsalicylic acid desensitization protocols have recurrent flare-ups of urticaria until the NSAID is withdrawn.23 In this subset of patients at the Scripps Clinic, acetylsalicylic acid desensitization was not accomplished.

Type III: Urticaria/Angioedema Induced by Multiple NSAIDs. Some patients without a history of underlying CIU develop urticaria/angioedema after treatment with more than one NSAID that inhibit COX-1. These patients will usually experience urticaria/angioedema that is limited to the skin and extremities without accompanying anaphylaxis. Patients at the Scripps Clinic in this subset were able to undergo desensitization therapy safely and effectively; however, no prospective controlled studies have been performed to confirm this observation.

Type IV: Urticaria/Angioedema Induced by a Single NSAID. In patients without known risk factors for a NSAID reaction who experience urticaria and/or angioedema to a single NSAID, the presumed mechanism is believed to be secondary to an immunologic phenomenon related to IgE antibody production. A single NSAID acts as a hapten with subsequent production of drug-specific IgE antibodies against the NSAID. On repeat exposure to the same NSAID, patients will experience an immune-mediated phenomenon with histamine release related to drug-specific IgE antibody production against the NSAID (Figure 1). Assays to detect the specific IgE antibodies against NSAID haptns have been difficult to develop, however specific IgE antibodies were identified against acetylsalicylic acid in a patient with single drug-induced anaphylaxis.24 Because these patients react to a single NSAID, antibodies to specific NSAIDs have been identified, and because these reactions occur after multiple exposures to the NSAID and no satisfying alternative mechanism has been discovered, it has been concluded that these reactions are probably IgE mediated.2 Patients with this type of NSAID sensitivity at the Scripps Clinic were able to undergo desensitization therapy the majority of the time; however, no prospective controlled studies have been performed to confirm this observation.

Mechanisms of Acetylsalicylic Acid Desensitization
A detailed discussion of the mechanisms of acetylsalicylic acid desensitization has been published previously.25 Briefly, acetylsalicylic acid desensitization therapy refers to the elimination of pharmacological and immunologic reactions by slowly increasing exposure to oral acetylsalicylic acid.

Type V: Anaphylaxis Induced by a Single NSAID. Similar to a type IV reaction, a single NSAID can induce anaphylaxis via a presumed IgE-mediated reaction. Patients will not cross-react with other NSAIDs, but are rarely desensitized to the specific drug that caused the reaction given that the reaction is drug-specific to a particular NSAID. Similar to a type IV reaction, no specific data exists regarding efficacy of desensitization therapy, but in our experience desensitization therapy is successful a majority of the time if acetylsalicylic acid is specifically needed.

Box. Patterns of Cross-Reactions Between Acetylsalicylic Acid and Various Nonsteroidal Anti-Inflammatory Drugs

Common nonsteroidal anti-inflammatory drugs (NSAIDs) that preferentially inhibit cyclooxygenase 1 (COX-1) and cross-react with acetylsalicylic acid, inducing respiratory and cutaneous pseudoallergic reactions:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Meclomenamate sodium</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Mefenamic acid</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Nabumetone</td>
</tr>
<tr>
<td>Fenoprofen calcium</td>
<td>Naproxen</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Naproxen sodium</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oxaprozin</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Sulindac</td>
</tr>
<tr>
<td>Ketorolac tromethamine</td>
<td>Tolmetin sodium</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Preferentially, but poorly, inhibits COX-1 and cross-reacts with acetylsalicylic acid.</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Preferentially inhibits cyclooxygenase 2 (COX-2), but at higher concentrations will also inhibit COX-1. At low therapeutic concentrations, it does not cross-react. At high doses, it cross-reacts poorly or not at all.</td>
</tr>
<tr>
<td>Celecoxib</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (removed from the market in October 2004)</td>
<td></td>
</tr>
<tr>
<td>Valdecoxib</td>
<td></td>
</tr>
</tbody>
</table>

Highly selective COX-2 inhibitors that do not cross-react with acetylsalicylic acid and NSAIDs:

- Celecoxib
- Rofecoxib (removed from the market in October 2004)
- Valdecoxib

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In patients with IgE-mediated reactions, the exact mechanism of desensitization is unknown; however, given the need for prior exposure and occasional presence of IgE antibodies we believe it is similar to penicillin desensitization. As in penicillin desensitization, repeated and sustained NSAID exposure leads to saturation of anti-NSAID IgE antibodies sites on basophils and mast cells. In addition, cross-linking of IgE antibodies results in limited mast cell and basophil activation. Ultimately, there is gradual depletion of intracellular mediators (ie, histamine) with continued exposure to the NSAID.

**Approach to Acetylsalicylic Acid Desensitization**

Acetylsalicylic acid desensitization therapy should be undertaken with a multidisciplinary approach ideally involving an allergist, internist, and if considered among patients with CAD, a cardiologist. When first evaluating a patient with suspected NSAID sensitivity, the mechanism of an adverse reaction to an NSAID should be determined. Differentiation between the 2 mechanisms is sometimes difficult because blended reactions do occur; however, historical clues to indicate a COX inhibition mechanism include reactions occurring with the first exposure to the medication and cross-reactivity to other COX-1-inhibiting NSAIDs. Similarly, clues to indicate an IgE-mediated mechanism are the lack of cross-reactivity with other NSAIDs and need for prior exposure to initiate an immune-mediated reaction. If COX-1 inhibition is suspected as the mechanism, then aspirin desensitization should be strongly considered. Even if the original offending drug was not acetylsalicylic acid, the patient will cross-react with acetylsalicylic acid given the similar COX-1 inhibition mechanism.

In contrast, if a patient’s sensitivity was consistent with an IgE mechanism and the reaction was not anaphylactic and the offending drug is a non–acetylsalicylic acid NSAID, then treatment with acetylsalicylic acid can be started safely without desensitization therapy. Antibodies against the non–acetylsalicylic acid NSAID may be present, but specific antibodies against acetylsalicylic acid should not be present.

Acetylsalicylic acid desensitization therapy can effectively be undertaken in the vast majority of patients with NSAID sensitivity, except in those individuals with CIU. However, in patients with acetylsalicylic acid sensitivity and concomitant CAD, data are limited to small case series regarding the safety and efficacy of desensitization therapy. Wong et al reported 9 patients with a history of aspirin-induced urticaria/angiœdema who underwent acetylsalicylic acid desensitization therapy at Scripps Clinic; we identified 8 patients with AERD and CAD who underwent acetylsalicylic acid challenges safely without an exacerbation of their underlying CAD. Furthermore, among 560 patients undergoing acetylsalicylic acid desensitization therapy at Scripps Clinic, we identified 8 patients with AERD and CAD who underwent acetylsalicylic acid challenges safely without an exacerbation of their underlying CAD. Similarly, in a case series of 3 patients with acetylsalicylic acid sensitivity and stable CAD, desensitization therapy with acetylsalicylic acid was undertaken without an exacerbation of coronary disease. Trials on desensitization therapy in patients with anaphylaxis induced by acetylsalicylic acid (type V reactions) and CAD have not been reported and therefore it has recently been recommended that acetylsalicylic acid challenge not be undertaken in this subset of patients.

In patients who do undergo desensitization therapy, it is usually performed in a supervised hospital setting unless they have a history of anaphylaxis to an NSAID, which mandates the oral challenge to be performed in the intensive care unit under controlled conditions. A variety of protocols have been developed, such as the algorithm outlined in Figure 2. Patients who are unstable should undergo coronary intervention and medical management first with a future evaluation and treatment of their NSAID sensitivity. In these patients, the optimal antiplatelet regimen is yet to be determined. We recommend the use of bare metal stents such as heparin-coated stents in lieu of a drug-eluting stent given the need for combination antiplatelet therapy with a thienopyridine and acetylsalicylic acid in patients receiving a drug-eluting stent. Mehra et al demonstrated a 1% rate of stent thrombosis at 30 days using only acetylsalicylic acid monotherapy with heparin-coated stents. Also, in a randomized trial of 243 patients comparing acetylsalicylic acid and ticlopidine combination therapy with ticlopidine monotherapy after bare metal stenting, Machraoui et al demonstrated an equivalent primary end point of in-hospital death, cardiac event, or vascular access-site complication. In that study, stent thrombosis did not occur in any of the patients treated with ticlopidine monotherapy.

Because patients usually do not have restenosis within the first month after initial stenting, there is usually enough time to have patients undergo aspirin desensitization therapy before the usual restenosis window occurs (ie, 1-6 months after stenting). This should allow patients with restenosis of bare metal stents to have placement of drug-eluting stents as they can now receive combination therapy with acetylsalicylic acid and a thienopyridine.

The adjunctive use of warfarin to prevent stent thrombosis and long-term clinical events. In the Warfarin, Aspirin, or Both After Myocardial Infarction (WARIS II) trial comparing aspirin with warfarin after a myocardial infarction, warfarin was found to be superior to aspirin for the prevention of the composite end point of death, nonfatal recurrent myocardial infarction, and thromboembolic cerebral stroke. However, bleeding complications increased in WARIS II. In addition to using bare metal stents and warfarin, other options to consider include the use of glycoprotein IIb/IIIa inhibitors and direct thrombin inhibitors during percutaneous intervention.
Controversies

The best treatment regimen for patients who cannot be desensitized to acetylsalicylic acid prior to stent placement (ie, chronic idiopathic urticaria, unstable patients) is debatable. Some patients may be able to tolerate long-term therapy with a thienopyridine or with warfarin without recurrent cardiac events. However, some patients with cardiac events despite thienopyridine or warfarin therapy may benefit from further treatment with acetylsalicylic acid for CAD. This may be of extreme importance in some patients with coexistent resistance to clopidogrel bisulfate. The current level of evidence demonstrating efficacy of aspirin desensitization is rather low—especially in patients with CAD—with no randomized trials published. Further study should include large-scale multicenter randomized trials to help identify which patients most benefit from aspirin desensitization, and to determine which desensitization techniques are most safe and cost-effective.

CONCLUSION

Acetylsalicylic acid desensitization therapy is safe and successful in many patients except in those with chronic idiopathic urticaria. In patients with a NSAID sensitivity and concomitant CAD, acetylsalicylic acid desensitization therapy may be considered given aspirin’s excellent clinical efficacy, low-risk profile, and cost-effectiveness. Nonetheless, it must be recognized that published data are limited and randomized trials are needed to determine optimal management approaches in these challenging situations.

REFERENCES