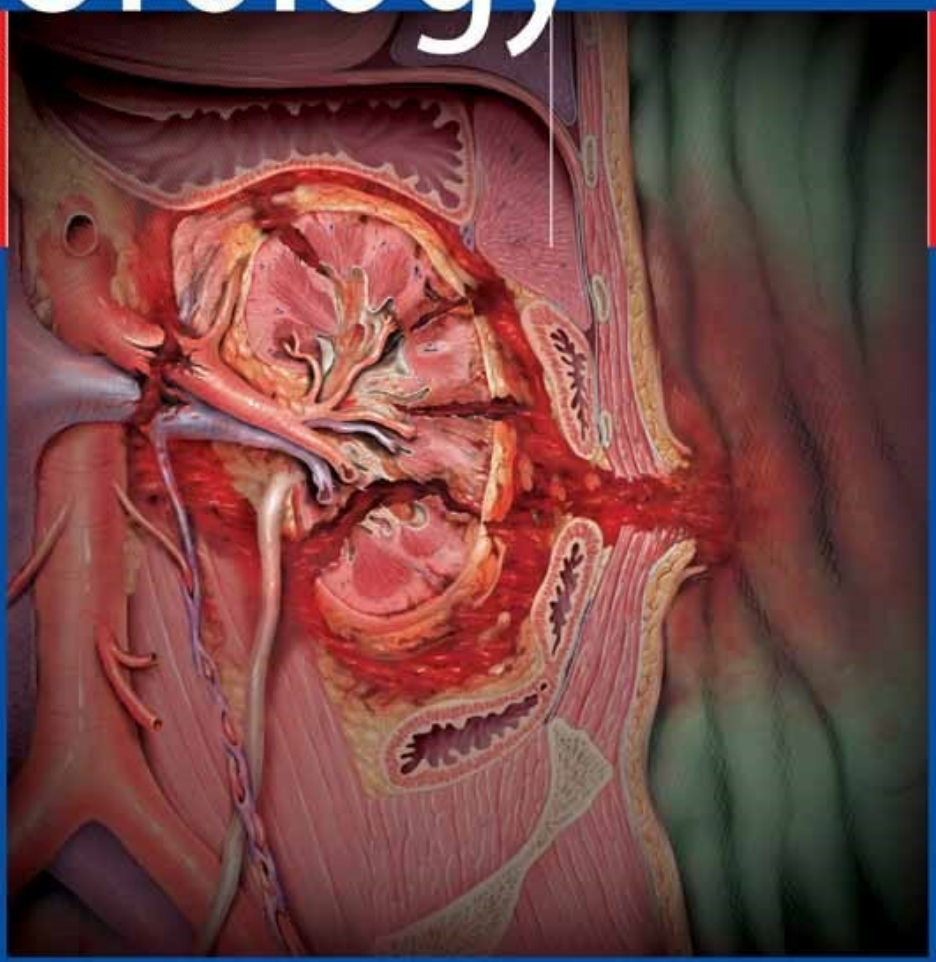
Markus Hohenfellner
Richard A. Santucci
*Editors*

# Emergencies in Urology



Springer

M. Hohenfellner · R.A. Santucci (Eds.)

# Emergencies in Urology

With 312 Figures and 161 Tables

Springer

Markus Hohenfellner, MD
Professor and Chairman
Department of Urology
Heidelberg University, Medical School
69120 Heidelberg, Germany

Richard A. Santucci, MD
Chief of Urology, Detroit Receiving Hospital
Associate Professor, Wayne State University School of Medicine
4160 John R., Suite 1017
Detroit, MI 48201, USA

ISBN 978-3-540-48603-9 Springer-Verlag Berlin Heidelberg New York

Library of Congress Control Number: 2006938751



Springer is a part of Springer Science+Business Media
http://www.springer.com



Printed in Germany



Editor: Dr. Ute Heilmann
Desk Editor: Meike Stoeck
Copy-editing: WS Editorial Ltd, Shrewsbury, UK
Illustrations: Stephan Spitzer, Frankfurt, http://www.medizillu.de and
Reinhold Henkel, Heidelberg, http://reinholdhenkel.illustration.de
Production Editor: Joachim W. Schmidt

Cover design: eStudio Calamar, Spain

Typesetting: FotoSatz Pfeifer GmbH, D-82166 Gräfelfing
Printed on acid-free paper – 24/3150 – 5 4 3 2 1 0

*To Ulrike and Christine*

# Preface

Emergencies in medicine are difficult on two fronts: they may challenge both the health of the patient and the skills of the doctor in charge. If the latter, the former may deteriorate rapidly. Thus, the definition of an emergency indeed depends on who is facing it. As we mature along our clinical pathways of education, training, and experience, the risk of going through a personal professional emergency is continuously reduced. Nevertheless, throughout our medical career, accurate self-assessment and subsequent control of our actions remain our most important qualities. This is true especially for anybody who endeavors into a surgical field.

This book focuses on both kinds of emergencies. It works to facilitate anticipation of potential situations, and therefore allow their competent management. This aim has only become possible with the support of some of the most distinguished urologists for this project. They contributed their rich experience not only in the classical form of textbook chapters but also by narrating their personal Armageddons as open-styled vignettes. These short stories are an impressive proof that persistent awareness and education are essential elements of a successful professional life. They also relay a golden rule to all of our readers, who still have the privilege to call somebody if needed: if in doubt – just do it. The so-called four big Cs: climb, communicate, confess, and comply are the basic actions for any pilot in distress and they may just be as applicable for any doctor facing a difficult situation that may exceed his experience and abilities. Our pride must be to consistently achieve the same result: *salus aegroti suprema lex* – only the best for our patients.

At this point, we want to extend our sincere thanks to the authors who have participated in this book. All of them are extremely busy, internationally renowned clinicians. Nonetheless, their effort and dedication to make *Emergencies in Urology* possible have surpassed all expectations, not only by the superb quality of the manuscripts but also by the timeliness and enthusiasm of their cooperation.

Special thanks are also extended to Stephan Spitzer, whose outstanding art and understanding of the author's picturesque suggestions created many of the ever-so-crucial illustrations.

The editors wish to thank the publishers at Springer-Verlag for a fantastic job. We are especially indebted to our Desk Editor, Meike Stoeck, who was in nearly daily contact with us for years. She helped us immeasurably to stay on time, on the job, and on focus. The final result has been inestimably improved by her efforts.

*Markus Hohenfellner*
*Richard A. Santucci*

# The artwork in this volume was kindly sponsored by:

| | |
|---|---|
| **Astellas** | 81606 München, Germany |
| **Ethicon** | 22861 Norderstedt, Germany |
| **Farco-Pharma GmbH** | 50670 Köln, Germany |
| **SIEMENS Medical Solutions** | 91052 Erlangen, Germany |
| **KARL STORZ GmbH & Co. KG** | 78532 Tuttlingen, Germany |
| **Takeda Pharma GmbH** | 52066 Aachen, Germany |
| **Richard Wolf GmbH** | 75438 Knittlingen, Germany |

# The Editors

## Markus Hohenfellner, MD

Dr. Hohenfellner is Professor of Urology and Chair of The Department of Urology of the University of Heidelberg, Medical School. His institution is consequently organized to function in a high-level interdisciplinary environment and addresses all the contemporary clinical challenges: urologic oncology, minimally invasive surgery, reconstructive surgery, pediatric urology, lower urinary tract dysfunction, stone disease, and andrology.

Dr. Hohenfellner is chairman of the EAU Working Group on Urologic Trauma. He is also the chief representative of the German Urological Association to establish guidelines on Urologic Trauma.

## Richard A. Santucci, MD, FACS

Dr. Santucci is the Chief of Urology at the Detroit Receiving Hospital, one of the nation's first Level I trauma centers and the only hospital built from the ground up to serve as a trauma hospital. He is an Associate Professor at Wayne State University and is a widely published expert in the field of trauma and emergency urology.

Dr. Santucci also serves as the Director of the Center for Urologic Reconstruction at Detroit Receiving Hospital. The Center is a regional referral center for difficult cases in urologic reconstruction, including urethral injury, urethral stricture, and complex reconstructive problems of the bladder, ureters and kidneys.

# Contents

# List of Contributors


**Arap, Marco A., MD**
Assistant Professor of Urology
University of São Paulo
School of Medicine
Av. Dr. Eneas de Carvalho Aguiar 255
05422-970, São Paulo, SP, Brazil

**Arap, Sami, MD**
Professor Emeritus of Urology
University of São Paulo
School of Medicine
Av. Dr. Eneas de Carvalho Aguiar 255
05422-970, São Paulo, SP, Brazil

**Bader, Pia, MD**
Urologische Klinik, Städtisches Klinikum Karlsruhe
Moltkestraße 90
76133 Karlsruhe, Germany

**Beck, Stephen D.W., MD, FACS**
Assistant Professor of Urology
Department of Urology
Indiana University
Indiana Cancer Pavilion
535 N Barnhill Dr
Indianapolis, IN 46202, USA

**Bella, Anthony J., MD, FRCSC**
Clinical Instructor and American Urological Association
Foundation Robert J. Krane Scholar
University of California, San Francisco
400 Parnassus Ave, A633
San Francisco, CA 94143-0738, USA

**Berger, Ingrid, MD**
Resident for Urology
Department of Urology and Andrology
Donauspital
Langobardenstraße 122
1220 Vienna, Austria

**Boccon-Gibod, Laurent, MD**
Professor of Urology
Hôpital Bichat
Clinique Urologique
46 rue Henri Huchard
Paris 75018, France

**Brant, William O., MD**
Northstar Urology
PO Box 40,000
Vail, CO 81658, USA

**Burkhard, Fiona, MD**
Klinik und Poliklinik für Urologie
Universitätsspital Bern
Inselspital
Freiburgstrasse
3010 Bern, Switzerland

**Buse, Stephan, MD**
Member of the Faculty
Department of Urology
University of Heidelberg, Medical School
69120 Heidelberg, Germany

**Chapple, Christopher R., BSc, MD, FRCS, FEBU**
Professor of Urology
Section of Female and Reconstructive Urology
and Urodynamics
Dept. of Urology
Royal Hallamshire Hospital
Glossop Road
Sheffield, S10 2JF, UK

**Cook, Anthony, BSc, MD, FRCSC, FAAP**
Assistant Clinical Professor
Division of Pediatric Surgery
University of Calgary
Pediatric Urology Fellowship Director
Alberta Children's Hospital
Calgary, Alberta

**Dall'Era, Marc A., MD**
Dept. of Urology
University of Washington School Medicine
Seattle, WA 98125, USA

**Diemer, Thorsten, MD**
Universitätsklinikum Gießen und Marburg GmbH
Klinik und Poliklinik für Urologie und
Kinderurologie
Rudolf-Buchheim-Straße 7
35385 Gießen, Germany

**Donatucci, Craig F., MD**
Associate Professor and Vice-Chair
Deptartment of Surgery
Division of Urology
Duke University Medical Center
DUMC 3274
Durham, NC 27710, USA

**Elliot, Sean P., MD**
Professor of Urology
Fellow in Urologic Trauma and Reconstruction
San Francisco General Hospital
1001 Potrero Avenue, 3A-20
San Francisco, CA 94110, USA

**Foster, Richard S., MD, FACS**
Professor of Urology
Department of Urology
Indiana University
Indiana Cancer Pavilion
535 N Barnhill Dr
Indianapolis, IN 46202, USA

**Fradet, Yves, MD**
Département de Chirurgie (Urologie)
Hotel Dieu Hospital
11 Côte du Palais
Québec, Québec G1R 2J6, Canada

**Frohneberg Detlef, MD**
Professor of Urology
Urologische Klinik, Städtisches Klinikum Karlsruhe
Moltkestraße 90
76133 Karlsruhe, Germany

**Gettman, Matthew T., MD**
Mayo Clinic
Department of Urology
200 First Street, SW
Rochester, MN 55905, USA

**Ghoneim, Mohamed A., MD**
Professor of Urology
Urology and Nephrology Center
Mansoura University
Mansoura, Egypt

**Gilfrich, Christian, MD**
Department of Urology
University of Heidelberg, Medical School
69120 Heidelberg, Germany

**Gil-Vernet, José M., MD**
Professor and Chair of Urology
Chair of Urology
Centro Medico Teknon
Vilana, 12
08022 Barcelona, Spain

**Gracia, Maurice M., MD**
Chief Resident
Dept. of Urology
400 Parnassus Ave, A-633
San Francisco, CA 94143-0738, USA

**Günther, Rolf W., MD**
Dept. of Diagnostic Radiology
University Hospital
University of Technology
Pauwelsstraße 30
52074 Aachen, Germany

**Haferkamp, Axel, MD**
Associate Professor of Urology
Senior Faculty
Department of Urology
Heidelberg University, Medical School
69120 Heidelberg, Germany

**Hartung, Rudolf, MD**
Professor Emeritus of Urology
Urologische Klinik und Poliklinik
Technische Universität München
Ismaninger Str. 22
81675 Munich, Germany

**Hermieu, Jean Francois, MD**
Hôpital Bichat
Clinique Urologique
46 rue Henri Huchard
Paris 75018, France

**Heyns, Christiaan F., MD**
Department of Urology
University of Stellenbosch and Tygerberg Hospital
P.O. Box 19063
Tygerberg 7505
South Africa

**Hohenfellner, Markus, MD**
Professor and Chairman
Department of Urology
Heidelberg University, Medical School
69120 Heidelberg, Germany

**Hohenfellner, Rudolf, MD**
Professor Emeritus of Urology
Department of Urology
Johannes Gutenberg University
Langenbeckstraße 1
55101 Mainz, Germany

**Ikoma, Fumihiko, MD**
Professor Emeritus of Urology
18-27, Higashiyama-cho
659-0091 Ashiya, Japan

**Jacobs, Micah, MD**
The Department of Urology
Lahey Clinic
Burlington, MA 01805, USA

**Jacobsen, Niels-Erik B., MD, FRCSC**
Fellow, Urologic Oncology
Department of Urology
Indiana University School of Medicine
Indiana Cancer Pavilion
535 N Barnhill Dr
Indianapolis, IN 46202, USA

**Jordan, Gerald H., MD**
Professor of Urology
Eastern Virginia Medical School
400 W. Brambleton Ave., # 100
Norfolk, VA 23510, USA

**Jünemann, Klaus-Peter, MD**
Professor and Chairman
Klinik für Urologie und Kinderurologie
Universitätsklinikum Schleswig-Holstein, Campus Kiel
Arnold-Heller-Straße 7
24105 Kiel, Germany

**Kavoussi, Louis R., MD**
The Department of Urology
Johns Hopkins Hospital
600 N. Wolfe Street, Suite 161
Jefferson Street Building
Baltimore, MD 21287, USA

**Khoury, Antoine Elie, MBBCH, FRCSC**
Professor
Department of Surgery
The University of Toronto
Division of Urology
Hospital for Sick Children
555 University Avenue
Toronto, ON M5G 1X8, Canada

**Kitrey, Noam D., MD**
Department of Urology
Sheba Medical Center
Tel-Hashomer
52621 Ramat-Gan, Israel

**Krieger, John N., MD**
Department of Urology
University of Washington School of Medicine
Seattle, WA 98125, USA

**Libertino, John, A., MD**
Lahey Clinical Medical Center
41 Mall Rd.
Burlington, MA 01805-0001, USA

**Lue, Tom F., MD**
Professor of Urology
Department of Urology
400 Parnassus Ave, A-633
San Francisco, CA 94143-0738, USA

**Månsson, Wiking MD, PhD**
Department of Urology
University Hospital
22100 Lund, Sweden

**Martin, Eike, MD**
Professor and Chairman
Department of Anesthesiology
University of Heidelberg, Medical School
Im Neuenheimer Feld 110
69120 Heidelberg, Germany

**Martínez-Piñeiro, José A., MD, PhD**
Professor of Urology
Clinica La Luz, Former Head
Department Urology
Hospital Universitario La Paz
Avenida de San Luis 95
Madrid 28033, Spain

**Martínez-Piñeiro, Luis, MD, PhD, FEBU**
Urology Department
La Paz University Hospital
Paseo Castellana 261
28046 Madrid, Spain

**Master, Viraj A., MD, PhD**
Assistant Professor
Department of Urology
Emory University
1365 Clifton Road, N.E., Building B
Atlanta, GA 30322, USA

**McAninch, Jack W., MD**
Professor of Urology, Chief of Urology
San Francisco General Hospital
1001 Potrero Avenue, 3A-20
San Francisco, CA 94110, USA

**Mor, Yoram, MD**
Department of Urology
Sheba Medical Center
Tel-Hashomer
52621 Ramat-Gan, Israel

**Motsch, Johann, MD**
Professor of Anesthesiology
Department of Anesthesiology
University of Heidelberg, Medical School
Im Neuenheimer Feld 110
69120 Heidelberg, Germany

**Mundy, Tony, AR**
Professor of Urology
Trust Headquarters
University College London Hospitals
NHS Foundation Trust
250 Euston Road
London NW1 2PG, UK

**Muntener, Michael, MD**
Department of Urology
Johns Hopkins Hospital
600 N. Wolfe Street
Baltimore, MD 21287, USA

**Nadu, Andrei, MD**
Department of Urology
Sheba Medical Center
Tel-Hashomer
52621 Ramat-Gan, Israel

**Olsson, Carl A., MD**
Columbia University Medical Center
Department of Urology
Herbert Irving Pavilion
161 Fort Washington Ave.
New York, NY 10032, USA

**Pansadoro, Vito, MD**
Professor of Urology
Vincenzo Pansadoro Foundation
Via Aurelia 559
00165 Rome, Italy

**Patterson, Jacob M., MBCHB, MRCS**
Section of Female and Reconstructive Urology
and Urodynamics
Dept. of Urology
Royal Hallamshire Hospital
Glossop Road
Sheffield, S10 2JF, UK

**Perez-Castro, Ellendt E., MD**
Department of Urology
C/General Rodrigo, 8
28003 Madrid, Spain

**Perovic, Sava, MD**
Department of Urology
University Children's Hospital
Tirsova 10
11000 Belgrade, Serbia and Montenegro

**Pfitzenmaier, Jesco, MD**
Associate Professor
Department of Urology
University of Heidelberg
Im Neuenheimer Feld 110
69120 Heidelberg, Germany

**Plas, Eugen, MD**
Associate Professor of Urology and Andrology
Department of Urology and Ludwig Boltzmann
Institute for Urology and Andrology
Hietzing Hospital
Wolkersbergenstr. 1
1130 Vienna, Austria

**Pontes, J. Edson**
Department of Urology
Wayne State University
4160 John P. Denort, 41 I 48201, USA

**Romero, Frederico R., MD**
The Department of Urology
Johns Hopkins Hospital
600 N. Wolfe Street, Suite 161
Jefferson Street Building
Baltimore, MD 21287, USA

**Santucci, Richard A., MD, FACS**
Associate Professor
Wayne State University School of Medicine
Department of Urology
4160 John R., Suite 1017
Detroit, MI 48201, USA

**Schiefer, Hans Gerd, MD**
Professor
Medizinische Mikrobiologie
Universitätsklinikum Gießen und Marburg
Schubertstraße 1
35392 Gießen, Germany

**Schlenker, Boris, MD**
Urologische Klinik und Poliklinik
Klinikum der Universität München – Großhadern
Ludwig-Maximilians-Universität München
Marchioninistraße 15
81377 Munich, Germany

**Schramm, Christoph, MD**
Department of Anesthesiology
University of Heidelberg, Medical School
Im Neuenheimer Feld 110
69120 Heidelberg, Germany

**Schumacher, Martin C., MD**
Klinik und Poliklinik für Urologie
Universitätsspital Bern
Inselspital
Freiburgstrasse
3010 Bern, Switzerland

**Segura, Joseph W., MD**
Mayo Clinic
Department of Urology
200 First Street, SW
Rochester, MN 55905, USA

**Seitz, Michael, MD**
Urologische Klinik und Poliklinik
Klinikum der Universität München – Großhadern
Ludwig-Maximilians-Universität München
Marchioninstraße 15
80336 Munich, Germany

**Serafetinides, Ephraim, MD**
Department of Urology
General Hospital 'Asklipieion' Voula
Vas. Pavlou 1
16673 Voula, Greece

**Shokeir, Ahmed A., MD, PhD, FEBU**
Urology and Nephrology Center
Mansoura University
Mansoura, Egypt

**Skinner, Donald G., MD**
Chairman and Professor of Urology
Department of Urology
University of Southern California
USC/Norris Cancer Center
1441 Eastlake Avenue
Los Angeles, CA 90089-9178, USA

**Stackl, Walter, MD**
Professor of Urology
Urologische Abteilung Rudolfstiftung
Juchgasse 25
1030 Vienna, Austria

**Stein, John P., MD, FACS**
Associate Professor of Urology
Department of Urology
University of Southern California
USC/Norris Cancer Center
1441 Eastlake Avenue
Los Angeles, CA 90089-9178, USA

**Stief, Christian, MD**
Professor of Urology
Urologische Klinik und Poliklinik
Klinikum der Universität München – Großhadern
Ludwig-Maximilians-Universität München
Marchioninstraße 15
80336 Munich, Germany

**Studer, Urs E., MD**
Professor of Urology
Klinik und Poliklinik für Urologie
Universitätsspital Bern
Inselspital
Freiburgstrasse
3010 Bern, Switzerland

**Theron, Pieter D., MD**
Department of Urology
University of Stellenbosch and Tygerberg Hospital
P.O. Box 19063
Tygerberg 7505, South Africa

**Tiguert, Rabi, MD**
Centre de recherche l'Hotel-Dieu Quebec
Centre hospitalier universitaire de Quebec
11, Cote-du-Palais, Quebec G1R2J6, Canada

**Trigo-Rocha, Flavio, MD**
Associate Professor of Urology
Division of Urology
Sao Paulo University
Sao Paulo, Brazil

**Türkeri, N. Levent, MD, PhD**
Professor of Urology
Marmara University Hospital
Department of Urology
Tophaneliolu Cad. No. 13 – 15
Altunizade 34662
Istanbul, Turkey

**Vaughan, Darracott Edwin Jr, MD**
Department of Urology
Weill Cornell University
525 East 68$^{th}$ Street
New York, NY 10021, USA

**Walsh, Thomas J., MD, MS**
Dept. of Urology
University of Washington School Medicine
Seattle, WA 98125, USA

**Wefer, Björn, MD**
Klinik für Urologie und Kinderurologie
Universitätsklinikum Schleswig-Holstein
Campus Kiel
Arnold-Heller-Str.7
24105 Kiel, Germay

**Weidner, Wolfgang, MD**
Professor of Urology
Universitätsklinikum Gießen und Marburg GmbH
Klinik und Poliklinik für Urologie und
Kinderurologie
Rudolf-Buchheim-Straße 7
35385 Gießen, Germany

**Wildberger, Joachim E., MD**
Dept. of Diagnostic Radiology
University Hospital
University of Technology
Pauwelsstraße 30
52074 Aachen, Germany

**Wimpissinger, Florian, MD, FEBU**
Urologische Abteilung Rudolfstiftung
Juchgasse 25
1030 Vienna, Austria

**Wolf, J. Stuart, Jr., MD**
Professor of Urology
University of Michigan
1500 E. Medical Center Dr.
TC 3875
Ann Arbor, MI 48109-0330, USA

**Wotkowicz, Chad, MD**
Department of Urology
Lahey Clinic
Burlington, MA 01805, USA

**Yoon, Gerald H., MD**
Department of Urology
University of Southern California
USC, Norris Cancer Center
1441 Eastlake Avenue
Los Angeles, CA 90089-9178, USA

**Zantl, Niko, MD**
Associate Professor of Urology
Urologische Klinik und Poliklinik
Technische Universität München
Ismaninger Str. 22
81675 Munich, Germany

# Urologic Emergencies: Overview

1

S.P. Elliott, J.W. McAninch

Compared to other surgical fields there are relatively few emergencies in urology. For this reason we may become unaccustomed to caring for the acutely ill patient. Therefore, it is important to keep certain guiding principles in mind when confronted with a patient with an emergent urologic condition.

First, remember that emergencies in urology are rarely life-threatening. Even some of the most concerning conditions such as pyonephrosis or renal trauma are urgent but usually not emergent. Remembering this principle will prevent one from making rushed decisions about management. Important questions to consider before acting are:

1. Is the patient well enough to undergo an operation?
2. Will an operation improve the situation or is a minimally invasive approach or patience a better course of action?
3. Have you considered possible concomitant pathology or injuries?
4. Should you involve a general surgeon, internist, or intensivist in the patient's care?
5. Would additional imaging be helpful?

By no means should an urgent problem go untreated but taking a couple of minutes to think through these questions could avoid misguided therapy.

Second, as mentioned above, avail yourself of imaging of the genitourinary tract. Radiology should be considered an extension of the physical exam in urology since many of the structures are difficult to examine by palpation. Contrast-enhanced computerized tomography of the abdomen and pelvis with delayed imaging of the urinary collection system plays a critical role in the evaluation and management of abdominal trauma involving the urinary system, ultrasound is often indispensable in the differentiation of orchitis and testicular torsion, and a cystogram diagnoses a bladder perforation as intraperitoneal or extraperitoneal. In each of these examples, findings on radiographic imaging will significantly alter one's choice of management. The urologist should be familiar with the options for imaging and the interpretation of those images.

Third, and perhaps most important, do not be afraid to involve other urologists or other services in the care of the patient, particularly if you are unfamiliar with the management of the acutely ill patient. As alluded to above, many of us have an office-based practice and perform mostly short-stay surgery. If one is uncomfortable managing an acutely ill patient one should not allow pride to prevent one from consulting a colleague early in the patient's hospital course.

# 2 The Clinical Approach to the Acutely Ill Patient

S. Buse, R. Santucci, M. Hohenfellner



## 2.1 Diagnosis

### 2.1.1 The Use of Guidelines and Algorithms

The first step in the management of urologic emergencies is to recognize the clinical significance. One must distinguish among genuinely life-threatening problems such as urosepsis or kidney rupture, urgent problems such as testicular torsion, and merely troublesome conditions such as cystitis in a healthy young woman. This may be more easily said than done. The practitioner is challenged both by the broad spectrum of urologic emergencies and by the even more numerous possible diagnoses mimicking urologic symptoms. For example, a patient with a long history of renal colic may present with acute flank pain, tachycardia, tachypnea, and hypotension. If renal ultrasound is normal (lack of upper tract dilatation) and urinalysis reveals no microhematuria, abdominal ultrasonography and/or computed tomography (CT), as indicated in a diagnostic algorithm, will lead to the correct diagnosis of ruptured abdominal aneurysm.

A useful source of immediate, compact information for clinicians is found in published clinical guidelines (e.g., from the European Association of Urology [EAU][Lynch et al. 2005], the American Urological Association [AUA][Montague et al. 2003], or others often based upon the classification for urologic trauma formulated by the American Association for the Surgery of Trauma [Baker et al. 1974; Moore et al. 1989]). Most preferable are guidelines classified by the level of evidence: S1 guidelines representing an informal consensus of experts, S2 a formal consensus, and S3 a formal consensus adhering to evidenced-based medicine, with the elaboration of clinical algorithms. Guidelines in this form are widely used in other fields such as emergency medicine (e.g., cardiovascular resuscitation, initial management of trauma patients) and are increasingly used in urology.

Algorithms lead the doctor through the different potential situations arising during a urologic emergency and communicate in a clear and rapid way how to proceed to the next step. Because they are presented in a stepwise fashion and are logical, they are often easy to memorize. The branching design of algorithms creates decision trees, and the management pathway cannot be continued until the proper test is ordered or the diagnostic solution found. Algorithms therefore provide what is essential and unique to emergency medicine: a simultaneity of diagnosis and therapy.

### 2.1.2 The Emergency Setting

The emergency setting is characterized by continuous and rapid changes in the patient, and thus the assessment can seldom be deemed complete. Accordingly, repeated checks of the patient and of the working hypothesis are warranted. It is also important to evaluate the results of each step in the therapeutic process.

The current availability of high-tech diagnostic tools does not supplant the need for a urologist who is able to identify the salient facts in the history and findings on physical examination, as these are the bases for the correct management choice. The urologist must also be skilled in extracting the relevant results from technical or laboratory tests and in integrating these into the given management pathway.

## 2.2 History

Urologic emergencies, even if life-threatening (e.g., sepsis or hemodynamically relevant postoperative bleeding), should not hinder history taking of the acute event. Information to elicit includes concurrent illness or operation (e.g., previous nephrectomy in a patient with traumatic kidney rupture), medication (e.g., fever in neutropenic patients after chemotherapy requires a different therapeutic approach), and (crucially) allergy. Any minimal delay in therapy is offset by the avoidance of any potential iatrogenic complication, possibly adding a second emergency to the one already under evaluation. The AMPLE history (Allergies, Medications, Past medical history, time of Last meal, Events preceding the injury) used in trauma surgery can be used as a template in traumatic and even nontraumatic emergencies. Other elements of the urgent history include localization, time dimension, intensity and mitigating/inducing factors of the current problem. Some patients may not be able to report their condition themselves. In young children, patients with dementia, and those who are severely ill (urosepsis or polytrauma) or whom we are asked to treat intraoperatively, the history may be obtained from family members, the rescue staff, or the operating team.

The importance of history taking in urologic emergency is illustrated by a prospective study (Eskelinen et al. 1998) addressing its accuracy in acute renal colic. The combination of gross hematuria, loin tenderness, pain lasting less than 12 h, and decreased appetite–all information easily available from history–detected renal colic with a sensitivity of 84 % and a specificity of 98 %.

## 2.3 Physical Examination

### 2.3.1 Primary Survey

In emergency urology, many decision trees branch on the vital signs of blood pressure, pulse rate, respiratory rate, temperature, and general assessment of the patient (i.e., toxic or well appearing). These should be available from nursing personnel before any history taking by the doctor; if not, they must be obtained quickly (and updated frequently). After the vital signs, the initial assessment follows. Although urologists will be tempted to emphasize the genitourinary physical examination, elements of airway, breathing, circulation, disability (neurologic) and exposure (environmental), making up the ABCs, must be assessed (even briefly) in emergency cases before getting down to the U for urology! The authors have witnessed patients with impressive gunshot wounds to the genitalia that completely diverted primary caregiver attention from chest gunshot wounds that ultimately required emergency thoracotomy.

The urologist will be better able to make use of modern diagnostic tools and management algorithms in a purposeful manner once the urologic history and physical examination are complete. They should not be bypassed. A prospective controlled study addressing the predictive value of abdominal examination in the diagnosis of abdominal aortic aneurysm, for instance, reported a negative predictive value higher than 90 % for aneurysms of 4 cm and a positive predictive value over 80 % for those larger than 5 cm (Vendatasubramaniam et al. 2004). Another group (van den Berg et al. 1999) compared the detection of groin hernia by different diagnostic tools and physical examination. Interestingly, physical examination achieved a sensitivity of 75 % and a specificity of 96 %. In patients with acute abdominal pain (Bohner et al. 1998), the variables with the highest sensitivity for bowel obstruction were distended abdomen, decreased bowel sounds, history of constipation, previous abdominal surgery, vomiting, and age over 50 years. The authors of this study calculated that, if only those patients presenting two of these variables had undergone imaging, radiography could have been avoided in 46 % without loss of diagnostic accuracy.

### 2.3.2 Secondary Survey

After vital signs and the initial assessment, the secondary assessment is conducted. If possible, the physical examination should be conducted in a systematic way in a fully exposed patient. In trauma patients, the risk of hypothermia must be considered even in the warmer months; nevertheless, it should not hinder complete exposure for examination and it will be reduced by warm infusions and by covering with external warming devices after assessment (ATLS Manual 2004a). With the exception of life-threatening emergencies requiring immediate evaluation and therapy, the secondary assessment should include organ systems other than those assumed to be affected. This will allow the discovery of physical signs not necessarily linked to the working hypothesis, as well as those arising from any additional disease (e.g., discovering a melanoma in a patient presenting with renal colic).

The reduced interrater reliability (Close et al. 2001) or accuracy (Weatherall and Harwood 2002) of some physical tests should not lead to a dismissal of the physical examination as a whole. For example, blood at the urethral meatus is only 50 % predictive of posterior urethral distraction injury, and a high-riding prostate is only 33 % predictive, but they are nonetheless useful features of the assessment. It remains the task of uni-

versities and training programs to support the teaching of these basic physical examination skills and their successful incorporation into diagnostic and therapeutic algorithms.

## 2.4 Laboratory Testing

Before trusting any laboratory value, one should always verify that the results actually stem from the patient and that laboratory or collection error has not occurred. Even in modern hospital systems, laboratory values are not completely reliable and blood or urine samples may have been exchanged. This is particularly important in episodes of mass casualty with numerous traumatized patients arriving simultaneously at the emergency room (ATLS Manual 2004b). In all cases, laboratory values that appear erroneous or do not make sense should be quickly rechecked before irrevocable steps are taken in the patient's care. Blood drawn from a vein above an intravenous infusion, for example, may show a very low hematocrit level indicating massive blood loss, but if the patient appears well and has normal vital signs the value might best be rechecked rapidly before acting.

In the management of emergencies, the time required for a particular test to return a result is a relevant issue. Diagnostic tools that are faster but less accurate may be substituted. For example, a patient with a suspected pulmonary embolus and a positive d-dimer blood test in the emergency room (fast but not 100% accurate) may be started on heparin while awaiting a more definitive spiral CT of the chest or angiogram. This provides the soonest effective therapy.

A peculiarity in urologic laboratory testing is found in the analysis of dipstick versus microscopic versus microbiological (culture) urine analysis. Culture results, particularly, will not be available for 48 – 72 h. It is imperative, however, to have collected a sample before starting empiric antibiotic treatment. The safest plan is to consider a complete urinalysis to consist not only of a dipstick test but also microscopic analysis and, if there are any nitrates or white blood cells present, an automatic Gram-positive and Gram-negative microbiologic culture.

Dipstick tests are quick but give both false-positive and false-negative results in the presence of some physicochemical urine properties as well as certain drugs. Blood detection might be hindered by captopril or vitamin C intake and leukocyte esterase by elevated specific gravity, glycosuria, proteinuria, and oxidating drugs, including some cephalosporins, tetracycline, and gentamicin (Simerville et al. 2005).

The sensitivity of dipstick urinalysis ranges from 91% to 96% for microscopic hematuria, 72% to 97% for abnormal leukocyte esterase, and 19% to 48% for nitrites; specificity ranges from 65% to 99%, 41% to 86%, and 92% to 100%, respectively(Simerville et al. 2005). Under the pressure of cost containment, numerous studies have addressed the diagnostic value of dipstick testing in the emergency room. Two prospective observational studies concluded that, in women with suspected UTI, over- and undertreatment rates were similar for various test cut-off values for urine dipstick and microscopic urine analysis (Lammers et al. 2001) and that microscopy prompted changes in only 6% of patients with suspected UTI and in none with suspected microhematuria (Jou and Powers 1998). On the other hand, Leman (2002) calculated that microscopy improved the specificity for UTI in women presenting to the emergency room. More importantly, the study revealed the dipstick urinalysis to be susceptible to systemic bias for UTI, resulting in different sensitivity and specificity values in patients with different clinical manifestations (Lachs et al. 1992; Grosse et al. 2005). In short, although the value of microscopy may be controversial in the general emergency room setting, it is not so in the urologic emergency room. In this specific population, many with severe or recurrent UTI, the practice of obtaining microscopy in addition to dipstick urinalysis is warranted.

## 2.5 Imaging

### 2.5.1 Sonography

History, physical examination and laboratory tests are usually completed by various imaging procedures. In Europe, the easiest test to access is commonly sonography; in the US it is probably CT. Sonography allows the evaluation of the size and position of the kidneys, parenchymal width, and the detection of masses, calculi (especially over 3 mm) (Heinz-Peer and Helbich 2001) and calcifications. Moreover, it is possible to diagnose urinary tract dilatation and assess the grade of hydronephrosis. In the lower urinary tract, sonography can show bladder tumors, clots, and bladder stones. Finally, after micturition the residual volume can be calculated.

Emergency indications for formal renal ultrasound include renal colic, renal failure, acute renal infection, urinary retention, and the detection of complications in renal transplant patients, as well as the exclusion of important nonurologic differential diagnoses such as spleen or liver rupture. However, because of the overwhelming diagnostic advantages of CT (Fowler et al. 2002; Sheafor et al. 2000), renal ultrasound is likely the second best choice for imaging calculi in suspected colic, except in children and pregnant women.

Emergency vascular evaluation by Doppler or duplex sonography is indicated in the acute scrotum to detect testicular torsion: the ultrasound finding of de-

creased or absent testicular flow achieves a sensitivity of up to 90 % and a specificity of over 98 % (Karmazyn et al. 2005). Emergency duplex sonography is also applicable for the detection of renal venous thrombosis (as a second choice after CT in patients who are pregnant or allergic to iodinated contrast) and perfusion disorders complicating renal transplantation, trauma, or urologic surgery.

### 2.5.2 Plain Abdominal Films

Although less useful, plain abdominal films (KUB) include information about the size and position of the kidneys, of the psoas shadow (poor identification may be a manifestation of retroperitoneal hematoma from a ruptured aortic aneurysm), and of intestinal gas distribution (e.g., postoperative ileus) and can aid the search for calculi and organ calcification, free intraabdominal gas, and bone pathology. For more than half a century, the plain abdominal film was the only tool available to detect urolithiasis. However, because of its limited accuracy for the direct detection of stones (Haddad et al. 1992; Levine et al. 1997; Mutgi et al. 1991), it is indicated only in follow-up of conservatively managed urolithiasis, of fragmentation results after lithotripsy (in combination with sonography), and for missed calculi after ureterorenoscopy (Grosse et al. 2005). Its advantages include availability, rapidity, and the ease of image evaluation even by a nonradiologist. Its only secondary effect is a small degree of radiation exposure, which is generally not a contraindication except in pregnant women and perhaps young children.

### 2.5.3 Intravenous Pyelography

Intravenous pyelography (IVP) allows additional qualitative analysis over KUB. It can determine the secretory function of each kidney, the presence of delay in filling of the renal pelvis (found in urinary obstruction), the post-void residual volume, and can describe the genitourinary anatomic pathology. Until 1995, IVP was the mainstay in the diagnosis of renal colic, but it has since been supplanted by helical CT. Its drawbacks are its generally lower sensitivity, the risk of forniceal rupture because of osmotic diuresis from contrast in the presence of occluding calculi, and the relatively long time to obtain the several images required for a complete IVP study. In some hospital systems, although the patient may be billed more for a CT scan than for an IVP (say US $ 2,000 for a noncontrast CT of the abdomen and pelvis versus US $ 650 for an IVP), the actual cost to the institution is much lower for CT. The specificities of IVP and helical CT for urolithiasis appear to be similar (Niall et al. 1999; Reiter et al. 1999).

Further disadvantages of IVP include the potential to mask stones through the secreted contrast product, the risks of iodinated contrast (including allergic reaction up to anaphylaxis), and an eventual induction of thyrotoxicosis in patients with clinically silent hyperthyroidism. The possibility of impaired renal function from IVP dye and the contraindication to injection in those with significant renal insufficiency cannot be forgotten. It is not without its benefits, however, and there are some situations in which IVP is actually preferred, as in the need for precise anatomic planning before complex ureteroscopy or percutaneous nephrolithotomy (Grosse et al. 2005).

### 2.5.4 Computed Tomography

Computed tomography is the gold standard in most urologic emergencies, including urolithiasis and renal trauma in the context of polytrauma. It is also useful in the exclusion of postoperative complications such as hemorrhage, abscess, or ileus (Balthazar 1994), or differential diagnoses such as abdominal aortic aneurysm (Hirsch et al. 2006).

The use of the nonenhanced helical CT to detect urolithiasis has been established since the ninetees (Liu et al. 2000; Miller et al. 1998) and has now mostly displaced IVP (Dalla Palma 2001). The sensitivity, depending on calculus size, amounts to nearly 100 % (Liu et al. 2000; Catalano et al. 2002; Fielding et al. 1997; Hamm et al. 2002). CT detects even nonradiolucent calculi, with the exception of stones composed of the protease-inhibitor indinavir (used to treat HIV). It can also predict the chances of spontaneous calculus discharge by its accurate size measurement and by the inverse correlation of the intensity of perinephric stranding with spontaneous discharge (Sandhu et al. 2003a, b).

Generally, exposure to radiation from CT is higher than with IVP, although newer low-dose nonenhanced helical CT protocols achieve radiation doses in the same range as IVP with comparable accuracy to standard CT imaging (Hamm et al. 2002).

CT urography (CT scan without, then with, contrast, followed by delayed images showing the urinary excretion phase) reaches an accuracy of 100 % in the detection of urolithiasis and it permits assessment of the retroperitoneum and renal vessels, facilitating the differentiation from other causes of acute flank pain. Its major drawbacks are its long duration, high radiation dose, and the necessity for contrast with the attendant potential secondary effects.

In the hemodynamically stable trauma patient, CT is the gold standard, as it accurately defines the location and severity of injuries, allowing a conservative surgical approach if appropriate. It also provides a view of the entire abdominal viscera, retroperitoneum and pel-

vis. Hemodynamic instability still mandates immediate operative exploration in patients with suspected renal trauma (Kawashima et al. 2001). Intraoperatively, a single-shot IVP can be obtained to image renal injury (Nicolaisen et al. 1985).

In the setting of hemodynamic stable polytrauma patient, CT cystography is an excellent alternative to conventional retrograde cystography (Deck et al. 2000), when necessary. Also, it allows the diagnosis of ureteral lesions resulting in contrast extravasation. In cases of persistent strong suspicion with negative CT, IVP or retrograde ureteropyelography (Lynch et al. 2005) should be adopted. To detect urethral injury, the recommended imaging method is still retrograde urethrography (Lynch et al. 2005).

### 2.5.5 Magnetic Resonance Imaging

Because of its excellent anatomic accuracy, MRI has become irreplaceable in modern uroradiology, but most indications concern oncology and only rarely is it used to evaluate urologic emergencies. An exception worth mentioning is the evaluation of penile rupture (when history and examination are unclear).

In MRI urography, the T2-weighted sequences are used to create an accurate anatomic representation of the urogenital organs and for the detection and analysis of hydronephrosis and hydroureters independent of renal function. T1-weighted contrast-enhanced MRI allows the analysis of excretory renal function and the evaluation of urinary outflow in the upper urogenital tract. MRI urography is particularly useful in the diagnosis of congenital disturbances in children (Nolte-Ernsting et al. 2001). The avoidance of iodinated contrast also makes MRI the primary choice in patients allergic to contrast material.

### 2.5.6 Chest X-Ray

For a more comprehensive view of the patient, to exclude nonurologic differential diagnoses (e.g., basal pneumonia with low posterior intercostal pain mimicking pyelonephritis) or complications of urologic disorders (e.g., lung metastases in testicular cancer), chest-x-ray should also be considered. In any case, an interdisciplinary diagnostic and therapeutic approach should always be adopted to optimize patient management.

## References

ATLS Manual (2004a) Advanced trauma life support for doctors, 7th edn. American College of Surgeons, Chicago, pp 18, 76

ATLS Manual (2004b) Advanced trauma life support for doctors, 7th edn. American College of Surgeons, Chicago, p 80

Baker SP, O'Neill B, Haddon W Jr et al (1974) The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 14:187

Balthazar EJ (1994) For suspected small-bowel obstruction and an equivocal plain film, should we perform CT or a small-bowel series? AJR Am J Roentgenol 163:1260

Bohner H, Yang Q, Franke C et al (1998) Simple data from history and physical examination help to exclude bowel obstruction and to avoid radiographic studies in patients with acute abdominal pain. Eur J Surg 164:777

Catalano O, Nunziata A, Altei F et al (2002) Suspected ureteral colic: primary helical CT versus selective helical CT after unenhanced radiography and sonography. AJR Am J Roentgenol 178:379

Close RJ, Sachs CJ, Dyne PL (2001) Reliability of bimanual pelvic examinations performed in emergency departments. West J Med 175:240

Dalla Palma L (2001) What is left of i.v. urography? Eur Radiol 11:931

Deck AJ, Shaves S, Talner L et al (2000) Computerized tomography cystography for the diagnosis of traumatic bladder rupture. J Urol 164:43

Eskelinen M, Ikonen J, Lipponen P (1998) Usefulness of history-taking, physical examination and diagnostic scoring in acute renal colic. Eur Urol 34:467

Fielding JR, Steele G, Fox LA et al (1997) Spiral computerized tomography in the evaluation of acute flank pain: a replacement for excretory urography. J Urol 157:2071

Fowler KA, Locken JA, Duchesne JH et al (2002) US for detecting renal calculi with nonenhanced CT as a reference standard. Radiology 222:109

Grosse A, Grosse CA, Mauermann J et al (2005) [Imaging techniques and their impact in treatment management of patients with acute flank pain]. Radiologe 45:871

Haddad MC, Sharif HS, Shahed MS et al (1992) Renal colic: diagnosis and outcome. Radiology 184:83

Hamm M, Knopfle E, Wartenberg S et al (2002) Low dose unenhanced helical computerized tomography for the evaluation of acute flank pain. J Urol 167:1687

Heinz-Peer G, Helbich T (2001) [Urological and nephrological emergency-value of diagnostic imaging]. Wien Med Wochenschr 151:560

Hirsch AT, Haskal ZJ, Hertzer NR et al (2006) ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 113:e463

Jou WW, Powers RD (1998) Utility of dipstick urinalysis as a guide to management of adults with suspected infection or hematuria. South Med J 91:266

Karmazyn B, Steinberg R, Kornreich L et al (2005) Clinical and

sonographic criteria of acute scrotum in children: a retrospective study of 172 boys. Pediatr Radiol 35:302
Kawashima A, Sandler CM, Corl FM et al (2001) Imaging of renal trauma: a comprehensive review. Radiographics 21:557
Lachs MS, Nachamkin I, Edelstein PH et al (1992) Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. Ann Intern Med 117:135
Lammers RL, Gibson S, Kovacs D et al (2001) Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. Ann Emerg Med 38:505
Leman P (2002) Validity of urinalysis and microscopy for detecting urinary tract infection in the emergency department. Eur J Emerg Med 9:141
Levine JA, Neitlich J, Verga M et al (1997) Ureteral calculi in patients with flank pain: correlation of plain radiography with unenhanced helical CT. Radiology 204:27
Liu W, Esler SJ, Kenny BJ et al (2000) Low-dose nonenhanced helical CT of renal colic: assessment of ureteric stone detection and measurement of effective dose equivalent. Radiology 215:51
Lynch TH, Martinez-Pineiro L, Plas E et al (2005) EAU guidelines on urological trauma. Eur Urol 47:1
Miller OF, Rineer SK, Reichard SR et al (1998) Prospective comparison of unenhanced spiral computed tomography and intravenous urogram in the evaluation of acute flank pain. Urology 52:982
Montague DK, Jarow J, Broderick GA et al (2003) American Urological Association guideline on the management of priapism. J Urol 170:1318
Moore EE, Shackford SR, Pachter HL et al (1989) Organ injury scaling: spleen, liver, and kidney. J Trauma 29:1664
Mutgi A, Williams JW, Nettleman M (1991) Renal colic. Utility of the plain abdominal roentgenogram. Arch Intern Med 151:1589
Niall O, Russell J, MacGrego, R et al (1999) A comparison of noncontrast computerized tomography with excretory urography in the assessment of acute flank pain. J Urol 161:534
Nicolaisen GS, McAninch JW, Marshall GA et al (1985) Renal trauma: re-evaluation of the indications for radiographic assessment. J Urol 133:183
Nolte-Ernsting CC, Tacke J, Adam GB et al (2001) Diuretic-enhanced gadolinium excretory MR urography: comparison of conventional gradient-echo sequences and echo-planar imaging. Eur Radiol 11:18
Reiter WJ, Schon-Pernerstorfer H, Dorfinger K et al (1999) Frequency of urolithiasis in individuals seropositive for human immunodeficiency virus treated with indinavir is higher than previously assumed. J Urol 161:1082
Sandhu C, Anson KM, Patel U (2003a) Urinary tract stones: Part II: current status of treatment. Clin Radiol 58:422
Sandhu C, Anson KM, Patel U (2003b) Urinary tract stones: Part I: role of radiological imaging in diagnosis and treatment planning. Clin Radiol 58:415
Sheafor DH, Hertzberg BS, Freed KS et al (2000) Nonenhanced helical CT and US in the emergency evaluation of patients with renal colic: prospective comparison. Radiology 217:792
Simerville JA, Maxted WC, Pahira JJ (2005) Urinalysis: a comprehensive review. Am Fam Physician 71:1153
Van den Berg JC, de Valois JC, Go PM et al (1999) Detection of groin hernia with physical examination, ultrasound, and MRI compared with laparoscopic findings. Invest Radiol 34:739
Venkatasubramaniam AK, Mehta T, Chetter IC et al (2004) The value of abdominal examination in the diagnosis of abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 27:56
Weatherall M, Harwood M (2002) The accuracy of clinical assessment of bladder volume. Arch Phys Med Rehabil 83:1300

# 3 New Developments in Anesthesia

J. Motsch, Ch. Schramm, E. Martin



## 3.1 Perioperative Cardiac Complications

Major cardiac complications presenting as myocardial infarction, myocardial ischemia, cardiac failure, or life-threatening dysrhythmias contribute significantly to perioperative morbidity and mortality. Preventive strategies are of major importance since even despite adequate treatment these events are associated with poor outcome.

### 3.1.1 Myocardial Ischemia

According to Poldermans and Boersma (2005), the incidence of a perioperative myocardial infarction is 0.185 % in the United States. Approximately 50,000out of 27 million patients who are given anesthesia for surgical procedures annually suffer perioperative myocardial infarction. The cause is a prolonged mismatch between myocardial oxygen demand and supply owing to the stress of surgery or as the result of a sudden rupture of a vulnerable plaque followed by thrombus formation and coronary artery occlusion.

Beta-blockers decrease the myocardial oxygen demand by reducing heart rate and myocardial contractility. Additionally they modulate the adrenergic activity leading to decreased levels of fatty acids, thus resulting in a shift in myocardial metabolism toward glucose uptake (Schouten et al. 2006). To identify patients who might benefit from a perioperative beta-blocker therapy, Lindenauer et al. (2005) conducted a retrospective cohort study on 782,969 patients using the validated Revised Cardiac Risk Index (RCRI) (Lee et al. 1999) to stratify patients as low cardiac risk (RCRI 0 and 1) and as high cardiac risk (RCRI 2, 3, 4 or more). The study demonstrated that perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high risk, but not low-risk patients undergoing major noncardiac surgery.

According to the meta-analysis of Schouten et al. (2006), in 1,077 patients with noncardiac surgeries, perioperative administration of beta-blockers lowers the risk of myocardial ischemia by 65 % ($p < 0.001$), the risk

of myocardial infarction by 56 % ($p = 0.04$), and the surrogate risk of cardiac death and nonfatal myocardial infarction by 67 % ($p = 0.002$). Administration of beta-blockers should be commenced prior to surgery, a dose-titration has to be carried out up to the induction of anesthesia, and a lifelong continuation of beta-blocker therapy is recommended in high-risk patients. The optimum time interval to start treatment with beta-blockers before surgery has not yet been defined by studies. The choice of the beta-blocker is of minor importance, since no specific beta-blocker demonstrated a superior effect in the perioperative setting. The side effects of perioperative administration of beta-blockers are a 4.3-fold increased risk of bradycardia ($p = 0.006$), but hypotension, atrioventricular block, pulmonary edema, and bronchospasm are not significantly associated with perioperative beta-blocker therapy. The following contraindications should be kept in mind prior to commencement of beta-blocker therapy: bradycardia, second or third degree atrioventricular block, sick sinus syndrome, and acute heart failure. Patients with asthma bronchiale have to be carefully evaluated as to whether they may benefit from primary protective cardiac effects or are harmed by side effects.

For a practical pathway concerning the perioperative beta-blocker therapy, please refer to Fig. 3.1.

### 3.1.2 Arrhythmias

Cardiac arrhythmias contribute significantly to morbidity and mortality in the perioperative period. Although the knowledge on antiarrhythmic drug use in nonsurgical settings is expanding rapidly, data on the use of these agents perioperatively are still scarce.

Antiarrhythmic pharmacology is focused on the cardiac ion channels and adrenergic receptors for management of arrhythmias in adults during surgery and anesthesia. Virtually all drugs that modulate heart rhythm work through the adrenergic receptor/second messenger system through one or more ion channels. Generally three classes of ion channels have to be considered based on the cation they conduct: sodium ($Na^+$), calcium ($Ca^{2+}$), and potassium ($K^+$) channels. Although ion channels as molecular targets are distinctive, the drug receptor sites are highly homologous, causing some class overlap associated with antiarrhythmic therapy. Table 3.1 lists the molecular targets of antiarrhythmic agents used perioperatively.

**Table 3.1.** Classification of antiarrhythmic drugs

| Receptor | Class | Drugs |
|---|---|---|
| $Na^+$, $K^+$ channels | IA | Amiodarone, procainamide, ajmaline, quinidine |
| $Na^+$ channels | IB | Lidocaine, phenytoin, mexiletine[a], tocainide[a] |
| | IC | Propafenone |
| Beta-adrenoceptors | II | Esmolol, amiodarone, propranolol, atenolol, sotalol[a] |
| $K^+$ channels | III | Bretylium, ibutilide, sotalol[a], dofetilide[a] |
| $Ca^{2+}$ channels | IV | Verapamil, diltiazem, amiodarone |

[a] Orally (only commercially available form)

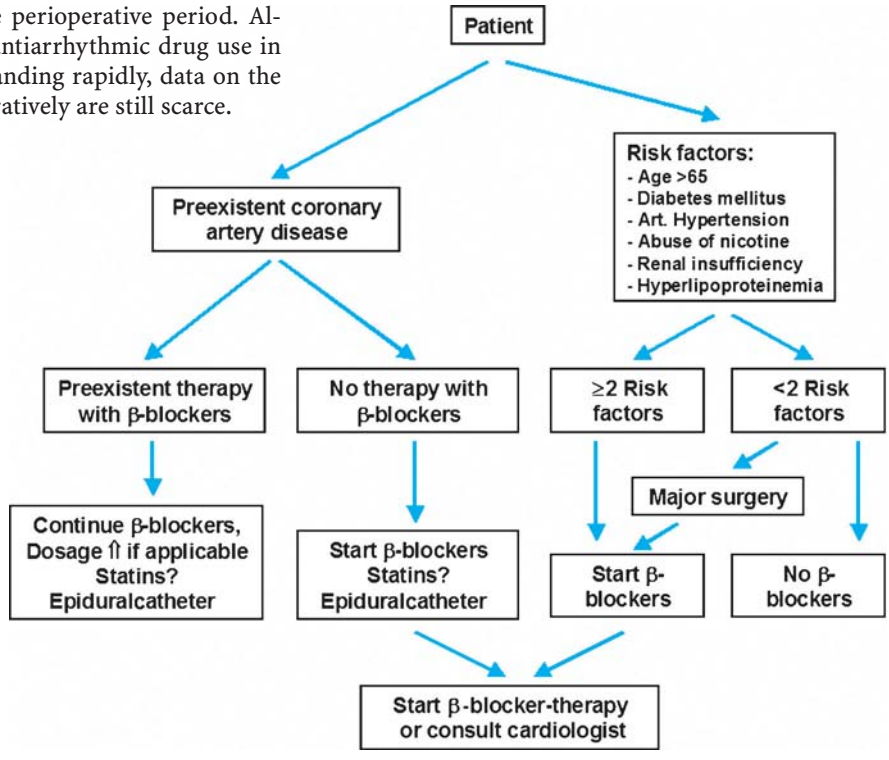



**Fig. 3.1.** Perioperative therapy with β-blockers. Patients with good left-ventricular function (LVF) receive metoprololsuccinate 95 mg once per day; patients with impaired LVF receive 47.5 mg once per day. For contraindications and further explanations see text. Modified from Teschendorf 2006

Perioperative arrhythmias are caused by physiologic and pathologic disturbances or by pharmacologic drug effects. Physiologic disturbances include hypoxemia, hypercapnia, acidosis, hypotension, hypovolemia, electrolyte imbalances, adrenergic stimulation (light anesthesia), vagal stimulation, and mechanical irritation (chest tube, pulmonary artery catheter). Pathologic cardiac disturbances include myocardial ischemia, infarction, acute heart failure, pulmonary embolism, and micro- or macrocirculatory shock. Therapy with proarrhythmic drugs must also be considered when arrhythmias occur perioperatively.

The primary indications for antiarrhythmics are compromised hemodynamics due to critical tachycardias or bradycardias with impaired cardiac output. Another indication is the increased risk for cardiac death due to malignant or potentially malignant arrhythmias. Since all of the antiarrhythmic drugs also bear a proarrhythmic effect, treatment with antiarrhythmics may harm the patient, as was demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST). Therefore, a thorough risk–benefit analysis is mandatory prior to long-term treatment with antiarrhythmics. Generally, the primary aim of antiarrhythmic therapy is to treat the underlying condition such as coronary heart disease or acute heart failure and not to cure symptoms.

In the perioperative setting, arrhythmias are observed quite commonly. Since in the operating room environment there are many reversible causes that predispose patients to arrhythmias, these conditions should be treated before considering pharmacological antiarrhythmic strategies. But in some patients perioperative arrhythmias pose the potential for rapidly developing life-threatening events necessitating immediate treatment.

#### *3.1.2.1 Bradycardia*

Bradycardia is defined as a heart rate below 60 beats per minute. In trained athlete patients as well as in patients with excessive beta-blocker therapy, the heart rate can drop below 40 beats per minute with no symptoms. When low cardiac output is associated with bradycardia, the following stepwise therapeutic approach is indicated, where continuously the next step should be taken on failure of the previous step:

- Start with the administration of a parasympatholytic drug such as atropine up to 3 mg intravenously.
- Then administer a beta-adrenergic drug, e.g., epinephrine in boluses of 10 µg i.v.
- Thereafter consider the application of a transient pacemaker, either as an external transthoracic stimulation with pads or via an esophageal stimulation probe.

When an external pacemaker is not available, a defibrillator with its stimulation mode may be used in case of emergency. Alternatively, internal stimulation with a temporary transvenous-inserted sterile stimulation probe is the treatment of choice in severe heart block.

#### *3.1.2.2 Supraventricular Tachyarrhythmias*

Various adverse physiological phenomena can evoke supraventricular tachyarrhythmias in anesthetized or critically ill patients. For management of the surgical patient, a thorough but rapid consideration of potential causes is required, because correction of reversible conditions may prevent life-threatening conditions. Antiarrhythmic therapy should only be considered after these etiologies have been excluded or in cases of extreme hemodynamic instability.

The origin of supraventricular tachyarrhythmias lies in the area of the atria, the sinus node, or the atrioventricular node (AV node).

- Paroxysmal supraventricular tachyarrhythmia *with* preexcitation is caused (most commonly) by congenital short-circuit conductive fibers leading to a bypass of the regular excitation from the sinus node over the atria to the AV node.

Wolff-Parkinson-White syndrome (WPW) is the most common preexcitation syndrome with the so-called Kent fiber being the accessory conductive fiber. In type A WPW syndrome, ECG recordings show a positive delta wave in V1 and Q waves in II, III, and aVF. In type B WPW syndrome, a negative delta wave is recorded in V1 of the ECG. The delta wave is defined as a slow upslope of the R in the widened QRS complex. The PQ interval is below 0.12 s. WPW syndrome is potentially life-threatening, because an atrial fibrillation with the fast conducting accessory Kent fiber may lead to ventricular tachycardia or ventricular fibrillation. For treatment, a short trial of vagal stimulation may be attempted initially by the Valsalva maneuver or massage of the carotid sinus. On failure, the antiarrhythmic ajmalin 50 mg is administered by slow intravenous injection under ECG monitoring. As an alternative, amiodarone, procainamide, or flecainide should be considered.

It should be noted that patients with accessory pathways may also develop atrial fibrillation. These patients are at increased risk for developing ventricular fibrillation when treated with classic AV-nodal blocking agents (digitalis, calcium channel blockers, beta-blockers, adenosine), because these agents reduce the accessory bundle refractory period.

- A type of paroxysmal supraventricular tachyarrhythmia (PSVT) *without* preexcitation is the AV

node reentry tachycardia. In two-thirds of patients, it is caused by a congenital defect of the cardiac conductive system, in one-third of patients, it is caused by a prolapse of the mitral valve, hyperthyroidosis, or other cardiac diseases. The ECG trace shows a heart rate of 180 – 200 beats/min, small QRS complexes, and a missing P wave. The symptomatic therapy consists of adenosine (6 mg bolus, after 3 min 12 mg bolus), verapamil (5 mg slow intravenous injection over 10 min), or overdrive pacing in circulatory stable patients. In unstable patients with a threat of cardiogenic shock, an electroconversion is indicated with initially 200 J, on failure with higher energy of 360 J. If the patient is conscious, a short-acting hypnotic such as etomidate or propofol should be used for sedation during the electroconversion. Causal therapy is high-frequency catheter ablation.

- Atrial fibrillation (AF) is the most common type of supraventricular tachyarrhythmia. The prevalence is about 0.5 % of the adult population, but at age greater than 60 years, the prevalence is 4 %. The etiology is primary or idiopathic in patients without cardiac disease or secondary due to a cardiac disease such as mitral valve disease, coronary heart disease, or due to extracardial causes such as arterial hypertension or alcohol-toxic effects on the heart ("holiday-heart"). The irregular conduction in the AV node leads to a tachyarrhythmia of the ventricles with frequencies of 100 – 150 beats/min. Treatment strategies include frequency control, conversion into sinus rhythm, and prophylaxis of recurrence. The frequency control is achieved by administering digitalis and verapamil (calcium channel blocker). ECG-triggered cardioversion is performed under short sedation with an initial energy of 100 J. It may be advisable to first establish a therapeutic level of an antiarrhythmic agent that maintains sinus rhythm (i.e., amiodarone, procainamide) in order to minimize the risk of SVT recurrence following electrical cardioversion. It is important to anticoagulate the patient before the cardioversion, if the AF persists longer than 48 h because intracardiac thrombi may have been formed. Thrombi formation can be checked by TTE (transthoracic echocardiography) or by TEE (transesophageal echocardiography). As an alternative, a drug-induced chemical cardioversion may be considered.

For intraoperative and postoperative patients developing new-onset AF who are stable and rate-controlled, pharmacological cardioversion of SVT is questionable. The 24-h rate of spontaneous conversion to sinus rhythm exceeds 50 % and many patients who develop SVT under anesthesia will remit spontaneously before or during emergence. Moreover, the antiarrhythmic agents with long-term activity against atrial arrhythmias have limited efficacy when used for rapid pharmacologic cardioversion. Improved rates have been seen with amiodarone, but further studies have to confirm this because of the potential for undesirable side effects. Finally, it should be kept in mind that in recent-onset perioperative SVT, reversible causes should be excluded or resolved before considering pharmacological antiarrhythmic therapies.

#### *3.1.2.3 Ventricular Tachyarrhythmias*

Morphology (monomorphic vs polymorphic) and duration (sustained vs nonsustained) characterizes ventricular arrhythmias. Nonsustained ventricular tachycardia (NSVT) is defined as three or more premature ventricular contractions that occur at a rate exceeding 100 beats/min and last 30 s or less without hemodynamic compromise. The origin of ventricular premature beats is below the bifurcation of the HIS fibers. Usually the sinus node is not stimulated backwards. This leads to a compensatory pause, which is felt by the patient as an extra beat of the heart. These arrhythmias are routinely seen in the absence of cardiac disease and may not require drug therapy in the perioperative period. In contrast, in patients with structural heart disease, these nonsustained rhythms do predict subsequent life-threatening ventricular arrhythmias. However, antiarrhythmic drug therapies in patients with structural heart disease may worsen survival. When nonsustained ventricular arrhythmias occur during or after major operations, early or late mortality of patients with preserved left ventricular function is not influenced. These patients usually do not require antiarrhythmic drug therapy. However, as in SVT, these arrhythmias may signal reversible etiologies that should be treated. For example, potassium- and magnesium-serum levels should be checked and elevated digitalis levels should be excluded.

Sustained ventricular tachycardia (VT) presents as monomorphic or polymorphic. In monomorphic VT, the amplitude of the QRS complex remains constant, while in polymorphic ventricular tachycardia the QRS morphology continually changes.

Ventricular tachycardia is characterized as a regular tachycardia of 100 – 200 beats/min with bundle-branch-block-like deformed, widened ventricular complexes. The underlying etiology is idiopathic, severe organic cardiac disease, intoxication of digitalis or treatment with other antiarrhythmics, or the Brugada syndrome (congenital mutation of the sodium channel). The underlying mechanism for monomorphic VT is formation of a re-entry pathway, e.g., around scar tissue from a healed myocardial infarction.

This is a life-threatening condition and immediate action is required. Although lidocaine has traditionally

been the primary drug therapy for all sustained ventricular arrhythmias, i.v. amiodarone is now also recommended for treatment of perioperative-occurring monomorphic VT.

Treatment strategies for sustained polymorphic ventricular tachycardia depend on the duration of the QT interval during a prior sinus rhythm. In the setting of a prolonged QT interval (torsades de points), emphasis is taken at reversal of QT prolongation. In addition to QT-prolonging antiarrhythmic drugs (class IA or III), a number of other medications used in the perioperative period may evoke QT prolongation and torsades de points. The management of torsades de points includes i.v. magnesium sulfate (2–4 g), repleting potassium, maneuvers increasing the heart rate (atropine, temporary atrial or ventricular pacing). Hemodynamic collapse requires asynchronous DC countershocks. When antiarrhythmic therapy is deemed necessary, i.v. amiodarone may be considered, because it bears the lowest risk of triggering torsades de points.

Unstable ventricular tachycardia and ventricular fibrillation are life-threatening arrhythmias in the operating room. The most important first maneuvers in patients who experience VF perioperatively are nonpharmacological: rapid defibrillation (360 J monophasic or 200 J biphasic), and correction of reversible etiologies. Amiodarone i.v. (300 mg) should be considered as pharmacological intervention in addition to other measures taken during resuscitation (Thompson and Balser 2004).

A new therapeutic option for the treatment of VT is the implantation of antitachycardic pacemakers. The implantable cardioverter defibrillator (ICD) is used in patients with increased risk of sudden cardiac death due to ventricular fibrillation in recurrent ventricular tachyarrhythmias or history of VF (ventricular fibrillation) with significantly impaired ventricular function. For supraventricular tachyarrhythmia, termination of the reentry mechanisms can be achieved by overdrive pacing with a stimulation frequency above the tachycardic frequency, programmable electrostimulation to terminate circulating impulses through premature impulses, or atrial high-frequency stimulation for the conversion of atrial flutter (Herold et al. 2006).

For an overview of the antiarrhythmic therapy, please refer to Fig. 3.2.

### 3.1.3 Acute Heart Failure

The acute heart failure (AHF) is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, abnormalities in cardiac rhythm, or preload and afterload mismatch. It is often life-threatening and requires urgent treatment.

#### *3.1.3.1 Etiology*

In the perioperative setting, AHF poses a serious threat to the patient, because these patients have a very poor prognosis. The 60-day mortality rate was 9.6 % and the combined rate for mortality and rehospitalization was 35.2 % in the largest randomized trial to date (Cleland et al. 2003). The most common cause of AHF in the elderly is coronary heart disease, whereas in the younger population it is caused by dilatative cardiomyopathy, arrhythmia, congenital or valvular heart disease, or myocarditis (see Table 3.2).

#### *3.1.3.2 Diagnosis*

The diagnosis of AHF is primarily based on clinical findings, electrocardiogram (ECG), laboratory tests, chest x-ray, and echocardiography.

An impaired right ventricular function may be suspected if prominent jugular veins are present. To a cer-

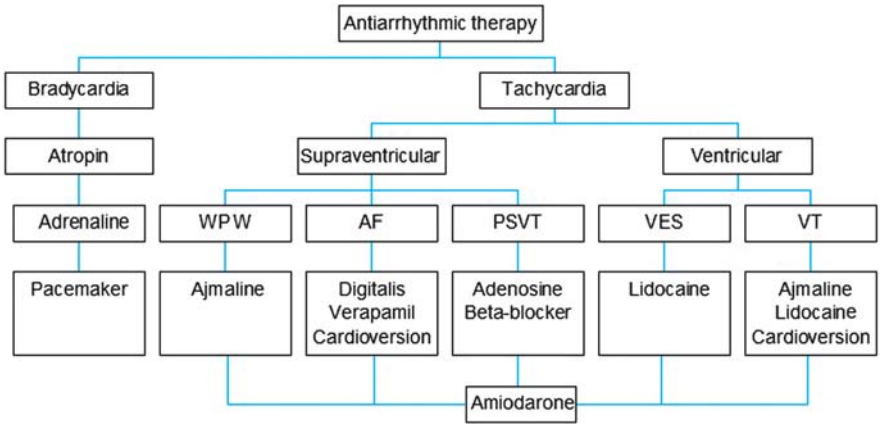



**Fig. 3.2.** Pathway for antiarrhythmic therapy. *WPW* Wolff-Parkison-White syndrome, *AF* atrial fibrillation, *PSVT* paroxysmal supraventricular tachycardia, *VES* ventricular extrasystole, *VT* ventricular tachycardia. Modified from Herold et al. (2006)

**Table 3.2.** Causes and precipitating factors in acute heart failure

| |
|---|
| Decompensation of preexisting chronic heart failure (e.g., cardiomyopathy) |
| Acute coronary syndromes: myocardial infarction/unstable angina with large extent of ischemia and ischemic dysfunction; mechanical complication of acute myocardial infarction; right ventricular infarction |
| Hypertensive crisis |
| Acute arrhythmia (ventricular tachycardia, ventricular fibrillation, atrial fibrillation or flutter, other supraventricular tachycardia) |
| Valvular regurgitation/endocarditis/rupture of chordae tendineae, worsening of preexisting valvular regurgitation |
| Severe aortic valve stenosis |
| Acute severe myocarditis |
| Cardiac tamponade |
| Aortic dissection |
| Postpartum cardiomyopathy |
| Noncardiovascular precipitating factors: lack of compliance with medical treatment, volume overload, infections, particularly pneumonia or septicemia, severe brain insult, after major surgery, reduction in renal function, asthma, drug abuse, alcohol abuse, pheochromocytoma |
| High output syndromes: septicemia, thyrotoxic crisis, anemia, shunt syndromes |

Modified from Nieminen (2005)

tain extent, measurement of the central venous pressure (CVP) allows quantification of the amount of congestion. The normal range of the CVP is 4 – 12 cm $H_2O$. Caution is necessary in the interpretation of high measured values of central venous pressure in AHF, as this may be a reflection of decreased venous compliance together with decreased right ventricular (RV) compliance even in the presence of inadequate RV filling. If the left ventricular function is impaired, wet rales in the lung fields are present during chest auscultation.

A chest x-ray confirms the diagnosis of left ventricular failure and allows the differential diagnosis to inflammatory or infectious lung diseases. Additionally the chest x-ray is used for follow-up of improvement or unsatisfactory response to therapy.

The ECG usually shows pathologic signs in patients with AHF. It determines the etiology of the AHF and may indicate strain of the left or right ventricle or the atria, acute coronary syndromes, arrhythmias, perimyocarditis, and preexisting conditions such as left or right ventricular hypertrophy or dilated cardiomyopathy.

The recommended laboratory test in AHF include arterial blood gas analysis (BGA), venous oxygen saturation, plasma B-type natriuretic peptide (BNP), and standard tests such as blood count, platelet count, urea, electrolytes, blood glucose, and creatinine phosphokinase. The arterial BGA allows assessment of oxygenation ($p_aO_2$), adequacy of respiratory function ($pCO_2$), and acid–base balance (pH). Venous oxygen saturation is determined by oxygen supply, oxygen consumption of the body and regional circulation. It is useful as an estimate of the total body oxygen supply–demand balance. Another useful laboratory test is the plasma BNP, which is released from the cardiac ventricles in response to increased wall stretch and volume overload. The decision cut-off point is proposed as 100 pg/ml.

Echocardiography is used in AHF to evaluate the functional and structural changes of the heart and to assess acute coronary syndromes. Additional information is gathered by echo-Doppler studies, which can estimate pulmonary artery pressures (from the tricuspid regurgitation jet) and left ventricular preload.

Additional diagnostic procedures such as angiography, CT scan, or scintigraphy may be indicated according to the etiology of the AHF.

#### *3.1.3.3 Therapy*

If the diagnosis of AHF is verified, the patient must be treated in specialized wards such as emergency units, chest pain units, or intensive care units. The physicians should be trained and should follow guidelines.

If immediate resuscitation is necessary, basic and advanced life support (BLS/ALS) is applied according to the applicable guidelines.

The patient in distress or pain requires treatment with a sedative or analgesic agent. In this context, morphine is recommended in the early stage of the treatment, when a patient is admitted with severe AHF presenting with the signs of restlessness and shortness of breath (dyspnea). Additional effects of morphine include venodilation, mild arterial dilation, and reduction of the heart rate. Intravenous boluses of 3 mg (2 – 5 mg) are recommended and may be repeated as needed.

To achieve adequate tissue oxygenation, an arterial oxygen saturation of greater than 95 % is favorable. It is important to realize that increased concentrations of oxygen to patients without evidence of hypoxemia may cause harm, because hyperoxemia can be associated with reduced coronary blood flow, reduced cardiac output, increased blood pressure, and increased systemic vascular resistance. When arterial oxygen saturation is too low, oxygen supply via a face mask with reservoir bag is effective to increase inspiratory oxygen concentration. In case of failure, ventilatory support without endotracheal intubation is supplied as noninvasive ventilation: continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BiPAP). If acute respiratory failure by AHF-induced respiratory muscle fatigue does not respond to vasodilators, oxygen therapy and noninvasive ventilation, the trachea has to be intubated and mechanical ventilation of the lungs commenced.

During bradycardia-induced AHF, external or internal pacing restores an adequate heart rhythm. Cardiac

arrhythmias or tachycardia can cause AHF. Since antiarrhythmic drugs and beta-blocking agents such as metoprolol have negative inotropic properties, they should be used with extreme caution in AHF. However, in patients with acute myocardial infarction, who stabilize after having developed AHF, beta-blockers should be initiated early.

In patients with AHF and absence of hypotension (mean blood pressure above 70 mm Hg) vasodilators are indicated. The primary pharmacologic treatment options include nitrates such as glyceryl trinitrate or isosorbide dinitrate, sodium nitroprusside, and the new agent nesiritide (atrial natriuretic peptide). The nitrates relieve pulmonary congestion without compromising stroke volume or increasing myocardial oxygen demand in acute left heart failure, particularly in patients with acute coronary syndrome. Their effect is limited to 16 – 24 h primarily due to development of tolerance. Sodium nitroprusside is indicated in patients with severe heart failure and in patients with predominantly increased afterload such as hypertensive heart failure or acute mitral regurgitation due to ruptured papillary muscle as a complication of severe myocardial infarction. The substance should be used cautiously, invasive monitoring of blood pressure is usually required, and toxicity of the cyanide metabolites should be taken into account. The new drug nesiritide is a recombinant human brain peptide, which is identical to the endogenous hormone produced by the ventricle (see description above). Nesiritide has venous, arterial, and coronary vasodilatory properties, reducing preload and afterload and thereby increasing cardiac output without direct inotropic effects. Calcium antagonists are contraindicated in AHF; ACE inhibitors are not indicated in the early stabilization phase of patients with AHF.

If the patients show symptoms of AHF secondary to fluid retention, diuretics are indicated. Usually loop diuretics such as furosemide or torasemide are administered. Hydrochlorothiazide (HCT) or spironolactone is added to loop diuretics in patients that are refractory to loop diuretics alone; a concomitant alkalosis is treated with acetazolamide. In refractory renal failure, hemodialysis or hemofiltration is initiated.

If the preload is low, a fluid challenge is indicated, but should be administered with extreme caution.

After executing all of the therapeutic steps mentioned above, the adequacy of cardiac output is assessed by reversal of metabolic acidosis, venous oxygen saturation, and clinical signs of adequate organ perfusion. The application of catecholamines or phosphodi-

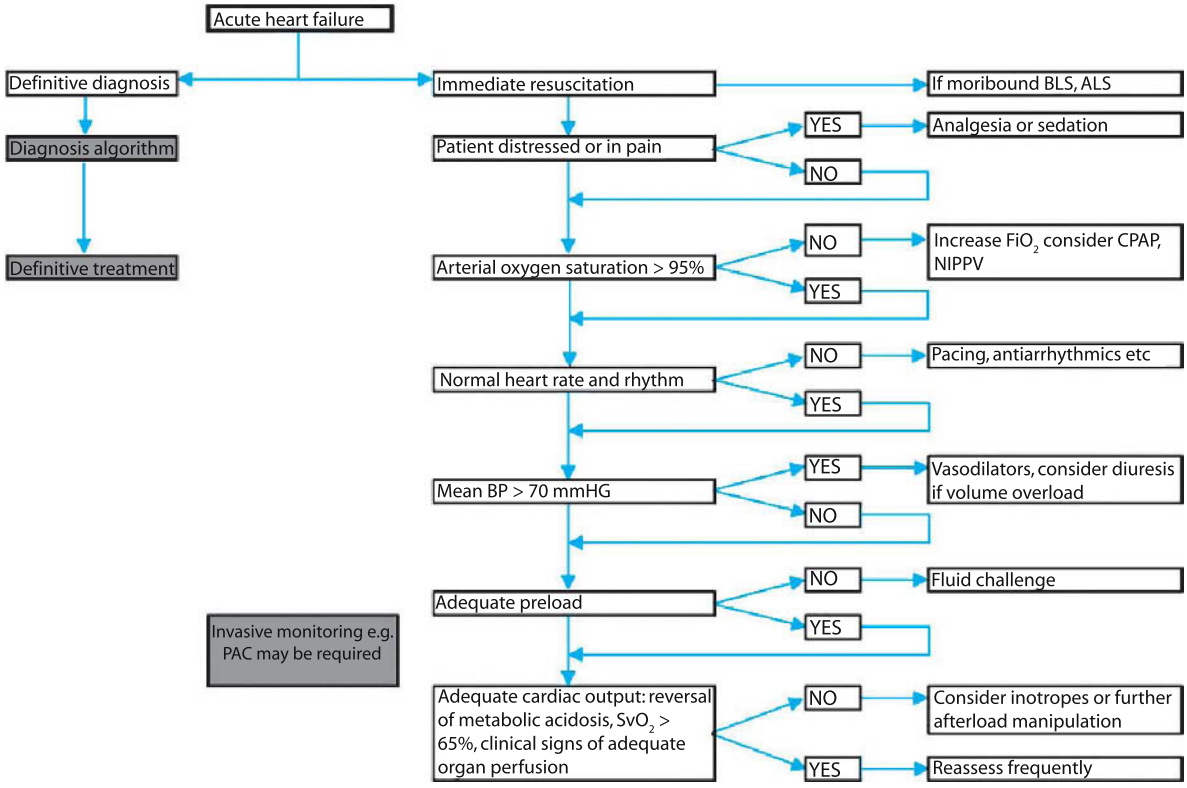



**Fig. 3.3.** Flow chart for immediate goals in treatment of the patients with acute heart failure. In coronary artery disease, the patient's mean blood pressure (mBP) should be higher to ensure coronary perfusion, mBP>70, or systolic >90 mm Hg. *BLS* basic life support, *ALS* advanced life support, *CPAP* continuous positive airway pressure, *NIPPV* noninvasive positive pressure ventilation. From Nieminen et al. (2005)

esterase inhibitors as inotropic agents is indicated in persistent heart failure, if tissue hypoperfusion does not suspend under the therapy described previously; but one must pay particular attention to these patients as catecholamines increase the oxygen consumption of the heart.

Dopamine incorporates dose-dependent properties of action on the receptors: it stimulates dopamine receptors at low doses (< 2 μg/kg/min), beta-adrenergic receptors at medium doses (2 – 5 μg/kg/min), and alpha receptors at high doses (> 5 μg/kg/min). Dopamine may be used as an inotropic (> 2 μg/kg/min i.v.) in AHF with hypotension. Infusion of low doses of dopamine (≤ 2 – 3 μg/kg/min i.v.) may be used to improve renal blood flow and diuresis in decompensated heart failure with hypotension and low urine output. However, if no response is seen, the therapy should be terminated, because no controlled trials regarding its long-term effects on renal function and survival have been conducted and concerns regarding its potential untoward effects on pituitary function, T cell responsiveness, gastrointestinal perfusion, chemoreceptor sensitivity, and ventilation have been raised.

Dobutamine stimulates beta1 receptors and beta2 receptors in a 3 : 1 ratio. The effect is a positive inotropic and chronotropic action as well as peripheral vasodilation. To increase cardiac output, dobutamine is initiated with an infusion rate of 2 – 3 μg/kg/min, which can be increased up to 20 μg/kg/min. After 24 – 48 h, beta-receptor tolerance decreases the effect of dobutamine. The indication for dobutamine is evidence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary edema refractory to volume replacement, diuretics, and vasodilators at optimal doses.

Phosphodiesterase inhibitors such as enoximone and milrinone have a site of action distal of the beta receptors, which results in persistent inotropic, lusitropic, and peripheral vasodilatory effects even in the presence of beta-blockers. Therefore, they are preferred to dobutamine in patients with concomitant beta-blocker therapy. In severe heart failure, a combination of phosphodiesterase inhibitors with epinephrine or norepinephrine is indicated in order to provide sufficient cardiac output with adequate perfusion pressure.

The new substance levosimendan (calcium sensitizer) has two main mechanisms of action: calcium sensitization of the contractile proteins, responsible for positive inotropic action, and smooth muscle potassium channel opening, responsible for peripheral vasodilatation. It is indicated in patients with symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension.

If the combined administration of inotropic substances and a fluid challenge fail to relieve the symptoms of AHF, a potent vasopressor such as epinephrine is indicated. Norepinephrine may be considered in right heart failure or in combination with phosphodiesterase inhibitors (Fig. 3.3) (Nieminen et al. 2005).

## 3.2 Deep Vein Thrombosis and Pulmonary Embolism

### 3.2.1 Risk Factors

Perioperative thromboembolic disease and pulmonary embolism contribute to morbidity and mortality in urological patients. Venous thromboembolism is a multifactorial disease involving clinical risk factors as well as genetic and environmental interactions. It is uncommon in the young, but after 40 years of age the incidence doubles with each decade of life. Hereditary risk factors include factor V Leiden mutation, G20210A prothrombin gene mutation, and deficiencies in protein C, protein S, and antithrombin. Hereditary and/or acquired risk factors are hyperhomocysteinemia and elevated levels of factor I, VIII, and IX. Acquired risk factors include malignancy, hospitalization/immobility, surgery, venous trauma, estrogen therapy, pregnancy, and the presence of antiphospholipid antibodies. Especially operations at the prostate activate the coagulation cascade. These patients are therefore prone to develop deep veins thrombosis and thrombosis in the pelvic vein bearing an increased risk of pulmonary embolism.

It is important to identify patients with risk factors for venous thromboembolism and pulmonary embolism and patients with contraindications for the regular prophylaxis, because routine surveillance and screening are not cost-effective in the perioperative setting, as they do not reduce symptomatic venous thromboembolism or fatal pulmonary embolism. In most cases, it is not necessary to initiate specific diagnostic procedures to identify the exact cause of the thrombophilia, but rather attach importance to a consequent perioperative antithrombotic strategy. Therefore, prevention using the standard protocol for prophylaxis is far more preferable. Anticoagulants are the first choice in the prevention of perioperative thromboembolic disease. There are widespread differences in the use of prophylaxis, however, although guidelines were published recently (Geerts et al. 2004).

One exception of the above-mentioned approach is a deficiency of antithrombin or protein C, which is usually known by the patient. After a targeted evaluation, a specific therapy with substitution of the deficient factor might by useful (Dempfle 2005).

According to a prospective study in 99 cancer patients by Sarig et al. (2005), F.V and F.VIII are elevated and can lead to acquired protein C resistance. These au-

**Table 3.3.** Risk factors for thromboembolic complications

| | |
|---|---|
| **Hereditary** | Factor V Leiden mutation<br>G20210A prothrombin gene mutation<br>Protein C deficiency<br>Protein S deficiency<br>Antithrombin III deficiency |
| **Hereditary and/or acquired** | Hyperhomocysteinemia<br>Anticardiolipin antibodies<br>Lupus anticoagulant<br>Elevation of F.I or F.VIII or F.IX |
| **Acquired** | Surgery requiring more than 30 min of anesthesia, especially cancer surgery<br>Malignancy<br>Fracture of pelvis, femur, or tibia<br>Age > 40 years<br>History of venous thromboembolism<br>Obesity<br>Pregnancy or recent delivery<br>Estrogen therapy<br>Prolonged immobilization, nursing home confinement<br>Cerebrovascular incident<br>Congestive heart failure<br>Permanent pacemaker, internal cardiac defibrillator<br>Chronic in-dwelling central venous catheter<br>Inflammatory bowel disease<br>Hypertension<br>Cigarette smoking<br>Long-haul air travel<br>Activated protein C resistance |

Modified from Motsch et al. (2006)

thors assume that acquired protein C resistance can serve as a possible risk factor for thromboembolic complications in cancer patients, but this needs to be further evaluated. In general, cancer is a major risk factor for developing thromboembolic complications. Therefore from the surgeon's point of view, it has been raised that patients presenting with the first episode of thromboembolic disease should always be screened for cancer. It should always be kept in mind that patients with prostate cancer are at increased risk for thrombosis or Trousseau syndrome, which is a manifestation of a chronic disseminated intravascular coagulopathy and clinically presents as a migratory superficial phlebitis. Table 3.3 summarizes the risk factors for thromboembolic complications.

### 3.2.2 Medical History

To reveal an increased risk for thromboembolism, the examiner should pay special attention to the following conditions in the patient's medical history: deep venous thrombosis, thrombophlebitis, pulmonary embolism, myocardial infarction, angina pectoris, other signs of coronary disease, cardiac arrhythmias, occlusion of arterial vessels, embolic events, strokes, prolonged ischemic deficits, anticoagulatory therapy, unexpected or allergic reactions to anticoagulants, immobilization before surgery, influenza-like diseases, and other conditions that initiate an acute phase reaction. Additionally, the medical history of relatives is important in order to detect a thrombophilic disposition: venous thromboembolism, arterial occlusion, cerebral ischemia, transitional neurologic deficits, and relatives with continuous anticoagulatory medication.

### 3.2.3 Therapy

After careful evaluation of the individual patient, an individual assessment of the degree of risk for perioperative thromboembolic complications is applied. Based on this evaluation, the appropriate prophylaxis is selected.

The basic preventive perioperative therapy against thromboembolism consists of early mobilization and the use of graduated elastic compression stockings. However, the backbone of specific strategies for perioperative prevention of venous thromboembolism is treatment with anticoagulants. The old drug, unfractionated heparin, is characterized by serious adverse effects and by large interindividual variability necessitating close monitoring. The new anticoagulants have a more predictable action, higher efficiency and are easier to handle because they no longer require routine monitoring, but effective antagonists are mostly lacking.

Although there are widespread differences in the use of prophylaxis, the following recommendations, which are based on recently published guidelines can be suggested. According to these guidelines (Motsch et al. 2006), low molecular weight heparins (LMWH) $\leq$3,400 U once daily or unfractionated heparin (UFH) 5,000 U every 8 h should be administered to general surgery patients without any additional risk factors for venous thromboembolism. High-risk patients should receive LMWH > 3,400 U daily. Cancer patients should be treated as patients at high risk. Therefore, LMWH greater than 3,400 U should be administered twice daily and continued for 28 days. For patients with prolonged postoperative intensive care unit treatment and with delayed recovery, a surveillance by venous ultrasonography should be considered, because of the high incidence of venous thrombosis in patients staying in intensive care units.

New agents, such as fondaparinux, idraparinux are superior to the standard treatment in the prevention of venous thromboembolism after high-risk major orthopedic surgery and for initial treatment of patients with venous thromboembolism. In orthopedic patients, the risk of venous thromboembolism was reduced by approximately 55%. Although major bleeding occurred

**Table 3.4.** Risk stratification and therapy recommendations in pulmonary embolism

| Risk category | Hemodynamic function | Therapy recommendations |
|---|---|---|
| 1 | Stable, no right ventricular dysfunction | Anticoagulation, using LMWH (or UFH) or fondaparinux |
| 2 | Stable, signs of right ventricular dysfunction | Anticoagulation, in some cases thrombolysis |
| 3 | Shock | Thrombolysis, except for strong contraindications |
| 4 | Cardiopulmonary resuscitation | Thrombolysis |

Modified from Motsch et al. (2006)

more frequently, the incidence of critical bleeding was comparable to patients receiving LMWH (enoxaparin). Such superior prophylactic effects of fondaparinux could not be confirmed in 2,297 patients undergoing abdominal surgery when compared to dalteparin in a double-blind study. Data for prophylaxis in major urologic operations are lacking. Therefore, these new anticoagulants such as fondaparinux need to be evaluated for the perioperative urologic setting.

Inferior vena cava filters are not advisable for long-term treatment, because they pose a nidus for recurrent thrombi, but may be considered as temporary retrievable filters in selected cases, when patients cannot receive anticoagulation.

If pulmonary embolism is present, the therapy is stratified according to the severity of the disease, ranging from the use of anticoagulants to thrombolysis (see Table 3.4).

## 3.3 Shock

### 3.3.1 Intraoperative and Postoperative Hemorrhage

In the case of massive perioperative hemorrhage, the administration/substitution of large quantities of crystalloid and colloid solution and blood products is required to maintain an adequate circulating volume with a sufficient organ and tissue perfusion.

The preparation for red blood cells is usually a leukocyte-depleted erythrocyte concentrate extracted from a whole blood donation. Another product is fresh frozen plasma (FFP), which is also extracted from a whole blood donation. FFP needs to be warmed for about 40 min at 37 °C, until it can be used. This long delay can be bridged in very urgent cases with readily available coagulation factors such as Prothrombin factor II, Proconvertin factor VII, Christmas-Factor (factor IX), Stuart-Prower-Factor (factor X) concentrate (PPSB), antithrombin 3 (AT III), fibrinogen, and recombinant factor VIIa. The third column of blood component therapy are platelets, which are available as a pool concentrate from four whole blood donations or as an apheresis preparation from one donor.

Other solutions to maintain an adequate intravascular volume are colloidal solutions such as hydroxyethyl starches, gelatin, and dextran, which remain for a longer period in the intravascular system. Crystalloid solutions such as ringer's lactate or normal saline have a disadvantage in severe hemorrhage in that they distribute throughout the extracellular space, e.g., to fill up 1 l of lost blood 3 – 4 l of crystalloid solution is needed for replacement.

A new approach for fluid resuscitation in severe hypovolemic shock in emergency medicine is to combine a hypertonic solution (e.g., 7.5 % sodium chloride solution) with hyperoncotic solutions (e.g., 6 % Hydroxy ethyl starch [HES]) to mobilize the interstitial fluid to

**Fig. 3.4.** High-flow blood and fluid warmer, System 1025, Level 1 (Level 1, Inc. 2006)

increase the intravascular volume. Since the dosage necessary is only 3–4 ml/kg of body weight in adults, this effective procedure is called small-volume resuscitation.

For the administration of fluid quantities required per time, large-bore intravenous cannulas of the highest possible diameters are useful. The diameter of appropriate peripheral cannulas is 14 gauge placed in the v. basilica or v. jugularis externa or 12-Fr catheters in the v. jugularis interna, v. subclavia, or v. femoralis. Special high-flow infusion lines and three-way-stop cocks should be used as well: because of the large diameter they allow the high required flows for fluid resuscitation. Fluid warming with special devices is advisable in order to prevent hypothermia with consecutive deterioration of the coagulation system and negative cardiac side effects. Pressure is applied to the infusion bags by compressing the infusion bags with a manually or automatically driven pressure bag. Figure 3.4 shows an example of a high-flow blood and fluid warmer, where up to 1,100 ml/min of fluid can be administered to the patient.

### 3.3.2 Anaphylaxis

The anaphylactic reaction (AR) is defined as an immediate humoral reaction due to preformed membrane-adherent immunoglobulins IgE, which lead to the release of histamine and other mediators. Anaphylaxis is the worst possible variant of an AR. The incidence for a severe intraoperative AR is 1:6,000 to 1:28,000.

Triggers for perioperative AR include neuromuscular blocking agents (60%–70%), latex (18%), colloidal solutions (5%), barbiturates, antibiotics, opioids, protamine, ethylene oxide, blood transfusions, and methylmethacrylate (bone cement). Cross reactions such as penicillin – cephalosporin or sulfonamide – loop diuretics should be considered, as the AR to one substance may also implicate the AR to the other substance.

#### *3.3.2.1 Symptoms and Treatment*

The symptoms vary from a light cutaneous reaction (degree 0) to cardiopulmonary arrest (degree 4). Symptoms and treatment of each stage are described below.

Degree 0 is a localized cutaneous reaction (urticaria). Discontinuing of the trigger substance, reassurance, and in most cases the establishment of an intravenous line is indicated.

Degree 1 is a light general reaction with the following symptoms: disseminated cutaneous reaction (flush, pruritus, generalized urticaria), reaction of the mucous membranes, edema (nose, conjunctivitis), and general symptoms (cephalgia, restlessness, vomiting). The therapeutic measure include discontinuation of the triggering agent, reassurance, placement of an intravenous line, fluid resuscitation (500 ml), corticosteroids (e.g., 250 mg prednisolone), and antihistaminics (e.g., 0.1 mg/kg dimethindene in combination with 5 mg/kg cimetidine).

Degree 2 is a pronounced general reaction (pulmonary and/or cardiovascular reaction), dysregulation of the circulatory system (tachycardia, hypotension, arrhythmias), Quincke edema, laryngeal edema, dyspnea, beginning bronchospasm, and urge for defecation and urination. The treatment consists of the discontinuation of the allergen, intubation, and mechanical ventilation in good time, intravenous line and fluid resuscitation (500–1,000 ml). Epinephrine should be administered in boluses of 5–50 µg i.v., corticosteroids and antihistaminics should be administered as described above, and bronchospasmolytics be administered as needed (inhalative beta-2-mimetics such as terbutaline, fenoterol, salbutamol, and intravenous theophylline 5 mg/kg i.v.).

Degree 3 is characterized by a general reaction with shock, bronchospasm, and unconsciousness. In addition to the measures taken in degree 2 anaphylactic reactions, mechanical ventilation should be provided with 100% oxygen, fluid resuscitation with 1,000–2,000 ml crystalloid and colloid solution, epinephrine (initial bolus 5–100 µg, followed by continuous infusion starting with 0.01 µg/kg/min effect-adjusted, dopamine infusion (3–7 µg/kg/min), prednisolone 500–1,000 mg i.v., and vasopressors (Caffedrine/theoadrenalin, etilefrine, or norepinephrine).

Degree 4 is a failure of vital organs resulting in cardiorespiratory arrest. Immediate basic and advanced life support must be initiated. In addition to the measures taken in degree 3 anaphylaxis, fluid resuscitation exceeding the amount of 2,000–3,000 ml and norepinephrine in boluses of 10–50 µg i.v. must be given (Heck and Fresenius 2004).

## 3.4 Sepsis

### 3.4.1 Definitions

#### *3.4.1.1 Systemic Inflammatory Response Syndrome*

If a patient presents with at least two of the criteria listed in Table 3.5, but lacks evidence for infection, the conditions for a systemic inflammatory response syndrome (SIRS) are met. The SIRS is the uniform answer of the body to a variety of diseases such as pancreatitis, major operation, severe trauma, or ischemia. Additionally a drop in the platelet count and the antithrombin-III levels (AT-III) is usually seen (Fresenius and Heck 2001).

**Table 3.5.** Definition of the systemic inflammatory response syndrome

| |
|---|
| Temperature > 38 °C or < 36 °C |
| Tachycardia > 90 beats/min |
| Respiratory insufficiency (at least one of the following three criteria) |
| Respiratory frequency > 20/min |
| Hyperventilation $p_aCO_2$ < 32 mm Hg (with spontaneous respiration) |
| $p_aO_2$ < 70 mm Hg (during spontaneous respiration) or $p_aO_2/F_IO_2$ < 175 (during mechanical ventilation with absence of pulmonary disease) |
| WBC > 12,000/µl or < 4,000/µl or > 10 % immature bands |

For the diagnosis of SIRS at least two criteria have to be met
From AACP/SCCM (1992); *WBC* white blood cell count

#### *3.4.1.2 Sepsis*

If the source of an infection can be located and the SIRS criteria are present, the definition of sepsis is met. The incidence of sepsis is five per 1,000 inpatients; the 28-day mortality varies between 25 % and 35 %, in severe sepsis up to 60 %.

The definition for severe sepsis includes the standard sepsis criteria in conjunction with signs of organ dysfunction, hypoperfusion, or sepsis-induced hypotension, which present as lactate acidosis, oliguria, encephalopathy, or thrombocytopenia.

A septic shock is the combination of sepsis with arterial hypotension, defined as arterial blood pressure below 90 mm Hg (or a decrease of more than 40 mm Hg from the baseline value for more than 1 h) despite adequate fluid resuscitation. It is accompanied by decreased perfusion or dysfunction of the organs.

### 3.4.2 Standard Therapy for Sepsis

The standard therapy for sepsis consists of the following:

- Identification and verification of the origin of the sepsis and removal of this focus (surgery and/or anti-infectious therapy)
- Accompanying antimicrobiologic treatment, initially as broad calculated antibiotic therapy using a combination of two or more antibiotics according to the CID (Centre of Infectious Disease) guidelines, after antibiogram testing-specific deescalating antibiotic treatment
- Optimization of organ perfusion and oxygen delivery with catecholamines
- Early mechanical ventilation
- Transfusion of red blood cells until the hematocrit reaches 30 %
- Volume resuscitation with crystalloid or colloid solutions
- Decreasing peripheral oxygen consumption by lowering of body temperature, analgesia, and sedation
- Early enteral nutrition

### 3.4.3 Early Goal-Directed Therapy for Sepsis

In 2001 Rivers et al. (2001) presented a new treatment strategy for sepsis that reduced the in-hospital mortality from 46.5 % to 30.5 % when compared to standard treatment with the so called early goal-directed therapy (EGDT). Patients were included in this study if they met the SIRS criteria and showed signs of global tissue hypoxia, which was defined by a systolic pressure of 90 mm Hg or below or a lactate level of 4 mmol/l or higher.

After assessment and consent, the patients were randomized either to the standard therapy group or the EGDT group. In both groups, treatment was commenced in the emergency room; after at least 6 h the patients were transferred to an intensive care unit, where the consecutive treatment did not differ between groups and where the intensivists were blinded to the initial treatment group assignments. In both groups, the central venous pressure (CVP) was kept at or above 8 – 12 mm Hg with boluses of 500 ml crystalloid solutions every 30 min, the mean arterial pressure (MAP) monitored with an arterial cannula was kept at or above 65 mm Hg with vasoactive agents and the urine output was kept at or above 0.5 ml/kg/h.

The particular feature of the EGDT was to install continuous central venous oxygen saturation monitoring ($ScvO_2$), which was achieved by inserting a specialized central venous catheter and monitoring system (Edwards Lifesciences, Irvine, CA, USA). $ScvO_2$ has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy. If $ScvO_2$ was below 70 %, transfusion of red cells was begun until the hematocrit reached 30 %. If $ScvO_2$ was still below 70 % infusion of dobutamine began. Dobutamine was started at a dose of 2.5 µg/kg/min that was increased by 2.5 µg/kg/min every 30 min until $ScvO_2$ reached 70 % or a maximum dose of 20 µg/kg/min was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives (see Fig. 3.5).

### 3.4.4 Heidelberg Sepsis Pathway

See Fig. 3.6 for the Heidelberg sepsis pathway.

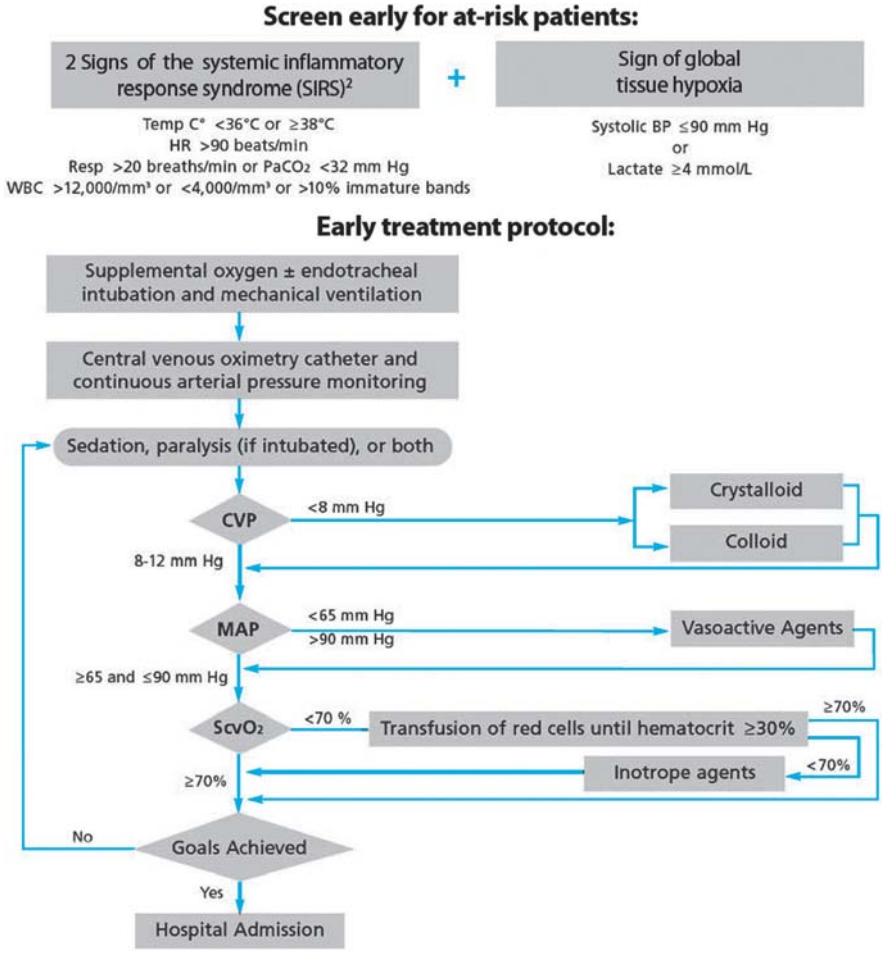



**Fig. 3.5.** Protocol for early goal directed therapy for sepsis. *CVP* central venous pressure, *MAP* mean arterial pressure, $ScvO_2$ central venous oxygen saturation. From Edwards Lifesciences (2006)

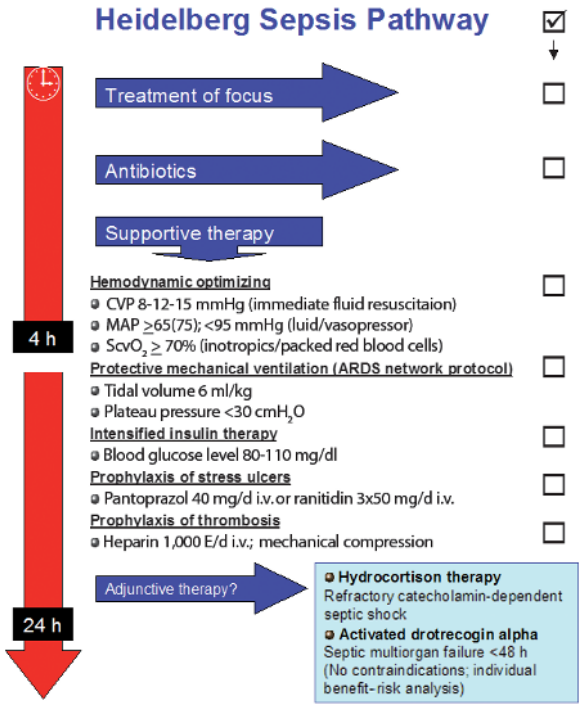



**Fig. 3.6.** Heidelberg sepsis pathway. *CVP* central venous pressure, *MAP* mean arterial pressure, $ScvO_2$ central venous oxygen saturation. Modified from Nieminen et al. (2005)

## 3.5 Intensive Care Procedures

### 3.5.1 Analgosedation

The use of analgetics and sedatives for the treatment of pain, anxiety, and agitation is a daily challenge in the intensive care environment. It is usually needed for the mechanically ventilated patient. To achieve a sufficient level of patient shielding while minimizing side effects and a short and cost-effective weaning period, the algorithm for analgosedation (AS) is an important task for the clinician. Emphasis should be placed on the consequent and correct implementation of a concept while the details of the concept are not as important. Another key aspect is the regular documentation of the indication for continuing AS, the definition of a therapeutic goal, the assessment of the patient's degree of agitation

and pain, and finally the adjustments in the drug therapy. If the underlying diseases permit, a regular daily suspension of the AS is advisable to evaluate the patient neurologically and discover a prolonged effect of the AS (Martin et al. 2005).

There are manifold causes of pain in the intensive care environment: preexisting disease, invasive procedures, trauma, monitoring and therapeutic devices (such as catheters, drains, noninvasive ventilating devices, endotracheal tubes), routine nursing care (airway suctioning, physical therapy, dressing changes, patient mobilization), and prolonged immobility. Unrelieved pain leads to inadequate sleep, causing exhaustion, disorientation, agitation, stress response (tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, persistent catabolism), pulmonary dysfunction through localized guarding of muscles around the area of pain and a generalized muscle rigidity or spasm that restricts movement of the chest wall and diaphragm.

The causes for anxiety in the intensive care unit can be secondary to an inability to communicate due to continuous noise (alarms, personnel, and equipment), continuous ambiguous lighting, excessive stimulation (inadequate analgesia, frequent measurements of vital signs, repositioning, lack of mobility, room temperature, sleep deprivation, and the underlying disease that led to ICU admission. Causes for agitation include extreme anxiety, delirium, adverse drug effects, and pain. If agitation is present, it is important to identify and treat any underlying physiological disturbances: hypoxemia, hypoglycemia, hypotension, pain, withdrawal from alcohol, and other drug effects. Special attention should be paid to the treatment of agitation, because it can pose a serious threat to patients by contributing to ventilator dyssynchrony, increase in oxygen consumption, or inadvertent removal of devices and catheters (Jacobi et al. 2002).

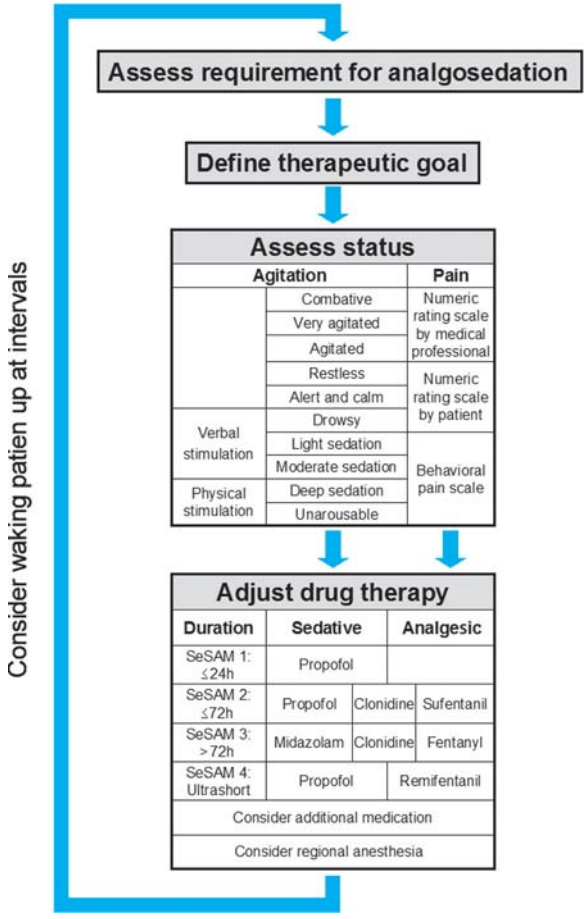



**Fig. 3.7.** Algorithm of analgosedation. Assembled from Jacobi et al. (2002); Martin et al. (2005); Martin and Messelken (1998)

### *3.5.1.1 Algorithm*

Before the start of analgosedation, it is important to assess the indication and define a therapeutic goal. Today the patients in the intensive care unit should react adequately to verbal stimulation, perceive their environment, communicate their needs, and tolerate the diagnostic and therapeutic measures.

The next step is to assess the degree of agitation and pain. A good approach is the concept by Martin and Messelken (1998), which implements the Richmond Agitation-Sedation Scale (RASS) (Sessler et al. 2002) at the outset and continues depending on the RASS score with an adequate pain score. For the unresponsive to lightly sedated patient, the behavioral pain scale (BPS) by Payen et al. (2001) is applicable, for the sleepy to restless patient the numeric rating scale (NRS: 0 = no pain to 10 = highest pain possible) assessed by the patient himself is applicable, and for the agitated to fighting patient the NRS rated by a medical professional (physician or nurse) is applicable. For details of the assessment of agitation and pain, please refer to Tables 3.6 and 3.7.

The last step is to schedule the duration of the AS and choose the appropriate drug accordingly. The SeSAM concept (Martin and Messelken 1998) provides four duration categories: up to 24 h, up to 72 h, more than 72 h, and ultrashort analgosedation (e.g., for short painful diagnostic procedures). The drugs were chosen such that the length of the context-sensitive half-life meets the requirements of the duration of AS needed and prolonged action is unlikely. For dosages of the drugs, please refer to Tables 3.8 and 3.9. Co-medication such as nonopioids should be considered to support the AS in an additive way, but strict adherence to the contraindications of these drugs is mandatory. Another therapeutic option is continuous regional anesthetic techniques such as epidural catheter analgesia

**Table 3.6.** Richmond agitation-sedation scale (RASS)

| Score | Term | Description | Procedure |
|---|---|---|---|
| +4 | Combative | Overtly combative or violent; immediate danger to staff | 1. Observe patient. Is patient alert and calm (score 0)? Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under "description")? |
| +3 | Very agitated | Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff | |
| +2 | Agitated | Frequent nonpurposeful movement or patient–ventilator dyssynchrony | 2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker. Patient has eye opening and eye contact, which is sustained for more than 10 s (score –1). Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score –2). Patient has any movement in response to voice, excluding eye contact (score –3). |
| +1 | Restless | Anxious or apprehensive but movements not aggressive or vigorous | |
| 0 | Alert and calm | | |
| –1 | Drowsy | Not fully awake, but has sustained (more than 10 s) awakening, with eye contact, to voice | |
| –2 | Light sedation | Briefly (less than 10 s) awakens with eye contact to voice | |
| –3 | Moderate sedation | Any movement (but not eye contact) to voice | 3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder. Patient has any movement to physical stimulation (score –4). Patient has no response to voice or physical stimulation (score –5). |
| –4 | Deep sedation | No response to voice, but any movement to physical stimulation | |
| –5 | Unarousable | No response to voice or physical stimulation | |

From Sessler et al. (2002)

**Table 3.7.** Behavioral pain scale (BPS)

| Item | Description | Score |
|---|---|---|
| **Facial expression** | Relaxed | 1 |
| | Partially tightened (e.g., brow lowering) | 2 |
| | Fully tightened (e.g., eyelid closing) | 3 |
| | Grimacing | 4 |
| **Upper limbs** | No movement | 1 |
| | Partially bent | 2 |
| | Fully bent with finger flexion | 3 |
| | Permanently retracted | 4 |
| **Compliance with ventilation** | Tolerating movement | 1 |
| | Coughing but tolerating ventilation most of the time | 2 |
| | Fighting ventilator | 3 |
| | Unable to control ventilation | 4 |

From Payen et al. (2001)

or continuous femoral nerve block. With the use of regional anesthesia techniques, a dose reduction of opioids and their side effects can be achieved. Spinal-applied local anesthetics provide sympathicolysis with improved bowel function and less postoperative ileus. A drawback of the continuous regional anesthesia techniques is the risk of infection at the puncture site and the risk of spinal hematoma formation, when a hypocoagulatory state is caused by disease or treatment with antithrombotic agents (therapeutic anticoagulation).

**Table 3.8.** Drugs for analgesia, sedation and vegetative attenuation. On usage of Ketamin-S cut dosages in half. All dosages refer to a middle aged adult of 60 – 80 kg.

| Drug | Loading (mg/50 ml) | Dosage [mg(µg)/kg/h] | | Application speed (ml/h) | | Metabolism | Active metabolites | Daily costs (Germany) |
|---|---|---|---|---|---|---|---|---|
| | | Low | High | Low | High | | | |
| Propofol 2% | 1,000 | 0.8 mg | 4 mg | 3.0 | 14 | Oxidation | No | +++ |
| Midazolam | 90 | 0.01 mg | 0.18 mg | 0.5 | 6.9 | Oxidation | Yes (prolonged sedation) | ++ |
| Remifentanil | 5 | 1.5 µg | 18 µg | 1 | 12 | Serum esterase | No | +++ |
| Fentanyl | 1.5 | 0.9 µg | 3.5 µg | 2.0 | 8.0 | Oxidation | No Accumulation | + |
| Sufentanil | 0.5 | 0.15 µg | 0.7 µg | 2.0 | 10.0 | Oxidation | No | ++ |
| Ketamine | 2,500 | 0.4 mg | 3.0 mg | 0.6 | 4.0 | Glucuronidized | Yes | +++ |
| Clonidine | 2.25 | 0.32 µg | 1.3 µg | 0.6 | 2.0 | Hydroxylized | No | + |

Modified from Martin et al. (2005)

**Table 3.9.** Co-medication to analgosedation.

| Drug | Dosage | Terminal half-life | Metabolism | Active metabolites | Cost per application |
|---|---|---|---|---|---|
| Piritramide | 3.75 – 15 mg i.v. | 4 – 10h | Oxidation | No | ++ |
| Pethidine | 12.5 – 50 mg i.v. | 3 – 12h | Demethyl. | No | ++ |
| Paracetamol | 4 × 1 g i.v./day | 2.7 – 3.5h | Conjugation | No | ++ |
| Metamizol | 1.0 – 2.5 g short infusion, max 5 g/day | 2.7 – 11.5h | Hydroxyliz. | Yes | ++ |
| Diclofenac | 50 – 100 mg supp, max 150 – 200 mg/day | 1 – 2h | Hydroxy-liz.+Conju-gation | No | + |
| CEA | Ropivacaine 0.2 % 10 – 20 mg/h, or in combination with an opioid (sufentanil or fentanyl) | 3h | Hydroxyliz | No | +++ |
| | Or 15 ml bupivacaine 0.25 % 3 – 4/day | 1.5 – 5.5h | | | + |
| Block of femoral nerve | Ropivacaine 0.2 % 20 – 30 ml Or bupivacaine 0.25 % 20 – 30 ml | | | | |

Please be aware of contraindications
Modified from Martin et al. (2005)
*CEA* continuous epidural anesthesia

#### *3.5.1.2 Assessment of Agitation and Pain*

See Tables 3.6 and 3.7 for the assessment of agitation and pain.

At regular intervals (e.g., once every 8-h shift), the algorithm for assessing sedation, pain, and agitation should be followed again.

#### *3.5.1.3 Drug Adjustment*

See Tables 3.8 and 3.9.

### 3.5.2 Monitoring

#### *3.5.2.1 Transesophageal Echocardiography*

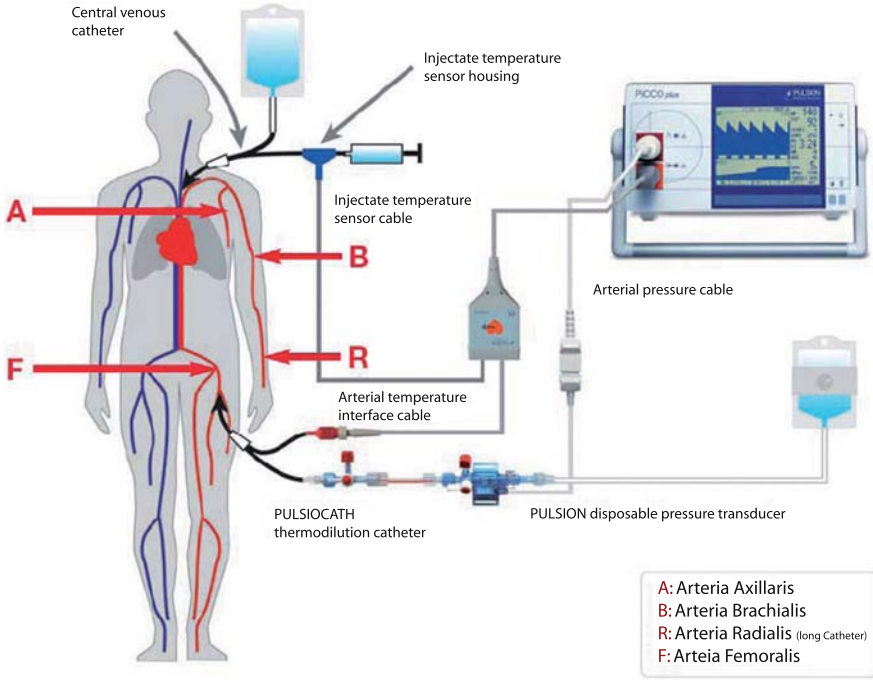
Transesophageal echocardiography (TEE) enables the experienced examiner to evaluate online the morphology of the anatomic structures of the heart and the large vessels, contractility of the ventricles, and blood flow.

The ACC/AHA/ASE 2003 guidelines (Cheitlin et al. 2003) state the following indication for an intraoperative TEE. Only the indications that apply to the urologic environment are stated:

- Class I (evidence or general agreement that a given procedure or treatment is useful and effective): evaluation of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment.
- Class IIa (weight of evidence/opinion is in favor of usefulness/efficacy): surgical procedures in patients at increased risk of myocardial ischemia, myocardial infarction, or hemodynamic disturbances.

#### *3.5.2.2 PiCCO*

With the PiCCO-system, cardiac output, the stroke volume index, the heart rate, the mean arterial pressure, the systemic vascular resistance, stroke volume variation (indicator of volume deficit), and left ventricular contractility can be measured continuously with a relatively noninvasive device. First a special arterial catheter must be placed in a large arteria (e.g., the femoral artery). This catheter has two functions: it has a transducer to measure the arterial pressure and a thermistor for the registration of changes in blood temperature for calibration. Second, a regular central venous catheter is needed to calibrate the system. After the setup, it should be calibrated at regular intervals (e.g., every 8 h), and changes in central venous pressure should be entered into the monitor to allow calculation of additional parameters. Please refer to Fig. 3.8 for the configuration of the PiCCO-system, to Table 3.10 for the overview of the complete parameters of the PiCCO-system, and to Fig. 3.9 for the decision tree and the therapeutic suggestions.




For the PiCCO-technology any central venous catheter with specific arterial PiCCO thermodilution catheter is required.

The specific PiCCO pressure transducer, validated and optimized for arterial pulse contour analysis

A pulmonary catheter is not required for the measurement of cardiac output and all other PiCCO parameters.

**Fig. 3.8.** Configuration of the PiCCO-System (Pulsion Technology 2006)

**Table 3.10.** Parameters and normal values of the PiCCO system

| Category | Parameter | Abbr. | Value | Unit |
|---|---|---|---|---|
| **Flow/afterload** | Cardiac Index | CI | 3.0 – 5.0 | l/min/m$^2$ |
| | Stroke Volume Index | SVI | 40 – 60 | ml/m$^2$ |
| | Heart rate | HR | 60 – 100 | 1/min |
| | Mean arterial pressure | MAP | 70 – 90 | mm Hg |
| | Systemic Vascular Resistance Index | SVRI | 1700 – 2,400 | dyn*s*cm$^{-5}$m$^2$ |
| **Volume management** | Global End-Diastolic Volume Index | GEDI | 680 – 800 | ml/m$^2$ |
| | Intrathoracic Blood Volume Index | ITBI | 850 – 1,000 | ml/m$^2$ |
| | Stroke volume variation | SVV | ≤ 10 | % |
| | Pulse pressure variation | PPV | ≤ 10 | % |
| **Lungs** | Extravascular Lung Water Index | ELWI | 3.0 – 7.0 | ml/kg |
| | Pulmonary Vascular Permeability Index | PVPI | 1.0 – 3.0 | |
| **Contractility** | Global ejection fraction | GEF | 25 – 35 | % |
| | Cardiac Function Index | CFI | 4.5 – 6.5 | 1/min |
| | Left ventricular contractility | dP/mx | | |

Continuous parameters/discontinuous parameters
Modified from Pulsion Technology (2006)

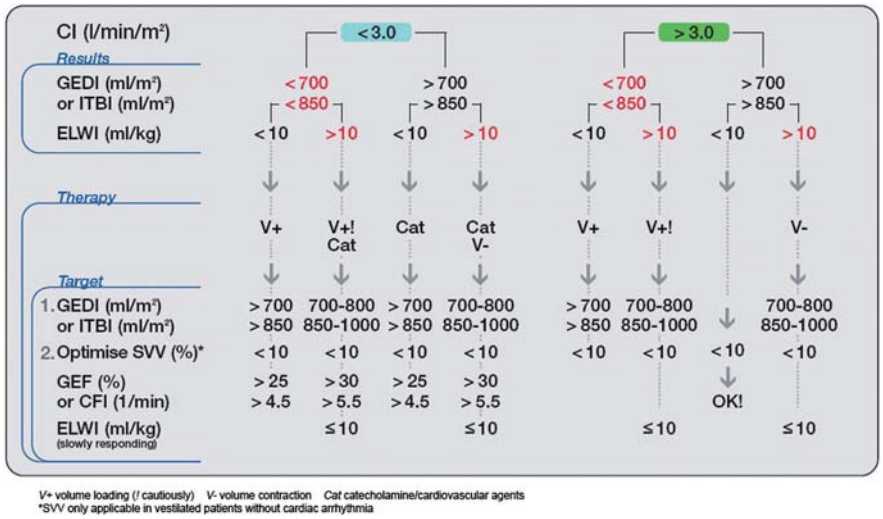



**Fig. 3.9.** PiCCO Decision Tree (Pulsion Technology 2006)

## 3.6 Intraoperative and Postoperative Procedures

### 3.6.1 TUR Syndrome

Many endoscopic procedures such as the transurethral resection of the prostate or bladder, operative hysteroscopies, cystoscopy, arthroscopy, rectal tumor surgery, vesical ultrasonic lithotripsy, or percutaneous nephrolithotripsy require the use of an irrigation fluid. If monopolar electrocauterization is necessary, the irrigation fluid must not contain any electrolytes. Accidental resorption of the irrigation fluid can therefore cause the so-called TUR syndrome, which poses a serious threat to the patient. The consequences for the patient depend on the rate, volume, and nature of the absorbed fluid. Possible symptoms are chest pain, bradycardia, hypertension, hypotension with drops over 50 mm Hg, poor urine output up to anuria despite diuretics, blurred vision to transient blindness, nausea, vomiting, uneasiness, confusion, tiredness, unconsciousness needing ventilatory support, and headache.

Traditional countermeasures to prevent TUR syndrome are limitation of the resection time, limiting the height of the bag containing the irrigating fluid to the maximum of 1 m above the patient, and inserting a suprapubic catheter. Early discovery of TUR syndrome is possible in patients under regional anesthesia by recognizing the symptoms described above. To quantify the amount of absorbed irrigation fluid, the latter must be mixed with a known quantity of ethanol. By measuring the exhaled ethanol concentration with an apparatus called Alcotest, absorption of irrigation fluid is detected and quantified.

Modern strategies to prevent TUR syndrome exchange the electrolyte-free irrigation solutions causing a hypotonic hyperhydration, hemolysis, hyponatremia, and specific symptoms of the other ingredients of the irrigation fluid (glycine, mannitol, sorbitol) for a normal saline solution. Closing vessels opened during resection when using electrolyte-containing irrigation solution is possible with bipolar cauterization or laser-evaporation or other techniques. In this case, absorption of irrigating fluid causes a normotonic hyperhydration, which is less dangerous (Hahn 2006).

### 3.6.2 Prevention of Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) is the second most common postanesthetic complication after pain, the most distressing for the patient. The overall incidence of PONV for all surgeries and patient populations varies between 25 % and 30 %, in high-risk groups PONV occurs in up to 70 % of all cases (Ho and Chiu 2005).

PONV is usually self-limiting and not associated with severe consecutive complications, but the patients' assessment classifies the prevention and treatment of PONV as important as pain (Apfel and Roewer 2004). Complications of PONV such as tension on suture lines, wound bleeding and dehiscence, increased intracranial pressure, pulmonary aspiration, dehydration, and electrolyte imbalance pose a threat to the patient and result in consecutive costs.

The pathophysiology of PONV still remains unclear, with the exception of the chemotherapy- or opioid-induced vomiting despite the identification of many anatomical and histological structures and the interconnections involved in the PONV process. The vomiting center in the brainstem receives stimuli from vagal afferents of the gastrointestinal tract (particularly serotoninergic), the vestibular system (particularly histaminergic), the chemoreceptor trigger zone (particularly

dopaminergic), and is connected to higher cerebral regions that are responsible for the perception of nausea and dizziness. The conclusions of the above-mentioned pathophysiological facts are: the multifactorial nature of PONV may necessitate combination therapy for prophylaxis and treatment. Vomiting is not an escalation of nausea, because vomiting is a vegetative reflex pattern, which can be triggered even without nausea, while cortical consciousness is a prerequisite of nausea.

#### *3.6.2.1 Risk Factors for PONV*

To adapt the therapeutic and prophylactic measures to the risk of PONV, it is essential to identify the risk factors with their correlated relevance and deduct an algorithm for the optimal and cost-effective measures to be taken. The clinically relevant patient-specific risk factors are:

- Female gender increases the risk of PONV threefold.
- Non-smoking increases the risk twofold.
- A history of former PONV or motion-sickness increases the risk.
- An age older than 5 years increases the risk.

The validated and clinically relevant anesthesiologic risk factors are:

- Use of volatile anesthetics (dependent on dosage) increases the risk of PONV compared to total intravenous anesthesia (TIVA).
- The use of nitrous oxide.
- The administration of postoperative opioids.
- The use of antagonists of nondepolarizing muscle relaxants (e.g., more than 2.5 mg neostigmine) also increases the risk.

There exists controversy over whether the type of surgery influences the rate of PONV in adults, because some studies have shown significant results, while others demonstrated no significance on the same type of surgeries. There is one study from Stadler et al. (2003) where the type of surgery was correlated with the incidence of nausea but not with the incidence of vomiting. In children, it was proved that the surgical technique can be related to the risk of PONV, e.g., in strabismus operations (Ruesch et al. 1999). Obesity, menstruation cycle, anxiety, or personality can definitely be ruled out as risk factors. Table 3.11 summarizes the degree of relevance and certainty of risk factors for PONV.

#### *3.6.2.2 Antiemetic Strategy*

A number of complicated scores and strategies taking the type of surgery into account exist to adapt the prophylaxis for PONV to the needs of the patient, while Apfel's simplified risk score (Apfel et al. 1999) with the four items

- Female gender
- Non-smoking status
- History of motion sickness or PONV
- Use of postoperative opioids

predicts PONV with the same reliability of about 70 %. Concerning the latter, the number of risk factors (0, 1, 2, 3, or 4) correlates with a PONV risk of 10 %, 20 %, 40 %, 60 %, or 80 % (see Fig. 3.10). The following limitations must be taken into account: The simplified risk score only applies to balanced anesthesia techniques in adults. It is unclear whether it yields reproducible results in outpatients.

**Table 3.11.** Risk factors for PONV, classified by evidence and clinical relevance

| | |
|---|---|
| Evidence demonstrated and clinically relevant | ●●● Female gender<br>●● Non-smoking status<br>●● Medical history for PONV or motion sickness<br>●●● General anesthesia<br>●● Volatile anesthetics<br>●● Duration of anesthesia<br>●● Postoperative opioids |
| Evidence demonstrated, but not as clinically significant | ● Young age and ASA status 1 or 2<br>● Nitrous oxide<br>● Neostigmine, Pyridostigmine |
| Controversial data | Type of surgery<br>Experience of anesthesiologist<br>Routine use of gastric tube |
| Insufficient data | Pain<br>Movements |
| Refuted | Obese patients (body mass index)<br>Menstruation cycle<br>Anxiety and personality |

Modified from Apfel and Roewer (2004)
● Moderate, ●● strong, ●●● very strong

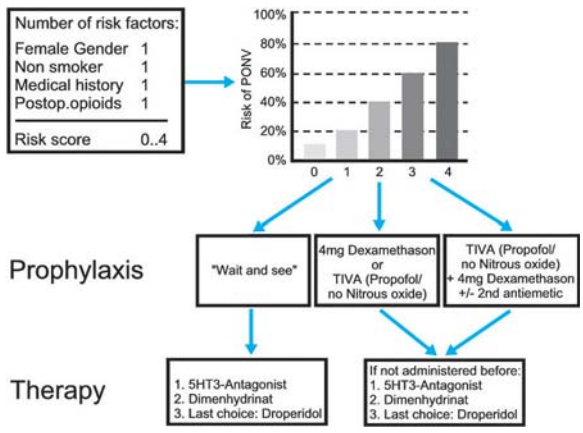



**Fig. 3.10.** Risk-adapted strategy for prophylaxis and therapy of PONV. modified from Apfel and Rozwer (2004)

In patients with none or only one risk factor, no prophylactic PONV therapy is required. If there are two risk factors, it is advisable to administer dexamethasone 4 mg i.v. or use total-intravenous anesthesia (TIVA) prophylactically. In TIVA, the induction and maintenance of the general anesthesia is achieved with intravenous agents, most commonly with propofol. Volatile anesthetics such as isoflurane, desflurane, sevoflurane, and nitrous oxide should be omitted. In patients with three or four risk factors for PONV, the combination of TIVA, dexamethasone prophylaxis, and optionally a second antiemetic drug is advisable.

To avoid the risk factors of volatile anesthetics and opioids, regional anesthetic techniques should be considered in patients at risk for PONV.

Every first-time vomiting or moderate nausea should be treated immediately. The dosage is approximately one-quarter of the antiemetic dosage needed for prophylaxis. Since it takes a few hours until the maximum antiemetic effect of dexamethasone is established, the use of a 5-$HT_3$-antagonist (e.g., ondansetron 1 mg i.v. or dolasetron 12.5 mg i.v.) or dimenhydrinate 32 mg i.v. is recommended. There is consensus on the fact that the next dose of an antiemetic drug should not be given in less than 6 h.

#### *3.6.2.3 Antiemetic Drugs*

Dexamethasone is proposed as a first-line antiemetic drug because it is effective and inexpensive, and it yields a low rate of side effects, although the antiemetic mechanism is unknown. Because of its delayed onset, dexamethasone should be given at the beginning of anesthesia.

Dimenhydrinate is an unspecific antagonist at the histamine-type 1 receptor with an antiemetic effect comparable to the other drugs mentioned. It should be used intravenously, since the amount of rectal absorption is uncertain.

Serotonin antagonists like ondansetron, tropisetron, dolasetron, or granisetron block the vagally mediated action of serotonin on the 5-hydroxytryptamin-type-3 receptor (5-$HT_3$). The most common side effect is a mild headache; they do not have any sedating or extrapyramidal potential. All serotonin antagonists are believed to demonstrate an equivalent antiemetic effect.

Droperidol is a highly potent neuroleptic drug acting as an antagonist at the dopamin-type-2 receptor. Because of the short duration of action, it is recommended to administer the drug at the end of surgery. The Food and Drug Administration (FDA) in the US has issued a black-box warning for the substance due to QT-interval prolongation resulting in fatal arrhythmogenic complications (prolonging of the QT interval in the electrocardiogram, torsades de points, tachycardia, bradycardia).

Metoclopramide was used by clinicians for decades, but an insufficient antiemetic effect was demonstrated by Henzi et al. (1999).

For an overview of antiemetic drugs and recommendations on dosages, please refer to Table 3.12.

## 3.7 Perioperative Management of Jehovah's Witnesses

Jehovah's Witnesses refuse to consent to transfusions of whole blood, red cells, plasma, platelets, white cells, and predonated autologous blood due to their religious beliefs. It is a matter of individual conscience whether Jehovah's Witnesses allow fractions derived from any primary component of blood (e.g., anti-D), medical procedures involving the use of autologous blood that do not involve storage (e.g., intraoperative cell salvage),

**Table 3.12.** Standard intravenous dosages of antiemetics (pediatric dosage should not exceed adult dosage), modified from (1)

| Substance | Point of action | Adult prophylaxis | Adult therapy | Pediatric prophylaxis |
|---|---|---|---|---|
| Ondansetron | 5-$HT_3$ | 4 mg | 1 mg[b,c] to 4 mg[a,b] | 50 µg/kg[b,c] to 100 µg/kg |
| Tropisetron | 5-$HT_3$ | 2 mg | 1 mg[c] to 2 mg[a] | 100 – 200 µg/kg[b,c] |
| Dolasetron | 5-$HT_3$ | 12.5 mg[a–c] to 50 mg[b,c] | 12.5 mg | 350 µg/kg[c] |
| Granisetron | 5-$HT_3$ | 0.35 – 1 mg[b,c], 3 mg[a] | 0.1 – 0.3 mg[c], 3 mg[a] | 10 – 20 µg/kg[c], 40 µg/kg (> 2years)[a] |
| Dexamethasone | Unsettled | 4 – 5 mg early[b,c], 8 – 20 mg preop[a] | Not recommended[c] 8 – 20 mg[a] | 150 µg/kg[a–c] to 500 µg/kg(> 2 years)[a] |
| Dimenhydrinate | $H_1$ | 62[a–c] to 124 mg[a] | 32 mg[c], 62 – 124 mg[a] | 500 µg/kg[b,c] to 1.25 mg/kg[a] |
| Droperidol | $D_2$ | 0.625 – 1.25 mg[b,c] | 0.625 mg[b,c] | 50 – 75 µg/kg[b,c] |
| Metoclopramide | Not recommended due to insufficient antiemetic effect | | | |

Modified from Apfel and Roewer (2004)
*5-$HT_3$* antagonist at 5-hydroxytryptamine (serotonin)-3 receptor, *$H_1$* antagonist at histamin-1-receptor, *$D_2$* antagonist at dopamin-2 receptor
[a] Scientific information
[b] Proved by studies
[c] Expert opinion

or organ transplant. Nevertheless, Jehovah's Witnesses request all other kinds of medical treatment to save their lives.

### 3.7.1 Legal Issues

Patient management depends on the laws of the country; e.g., in the United States, it is the right of a competent adult to refuse transfusion even though the result of such a refusal may be death of the individual.

The perioperative strategy seems to be quite easy if the patient can express his or her wish not to receive any blood or blood products in an elective setting. The key conditions for a legal informed consent are "competency" and "adulthood". There should be a high grade of suspicion concerning competency if the patient has abnormal or unstable vital signs, altered mental status, evidence of impaired judgment as from a central nervous system injury or illness, or any sign of alcohol or drug intoxication. In regard to the definition of a minor, individuals are generally considered too young to make a decision for themselves if they are under the age of 18; however, exceptions can be made for self-sufficient minors and emancipated minors. A self-sufficient minor is one who is age 15 or older and lives separately and apart from his or her parents or legal guardian. An emancipated minor is any person under the age of 18 who has entered into a valid marriage.

Concerning minors, the courts have ordered transfusions for children in life-threatening situations despite the objections or their parents or legal guardians. The same applies to incompetent adult patients, where courts have predominantly ruled that a physician has a legally recognized right to proceed with emergency procedures such as transfusion therapy even over the objections of the relatives (Rashad Net University 2006).

### 3.7.2 Physiology of Anemia

To understand the physiology and compensatory measures of a reduced hemoglobin concentration and deduct possible strategies to maintain oxygen supply of the body, the following parameters should be discussed.

The oxygen delivery of the organism ($DO_2$) is the product of the cardiac output (CO) and the arterial oxygen content of the blood ($c_aO_2$).

$$DO_2 = CO \times c_aO_2 \quad (3.1)$$

$DO_2$ Oxygen supply, normal range 900 – 1,200 ml/min
CO Cardiac output, normal range: 4 – 8 l/min
$c_aO_2$ Oxygen content of the arterial blood, normal range: 19±1 ml/dl

The content of oxygen of the arterial blood consists of the major part of 98.5 % that is stored in the hemoglobin ($S_aO_2$*Hb*1.39) and the minor part of 1.5 % that is physically stored ($p_aO_2$*0.003).

$$c_aO_2 = SaO_2 \times Hb \times 1.39 + p_aO_2 \times 0.003 \quad (3.2)$$

$S_aO_2$ Oxygen saturation of the arterial blood, normal range 96 % – 100 %
Hb Hemoglobin concentration, normal range 12 – 16 g/dl in women, 14 – 18 g/dl in men
$p_aO_2$ Partial pressure of oxygen in arterial blood, normal range 70 – 100 mm Hg (Fresenius and Heck 2001)

Physiologic compensation of anemia (decrease in hemoglobin concentration) to maintain adequate oxygen delivery is achieved by increased cardiac output (tachycardia, increased contractility). Therapeutic measures include lowering oxygen consumption and administering high inspiratory oxygen concentrations (increase in $S_aO_2$ and $p_aO_2$) by sedation and mechanical ventilation. Oxygen consumption can also be lowered (7 % per °C) by hypothermia. When the hemoglobin concentration is very low, the oxygen content of the blood decreases dramatically, because the physically stored oxygen ($p_aO_2$ * 0.003) is only a minor part of oxygen transport in the blood. The physically stored oxygen can only be increased significantly in hyperbaric conditions.

Other mechanisms to improve tissue oxygenation include lowering of the hematocrit with consecutive decrease in viscosity and improvement of blood flow. The peripheral vascular resistance is lowered to additionally increase blood flow. The oxygen saturation curve, which describes the dependency of saturation on the partial pressure, shifts to the right due to acidosis, anemia, and an increase in 2,3-diphosphoglycerate and consecutively improves donation of oxygen to the tissues (Rashad Net University 2006).

### 3.7.3 Strategies to Avoid Blood Transfusions

Perioperative care of Jehovah's Witnesses should ideally start weeks before the surgical procedure. After a positive benefit–risk analysis by the surgeon that includes the determination of the possible blood loss, the patient should also be assessed by the anesthesiologist to determine the patient's preferences and preclusions. After all parties agree on how to proceed with medical management, the patient must sign a consent form memorializing his or her request not to transfuse under any circumstances. At this early stage of planning, an oral iron medication should be considered.

Donation and deposition of autologous blood is commonly not accepted by the patients, but the preoperative acute normovolemic hemodilution can be an option to reduce intraoperative blood loss if the collect-

ing system "maintains in the circulatory system". Additionally a cell-saving device can be used intraoperatively, if no contraindications exist and the patient accepts its use.

Deliberate hypotension with the reduction of the systolic blood pressure to 80 – 90 mm Hg decreases intraoperative blood loss. Contraindications are cardiovascular disease, particularly coronary artery disease and congestive heart failure, poorly controlled hypertension, raised intracranial pressure, and coexistent central nervous system pathologies. Additional side effects of deliberate hypotension are increased alveolar dead space and decreased renal blood flow, so monitoring arterial blood gases and urinary output is advis-

**Table 3.13.** Perioperative management to avoid blood transfusions

| Strategy | Measures | Effect |
|---|---|---|
| Fluids | Ringer's lactate | Maintain blood volume |
| | Hydroxyethyl starch | |
| | Dextran | |
| | Gelatin solutions | |
| | Oxygen transporting solutions | Transport of oxygen |
| Drugs | Erythropoietin | Stimulation of red blood cells |
| | Interleukin-11 | Stimulation of platelets |
| | GM-CSF, G-CSF | Stimulation of white blood cells |
| | Aprotinin, Tranexamic acid | Antifibrinolytics |
| | Desmopressin | Release of vWF |
| | Vitamin K | Vitamin K-dependent coagulation factors |
| | Recombinant Factor VIIa, VIII | Activation of extrinsic pathway |
| Biological hemostats | Collagen pad | Direct sealing of wounds |
| | Cellulose woven pad | |
| | Fibrin glue | |
| Blood salvage | Cell-saving machines | Recovery of red blood cells |
| Surgical techniques | Thorough operative planning | Minimizing blood loss during procedure |
| | Prompt action to stop bleeding | |
| | Dividing large surgeries into smaller ones | |
| | Minimally invasive procedures | |
| | Endoscopic procedures | |
| | Arterial embolization | |
| | Applied direct pressure | |
| | Ice packs | |
| | Positioning of body | |
| | Tourniquet | |
| Surgical tools | Electrocautery or electrosurgery | Closing vessels |
| | Laser surgery | |
| | Argon beam coagulator | |
| | Gamma knife radiosurgery | |
| | Microwave coagulating scalpel | |
| | Shaw hemostatic scalpel | |
| | Ultrasonic scalpel | |
| | Cryosurgery | |
| Anesthesiologic techniques | Controlled hypotension | Reduced blood pressure |
| | Regional anesthesia | |
| | Maintaining normothermia | Maintain coagulation |
| | Acute normovolemic hemodilution | Reduced blood loss |
| | Pediatric microsampling equipment | Reduced sample volumes |
| | Multiple tests per sample | |
| Management of anemia | Stop the bleeding | Basis of all efforts |
| | Oxygen support | Increased $S_aO_2$ |
| | Maintain intravascular volume | |
| | Iron | Erythropoiesis |
| | Folic acid | |
| | Vitamin $B_{12}$ injection | |
| | Hyperbaric oxygen chamber | Increased $p_aO_2$ |
| | Mechanical ventilation | Reduced oxygen consumption |

able. Hypotension can be achieved by inhalational anesthetics, sodium nitroprusside, nitroglycerin, and trimethaphan. Neuroaxial blocks such as spinal or epidural anesthesia also lower the blood pressure, but controlling the amount of hypotension is more difficult.

Positioning the patient so that the surgical field is at a high point may result in less blood loss.

Mild hypothermia is another possible measure to reduce oxygen demand in anemic patients, as mentioned before. A target core temperature of 30 – 32 °C is typically chosen to balance the reduction of oxygen consumption with the side effects of cardiac arrhythmias and the hypocoagulatory state. Desmopressin, a synthetic analog of the antidiuretic hormone, can elevate the coagulation factor VIII and von-Willebrand factor. Aminocaproic acid and other antifibrinolytics can reduce blood loss by inhibiting the physiologic or increased lysis of already formed clots. Recombinant human erythropoietin stimulates the synthesis of erythrocytes but takes a while to produce an effect and is quite expensive. The artificial substances such as perfluorocarbon that transport oxygen are not as effective as hemoglobin and still need further development.

Table 3.13 lists the possible strategies, measures, and effects to avoid blood transfusions. From this summary, the treating physician should extract the measures applicable to a specific patient.

### 3.7.4 Conclusion

If a hospital anticipates they might administer emergency care to Jehovah's Witnesses, it should establish a protocol for such treatment to help avoid any medical, ethical, or legal dilemmas that may arise.

All the blood-saving techniques discussed above also apply to the regular patient in order to minimize blood loss and the need for transfusions.

## References


ACCP/SCCM (1992) Consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM). Des Plains, IL, August 1991

Apfel CC, Roewer N (2004) Postoperative Nausea and Vomiting. Anaesthesist 53:377

Apfel CC, Laara F, Koivurante M et al (1999) A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross validations between two centers. Anesthesiology 91:693

Boettiger BW, Motsch J, Teschendorf P et al (2004) Postoperative 12-lead ECG predicts perioperative myocardial ischaemia associated with myocardial cell damage. Anaesthesia 59:1083

Cheitlin MD, Armstrong WF, Aurigemma GP et al (2003) ACC/AHA/Ase 2003 Guidline update for the clinical application of echocardiography: summary article. Circulation 108:1146

Cleland JG, Swedberg K, Follath F et al (2003) The Euroheart failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnostics. Eur Heart J 24:442

Dempfle CE (2005) Perioperative coagulation diagnostics. Anaesthesist 54:167

Edwards Life Sciences (2001) Protocol for Early Goal-Directed Therapy for Sepsis. Edwards Life Sciences, Irvine, CA, USA

Fresenius M, Heck M (2001) Repetitorium of Intensive Care. Springer, Berlin Heidelberg New York

Geerts WII, Pieno GF, Heit JA et al (2004) Prevention of venous thromboembolism:the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126:338S

Hahn RG (2006) Fluid absorption in endoscopic surgery. Br J Anaesth 1:8

Heck M, Fresenius M (2004) Repetitorium Anaesthesiology. 4th edn. Springer, Berlin Heidelberg New York

Henzi I, Walder B, Tramer MR (1999) Metoclopramide in the prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized, placebo-controlled studies. Br J Anaesth 83:761

Herold G et al (2006) Text of internal medicine. Gerd Herold, Cologne

Ho KY, Chiu JW (2005) Multimodal antiemetic therapy and emetic risk profiling. Ann Acad Med Singapore 34:196

Jacobi J, Fraser GL, Coursin DB et al (2002) Clinical practice guidelines for the sustained use of sedatives and analgetics in the critically ill adult. Crit Care Med 1:119

Larsen R (1999) Textbook of Anaesthesia, 6th edn. Urban and Schwarzenberg, Munich

Lee TH, Marcantonio ER, Mangione CM et al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100:1043

Level 1, Inc. 160 Weymouth Street, Rockland, MA, USA. http://www.smiths-medical.com. Cited 6 November 2006

Lindenauer PK, Pekow P, Wang K et al (2005) Perioperative beta-blocker therapy and mortality after major noncardiac surgery. N Engl J Med 4:349

Larsen R, Lahme T, Wilhelm W et al. (2002) Manual of Anaesthesia, University Hospital of the Saarland, Homburg

Martin J, Messelken M (1998) Sequential management of sedation and analgesia in the intensive care medicine. W. Zuckschwerdt, Munich

Martin J, Baesell K, Buerkle H et al (2005) Analgesia and sedation in the intensive care unit. S2: guidelines of the German society of anaesthesiology and intensive care medicine. Anaesth Intensivmed 1:S1

Motsch J, Walther A, Bock M, Boettiger BW (2006) Update in the prevention and treatment of deep vein thrombosis and pulmonary embolism. Curr Opin Anaesthesiol 19:52

Murray MJ, Cowen J, DeBlock H et al (2002) Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 1:142

Nieminen MS, Boehm M, Cowie MR et al (2005) Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 26:384

Payen JF, Bru O, Bosson JL et al (2001) Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 12:2258

Poldermans D, Boersma E (2005) Beta-blocker therapy in noncardiac surgery. N Engl J Med 4:412

Pulsion Technology. PiCCO-System, Pulsion Technology, http://www.pulsion.com. Cited 6 Novemer 2006

Rashad Net University (2006) The Jehovah Witness Patient. Published online by the Rashad Net University, Santa Monica, California, USA. http://www.rashaduniversity.com. Cited 6 November 2006

Rivers M, Nguyen B, Havstad S et al (2001) Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 19:1368

Ruesch D, Happe W, Wulf H (1999) Is TIVA with remifentanil/propofol superior to sevoflurane/N2O regarding PONV in children undergoing strabismus surgery. Anaesthesist 48:80

Sarig G, Michaeli Y, Lanir N (2005) Mechanisms for acquired activated protein C resistance in cancer patients. J Thromb Hemost 3:589

Schouten O, Shaw L, Boersma E et al (2006) A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of non-cardiac surgery. Coron Artery Dis 2:173

Sessler CN, Gosnell MS, Grap MJ et al (2002) The Richmond Agitation-Sedation Scale – validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338

Stadler M, Bardieu F, Seidel L et al (2003) Difference in risk factors for postoperative nausea and vomiting. Anaesthesiology 98:46

Teschendorf P (2006) Standard Operating Procedure – Perioperative Beta-Blockers. Department of Anaesthesia, University Hospital of Heidelberg, Germany

Thompson A, Balser JR (2004) Perioperative cardiac arrhythmias. Br J Anaesth 93:86

Weigand MA, Hofer S, Plachky J (2004) Heidelberg sepsis pathway – Recommendations for the therapy of sepsis. University Hospital Heidelberg, Germany

# 4 Anaphylaxis

P. Bader, D. Frohneberg



## 4.1 Definition

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction resulting from the sudden release of mast cell and basophil-derived mediators (Kemp and Lockey 2002).

The European Academy of Allergology and Clinical Immunology (EAACI) suggested that anaphylactic-type reactions should be reclassified as allergic and nonallergic anaphylaxis (Johansson et al. 2001). Allergic anaphylaxis is classified as IgE- or non-IgE-mediated reactions. However, these terms have not been adopted worldwide and *anaphylactoid* and *anaphylactic* remain commonly used in differentiating non-IgE-mediated and IgE-mediated reactions (Kemp and Lokkey 2002).

**Table 4.1.** Common agents that cause perioperative anaphylaxis

| |
|---|
| **Anaphylactic (IgE-dependent)** |
| Medications (e.g., penicillin) |
| Latex |
| Aspirin and other nonsteroidal anti-inflammatory drugs (probably) |
| **Anaphylactoid (IgE independent): Multimediator complement activation, activation of contact system** |
| (Radio)contrast media |
| **Nonspecific degranulation of mast cells and basophils** |
| Opioids |
| Muscle relaxants |
| **Immune aggregates** |
| Dextran (possibly) |
| **Cytotoxic** |
| Transfusion reactions to cellular elements (IgG, IgM) |

The incidence of anaphylaxis during general anesthesia is 1:13,000 in a French study with a mortality of 6% (Laxenaire 1999). The most frequent causes of anaphylaxis during surgical and medical procedures are muscle relaxants, natural rubber latex, antibiotics, and anesthesia induction agents (Lieberman 2002). Colloids, opioids, and (radio)contrast media account for less than 10% of all reactions. An overview of the types of reactions is listed in Table 4.1.

## 4.2 Immunological Mechanism

Coombs and Gell (1975) first classified four types of hypersensitivity (immunopathologic) reactions (Table 4.2).

Type I: Immediate (IgE-dependent)
Type II: Cytotoxic (IgG, IgM-dependent)
Type III: Immune complexes (IgG, IgM-dependent complex)
Type IV: Delayed (T lymphocyte-dependent)

**Table 4.2.** Classification of hypersensitivity (Coombs and Gell 1975)

| Type | Time to maximal reaction | Immunological components | Examples |
|---|---|---|---|
| I | 30 Min and 6 – 12 h | IgE antibodies<br>Mast cells<br>Biphasic reaction | Allergic asthma |
| II | days | Cytotoxic reaction | Graft-versus-host reaction |
| III | 6 – 8 h | Antigen–antibody complexes<br>Complement activation | Vasculitis<br>Glomerulonephritis<br>Blood transfusion reactions |
| IV | 40 – 72 h | Antigen-dependent T cell reaction and leukotriene production | Cutaneous contact allergy |

After Coombs and Gell (1975)

### 4.2.1 IgE-Dependent Anaphylaxis

Classical IgE-dependent anaphylaxis is a type I immunologic reaction, which can happen when a sensitized person is re-exposed to an allergen, usually at least a few weeks after the first exposure. Allergens are usually bivalent proteins with a molecular weight between 10,000 and 70,000 D. Allergen-specific IgE antibodies – synthesized by plasma cells after the first allergen contact – reversibly bind with the $F_c$ portion to receptors on mast cells and basophils. The antigen-binding part of the IgE antibodies (the $F_{ab}$ portion) extends into the extracellular space. During a subsequent antigen contact, the bivalent antigen can then build a bridge between two cell-attached IgE antibodies, which will cause a release of preformed mediators, mainly histamine, from intracellular granules. It also causes the quick synthesis of other mediators such as leukotrienes C4, D4, and E4, triggered from membrane-attached phospholipids. These primary mediators cause the clinical appearance of anaphylaxis. Both mast cells and basophils additionally release chemotactic factors to attract other cells of the immune system. The eosinophils partly decrease the anaphylactic reaction by inactivating histamine and leukotrienes. Neutrophils and thrombocytes with their products are thought to be part of the delayed anaphylactic reaction 6 – 12 h after the initial type I reaction.

Besides this classical route of anaphylactic reaction, another type has been described: type III anaphylactic reaction. Characteristically, this type of reaction occurs in patients with a hereditary deficiency of IgA (for example, during blood transfusion) (see Sect. 4.8).

### 4.2.2 Non-IgE-Dependent Anaphylaxis

In non-IgE-dependent anaphylaxis, the release of the mediators can be initiated by different factors that directly interfere with the mast cells and basophils: physical (e.g., cold temperature), osmotic (e.g., contrast media), or chemical stimuli (e.g., opioids). For this type of a reaction, no sensitization is needed, and therefore this type of anaphylactic reaction may occur with the first contact to the allergen.

The main primary mediator, histamine, activates $H_1$ and $H_2$ receptors. Pruritus, rhinorrhea, tachycardia, and bronchospasm are caused by the $H_1$ receptors, whereas both $H_1$ and $H_2$ receptors mediate headache, flushing, and hypotension. Gastrointestinal signs and symptoms are associated with histamine more so than with tryptase levels.

| The different routes of histamine release: | | | |
|---|---|---|---|
| IgE-dependent: | Antigen | Basophils | Histamine<br>Leukotrienes |
| | | Mastocytes | Histamine<br>Leukotrienes<br>Tryptase |
| Nonspecific:<br>Idiosyncratic | Chemotoxicity<br>Physical stimuli | Basophils | Histamine |

## 4.3 Clinical Presentation and Differential Diagnosis

The severity of the hypersensitivity reaction is classified into four grades (see Table 4.3): IgE- or non-IgE-mediated reactions and anaphylactoid or anaphylactic reactions, respectively, cannot be differentiated clinically.

The most important clinical signs are (Chiu and Kelly 2005):

- Cutaneous reactions (erythema, urticaria ) and soft tissue swelling (e.g., eyelids, lips)
- Hypotension and tachycardia

**Table 4.3.** Severity of immediate hypersensitivity reactions

| Grade | Symptoms |
|---|---|
| Grade 1 | Only cutaneous signs: diffuse erythema, urticaria |
| Grade 2 | Same as grade 1 + nausea, cough, dyspnea, tachycardia, hypotension |
| Grade 3 | Same as grade 2 + vomiting, diarrhea, bronchospasm, cyanosis, shock |
| Grade 4 | Cardiovascular arrest (apparent death) |

After Ring and Messmer (1977)

- Respiratory symptoms (cough, dyspnea, bronchospasm, laryngeal edema, and cyanosis)
- Gastrointestinal reactions (nausea, vomiting, diarrhea)
- Neurological reaction (loss of consciousness)

Other diagnoses that might mimic anaphylaxis should be considered, since there are several conditions that can also cause abrupt and dramatic patient collapse. Acute reactions should be excluded if possible; these include vasodepressor (vasovagal) reactions, acute anxiety (e.g., panic attack or hyperventilation syndrome), myocardial dysfunction, pulmonary embolism, aspiration, and hypoglycemia.

The clinical presentation of an anaphylactic/anaphylactoid reaction can differ greatly in each patient; it is also very much dependent on the route of allergen exposure, the rate of absorption, and the grade of sensitivity to the allergen. The symptoms may appear only seconds or minutes after the contact with the allergen.

In more than 90 % of all cases, cutaneous symptoms such as pruritus, flush, or erythema happen prior to systemic reaction. However, cutaneous manifestations might be delayed or absent in rapidly progressive anaphylactic shock.

Obstruction of the pulmonary system is very common and can be life threatening. The reason may be extrathoracic (caused by swelling of the larynx or pharynx) or intrathoracic (caused by obstruction of the bronchi). Most often the swelling of the larynx is the cause of death in anaphylactoid reactions and starts with hoarseness, wheeze, and stridor. As in acute shock, edema of the larynx may be the only symptom of anaphylaxis.

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, bowel urgency are caused by disturbance of the permeability of the gastrointestinal system and additionally by the hypermobility of the bowels due to stimulation of histamine receptors.

The exact mechanism of hemodynamic reactions is not fully understood. Leading symptoms are hypovolemia due to vasodilatation and fluid shift into the interstitium, and tachycardia as well as decreased cardiac filling pressure.

It is unknown whether cerebral signs such as dizziness, syncope, cramps, and unconsciousness are caused by cerebral lack of perfusion or a direct effect of the mediators.

## 4.4 Diagnostic Tests and Risk Factors

There are many different diagnostic tests, including serum tryptase, plasma histamine, specific IgE-level measurements, and skin tests. However, all of these tests have their pitfalls.

An elevated tryptase level 1 – 6 h after a suspected anaphylactic reaction indicates mast cell degranulation. Together with a suggestive history and clinical findings, this supports the diagnosis of anaphylaxis (Fisher and Baldo 1998). However, serum tryptase concentration may be normal even in fatal anaphylaxis.

Plasma histamine level reaches a peak within 15 – 30 min of the onset of anaphylaxis and returns to baseline values within 1 h. This test is therefore of very limited use and only helpful in some patients.

### 4.4.1 Diagnosis of Serious or Fatal Reaction to Contrast Media

During anaphylaxis/anaphylactoid reaction, histamine is released from both basophils and mast cells, while tryptase is absent from basophils but released from the granules of mast cells together with histamine. New highly reliable assays are becoming available for measuring tryptase and histamine in plasma (Laroche et al. 1998). Tryptase's half-life is about 90 min, and the best time for measuring is 1 – 2 h after the reaction (not later then 6 h). Only very high concentrations of serum tryptase should be regarded as specific for fatal anaphylaxis/anaphylactoid reactions (Brockow et al. 1999). Histamine has a very short half-life (approximately 2 min), and the best time for measuring its plasma level is between 10 min and 1 h after the reaction. Consequently, blood samples for histamine analysis should be drawn as soon as possible after the reaction. For tryptase, blood sampling 1 – 2 h after onset of the symptoms has been recommended. To enable comparison with baseline levels, new blood samples should be collected 1 – 2 days after the reaction (Brockow et al. 2005a).

The level of histamine release has been demonstrated to have a direct relationship to the severity of the immediate reaction to iodinated contrast media (CM) (Laroche et al. 1998). The proof of an increased histamine or tryptase level during the acute reaction can help to diagnose an anaphylactic reaction, even retrospectively.

Muscle relaxants and natural rubber latex are very significant and potent allergens in the perioperative period. In patients with a suspicious history, a search for specific IgE antibodies can be done prior to the operation to minimize the risk of a potential anaphylactic reaction (see Sects. 4.8 and 4.9). If a latex allergy is suspected, a skin prick test is recommended (see Sect. 4.9).

In suspected penicillin incompatibility, a prior skin test might be very helpful, because it has a high negative predictive value (see Sect. 4.8).

All patients with an anaphylactic reaction should undergo an consultation with an allergy and immunology specialist, and the results documented in an allergy

card. After a severe reaction, the patient should be taught to do initial self-treatment in the event of contact to the allergen. In such cases, patients should therefore carry an emergency kit with them. This should include an H1-antagonist (e.g., dimetindene maleat, 2 ml = 2 mg) as a liquid and an quick effective corticosteroid in a liquid form (e.g., celestamine liquidum, 5 ml = 0.5 mg betamethasone) or for inhalation (e.g., Primatene mist epinephrine) and an adrenaline pen for self- intramuscular injection (e.g., Fastjekt or EpiPen, 0.3 ml = 0.30 mg epinephrine).

Generally, all patients with a history of asthma or atopy (including hay fever and food allergies) have an increased risk of anaphylactic/anaphylactoid reactions in the perioperative interval. Risk factors have been clearly demonstrated for two major allergens commonly found in hospital:

1. Although reactions to iodinated radiographic CM are not true allergic ones, patients with a history of a previous reaction to contrast material have a three- to fourfold greater risk of subsequent reaction than the general population (Katayama et al. 1990; Morcos and Thomsen 2001). Other important risk factors include asthma and a history of atopy, including hay fever and food allergies, increasing the risk of anaphylaxis eight- to tenfold (Morcos and Thomsen 2001; Shehadi 1982). In addition, patients treated with β-adrenergic blockers and interleukin-2 are at increased risk of acute adverse reactions to CM (Thomsen et al. 2004; Morcos 2005) (see Sect. 4.7).
2. The risk of latex hypersensitivity in patients who require chronic bladder care (e.g., individuals with bladder extrophy or meningomyelocele) has been reported to be as high as 72 % (Ricci et al. 1999). The risk of anaphylaxis in the operating room is 500-fold greater in patients with spina bifida as compared with control groups (Taylor and Erkek 2004). In individuals of occupations with regular exposure to latex gloves (e.g., health care workers, hair dressers, cleaners, housekeepers) the incidence of latex sensitization is up to 12 %, compared to 1 % – 6 % in the general population (Lieberman 2002) (see Sect. 4.9).

## 4.5 Prevention and Treatment of Anaphylactic Reactions

Medical prevention of anaphylaxis is useful in avoiding reactions to iodinated radiographic contrast media. It is recommended in patients with a high risk for anaphylactic/anaphylactoid reaction to CM as defined earlier (Sect. 4.4). Premedication has not been proven to have any benefit in all other perioperative anaphylactic/anaphylactoid reactions, e.g., reactions to latex or muscle relaxants.

The treatment of anaphylaxis is based on a few very important factors (for details, see Table 4.4).

- Supine position, elevated legs
- Oxygen (6 – 10 l/min)
- Volume substitution
  - Crystalloids (saline or ringer solution) 30 ml/kg i.v.

**Table 4.4.** Treatment of immediate hypersensitivity reactions
*HES* = Hespan

| Grade | Type of reaction Dermatological | Respiratory tract | Cardiovascular | Progression suspected |
|---|---|---|---|---|
| I | H1- (+H2-) antagonists | As needed:<br>i.v. line<br>Oxygen | As needed:<br>i.v. line<br>Oxygen | Corticoids i.v.<br>H1-(+H2-) antagonists |
| II | H1- (+H2-) antagonists | Mandatory:<br>i.v. line<br>Oxygen<br>$\beta_2$-Sympathicomimetica inhalation<br>Prednisolone (250 – 500 mg i.v.) | Mandatory:<br>i.v. line<br>Oxygen<br>Colloids, Ringer solution, HES | Corticoids i.v.<br>H1-(+H2-) antagonists<br>Adrenaline 0.1 mg i.v. |
| III | H1- (+H2-) antagonists | Mandatory:<br>i.v. line<br>Oxygen<br>$\beta_2$-sympathicomimetica inhalation<br>Prednisolone (0.5 – 1 g i.v.) | Mandatory:<br>i.v. line<br>Oxygen<br>Colloids, Ringer solution, HES<br>Adrenaline 0.1 mg i.v. repeated every 3 min | Corticoids i.v.<br>H1-(+H2-) antagonists<br>Adrenaline 0.1 mg i.v.<br>Dopamine and/or noradrenaline as needed |
| IV | Cardiopulmonary Resuscitation and intubation | | | |

From Kemp 2002

| Grade of reaction | Step | What to do? |
|---|---|---|
| **Grade I** (slight to moderate general reaction) | 1 | Stop the cause, stop the antigen |
| | 2 | Give oxygen by mask (6 – 10 l/min) |
| | 3 | Place an i.v. line and apply volume (500 ml saline, Ringers solution or HES) |
| | 4 | Measure blood pressure and pulse rate |
| | 5 | Elevate patient's legs if hypotensive |
| | 6 | Inject an H1-antagonist i.v. (e.g., diphenhydramine 25 – 50 mg, clemastine 4 mg or dimetindene maleat 8 mg)<br>Optionally inject an H2-antagonist (e.g., cimetidine 400 mg or ranitidine 100 mg) |
| **Grade II** (severe general reaction) | 7 | Call resuscitation team |
| | 8 | Give corticosteroids i.v. (e.g., prednisolone 500 – 1,000 mg) |
| | 9 | Give adrenaline 1 : 1000 i.m. (0.2 – 0.5 mg) |
| | 10 | In case of bronchospasm give $\beta_2$-sympathicomimetica (e.g., fenoterol inhalation 100 – 200 µg or terbutaline 0.25 – 0.5 mg SC) |
| **Grade III** (life threatening general reaction) | 11 | ECG monitoring |
| | 12 | Give adrenaline 1 : 1,000 i.v. (0.1 mg, repeated every 3 min) |
| | 13 | Cardiopulmonary resuscitation and intubation |

**Table 4.5.** Step-by-step algorithm for the treatment of anaphylactic reactions in correlation to the grade of anaphylactic reaction

See also Table 4.4

- Antihistamines (H1 and H2)
- Corticoids
- Adrenaline (diluted 1 : 1,000)

A step-by-step algorithm on what to do with a patient presenting with an anaphylactic reaction is provided in Table 4.5.

Treatment for anaphylaxis is supportive and includes epinephrine/adrenaline as the first-line pharmacological agents. An incidence of 6 % for a biphasic anaphylactic reaction in pediatric patients was reported. A delay in administering epinephrine was associated with increased incidence of biphasic reactions, and *unavailability of epinephrine was associated with death* (Lee and Greenes 2000; Chiu and Kelly 2005).

Therefore, patients with an anaphylactic reaction need continuous surveillance for 24 h in hospital. This is also necessary in patients with a good reaction to appropriate therapy because of the possibility of recurrence and the delayed reaction (up to 12 h after the initial reaction) with arrhythmia, myocardial ischaemia or respiratory insufficiency (Haupt 1995).

Monitoring vital functions must include continuous ECG monitoring, pulse oximetry, and blood pressure monitoring.

Management of anaphylactic shock in general is described in great detail by Kemp and Lockey (2002) and is analogous to the management of the immediate reactions to contrast media (Table 4.8).

Guidelines for the management of the cardiovascular shock are published by the American Heart Association (Cummins and Hazinski 2000), the British Resuscitation Council, and the National Guideline Clearinghouse of the United States (NGC) (for addresses of the websites, see Sect. 4.10).

## 4.6 The Role of Skin and Provocation Tests

The diagnostic value of skin tests has not been fully evaluated during the last decade. Reliable skin test procedures are generally lacking, and test concentrations are unknown or poorly validated for most drugs (Demoly 2005). Skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism. They should be performed 4 – 6 weeks after the reaction by specialists in an appropriate setting, since the tests themselves can induce an anaphylactic reaction, although rarely.

Depending on the drug, the sensitivity and predictive values of tests vary from excellent (penicillin, muscle relaxants) to satisfactory (opioids, thiopental) all the way to poor or unknown (local anesthetics, paracetamol, sulfonamide, contrast media, nonsteroidal antiinflammatory drugs). For details, see Sects. 4.7 and 4.8.

The best standardized skin test exists for the β-lactam ring of penicillin. An IgE-dependent hypersensitivity can be demonstrated by a positive skin prick test and/or intradermal test after 20 min (Brockow et al. 2002).

A drug provocation test is carried out for diagnostic/therapeutic purposes and consists of the controlled administration of the drug to a patient with a history that suggests drug allergies. The European Network of Drug Allergy from the European Academy of Allergology and Clinical Immunology recommends the use of a provocation test when skin tests and biological tests are not available or not validated. This approach has elicited some controversial discussion, because with the exception of aspirin and β-lactams, results of tests are only available for very small patient groups. One of the most important reports on drug provocation tests, con-

ducted in 1,372 patients, could show true drug hypersensitivity in only 17.6 % of the patients (Demoly 2005). This is of crucial importance for the therapeutic future of these patients. Drug provocation tests should nevertheless be regarded as a serious and potentially dangerous procedure (Aberer et al. 2003).

## 4.7 Immediate and Nonimmediate Reactions to Contrast Media

Since their development in the 1950s tri-iodinated benzene derivates have been used for opacification of the urinary tract. The radiopacity of such compounds is produced by molecular iodine, which is attached to the benzene ring. The agents are further characterized by their ionic and nonionic side chains as well as their monomeric or dimeric ring structure.

Contrast media are used in many diagnostic and interventional procedures, including intravenous urography, CT scan, angiography, intraoperative antegrade or retrograde pyelography, urethrogram, and cystogram.

Adverse effects of contrast media are generally classified into two large groups: chemotoxic effects and idiopathic or anaphylactoid reactions. Chemotoxic effects are thought to be dose-related and have a direct toxic effect on the target organ, such as the nephrotoxicity of contrast media.

Anaphylactoid reactions simulate a true allergic reaction, but are not mediated by immunoglobulins. No antibodies to contrast material have ever been demonstrated. The diagnosis of contrast media-associated nonallergic anaphylaxis is based on clinical history alone.

Serious reactions to CM are comparable to type 1 hypersensitivity reactions (anaphylaxis), which begin within minutes after antigen exposure and are mediated by a variety of chemotactic, vasoactive, and spasmogenic compounds. Histamine seems to be the primary mediator of anaphylaxis/anaphylactoid reaction and is responsible for the intense immediate manifestations. Preformed histamine is present in basophils and mast cells and is released rapidly by degranulation of these cells in a response to a variety of stimuli. There are several other biological mediators produced by mast cells and basophils, including leukotrienes, prostaglandins, enzymes, and a variety of cytokines. These substances act in an autocrine, paracrine, and endocrine fashion, triggering a cascade of inflammatory mediators. They induce vasodilatation, an increase in vascular permeability leading to edema, contraction of smooth muscle cells precipitating bronchospasm, and an increase in airway mucous secretion. The cytokines and chemotactic factors recruit leukocytes, eosinophils, basophils, monocytes, and T cells, which release additional waves of mediators and cytokines (Morcos 2005).

The mechanisms by which CM activate basophils and mast cells to release histamine and other mediators are not completely understood. They may include direct effects of CM particles on these cells or activation of immunological mechanisms involving IgE antibodies, thymus-derived lymphocytes (T cells) or the complement system (Morcos 2005).

Hypersensitivity reactions to all classes of contrast media (CM) occur either immediately within the first hour after CM administration, or nonimmediately, more than 1 h after CM exposure.

Mild immediate reactions occur in 0.7 % – 3.1 % of patients receiving lower-osmolar/nonionic CM (Brokkow et al. 2005a). Pruritus and mild urticaria are the most common immediate manifestations. More severe reactions involve the respiratory and cardiovascular systems.

The frequency of nonimmediate hypersensitivity reactions appears to range from 1 % to 3 %, and skin reactions of the maculopapular exanthematous and urticarial/angioedematous types account for the majority of them. At present, the exact pathogenesis of these delayed reactions is still unclear. There is, however, increasing evidence that a significant proportion of the reactions is T cell-mediated (Christiansen et al. 2000).

In a large study of over 330,000 patients, Katayama et al. evaluated the incidence of severe and very severe reactions following intravascular administration of CM. He found an incidence of 0.22 % and 0.04 %, respectively, after administration of high-osmolar contrast media (HOCM), but only 0.04 % and 0.004 %, respectively, after low-osmolar contrast media (LOCM) (Katayama et al. 1990; Table 4.6). The study concluded that the use of LOCM has resulted in reducing the incidence of severe and very severe reactions by a factor 10 in comparison to HOCM. However, no difference was observed in the incidence of fatal reactions to both types of CM, which were exceedingly rare (1 : 170,000). Nevertheless, iodinated CMs are one of the top ten drugs responsible for anaphylaxis/anaphylactoid reactions (Wang et al. 1998), with a mortality rate of 0.9 per 100,000 examinations (Pumphrey 2000; Caro 2001).

**Table 4.6.** Frequency of adverse reactions to contrast media (338,000 patients)

| Adverse reactions | High-osmolar/ ionic contrast media | Low-osmolar/ nonionic contrast media |
|---|---|---|
| Total | 12.66 % | 3.13 % |
| Severe | 0.22 % | 0.04 % |
| Very severe | 0.04 % | 0.0004 % |
| Fatal | 0.0006 % | 0.0006 % |

After Katayama et al. 1990

### 4.7.1 Diagnostics

#### *4.7.1.1 Immediate Hypersensitivity Reactions*

Immediate hypersensitivity reactions to CM are at least in part associated with histamine and tryptase release from basophils and mast cells (Laroche et al. 1998). The role of skin prick tests and intradermal tests (IDT) in diagnostic procedures has been evaluated for many years, but positive tests have only been reported in patients with a history of severe reactions (Brockow 2005a). Determination of plasma histamine and tryptase immediately after reactions to CM may confirm basophil or mast cell mediator release (Laroche et al. 1998). However, recent results indicate that these tests may be of limited value (Laroche 2004). Only two out of 20 patients with immediate reactions had increased levels of these mediators after CM exposure. Both patients had experienced a life-threatening reaction. Whereas tryptase levels remain relatively stable within at least 2 h, histamine is rapidly degraded, and levels have to be determined as soon as possible after the reaction.

Some investigators have reported the presence of CM-specific IgE antibodies in the serum of patients with an immediate reaction, but the frequency of positive test results varies widely between 2 % and 47 %. No commercial assay is available for routine measurement, and the relative merit of the test in diagnosing severe immediate reactions has yet to be established (Brockow 2005a).

Additionally, the role of a histamine release test and other in vitro basophil activation tests in the diagnosis of allergic reactions to CM has not yet been defined.

#### *4.7.1.2 Skin Reactions*

Skin reactions of the maculopapular exanthematous and urticarial/angioedematous types account for the majority of nonimmediate hypersensitivity reactions to CM. There is increasing evidence that a significant proportion of the reactions are T cell-mediated (Christiansen et al. 2000). Skin tests have been widely used to confirm such delayed hypersensitivity. CM have consistently tested positively as an allergen in patch tests and/or delayed intradermal tests (IDT) in reactors but not in controls (Brockow et al. 2005a). These tests may be useful in allergy diagnosis of nonimmediate skin reactions to CM, but further evaluation is needed with regard to the sensitivity and specificity as well as of the positive and negative predictive value of such tests.

More data from larger studies are needed to assess the usefulness of the skin tests and other diagnostic tests as routine tools in the follow-up of patients with either immediate or nonimmediate hypersensitivity reactions after CM exposure. *At present such tests cannot yet be recommended for routine clinical practice* (Brokkow 2005b).

### 4.7.2 Risk Factors

Although the majority of anaphylactoid reactions occur unpredictably, certain risk factors have been well documented. Even though these reactions are not true allergic reactions, patients with a history of a previous adverse response to contrast material have a risk of subsequent reaction that is three- to fourfold greater than the general population (Katayama et al. 1990; Morcos and Thomsen 2001). Other important risk factors include asthma and a history of atopy, including hay fever and food allergies (Morcos and Thomsen 2001; Shehadi 1982). In addition, patients treated with β-adrenergic blockers and interleukin-2 are at increased risk of acute adverse reactions to CM (Thomsen and Morcos 2004; Morcos 2005).

### 4.7.3 Prevention

The European Society of Urogenital Radiology (ESUR) has produced guidelines on prevention of generalized reactions to CM (Morcos et al. 2001; Table 4.7). They recommend the use of nonionic CM to decrease the risk of generalized CM reactions; they also recommend premedicating high-risk patients with prednisolone (30 mg orally) or methylprednisolone (32 mg orally) 12 and 2 h before CM exposure. However, the value of such premedication in the prevention of severe reactions to lower-osmolar CM has not been conclusively demonstrated. It has yet to be definitively decided whether antihistamines H1 and H2 are of additional benefit in premedication (Morcos et al. 2001; Morcos 2005).

In case of emergency administration of CM in patients with a high risk of severe reactions to CM, particularly those with a history of previous serious reaction to CM, pretreatment is recommended with hydrocortisone (200 mg intravenously) immediately and every 4 h until the procedure is completed, as well as with diphenhydramine (50 mg intravenously) before the procedure and the use of low-osmolar nonionic CM (Greenberger et al. 1986).

However, the best prevention of acute reactions to iodinated contrast media is to avoid its administration (Morcos 2005). Therefore in high-risk patients, imaging procedures that use other contrast media should be considered. Anaphylaxis to gadolinium-based contrast media used in magnetic resonance imaging is very rare and is a safe alternative.

**Table 4.7.** Prevention of generalized reactions to contrast media

**A. Risk factors for reactions**
- Previous generalized reaction to a contrast medium, either moderate (e.g., urticaria, bronchospasm, moderate hypotension) or severe (e.g., convulsions, severe bronchospasm, pulmonary edema, cardiovascular collapse)
- Asthma
- Allergy requiring medical treatment

**B. To reduce the risk of generalized contrast medium reactions**
- Use nonionic agents

**C. Premedication is recommended in high-risk patients (defined in A)**
- When ionic agents are used
- Opinion is divided about the value of premedication when nonionic agents are used

**D. Recommended premedication**
- Corticosteroids
  Prednisolone (30 mg orally) or methylprednisolone (32 mg orally) 12 and 2 h before contrast
  Medium is administered. Corticosteroids are not effective if given less than 6 h before contrast medium
- Antihistamines H1 and H2 may be used in addition to corticosteroids, but opinion is divided about the merits of this approach
  Remember for all patients
- Have a trolley with resuscitation drugs in the examination room
- Observe patients for 20 – 30 min after contrast-medium injection

**F. Extravascular administration**
- When absorption or leakage into the circulation is possible, take the same precautions as for intravascular administration

After Morcos et al. (2001b); www.esur.org

### 4.7.4 Treatment

Severe, even life-threatening reactions may still occur in patients who receive both corticoid premedication and low-osmolar contrast media. Prompt recognition and treatment of adverse side effects to CM can be invaluable in diminishing the response and may prevent a reaction from becoming severe or even life-threatening (Morcos and Thomsen 2001). For at least 20 min after a CM injection, the patient should never be left alone, because 94 % – 100 % of severe and fatal reactions occur in that interval. Knowledge, training, and preparation are very important for effective treatment of an adverse contrast-related reaction. Therefore, all personnel involved in intravascular application of CM should be adequately trained in cardiopulmonary resuscitation, and all equipment for resuscitation (crash cart, defibrillator, necessary drugs) should be checked regularly.

Mild reactions are usually self-limiting and do not require active treatment. However, the application of the agents must be stopped immediately, and the patient should be observed until full recovery.

**Table 4.8.** Simple guidelines for first-line treatment of acute reactions to CM

**Nausea or vomiting**
- Transient: supportive treatment
- Severe, protracted: appropriate antiemetic drugs should be considered

**Urticaria**
- Scattered, transient: supportive treatment including observation
- Scattered, protracted: appropriate H1-antihistamine intramuscularly or intravenously should be considered; drowsiness and/or hypotension may occur
- Profound: consider adrenaline 1:1,000, 0.1 – 0.3 ml (0.1 – 0.3 mg) intramuscularly up to 0.3 maximum in children. Repeat as needed

**Bronchospasm**
- Oxygen by mask (6 – 10 l/min)
- β-2-agonist metered dose inhaler (two to three deep inhalations)
- Adrenaline

*Normal blood pressure*
Intramuscular: 1:1,000, 0.1 – 0.3 ml (0.1 – 0.3 mg) (use smaller dose in a patient with coronary artery disease or elderly patient)
In pediatric patients: 0.01 mg/kg up to 0.3 mg maximum

*Decreased blood pressure*
Intramuscular: 1:1,000, 0.5 ml (0.5 mg), (in pediatric patients: 0.01 mg/kg intramuscularly)

**Laryngeal edema**
- Oxygen by mask (6 – 10 l/min)
- Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) for adults, repeat as needed

**Hypotension**
*Isolated hypotension*
- Elevate patient's legs
- Oxygen by mask (6 – 10 l/min)
- Intravenous fluid: rapidly, normal saline or lactated Ringer's solution
- If unresponsive: adrenaline: 1:1,000, 0.5 ml (0.5 mg) intramuscularly, repeat as needed

*Vagal reaction (hypotension and bradycardia)*
- Elevate patient's legs
- Oxygen by mask (6 – 10 l/min)
- Atropine 0.6 – 1.0 mg intravenously, repeat if necessary after 3 – 5 min, to 3 mg total (0.04 mg/kg) in adults. In pediatric patients, give 0.02 mg/kg intravenously (max. 0.6 mg per dose) repeat if necessary to 2 mg total
- Intravenous fluid: rapidly, normal saline or lactated Ringer's solution

**Generalized anaphylactoid reaction**
- Call for resuscitation team
- Suction airway as needed
- Elevate patient's legs if hypotensive
- Oxygen by mask (6 – 10 l/min)
- Intramuscular adrenaline (1:1,000), 0.5 ml (0.5 mg) in adults. Repeat as needed. In pediatric patients, 0.01 mg/kg to 0.3 mg (maximum dose)
- Intravenous fluids (e.g., normal saline, lactated Ringer's)
- H1-blocker, e.g., diphenhydramine 25 – 50 mg i.v.
- β-2-agonist metered dose inhaler for persistent bronchospasm: two or three inhalations

After Thomsen et al. (2004); www.esur.org

The management of acute adverse reactions to contrast media is well defined and all other anaphylactic reactions, for example to latex and drugs, are managed in the same way. This includes establishment of an adequate airway, oxygen supplementation, administration of intravascular physiological fluids, and measurement of the blood pressure and heart rate. Talking to the patient while checking the pulse rate provides useful initial information: breathing is assessed, the possibility of a vagal reaction (bradycardia) is determined, and a rough estimation of systolic pressure is obtained. H1-antihistamine and adrenaline are administered in correlation with the severity of the reaction.

Wherever an anaphylactic reaction may occur (e.g., the ward, the operating room, the examination room of the radiology department), the following basic medical equipment should be available:

- Oxygen
- Adrenalin 1:1,000 (suitable for injection)
- Antihistamine H1 (suitable for injection)
- Atropine
- β2-agonist metered-dose inhaler
- i.v. fluids: normal saline or Ringers solution
- Anticonvulsive drugs (diazepam)
- Sphygmomanometer
- One-way mouth breather apparatus

Guidelines on first-line treatment have been published by the European Society of Urogenital Radiology (ESUR) (Thomsen and Morcos 2004; Table 4.8, www.esur.org). The subsequent management of severe adverse reactions (including the administration of second-line drugs) should be handled by the resuscitation team.

H2 antihistamines and H2 receptor blockers have a limited role in treating contrast media reactions. They are used primarily to reduce symptoms from skin reactions. High-dose intravenous corticoids do not play a role in the first-line treatment of acute adverse reactions. Standard doses can be effective in reducing delayed recurrent symptoms, occurring up to 48 h after the initial reaction (intravenous prednisolone 250 mg or methylprednisolone 50 mg). However, very high doses may have an immediate stabilizing effect on the mast cell membrane and can be used in the second-line treatment (intravenous prednisolone 500–1,000 mg or methylprednisolone 100–200 mg). It can take 6 h before corticoids are fully active (Thomsen and Morcos 2004).

## 4.8 Reactions to Perioperative Drugs

### 4.8.1 General Anesthetic Agents and Neuromuscular Blocking Agents

The main agents used for induction of anesthesia are hypnotics (thiopentone, propofol, and etomidate), opioids (fentanyl), neuroleptics, and benzodiazepines (Thong and Yeow-Chan 2004). The majority of intraoperative anaphylactic reactions are caused by the neuromuscular blocking agents commonly used to induce paralysis to facilitate endotracheal intubation or to optimize surgical exposure (Birnbaum et al. 1994).

The use of intradermal skin tests for the diagnosis of IgE-mediated anaphylaxis to agents during general anesthesia is well established (Moscicki et al. 1990; Rose and Fisher 2001). Some authors have reported the usefulness of skin prick tests (Fisher and Bowey 1997). The advantage of skin prick tests is that by doing intradermal testing, potentially dangerous reactions can be prevented. However, there are no data available on the safety of subsequent anesthesia based on the results of prick testing alone, and reliability over time has not been assessed.

Skin testing is useful because alternative muscular relaxants that produce a negative skin test reaction may be used safely if skin tests show that a neuromuscular agent could cause problems (Fisher 1994). However, the true-negative predictive value for these skin tests is unknown, and false-negative skin reactions have been reported (Fisher et al. 1999).

Patients with previous reactions to an agent used during general anesthesia should have intradermal testing done for both putative agents and an alternative neuromuscular block. Low-risk agents such as pancuronium should be given preference over high-risk agents such as succinylcholine, if both yield negative skin tests. However, a negative skin test result does not eliminate the possibility of developing a reaction to one of these agents. Pretreatment for neuromuscular blocking agent allergy has been found to be ineffective.

Drug-specific IgE can be demonstrated by radioimmunoassay and radioallergosorbent testing (RAST). However, there is only one commercially available test for muscular relaxants (suxamethonium; Pharmacia, Uppsala, Sweden).

### 4.8.2 Local Anesthetic Agents

Adverse reactions to local anesthetics are not uncommon, but less than 1% are true allergic reactions (Schatz 1984.)

Positive skin test reactions may occur in approximately 15% of patients with no history of adverse reac-

tions to local anesthetic agents (false positive). False-negative test results are rare but are nevertheless reported in the literature (Thong and Yeow-Chan 2004).

### 4.8.3 Antibiotics

The most common antibiotics given perioperatively are penicillins, cephalosporins, gentamicin, and vancomycin (in patients with methicillin-resistant *Staphylococcus aureus*) (Thong and Yeow-Chan 2004). β-Lactam antibiotics are estimated to cause 400 – 800 fatal anaphylactic episodes per year. The skin test is the most reliable method for evaluating suspected anaphylaxis to penicillin; 97 % of patients with a negative skin test reaction will tolerate penicillin administration. Thus the skin test has a high negative predictive value. With the presence of a positive history and a positive skin test reaction, the patient has at least a 50 % risk of an immediate reaction to penicillin (Bernstein et al. 1999). Positive drug-specific IgE test results may suggest a diagnosis of penicillin allergy; however, negative tests are unreliable. Thus, skin tests are preferred.

The cross-hypersensitivity between penicillins and cephalosporins is less than 5 % – 10 %. Skin tests for cephalosporins are not standardized, and the negative predictive value is unknown.

Desensitization may be considered for patients with a positive skin test reaction to penicillin who require penicillin or cephalosporin in absence of suitable non-β-lactam alternatives (Borish et al. 1987; Kelkar and Li 2001).

Vancomycin hypersensitivity usually leads to skin flush (red man syndrome) and commonly occurs from direct mast cell histamine release. Diagnosis is made from clinical history. If the flush does not respond to a slower rate of infusion, a protocol similar to desensitization may be considered (Wazny and Daghigh 2001).

### 4.8.4 Opioids

Opioids are often used perioperatively for analgesia and sedation, and as adjuvants to anesthetics. Morphine, codeine, and synthetic opioids such as pethidine can cause direct mast cell degranulation without the presence of specific IgE antibodies. This explains why the skin prick test is not helpful in the diagnosis of opioid hypersensitivity (Nasser and Ewans 2001).

### 4.8.5 Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs), given for pain relief in the perioperative period, may cause both anaphylactic and anaphylactoid reactions. Anaphylaxis to NSAIDs is typically drug-specific and not common to the entire group of agents.

### 4.8.6 Heparin

Perioperative heparin prophylaxis can cause thrombocytopenia. There are two types of heparin-induced thrombocytopenia (HIT). HIT I is characterized by a transitory, slight, and asymptomatic reduction in platelet count during the first 1 – 2 days of treatment. It resolves spontaneously and does not require discontinuation of the drug. The origin of HIT I is not completely understood, but may be caused by a heparin-induced platelet clumping.

The other type of heparin-induced thrombocytopenia, HIT II, has an immunological origin. It is characterized by a significant reduction in platelets (reduction $>50\,\%$ or to levels $<100 \times 10^3/\mu l$), generally observed after the $5^{th}$ day of treatment, and usually resolves in 5 – 15 days after heparin has been suspended. However, in some cases it may take months. HIT II is the most frequent and dangerous side effect of heparin. It may appear in patients who were exposed to heparin earlier. Laboratory tests confirm that the prevalence seems to be 1 % – 3 % for unfractionated heparin and 0 % – 0.8 % for low-molecular-weight heparin. There is a greater risk in those patients receiving heparin of bovine compared with porcine origin (Fabris et al. 2000; Menajovsky 2005 ).

The immunologic etiology of HIT II is largely accepted: platelet factor 4 (PF4) displaced from endothelial heparin sulphate or directly from the platelets binds to the heparin molecule to form an immunogenic complex. The IgG anti-heparin/PF4 immunocomplexes activate platelets and provoke an immunologic endothelial lesion with thrombocytopenia and/or thrombosis. Cutaneous allergic manifestation at the heparin injection sites and skin necrosis may be present as well. Interestingly, hemorrhagic events are not frequent, while the major clinical complications in at least 30 % of the patients are both arterial and venous thrombosis, with a 20 % mortality rate. The exact pathomechanism of this reaction is not clear.

During heparin therapy, platelet counts should be checked regularly, at least twice weekly. The diagnosis of HIT is based primarily on clinical criteria and in vitro demonstration of heparin-dependent antibodies. Among the different assays available, the PF4-heparin enzyme linked immunosorbent assay (ELISA) and the $^{14}C$-serotonin release assay (SRA) are the most widely used tests.

If HIT II is suspected, heparin must be immediately discontinued and an alternative anticoagulation should be initiated until the resolution of the thrombocytopenia is completed. Heparinoids such as danaparoid sodi-

um (Orgaran; no longer available in the US) or direct thrombin inhibitors such as hirudin are the safest and most effective drugs against the symptoms of HIT, significantly reducing mortality due to thrombotic complications (Fabris et al. 2000). Administration of low-molecular-weight heparin is not recommended, because there is a 60 % – 100 % cross-reactivity of the heparin-induced antibodies.

### 4.8.7 Colloid Infusion Products

Colloid infusion products used as a plasma expander may cause anaphylaxis during surgery (Thong and Yeow-Chan 2004). The exact pathophysiologic mechanisms are unclear. Gelatin-specific IgE and positive skin prick test as well as positive intradermal test have been demonstrated in some cases, suggesting an IgE-mediated mechanism (Laxenaire et al. 1994).

In a prospective multicenter trial, 69 cases of nonallergic anaphylaxis were observed among 200,906 infusions of colloid volume substitutes. The frequency of severe reactions such as shock, cardiac, or respiratory arrest was 0.003 % for plasma-protein solutions, 0.006 % for hydroxyethyl starch, 0.008 % for dextran, and 0.038 % for gelatin solutions (Ring and Messmer 1977).

### 4.8.8 Blood Products

A systemic reaction following transfusion of properly matched blood is related to a deficiency of IgA; this in turn is due to either selective IgA immunodeficiency, affecting approximately 1 in 600 individuals in the Western world, or due to common variable immunodeficiency (1 in 25,000 Caucasians) (Hammarstrom et al. 2000). A systemic anaphylactic reaction to blood transfusion is triggered by IgE and IgG antibodies to IgA in some IgA-deficient recipients (type III hypersensitivity reaction). These reactions are very rare, estimated to occur in 1 in 20,000 – 47,000 transfusions. The diagnosis is established by detecting an anti-IgA antibody in the patient's serum (Sandler et al. 1995). Nevertheless, no exact level of antibodies has been defined that will predict the risk of anaphylaxis due to blood products.

Treatment of all anaphylactic/anaphylactoid reactions to perioperative drugs and infusions is recommended according to the guidelines (see Sect. 4.5; Tables 4.4, 4.5, 4.8). There are no special recommendations beyond these.

## 4.9 Latex Allergy: Diagnosis and Management

Natural rubber latex is a ubiquitous component of modern life. It consists of proteins from the sap of the *Hevea brasiliensis* tree. Anaphylaxis to latex is one of the most feared and frequent anaphylactic reactions during surgery and medical procedures, and the number of reactions are increasing. In the year 2000, reactions to latex accounted for 16.6 % of anaphylactic reactions during surgery.

The populations who are at risk for anaphylaxis to latex are as follows:

- Individuals with a genetic predisposition (atopic individuals)
- Individuals with increased previous exposure to latex (e.g., anyone who requires chronic bladder care with repeated insertion of a latex catheter or chronic indwelling catheters, children with spina bifida and meningomyelocele)
- Healthcare workers who are exposed to latex mainly by inhalation
- In some cases, patients who have undergone multiple surgical procedures

The incidence of latex sensitivity in the general population ranges from 0.8 % to 6.5 %. The two main risk groups for latex allergy are physicians and nurses, with an incidence of 7 % to 18 %. The highest incidence of latex sensitivity has been reported for patients who require chronic bladder care, e.g., children with bladder exstrophy, spina bifida, or meningomyelocele, who have a risk as high as 72 % (Ricci et al. 1999; Taylor and Erkek 2004; Chiu and Kelly 2005).

There are two types of allergic reactions: The delayed hypersensitivity (type IV), which is seen usually in form of a dermatitis reaction. It is a cell-mediated reaction which develops 24 – 48 h after exposure and can be diagnosed by patch testing. Immediate hypersensitivity (type I) is the more dangerous type of allergy, and its incidence has been rapidly increasing over the last two decades. It represents a latex protein-specific IgE-mediated hypersensitivity with a clinical manifestation ranging from contact urticaria to fatal anaphylactic shock (Taylor and Erkek 2004). Exposure to latex antigen can occur by cutaneous (latex gloves), respiratory (opening latex gloves in the operating room), mucosal (gynecological examination with latex gloves), and parenteral routes (i.v. medication with latex-containing infusion sets), with the latter two having the highest risk of anaphylaxis.

There are allergic cross-reactions in patients with fruit or food sensitivities to avocado, banana, chestnut, potato, tomato, passion fruit, and kiwi (Taylor and Erkek 2004). Therefore, a preexisting fruit allergy may be an additional risk factor for clinically relevant latex allergies.

A diagnostic evaluation is recommended for high-risk patients (e.g., children with urological malformations), and for anyone with a history of urticaria or angioedema of the lips when inflating balloons or with itching or contact urticaria when donning gloves, a latex allergy should be suspected. This evaluation should become more comprehensive as needed.

Latex-specific IgE antibodies in serum can be demonstrated in vitro and quantified with RAST or ELISA. Currently, there are three FDA-approved in vitro serologic assays for the diagnosis of latex allergy available on the market (ImmunoCAP, Pharmacia-Upjohn, Sweden; AlaSTAT FEIA, Diagnostic Products Corp., Los Angeles, CA, USA; HYTEC EIA, Hycor Biomedical Inc., Garden Grove, CA, USA). All of them have a relatively high rate of false-negative results. Further disadvantages are the costs, delayed results, low sensitivity, and accessibility compared to in vivo tests. However, serology should be the initial diagnostic step for suspected latex allergy because it is safer than in vivo tests.

The skin prick test is the gold standard. It is easy to perform and provides immediate results (5 – 30 min). Sensitivity is highly influenced by the quality of the latex extract used, but can be as high as 87 %. Additionally, at 66 % the specificity of the skin prick test is higher than the in vitro tests (RAST, ELISA). There is a standardized commercial skin prick test kit available in Europe (Stallergenes SA, Antony, France), but so far no FDA-approved test is available.

The skin prick test as an in vivo test is comparable to a small-scale provocation test. Therefore it should be performed by experienced staff and with oxygen, epinephrine, and latex-free resuscitation equipment at hand. Because of rare anaphylactic reactions to the prick test, the in vitro diagnostic work-up should be performed prior to the prick test.

Another possibility is a provocation test by wearing a latex glove. This may be employed when there is a discrepancy between prick test or specific IgE results and clinical history. It begins as a one-finger test, and extended to a whole-hand test if there is no urticarial reaction after 20 min. Nonlatex vinyl gloves are used as a control. The testing staff has to be aware of the possibility of sudden anaphylactic reactions.

Corticoids and H1 and H2 antagonists can be used to pretreat patients with known latex allergy prior to medical procedures. However, *pretreatment is not very effective* in preventing reactions to latex, unlike prevention measures for reactions to contrast media. Therefore, the most important factor is avoiding exposure to the allergen. This means taking a thorough patient history, testing for latex allergy in high-risk patients, preadmission measures, and establishing a latex-free environment while the patient is hospitalized, particularly in the operating and recovery rooms (Lieberman 2002). The charts of latex allergic patients should be labeled, and surgery should be scheduled as the first case of the day to reduce exposure to the aerosolized latex allergens. Latex-free equipment should be stored separately: nonlatex gloves, glass syringes, nonlatex tape, synthetic catheters and tubes, latex-free blood pressure cuffs, and three-way stopcocks for i.v. administration of medication.

Allergic reactions to latex are treated in a manner that is analog to all other anaphylactic reactions (compare treatment recommendations in Tables 4.4, 4.5, and 4.8).

## References


Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, Brockow K, Pichler WJ, Demoly P (2003) European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersenitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions:general considerations. Allergy 58:854

Bernstein IL, Gruchalla RS, Lee RE et al (1999) Executive summary of disease management of drug hypersensitivity:a practice parameter. Joint task force on practice parameters, the American Academy of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol 83:665

Birnbaum J, Porri F, Pradal M, Charpin D, Vervloet D (1994) Allergy during anaesthesia. Clin Exp Allergy 24:915

Borish L, Tamir R, Rosenwasser LJ (1987) Intravenous desensitization to beta–lactam antibiotics. J Allergy Clin Immunol 80:314

Brockow K, Vieluf D, Puschel K, Grosch J, Ring J (1999) Increased postmortem serum mast cell tryptase in a fatal anaphylactoid reaction to nonionic radiocontrast medium. J Allergy Clin Immunol 104:237

Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P (2002) General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 57:45

Brockow K (2005) Contrast media hypersensitivity – scope of the problem. Toxicology 209:189

Brockow K, Christiansen C, Kanny G, Clément O, Barbaud A, Bircher A, DeWachter P, Guéant J–L, Guéant R-M R, Mouton–Faivre C, Ring J, Romano A, Sainte–Laudy J, Demoly P, Pichler WJ for ENDA and the EAACI interest group on drug hypersensitivity (2005) Management of hypersensitivity reactions to iodinated contrast media. Allergy 60:150

Caro JJ, Trinidade E, McGregor M (1991) The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta–analysis. AJR Am J Roentgenol 156:825

Chiu AM, Kelly KJ (2005) Anaphylaxis: drug allergy, insect stings, and latex. Immunol Allergy Clin N Am 25:389

Christiansen C, Pichler WJ, Skotland T l (2000) Delayed allergy-like reactions to X-ray contrast media:mechanistic considerations. Eur Radio 10:1965

Coombs RRA, Gell PGH (1975) Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA, Lachmann PJ (eds) Clinical aspects of immunology, 3rd edn. Blackwell, Oxford, pp 761

Cummins RO, Hazinski MR (2000) The most important changes in the international ECC and CPR guidelines 2000. Circulation 102 [8 Suppl]:1371

Demoly P (2005) Anaphylactic reactions – value of skin and provocation tests. Toxicology 209:221

Fabris F, Luzzatto G, Stefani PM, Girolami B, Cella G (2000) Heparin-induced thrombocytopenia. Haematologica 85:72

Fisher MM, Bowey CJ (1997) Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. Br J Anaesth 79:59
Fisher MM, Baldo BA (1998) Mast cell tryptase in anaesthetic anaphylactoid reactions. Br J Anaesth 80:26
Fisher MM, Merefield D, Baldo BA (1999) Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. Br J Anaesth 82:770
Greenberger PA, Halwig JM, Patterson R, Wallemark CB (1986) Emergency administration of radio contrast media in high–risk patients. J Allergy Clin Immunol 77:630
Hammarstrom L, Vorechivsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID) (2000) Clin Exp Immunol 120:225
Haupt MT (1995) Anaphylaxis and anaphylactic shock. In: Parillo JE, Bone RC (eds) Critical care medicine. Mosby Year Book, St. Louis, pp 433
Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel–Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wuthrich B (2001) EAACI (the European Academy of Allergology and Clinical Immunology) nomenclature task force: a revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 56:813
Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K (1990) Adverse reactions to ionic and nonionic contrast media. A report from the Japanese committee on the safety of contrast media. Radiology 175:621
Kelkar PS, Li JT (2001) Cephalosporin allergy. N Engl J Med 345:804
Kemp SF, Lockey RF (2002) Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol 110:341
Laroche D, Aimone–Gastin I, Dubois F, Huet H, Gerard P, Vergnaud MC, Mouton–Faivre C, Gueant JL, Laxenaire MC, Bricard H (1998) Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology 209:183
Laroche D, Dewachter P, Mouton–Faivre C, Clément O (2004) Immediate reactions to iodinated contrast media :the CIRTACI study (abstract no. 56). Allergologie 27:165
Laxenaire MC, Charpentier C, Feldman L (1994) Anaphylactoid reactions to colloid plasma substitutes:incidence, risk factors, mechanisms. A French multicenter prospective study (in French). Ann Fr Anesth Reanim 13:301
Laxenaire MC (1999) Again and always allergy. Ann Fr Anesth Reanim 18:831
Lee JM, Greenes DS (2000) Biphasic anaphylactic reactions in pediatrics. Pediatrics 106:762
Lieberman P (2002) Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol 110:S64
Menajovsky (2005) LB Heparin-induced thrombocytopenia: clinical manifestations and management strategies. Am J Med 118:21S
Morcos SK (2005) Review article: Acute serious and fatal reactions to contrast media: our current understanding. Br J Radiol 932:686
Morcos SK, Thomsen HS (2001) Adverse reactions to iodinated contrast media. Eur Radiol 11:1267
Morcos SK, Thomsen HS, Webb JA (2001) Contrast Media Safety Committee of the European Society of Urogenital Radiology. Prevention of generalized reactions to contrast media: a consensus report and guidelines. Eur Radiol 11:1720
Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ (1990) Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 86:325
Nasser SM, Ewans PW (2001) Opiate-sensitivity: clinical characteristics and the role of skin prick testing. Clin Exp Allergy 31:1014
Pumphrey RS (2000) Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 30:1144
Ricci G, Gentili A, Di Lorenzo F, Righetti F, Pigna A, Masi M, DeCastro R (1999) Latex allergy in subjects who had undergone multiple surgical procedures for bladder exstrophy: relationship with clinical intervention and atopic diseases. BJU Int 84:1058
Ring J, Messmer K (1977) Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1:466–469
Rose M, Fisher M (2001) Rocuronium: high risk for anaphylaxis? Br J Anaesth 86:678
Schatz M (1984) Skin testing and incremental challenge in the evaluation of adverse reactions to local anesthetics. J Allergy Clin Immunol 74:606
Sandler SG, Mallory D, Malamut D, Eckrich R (1995) IgA anaphylactic transfusion reactions. Transfus Med Rev 9:1
Shehadi (1982) WH Contrast media adverse reactions: occurrence, recurrence, and distribution patterns. Radiology 143:11
Thomsen HS, Morcos SK (2004) Contrast Media Safety Committee of European Society of Urogenital Radiology. Management of acute adverse reactions to contrast media. Eur Radiol 14:476
Taylor JS, Erkek E (2004)Latex allergy:diagnosis and management. Dermatologic Therapy 17:289
Thong BY-H, Yeow-Chan (2004) Anaphylaxis during surgical and interventional procedures. Ann Allergy Asthma Immunol 92:619
Wang DJ, Forslund C, Persson U, Wiholm BE (1998) Drug-attributed anaphylaxis. Pharmacoepidemiol Drug Saf 7:269
Wazny LD, Daghigh B (2001) Desensitization protocols for vancomycin hypersensitivity. Ann Pharmacother 35:1458

## Further Reading

### Guidelines for the Management of Cardiovascular Shock

American Heart Association: www.americanheart.org. Cited 6 November 2006
Anonymous (2000) http://circ.ahajournals.org/cgi/content/full/102/suppl_1/I-1. Cited 6 November 2006
European Resuscitation Council (2000) Part 8: advanced challenges in resuscitation. Section 3: special challenges in ECC. 3D: anaphylaxis. Resuscitation 46:285
British Resuscitation Council: www.resus.org.uk. Cited 6 November 2006
National Guideline Clearinghouse of the United States (NGC) (2006) The diagnosis and management of anaphylaxis: an updated practice parameter. http://www.guideline.gov/summary/summary.aspx?doc_id=6887. Cited 6 November 2006

# Urosepsis

5

H.G. Schiefer, Th. Diemer, W. Weidner



## 5.1 Definition

Urosepsis is caused by the invasion, from a focus in the urinary tract, of pathogenic or commensal microorganisms, or their constituents into the body, prompting a complex response by the synthesis of endogenous mediators responsible for the clinical phenomena (Dinarello 1984; Van Amersfoort et al. 2003). Progress of sepsis to severe sepsis and septic shock correlates with an increased risk of death.

## 5.2 Epidemiology of Sepsis

US data demonstrate an incidence of sepsis of approximately 750,000 cases/year, responsible for up to 250,000 deaths/year in the United States. In relation to the whole population, a yearly incidence of 3 cases per 1,000 persons and of 26 cases per 1,000 persons in the elderly population (older than 65 years) is reported. In approximately 50 % of cases, sepsis arises from the urinary tract (Bernard et al. 2001; Hotchkiss and Karl 2003; Russell 2006; Van Amersfoort et al. 2003).

## 5.3 Etiology of Urosepsis

Urosepsis is caused by Gram-negative bacteria (e.g., *Escherichia coli,* 52 %; other *Enterobacteriaceae* spp., 22 %, *Pseudomonas aeruginosa*, 4 %), Gram-positive bacteria (e.g., *Enterococcus* spp., 5 %, *Staphylococcus aureus*, 10 %), and other pathogenic bacteria in nosocomial urosepsis (1 % of all cases) (multidrug resistant bacteria, e.g., *Pseudomonas aeruginosa).*

## 5.4 Pathophysiology

Sepsis is caused by the invasion of intact pathogenic or commensal bacteria or bacterial cell wall constituents, especially lipopolysaccharides (LPS), in particular lipoid A = endotoxin of the outer membrane of Gram-negative bacteria, or peptidoglycan, teichoic and lipoteichoic acids of Gram-positive bacteria, or toxins, e.g., toxic-shock-syndrome-toxin 1 and *Staphylococcus aureus* toxin A. They bind to cellular receptors and co-receptors, e.g., CD14, toll-like receptors TLR2 and TLR4, CD18 ($\beta_2$ integrins), and selectins, on the surfaces of monocytes/macrophages, neutrophils, and endothelial cells. Via intracellular signaling molecules, e.g., NF-κB and protein kinase C, they activate the transcription of mediator genes to induce the synthesis and release of numerous endogenous mediators, i.e., cytokines such as interleukin (IL)-1, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor (TNF), and platelet-activating factor (PAF). These pro-inflammatory and anti-inflammatory mediators often originate in an inflammed local site. They are formed and released with various kinetics. They act in part synergistically and in part antagonistically, mainly via additional mediators (chemokines, prostaglandins, thromboxanes, leukotrienes, and endogenous vasodilators nitric oxide [NO]), on target organs, and are responsible for a plethora of local and systemic effects in the host organism (Bernard et al. 2001; Dellinger 2003; Gerard 2003; Gogos et al. 2000; Hotchkiss and Karl 2003; Russell 2006; Van Amersfoort et al. 2003; Wilson et al. 1998).