Iatrogenic Diseases as a Reason for Admission to the Intensive Care Unit

Incidence, Causes, and Consequences

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Background: Data on iatrogenic diseases (IDs) have been recorded for the past 25 years. We determined whether aging of the general population and medical advances, including more powerful drugs and complex procedures, have altered the incidence, causes, and consequences of severe IDs during this period.

Methods: One-year retrospective study was conducted in an adult medical-surgical intensive care unit (ICU) affiliated with a French general hospital in an area of 200 000 inhabitants. All the patients admitted to the ICU during 1994 were screened for IDs. Patients with community or hospital-acquired IDs on admission were included. Follow-up assessed morbidity, mortality, workload, and costs of care for IDs, and the rate of preventable IDs.

Results: Of 623 patients admitted to the ICU, 68 (10.9%) were included; the cause of the ID was drugs in 41, medical acts in 12, and surgical acts in 15. These 68 patients were in the ICU for 472 days, with a 13% fatality rate (9 patients) and a financial cost of US $688 470. They were not different from the 555 other ICU patients in terms of severity, mortality, workload, and length of stay in the ICU. Risk factors for ID were old age and the number of prescribed drugs. The rate of preventable ID was 51%.

Conclusions: Iatrogenic diseases are a persistent and important reason for admission to the ICU, and the risk factors, causes, and consequences remain unchanged since 1980. Despite 25 years of experience with high-technology medicine, ID still has a negative impact on the health and resources of society.

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THERE HAVE been numerous North American and European studies on iatrogenic diseases (IDs) during the past 3 decades. Although the incidence of community-acquired ID is not precisely known, it seems to account for 2% to 10% of outpatient consultations[1,2] and 3% to 7% of hospital admissions,[3-10] most of them (95%) after drug exposures. These patients spend 8 to 10 days in the hospital and have a fatality rate of 2% to 6% and a rate of preventable events of 50%.[1,4-6,10] The elderly are most at risk.[2,6,10,11] Hospital-acquired ID occurs in 2% to 36% of hospitalized patients[6,12-19] and can be caused by drug-induced illness or events after medical and surgical procedures (35%-75% of cases). Hospital-acquired ID increases the length of stay and has a fatality rate of 3.7% to 14.0% and a permanent disability rate of 6.5%.[10,14] The rate of preventable events is 20% to 50%.[10,14-16] Once again, the elderly are more at risk,[6,10,11,13,17,18] but the severity of the underlying diseases,[5,20-22] the number of prescribed drugs,[13,23] and the pattern and location of care[14,15,24] are also factors. The risk of ID is high in neurologic, thoracic, vascular, and cardiac surgery units; intensive care units (ICUs); emergency departments; and interventional radiology because the association of severe coexisting diseases and the complexity of treatment are likely to lead to iatrogenic events.

Severity is closely linked to the nature of the adverse event and the underlying medical condition. Iatrogenic complications are life-threatening in 10% to 26% of cases.[13,15,17,18,24] Trunet et al[25] found that ID accounted for 12.6% of admissions in the ICU, with a fatality rate of 20.0%, in an adult medicosurgical ICU affiliated with a French tertiary care university hospital.

Most of the studies published during the past 25 years have shown the negative effects of ID on population health, the cost of medical care,[26,27] and the rate of malpractice claims. Health care providers have reacted by developing quality-of-care initiatives,[28-30] including better identification of ID,[31-34] determination of risk fac-

PATIENTS AND METHODS

STUDY POPULATION

This study was conducted in the 15-bed medicosurgical ICU (MSICU) affiliated with the 500-bed General Hospital at Compiègne, France. Cardiac surgery, neurosurgery, and organ transplantation are not performed in this institution. In addition to the MSICU, a 6-bed cardiac care unit takes care of patients with cardiovascular emergencies in the absence of other severe organ failure. Admission to the MSICU of any patient with at least 1 life-threatening organ failure or metabolic disorder, or requiring emergency dialysis or mechanical ventilation, is authorized by 1 of the permanent or on-duty MSICU senior physicians after discussion with the physician (emergency department, operating room, or wards) caring for the patient. All the patients admitted to the MSICU between January 1, 1994, and December 31, 1994, were retrospectively screened for ID as the purpose of admission to the unit. Screening was performed by house staff composed of 3 board-certified anesthesiologists (B.D., E.L.M., E.B.), 1 cardiology and internal medicine board-certified intensivist (Y.D.), and 1 resident (B.F.). Each patient was identified as having ID or not by consensus, and the causes, relationship between prescription or procedure and ID, preventability, and severity of the iatrogenic events were determined. If consensus was not obtained, the patient was not included. Each assessment was made according to the following criteria and definitions.

DEFINITIONS

Iatrogenic disease was defined as a disease induced by a drug prescribed by a physician; or after a medical or surgical procedure, excluding intentional overdose, nonmedical intervention; or unauthorized prescription, and environmental events (falls, equipment defect).

Adverse event was defined as an unintended and noxious event caused by medical management carried out according to the best of medical science.

Preventable event was defined as an event that should not occur if management is the best that medical science can provide.

Nosocomial infection was defined as a localized or systemic infection, occurring at least 48 hours after hospital admission, that was not present or incubating at the time of admission.[44]

Iatrogenic infection was defined as an infection after medical or surgical management, whether or not the patient was hospitalized.

RELATIONSHIP BETWEEN PRESCRIPTION OR PROCEDURE AND IATROGENIC DISEASE

Drug-Induced Disease

We used the progressive criteria of Karch and Lasagna.[45] The relationship between a drug and an adverse reaction was divided into the following 5 levels: *definite*: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known response pattern to the suspected drug, and that is confirmed by dechallenge and rechallenge; *probable*: a reaction that follows a reasonable temporal sequence from administration, that follows a known response pattern to the suspected drug, that is confirmed by dechallenge, and that could not be reasonably explained by the the patient's condition; *possible*: a reaction that follows a reasonable temporal sequence from administration and that follows a known response pattern to the suspected drug, but that could have been produced by the patient's clinical condition or other therapy given to the patient; *conditional*: a reaction that follows a reasonable temporal sequence from administration

tors,[14-16,24,35-38] and studies on the epidemiology of malpractice claims.[39-43] Nevertheless, medicine has changed considerably during the past few decades, with general aging of the population and the development of increasingly complex or advanced procedures, such as invasive cardiology and radiology and laparoscopic surgery. We have attempted to assess the impact of these changes on ID in a retrospective study. We compared the rate of ID-related admissions with the results reported by Trunet et al[25] 15 years ago, and analyzed the causes, risk factors, and consequences of these diseases.

RESULTS

A total of 24 555 patients were hospitalized at the General Hospital in Compiegne during 1994. Of these, 16 746 went to adult medical and pediatric wards, 7186 to surgical and obstetric wards, and 623 to the adult medicosurgical ICU. Among these 623 patients, 68 were admitted to the ICU because of 68 IDs, accounting for 10.9% of the ICU admissions. Twenty-seven (40%) were referred from home and 41 (60%) from hospital wards. The mean age was 69.4 ± 17.2 years, the sex ratio (male-female) was 0.66, and the mean Simplified Acute Physiology Score was 13.4 ± 6.7. The ID cases included 41 patients with drug-related ID (**Table 1**), 12 patients whose ID was linked to medical procedures (**Table 2**), and 15 whose ID was linked to surgical procedures (**Table 3**). Iatrogenic disease was life-threatening for 14 patients (21%) and fatal for 9 patients (13%). The rate of preventable ID was 51%.

The 41 drug-induced ID cases accounted for 60% of ID admissions to the ICU (24 from home, 27 from the hospital) and included 11 adverse events and 30 preventable events. The symptoms were severe in 11 instances and resulted in death in 6 cases. The relationship between drug and ID was definite in 14, probable in 14, and possible in 13. Fifty-five drugs were involved. Morbid combinations (ie, angiotensin-converting enzyme inhibitors ± nonsteroidal anti-inflammatory drugs ± diuretics) were encountered in several instances, but a single drug (antibiotic, vitamin K antagonist, etc) was responsible for ID in 22 cases (**Table 4**).

and that does not follow a known response pattern to the suspected drug, but that could not be reasonably explained by the known characteristics of the patient's clinical condition; and *doubtful*: any reaction that does not meet the above criteria.

Disease After Medical or Surgical Procedure

As there is no standard definition, we used the same criteria as Trunet et al.[25] The relationship was good if the following 4 criteria were all satisfied; otherwise the relationship was conditional: the complication is known and recorded in the medical literature; it is not reasonably explained by the patient's underlying diseases; there is a reasonable temporal sequence from the procedure to the complication; and a relationship can be established from anatomical criteria (such as colonic perforation linked to endoscopy), microbiologic criteria (such as urinary tract infection after urinary catheterization), or chemical criteria (such as radiocontrast and renal failure).

SEVERITY

The severity of the ID was classified as fatal, life threatening, or moderate. A *fatal* event is a complication principally responsible for death. *Life-threatening* ID requires intensive care (mechanical ventilation, vasopressors, hemodialysis, cardiac catheterization or pacing, tube thoracostomy, surgery, etc). Complication was judged to be *moderate* if only routine management and monitoring were needed.

DATA COLLECTION

The following data were recorded for each patient admitted to the ICU during the study period: age, sex, number of prescribed drugs before admission to the ICU, origin of patient (home or hospital), length of stay, and outcome in the ICU. The Simplified Acute Physiology Score[46] was calculated within 24 hours after admission to the ICU as an index of disease severity. The McCabe score[47] (3 classes: fatal during hospitalization, ultimately fatal within 5 years, and not fatal) was used as an index of the severity of the underlying medical condition. The Omega score was calculated at the end of the patient's stay as an index of total workload (**Figure**). The Omega score system is an ICU-specific activity scoring system used in the French ICUs since 1990, validated by the French Health Department and the Société de Réanimation de Langue Française.[48] It is highly correlated with the Nursing Research Project 1987 scoring system used in Canada. The Omega score is calculated by summing up 47 therapeutic interventions collected during each patient's ICU stay and scored from 1 to 10. For instance, tracheostomy is scored as 6 points per hospitalization; hemodialysis, 10 points per course; and mechanical ventilation, 10 points per day. We also recorded the nature and relationship between disease and procedure, and the severity and the preventability of disease for each patient with ID. The cost of care in the ICU was calculated by means of the global "day's fare" allocated to our ICU by the French care system, which was Fr 8122 per day for 1994 (US $1500 per day).

STATISTICAL ANALYSIS

The characteristics of the patients are expressed as means ± SDs or as the number of patients or events. Comparisons between patients were made by Student *t* test for continuous variables and the χ^2 test with Yates correction when indicated for categorical variables. A *P* value of less than .05 was considered statistically significant. Data were stored on Microsoft EXCEL (Version 4.0; Microsoft Inc, Redmond, Wash), and all probability calculations were performed with SAS Macro software (SAS Institute Inc, Cary, NC).

Twelve patients were admitted for ID after a medical procedure (3 performed out of hospital). The relationship was good in all cases, and ID was preventable in 3 of the 12 cases. Symptoms were severe in 7 instances, resulting in death in 2 cases. Six patients had iatrogenic infections, among which 3 were nosocomial infections and 3 were community-acquired infections (tetanus, bacteremia after lower-limb venous sclerotherapy and urinary catheter).

Fifteen patients had surgical complications, all of which occurred in the operating theater, in the recovery room, or on surgical wards. The relationship was good in 14 of the 15 cases, and the complication was preventable in 2 instances. Symptoms were severe in 5 cases, leading to death in 1 patient.

Overall, these 68 admissions resulted in 472 days of hospitalization in the ICU, with a mean length of stay of 6.9 ± 9.3 days (range, 1-52 days). The workload required was 3612 Omega points, with a mean of 53 points per patient and a density rate of 7.7 points per day of hospitalization. The fatality rate in the ICU was 13% (9/68 patients). Cost of medical care in the ICU for these 68 patients was estimated at US $688 470.

About half (35/68) of these IDs were considered to be preventable. The 30 preventable events after drug-induced ID were caused by the use of inappropriate drugs in 6 cases, an error in dose in 8 cases, inadequate follow-up of therapy in 14 cases, and failure to use prophylactic treatment in 2 cases. Three events were linked to medical procedures (radiocontrast infusion in 2 and hemorrhoid sclerotherapy in 1). Two were caused by surgical procedures (suprapubic cystotomy tube and epistaxis tamponade). These 35 preventable IDs resulted in 189 days of hospitalization in the ICU and 5 deaths (14%). Cost of medical care in the ICU was evaluated at US $275 680, with a workload of 1434 Omega points (41 points per patient, 7.6 points per day).

The 623 patients admitted to the ICU during the study period were divided into group 1 (n = 555), patients without IDs; group 2 (n = 41), patients with drug-induced IDs; and group 3 (n = 27), patients with IDs after medical or surgical procedures (**Table 5**). Groups 2 and 3 were next compared individually with group 1.

Omega Scoring System

Category 1: Record *once during stay*	ICR
Enteral Nutritional Support: ≥35 kcal/kg per day during 10 d	3
Parenteral Nutrition: ≥35 kcal/kg per day during 10 d	6
Continuous Neurologic Monitoring	1
Cardioversion and Defibrillation	3
Arterial Line Placement	3
Pulmonary Artery Catheter	6
Central Venous Catheter	3
Suprapubic Catheter	1
CSF Drainage	1
Pericardial Drainage	6
Chest Tube	6
Home Ventilation Training	6
Endotracheal Intubation	6
Gastric Lavage	1
Massive Blood Transfusion (>50% Blood Mass)	10
Diagnostic Peritoneal Lavage	3
Continuous Intravenous Sedation: ≥24 h	6
Arteriovenous Shunt	10
Temporary Cardiac Pacing	3
Ureterostomy Tube	3
Gastroesophageal Varices Tamponade	3
Tracheotomy	6
External Skeletal Traction	6
Treatment of Cardiac Arrest	10
Use of Vasopressors	6
Use of Fibrinolytic Drug	10
Total 1	

Category 2: Record *each time*	ICR	Nb	Tot
Angiography in the ICU	10		
Echography in the ICU	3		
Bronchoscopy	3		
Gastroscopy and Coloscopy	3		
Hemodialysis	10		
Plasmapheresis	10		
Transport Outside the ICU and/or Return to the Unit (Operating Room, CT Scan, Echography, etc)	6		
Admission of the Patient to the ICU	1		
Use of Radioactive Tracer for Investigation	6		
Total 2			

Category 3: Record *each day*	ICR	Nb	Tot
Continuous Hemodiafiltration, Peritoneal Dialysis	10		
Protective Isolation	10		
Complex Surgical Dressing, Laparotomy, Multiple Colostomies, or Enterostomies	10		
Continuous Positive Airway Pressure	10		
Mechanical Ventilation	10		
Continuous Monitoring in the ICU	1		
Total 3			

ICR Omega = Total 1 + 2 + 3 =

Sample of tally sheet used for calculating the Omega score, an index of the total workload for a patient's stay in the intensive care unit (ICU). ICR indicates relative complexity index (the value of each act in terms of workload); Nb, number of acts; Tot, total; CSF, cerebrospinal fluid; and CT, computed tomographic.

Group 2 patients were older and had an inverted sex ratio (29 women and 12 men), a higher Simplified Acute Physiology Score, and more prescribed drugs on admission. Group 3 patients were also older and stayed longer in the ICU. Nevertheless, groups 2 and 3 did not differ from group 1 with respect to workload in the ICU (Omega score) or mortality. Likewise, patients who experienced adverse events were compared with those who experienced preventable events (**Table 6**). The only factor increasing the risk of preventable events was age. The location of drug prescription (home or hospital) was not a risk factor for drug-induced ID.

COMMENT

This study, conducted 15 years after the one by Trunet et al,[25] clearly confirms the persistence and the paramount importance of ID as a cause of admission to the ICU. Trunet et al found that 12.6% of the ICU admissions were linked to ID. The rate was 10.9% in the present study, with the use of the same criteria and definitions. There was also a high rate of preventable events, accounting for 51% of the ID in our study, while Trunet et al found 41%. The stability of these rates over this long time is somewhat surprising, as a decrease might have occurred because of better recognition, care, and prophylaxis for ID or an increase because of more powerful and/or invasive treatment for more sick and aged patients. The 2 trends may well have canceled each other out.

We believe that this exhaustive review, although retrospective, of all ICU charts and medical reports from the 623 patients admitted during 1994, done early in the following year by the permanent clinical team taking care of these patients, provides a sensitive investigation. However, this advantage is probably outweighed by the method of identification of ID, requiring unanimity of judgment for a definitive inclusion. Although this procedure provided reliability of assessments, we believe that it led to an underestimation of the number of included IDs.

The drugs implicated in ID remained standard. Cardiovascular drugs accounted for 31%, anti-inflammatory and analgesic drugs for 20%, and antibiotics for 11% of cases of drug-induced ID. This has not changed in 20 years,[4,5] but there have been striking changes in each class of drugs.

Angiotensin-converting enzyme inhibitors (alone or associated with diuretics) are the leading class of cardiovascular drugs involved in ID, before diuretics and oral anticoagulants, whereas digitalis compounds and older antihypertensive drugs have almost disappeared. Few IDs related to antiarrhythmic or thrombolytic drugs were encountered in this study, because of the presence of a 6-bed cardiac care unit in the same hospital. Nonsteroidal anti-inflammatory drugs emerged as the leading anti-inflammatory and analgesic drugs causing iatrogenic events, and there were no complications linked to corticosteroids or aspirin. These changes probably reflect changes in prescription habits.

Trunet et al[25] found 2 incompatible blood transfusions among the 23 drug-induced IDs, whereas we observed no complication linked to the transfusion of blood products. The drastic vigilance guidelines regarding blood products enforced in France in 1992 after the "contaminated blood products affair" have reduced the frequency of gross compatibility accidents.[49] We also saw no severe ID caused by antidiabetic drugs, perhaps as a result of improved education of diabetic patients by the endocrinological staff of our hospital. Finally, only 2 of

Table 1. Patients With Iatrogenic Disease After Drug Exposure (N = 41)*

No. of Patients	Type of Drug	Iatrogenic Illness (No.)	Severity (No.)†	Preventability, No.
4	Diuretics alone	Hypokalemia (2), hyperkalemia (2)	M (2), LT (1), F (1)	2/4
1	ACEIs alone	Acute renal failure (1)	M (1)	1/1
3	ACEIs + diuretics	Hyperkalemia (1), dehydration (1), mesenteric infarction (1)	M (2), F (1)	3/3
3	Oral anticoagulants alone	Severe bleeding (3)	M (2), F (1)	3/3
3	Oral anticoagulants + interactive drug	Severe bleeding (3)	M (2), F (1)	3/3
4	NSAIDs alone	Gastrointestinal tract bleeding (4)	M (4)	2/4
5	Anesthesia	Cardiac failure (2), respiratory failure (3)	M (4), LT (1)	3/5
5	Intravenous fluid infusion	Fluid overload (4), hemodilution (1)	M (4), LT (1)	5/5
2	Amiodarone	Pneumonitis (2)	M (1), F (1)	0/2
2	Antibiotics	Hepatitis (1), allergic skin reaction (1)	M (2)	1/2
2	Cytotoxic drugs	Acute renal failure (1), aplastic marrow (1)	LT (1), F (1)	1/2
7	Miscellaneous‡	Coma (1), metabolic disorders (4), respiratory failure (1), serum sickness (1)	M (6), LT (1)	6/7

**ACEI indicates angiotensin-converting enzyme inhibitor; NSAID, nonsteroidal anti-inflammatory drug.*
†*M indicates moderate; LT, life-threatening; and F, fatal.*
‡*Including potassium and calcium oral therapies, digitalis, neuroleptics, theophylline, β-blockers, and influenza vaccine.*

Table 2. Patients With Iatrogenic Disease After Medical Procedure (N = 12)

No. of Patients	Type of Procedure	Iatrogenic Illness (No.)	Severity (No.)*	Preventability, No.
2	Radiocontrast infusion in patients with renal failure	Acute renal failure (2)	M (1), LT (1)	2/2
3	Radiotherapy	Radiation enteritis (2), acute myeloblastic leukemia (1)	M (2), LT (1)	0/3
2	Peripheral venous catheterization	Bacteremia (2)	M (1), LT (1)	0/2
2	Urinary tract catheterization	Urinary tract infection with bacteria (2)	LT (1), F (1)	0/2
1	Lower-limb venous sclerotherapy	Bacteremia (1)	M (1)	0/1
1	Hemorrhoidal sclerotherapy	Generalized tetanus (1)	LT (1)	1/1
1	Cardiac catheterization	Ventricular arrhythmia (1)	F (1)	0/1

**M indicates moderate; LT, life-threatening; and F, fatal.*

Table 3. Patients With Iatrogenic Disease After Surgery (N = 15)

No. of Patients	Type of Procedure (No.)	Iatrogenic Illness (No.)	Severity (No.)*	Preventability, No.
2	Colonic surgery	Colonic anastomotic leakage (2)	M (2)	0/2
3	Abdominal (2), and orthopedic (1) surgery	Thromboembolism (3)	M (2), LT (1)	0/3
3	Endoscopy (2) and peritoneoscopy (1)	Bladder (1), large-bowel (1), gallbladder (1) perforations	M (1), LT (1), F (1)	0/3
1	Aortobifemoral graft	Rectal ischemia (1)	LT (1)	0/1
2	Subphrenic (1) and cervical (1) surgery	Pneumothorax (2)	M (2)	0/2
1	Suprapublic cystotomy tube	Bladder rupture (1)	M (1)	1/1
1	Total hip arthroplasty	Nonhemorrhagic shock (1)	M (1)	0/1
1	Epistaxis tamponade	Acute laryngeal obstruction (1)	LT (1)	1/1
1	Abdominal surgery	Postoperative hypoxemia (1)	M (1)	0/1

**M indicates moderate; LT, life-threatening; and F, fatal.*

the 41 patients with drug-induced ID had allergic reactions severe enough to require ICU admission. This recruitment bias explains the differences of distribution for drug-induced ID, when compared with out-of-hospital or ward studies.[6,10,13,15,17]

The 12 IDs caused by medical procedures included 6 severe infections, 3 of them hospital acquired (2 cases of bacteremia after peripheral venous catheterization and 1 after urinary tract catheterization). We could not assess the preventability of these catheter-related infections because we had no information about their real need and the adherence to aseptic guidelines for their insertion and care.

The preventability of an iatrogenic accident after surgery is often difficult to determine because the surgeon is both judge and judged. This probably lowers the ability to distinguish between an adverse event and a preventable event. The 2 surgical iatrogenic events defined

as preventable included (1) a laborious attempt at suprapubic cystotomy drainage, without previous echographic verification of the bladder repletion, leading to a bladder laceration, and (2) a mispositioned nasopharyngeal balloon tamponade (inflated through the larynx) for active epistaxis, which was followed by acute respiratory distress. These 2 procedures were performed by residents, with a delayed call to senior staff because of the disaster.

The overall fatality rate of patients with ID was 13% (9/68 patients), not significantly different ($\chi^2 = 0.55$; $P > .50$) from the 17% fatality rate of the patients admitted to the ICU for other reasons (93/555). The fatality rate in the study by Trunet et al[25] was 19.5% (not significantly different from our study [$\chi^2 = 0.76$; $P > .50$]).

The risk factors identified herein are the same as in earlier studies [6,10,11,13,17,18]: old age (probably mainly women in our country) and the number of drugs prescribed before admission.[13,14,23] Drug-induced iatrogenic events, and particularly the preventable ones, are as likely to occur at home as in the hospital.

We distinguished preventable iatrogenic events from adverse events because the implications for responsibility of physicians are obviously quite different. An adverse event is an unexpected, unavoidable deleterious event after a medical prescription or procedure. That is the price we pay for using powerful drugs and sophisticated procedures. These modern medical tools may result in an overall increase in life expectancy, but the individual benefit-risk ratio decreases in older patients, patients with organ insufficiency, and patients receiving multiple medications.[11,13,20-23] Steel et al[13] and Ponge et al[50] have shown that the multiple drugs prescribed for patients hospitalized for drug-induced ID could be reduced by 25% to 40% without further damage.

A preventable event is an event that could have been avoided if the medical act or prescription had respected the state of the art of medical science. The 51% rate of preventable events (35/68 patients) found in our study agrees with the results of others.[10,14-16,25,32,51] This high rate results in part from biased recruitment to the ICU, as the severity of iatrogenic disease seems to be correlated with errors.[14] The immediate causes of preventable ID recorded are unremarkable[15,18,25]: dosage error, contraindication or drug interaction unawareness, prophylaxis or monitoring omission, and technical error. However,

Table 4. The 55 Drugs Involved in Iatrogenic Diseases

Type of Drug	No. (%)
Diuretics	7 (13)
Oral anticoagulants	6 (11)
Nonsteroidal anti-inflammatory drugs	6 (11)
Antibiotics	6 (11)
Anesthesia	5 (9)
Intravenous fluid infusion	5 (9)
Angiotensin-converting enzyme inhibitors	4 (7)
Miscellaneous*	16 (29)

*Includes influenza vaccine, amiodarone, cyclic antidepressants, oral calcium and potassium therapies, theophylline, digitalis, neuroleptics, cytotoxic drugs, β-blockers, and corticosteroidal anti-inflammatory drugs.

Table 6. Comparison of Patients Having Adverse Effects and Those With Preventable Events*

	Adverse Effects (n = 33)	Preventable Events (n = 35)	P
Age, mean ± SD, y	62.7 ± 14.0	75.7 ± 17.0	.001
Sex, No. M/F	17:16	11:24	.03
SAPS, mean ± SD	14.1 ± 7.0	12.3 ± 6.0	.26
McCabe score, No. of patients			
Fatal or ultimately fatal within 5 y	11	16	.88
Nonfatal	12	19	.58
Omega score, mean ± SD	51.0 ± 51.0	37.5 ± 130.0	.59
Length of stay in ICU, mean ± SD, d	6.3 ± 5.7	5.0 ± 12.5	.59
No. of drugs in drug-related diseases, mean ± SD	3.6 ± 2.1	4.4 ± 2.6	.17
Location of drug exposure before admission, No.			
Home	6	18	.75
Hospital	5	12	
No. of deaths	4	5	.79

*SAPS indicates Simplified Acute Physiology Score; ICU, intensive care unit.

Table 5. Characteristics of Patients With Iatrogenic Disease After Drug Exposure and After Medical and Surgical Procedures, and the Noniatrogenic Patients*

	Noniatrogenic Patients (n = 555)	Drug Exposure (n = 41)	P	Medical and Surgical Procedures (n = 27)	P
Age, mean ± SD, y	53.1 ± 20.0	70.8 ± 17.0	<.001	64.8 ± 17.0	.003
Sex, No. M/F	322:233	12:29	<.001	15:12	.80
SAPS, mean ± SD	11.1 ± 7.0	14.1 ± 5.0	.008	12.5 ± 8.0	.13
McCabe score, No. of patients					
Fatal or ultimately fatal within 5 y	198	18	.23	9	.06
Nonfatal	357	23	.13	18	.12
Omega score, mean ± SD	55 ± 86	32 ± 35	.09	86 ± 124	.08
No. of drugs before admission, mean ± SD	2.1 ± 2.2	4.0 ± 2.6	<.001	2.1 ± 2.2	.94
Length of stay in ICU, mean ± SD, d	6.0 ± 7.5	4.3 ± 2.9	.14	9.3 ± 13.7	.04
No. of deaths	93	6	.73	3	.44

*SAPS indicates Simplified Acute Physiology Score; ICU, intensive care unit.

the in-depth underlying causes of human fallibility and malpractice leading to these mishaps are worth examining. There are 3 types of error: error resulting from ignorance, negligence, or misjudgment.

Errors caused by ignorance (2 of 35 errors in this study) might be illustrated by a physician who does not recognize an unusual disease or does not perform exceptional care, although he or she took attentive care of the patient according to the best of his or her own knowledge. Such errors are probably difficult to avoid as the complexity and field of medical knowledge increase.

Errors caused by negligence (22 of 35 errors in this study) include acts that are knowingly below acceptable standards, as are violations of aseptic guidelines or omission of allergy checking. This lack of rigor probably is prompted by multiple factors, such as exhaustion, business factors, and loss of motivation.

Couch et al[12] originally identified 5 causes of medical misjudgment in surgery, easily transposable to any medical activity: (1) misplaced optimism, (2) unwarranted urgency, (3) an urge for perfection, (4) fashionable therapy, and (5) insufficient restraint and deliberation.

The cost of ID for these 68 patients in human (472 days in the ICU, 9 deaths) and financial (US $688 470) terms is probably underestimated. The financial costs were calculated by means of a daily set price calculated and revised each year by the hospital financial services. The morbidity, sequelae, and later morbidity attributable to ID after the survivors left the ICU were not followed up. If the present study group (68 patients per year per 200 000 inhabitants) is considered to be representative, extrapolation leads to 45 deaths, 2360 days of hospitalization in the ICU, and US $3.44 million per 1 million inhabitants per year. These amazing figures do not include IDs occurring in other high-risk units not present in our hospital and cases treated outside the ICU, at home, or unrecognized. Indirect iatrogenic events, such as crashes and occupational or domestic accidents experienced by patients who are prescribed psychotropic drugs, are also not recorded as IDs. The type of severe iatrogenic events we investigated may well be only the tip of the ID iceberg.

We confirmed that ID is still a major cause of hospitalization in the ICU, accounting for 11% of admissions, half of which are preventable. The morbidity, mortality (13% in our study), and cost of ID are certainly biased by the design of this study (patients with ID severe enough to require treatment in the ICU). Nevertheless, the global impact of ID on the health and resources of society is probably underestimated. The challenge, in this era of high-technology medicine, is to better understand the in-depth underlying causes of errors, to reduce the incidence of preventable iatrogenic events. This could provide a better quality of care at a lower cost.

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REFERENCES

1. Burnum JF. Preventability of adverse drug reactions. *Ann Intern Med.* 1976;85:80-81.
2. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use: a study of community-dwelling persons 65 years of age and older (see comments). *Ann Intern Med.* 1992;117:634-640.
3. Miller RR. Hospital admissions due to adverse drug reactions:a report from the Boston Collaborative Drug Surveillance Program. *Arch Intern Med.* 1974;134:219-223.
4. Caranasos GJ, Stewart RB, Cluff LE. Drug-induced illness leading to hospitalization. *JAMA.* 1974;228:713-717.
5. Lakshmanan MC, Hershey CO, Breslau D. Hospital admissions caused by iatrogenic disease. *Arch Intern Med.* 1986;146:1931-1934.
6. Hugues FC, Le Jeunne C, Boutot F, Lowenstein W, Haas C. Evaluation de l'incidence de la pathologie d'origine medicamenteuse dans un service de medecine interne. *Ann Med Interne (Paris).* 1986;137:41-45.
7. Hallas J, Harvald B, Gram LF, Grodum E, Damsbo N. Drug-related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med.* 1990;228:83-90.
8. Hallas J, Haghfeld T, Gram LF, Grodum E, Damsbo N. Drug-related admissions to a cardiology department: frequency and avoidability. *J Intern Med.* 1990;228:379-384.
9. Hallas J, Davidsen O, Grodum E, Damsbo N, Gram LF. Drug-related illness as a cause of admission to a department of respiratory medicine. *Respiration.* 1992;59:30-34.
10. Roblot P, de Bayser L, Barrier J, Marechaud R, Becq-Giraudon B. Primum non nocere: etude prospective de 115 observations de pathologies iatrogènes recueillies en 1 an chez 106 malades. *Rev Med Interne.* 1994;15:720-726.
11. Schneider JK, Mion LC, Frengley JD. Adverse drug reactions in an elderly outpatient population. *Am J Hosp Pharm.* 1992;49:90-96.
12. Couch NP, Tilney NL, Rayner AA, Moore FD. The high cost of low-frequency events: the anatomy and economics of surgical mishaps. *N Engl J Med.* 1981;304:634-637.
13. Steel KS, Gertman PM, Crescenzi C, Anderson J. Iatrogenic illness on a general medical service at a university hospital. *N Engl J Med.* 1981;304:638-642.
14. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. *N Engl J Med.* 1991;324:370-376.
15. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. *N Engl J Med.* 1991;324:377-384.
16. Brennan TA, Hebert L, Laird NM, et al. Hospital characteristics associated with adverse events and substandard care. *JAMA.* 1991;265:3265-3269.
17. Queneau P, Chabot JM, Rajaona H, Boissier C, Grandmottet P. Iatrogenie observee en milieu hospitalier, I: a propos de 109 cas colliges a partir d'une enquete transversale de l'APNET. *Bull Acad Natl Med.* 1992;176:511-529.
18. Queneau P, Chabot JM, Rajaona H, Boissier C, Grandmottet P. Iatrogenie observee en milieu hospitalier, II: analyse des causes et propositions pour de nouvelles mesures preventives. *Bull Acad Natl Med.* 1992;176:651-667.
19. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implication for prevention: ADE Prevention Study Group. *JAMA.* 1995;274:29-34.
20. Lefevre F, Feinglass J, Potts S, et al. Iatrogenic complications in high-risk elderly patients. *Arch Intern Med.* 1992;152:2074-2080.
21. Davidman M, Olson P, Kohen J, Leither T, Kjellstrand C. Iatrogenic renal disease. *Arch Intern Med.* 1991;151:1809-1812.
22. Harb GE, Alledredge BK, Colemen R, Jacobson MA. Pharmacoepidemiology of adverse drug reactions in hospitalized patients with human immunodeficiency virus disease. *J Acquir Immune Defic Syndr.* 1993;6:919-926.
23. Beers MH, Storries M, Lee G. Potential adverse drug interactions in the emergency room. *Ann Intern Med.* 1990;112:61-64.
24. Giraud T, Dhainaut JF, Vaxelaire JF, et al. Iatrogenic complications in adult intensive care units: a prospective two-center study. *Crit Care Med.* 1993;21:40-51.
25. Trunet P, Le Gall JR, Lhoste F, et al. The role of iatrogenic disease in admission to intensive care. *JAMA.* 1980;244:2617-2620.
26. Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. *Arch Intern Med.* 1995;155:1949-1956.
27. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients: Adverse Drug Events Prevention Study Group. *JAMA.* 1997;277:307-311.
28. Cheney FW, Posner K, Caplan RA, Ward RJ. Standard of anesthesia and anesthesia liability. *JAMA.* 1989;261:1599-1603.
29. Laffel G, Blumenthal D. The case for using industrial quality management science in health care organizations. *JAMA.* 1989;262:2869-2873.

30. Berwick DM. Continuous improvement as an ideal in health care. *N Engl J Med*. 1989;320:53-56.
31. Brennan TA, Localio RJ, Laird NL. Reliability and validity of physician judgments about adverse events suffered by hospitalized patients. *Med Care*. 1989; 27:1148-1158.
32. Brennan TA, Localio AR, Leape LL, et al. Identification of adverse events occurring during hospitalization. *Ann Intern Med*. 1990;112:221-226.
33. O'Neil AC, Petersen LA, Cook EF, Bates DW, Lee TH, Brennan TA. Physician reporting compared with medical-record review to identify adverse medical events. *Ann Intern Med*. 1993;119:370-376.
34. Husi F, Stalder H. Arztliche Selbstkontrolle zur Erfassung iatrogener Krankheiten. *Schweiz Med Wochenschr*. 1986;116:346-351.
35. Wenneker M, Epstein AM. Racial inequalities in the use of procedures for patients with ischemic heart disease in Massachusetts. *JAMA*.1989;261:253-257.
36. Hartz AJ, Krakauer H, Huhn EM. Hospital characteristics and mortality rates. *N Engl J Med*. 1989;321:1720-1725.
37. Kahn KL, Rubenstein LV, Draper D, et al. The effects of the DRG-based prospective payment system on quality of care for hospitalized Medicare patients: an introduction to the series. *JAMA*. 1990;264:1953-1955.
38. Burstin HR, Lipsitz SR, Brennan TA. Socioeconomic status and risk for negligent injury in hospitals [abstract]. *Clin Res*. 1991;39:189A.
39. Hiatt HH, Barnes BA, Brennan TA, et al. A study of medical injury and medical malpractice. *N Engl J Med*. 1989;321:480-484.
40. Localio AR, Lawthers AG, Brennan TA, et al. Relation between malpractice claims and adverse events due to negligence. *N Engl J Med*. 1991;325:245-251.
41. Taragin MI, Willett LR, Wilczek AP, Trout R, Carson JL. The influence of standard of care and severity of injury on the resolution of medical malpractice claims. *Ann Intern Med*. 1992;117:780-784.
42. Burstin HR, Johnson WG, Lipsitz SR, Brennan TA. Do the poor sue more? a case-control study of malpractice claims and socioeconomic status. *JAMA*. 1993;270: 1697-1701.
43. Brennan TA, Sox CM, Burstin HR. Relation between negligent adverse events and the outcomes of medical-malpractice litigation. *N Engl J Med*. 1996;335:1963-1967.
44. Wenzel RP. *Prevention and Control of Nosocomial Infections*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1993:143-145.
45. Karch FE, Lasagna L. Adverse drug reactions: a critical review. *JAMA*. 1975;234: 1236-1241.
46. Le Gall JR, Loirat P, Alperovitch A. A simplified acute physiology score for ICU patients. *Crit Care Med*. 1984;12:975-977.
47. McCabe WR, Jackson GG. Gram-negative bacteremia, I and II: etiology and ecology. *Arch Intern Med*. 1962;110:847-864.
48. Commission d'Évaluation et Commission Informatique. Score d'activité Oméga. In: Société de Réanimation de Langue Française, ed. *Guide des Outils d'Évaluation en Réanimation*. Paris, France: Arnette-Blackwell; 1995:39-44.
49. Hergon E, Crespeau H, Rouger P. Failure mechanisms in the transfusion process: importance of anticipatory operational safety analysis. *Transfus Clin Biol*. 1994;5:379-386.
50. Ponge T, Cottin S, Fruneau P, Ponge A, van Wassenhove L, Larousse C. Pathologie iatrogene: enquete prospective, lien avec la consommation médicamenteuse. *Therapie*. 1989;44:63-66.
51. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The quality in Australian health care study. *Med J Aust*. 1995;163:458-471.