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Cause of death in the ICU – autopsy findings

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Relevance of autopsy in ICU over time: unchanged

1) a necessary control mechanism for the accuracy of existing diagnostic tools

   validation of Galactomannan or Beta-D-Glucan in BAL for invasive aspergillosis

2) a vital means for improving our understanding of pathophysiology

   predilection of Zika virus for cells of the fetal central nervous system

   MERS-Corona virus targets pneumocytes

3) an irreplaceable instrument for quality control and clinical accountability (if used systematically)

➔ to determine the cause of death

1) What are the most frequent causes of death revealed by autopsy in the ICU?

2) What are the most frequent infections revealed by autopsy in the ICU?

Background: definition of misdiagnosis, diagnostic discrepancies or diagnostic errors

1) Diagnostic discrepancy, error or misdiagnosis: missed, wrong or delayed diagnosis

2) Autopsy-detected misdiagnosis according to Goldman criteria:

based on clinical relevance and the potential that timely therapy would have changed outcome

<u>Major errors: class I + class II</u>

class I = major missed diagnosis with potential adverse impact on survival

had the diagnosis been known it would changed management and possibly outcome

class II = major missed diagnosis that did not have an impact on survival

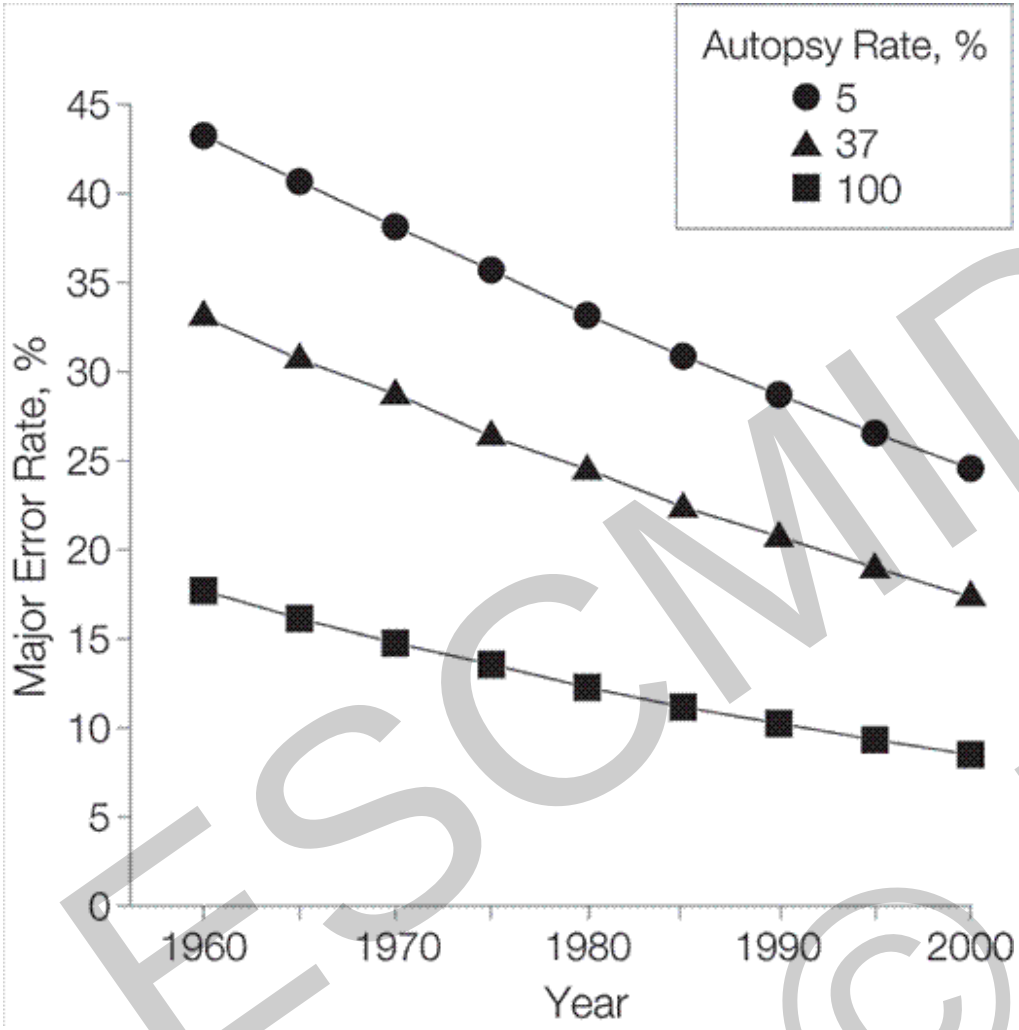
<u>Minor errors: class III + IV</u>

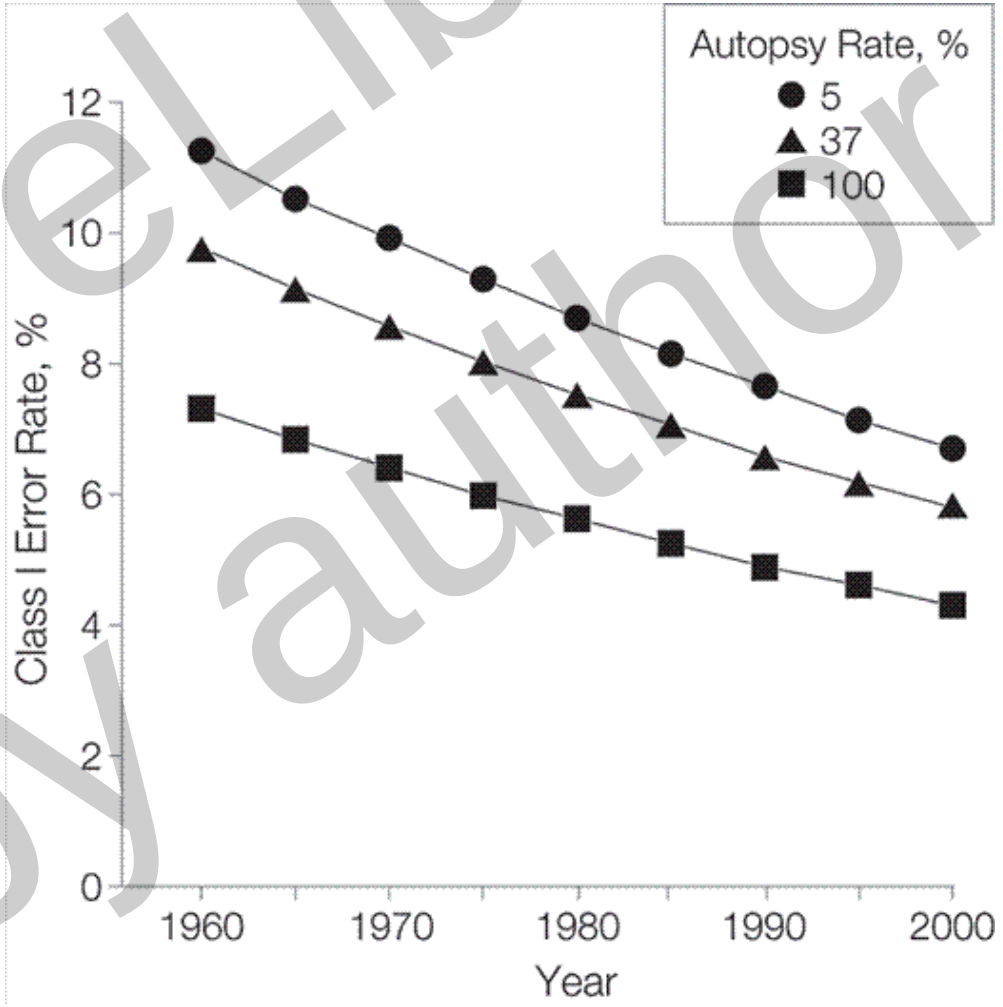
class III = minor missed diagnosis related to a terminal disease but not to the cause of death

Class IV = other missed minor discrepancies

Goldman et al. The value of autopsy in three medical eras. N Engl J Med 1983;28;308(17):1000-5

Background: autopsy and diagnostic discrepancies over time





Shojania K et al. JAMA 2003 (9% class I errors, 15% class II errors)

Autopsy studies in the ICU: systematic review BMJ 2012

Aim: prevalence and distribution of autopsy-confirmed diagnostic errors in the ICU

Table 1 Included studies of intensive care unit (ICU) misdiagnoses in general

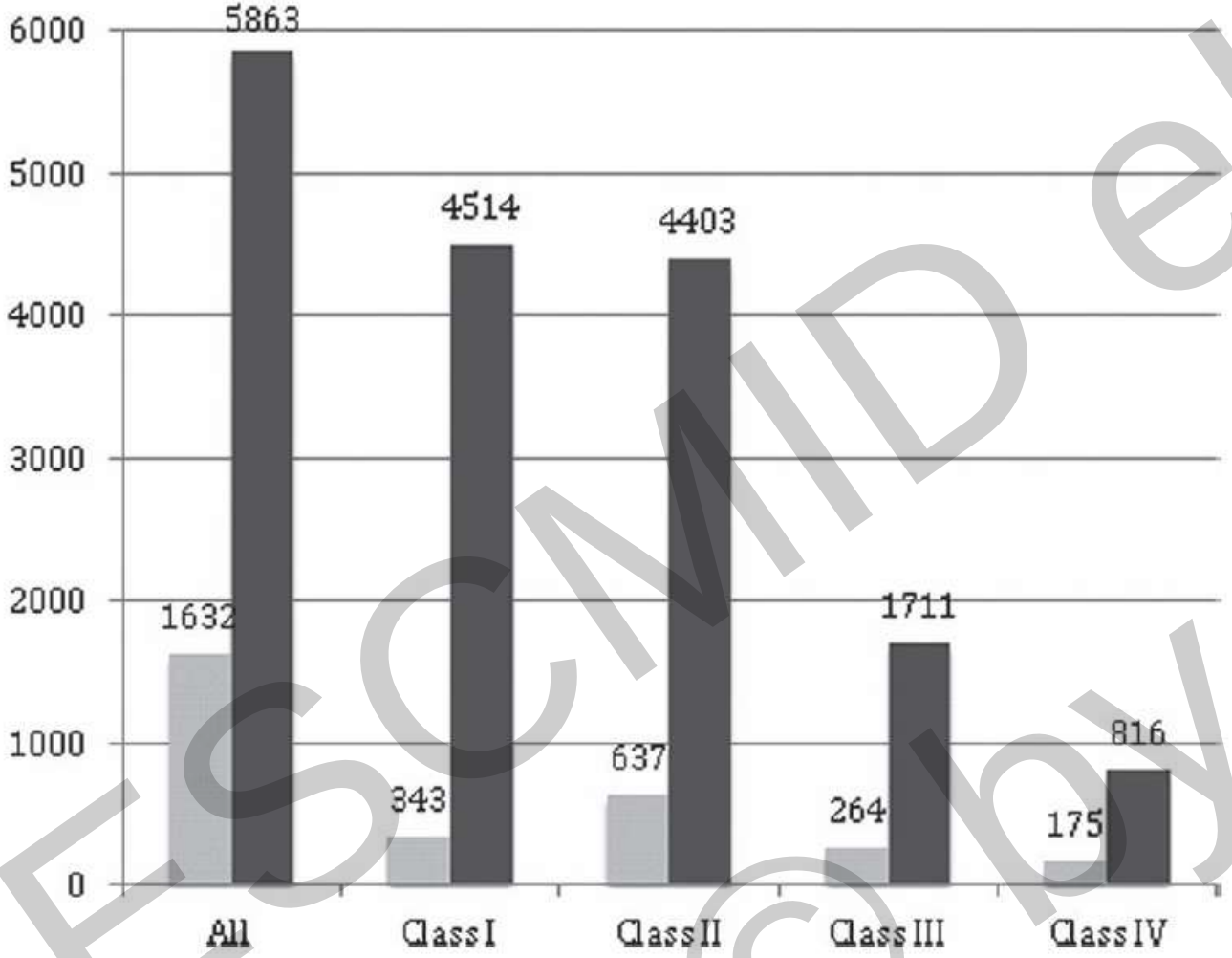
Author	Year	Country	Type of study	Length of study period (months)	ICU type	Total # of deaths	No of autopsies used for analysis
Berlot[7]	1999	Italy	Retrospective	36	Mixed	346	159
Blosser[8]	1998	USA	Retrospective	12	Med/ coronary	132	41
Combes[9]	2004	France	Prospective	36	Med/surg	315	167
Dimopolous[10]	2004	Belgium	Retrospective	12	Med/surg	489	222
Duke[11]	1999	Australia	Retrospective	24	Not given	238	Not given
Fernandez-Segoviano[12]	1988	Spain	Prospective	30	Mixed	Not given	100
Fish[13]	2000	USA	Retrospective	72	Burn	94	88
Gerain[14]	1990	Belgium	Retrospective	11	Oncology	48	34
Gut[15]	1999	Brazil	Retrospective	36	Med/surg	152	30
Kallinen[16]	2008	Finland	Retrospective	72	Burn	74	71
Koch[17]	2008	Germany	Retrospective	120	Medical	1205	1205
Magret[18]	2006	Spain	Retrospective	46	Mixed	525	80
Maris[19]	2007	Belgium	Retrospective	24	Med/surg	786	289
Mort[20]	1999	USA	Retrospective	72	Surg	560	149
Nadrous[21]	2003	USA	Retrospective	24	Multiple	1597	455
Ong[22]	2002	USA	Retrospective	24	Trauma/burn	158	153
Palazon-Sanchez[23]	1999	Spain	Retrospective	12	Med/surg	67	24
Papadakis[24]	1991	USA	Retrospective	24	Medical	401	172
Pastores[25]	2007	USA	Retrospective	69	Med/surg	658	86
Perkins[26]	2003	Great Britain	Retrospective	42	Med/surg	636	38
Podbregar[27]	2001	Slovenia	Retrospective	24	Medical	270	126
Podbregar[28]	2011	Slovenia	Retrospective	20	Medical	373	170
Roosen[29]	2000	Belgium	Retrospective	24	Medical	108	100
Saad[30]	2007	Brazil	Retrospective	24	Coronary	Unclear	161
Sharma[31]	2005	India	Retrospective	36	Trauma/burn	249	163
Silfvast[32]	2003	Finland	Retrospective	48	Mixed	388	346
Simon[33]	2001	Hungary	Retrospective	12	Medical	163	110
Tai[34]	2001	USA	Retrospective	24	Medical	401	91
Tejerina	2010	Spain	Retrospective	300	Mixed	2857	866
Twigg[36]	2001	Great Britain	Retrospective	36	Med/surg	252	97
Yalamarthi[37]	1998	Great Britain	Retrospective	24	Not given	233	70

Autopsy rates 6 -100%

Study periods from 11 to 300 months

Winters B et al:. BMJ Qual Saf 2012 (n=31 articles, 5863 autopsies)

Autopsy studies in the ICU: systematic review BMJ 2012: misdiagnosis by class



class I error = 8%

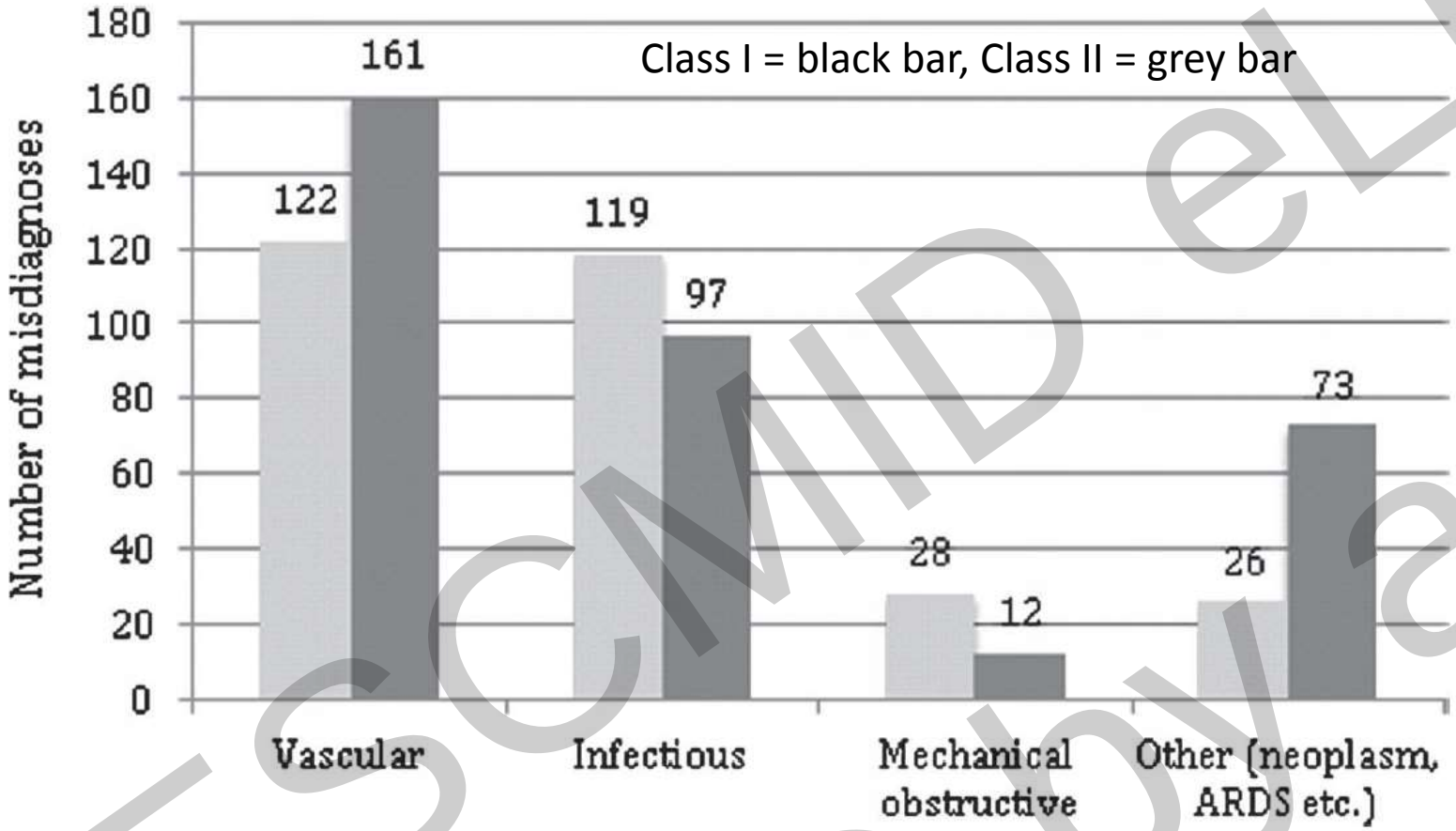
Class II error = 15%

Class III error = 15%

Class IV error = 21%

Winters B et al:. BMJ Qual Saf 2012 (n=31 articles)

Autopsy studies in the ICU: systematic review BMJ 2012: misdiagnosis by disease category



<u># of class I misdiagnosis</u>

97 Infectious

Vascular

37 pulmonary embolus

33 myocardial infarction

21 abdominal bleed

13 bowel infarction

11 aortic dissection

Mechanical obstructive

10 cardiac tamponade

9 perforated viscus

6 malignancy

Winters B et al:. BMJ Qual Saf 2012 (n=31 articles)

# of class I misdiagnosis (without infections)

37 pulmonary embolus

33 myocardial infarction

21 abdominal bleed

13 bowel infarction

11 aortic dissection

10 cardiac tamponade

9 perforated viscus

6 malignancy

Diagnoses	# of Class I diagnoses
Cardiac tamponade	5
Retroperitoneal or intra-abdominal hemorrhage	4
Myocardial infarction	3
Cancer	1
Giant cell myocarditis	1
Aortoenteric fistula	1
Pulmonary embolism	0

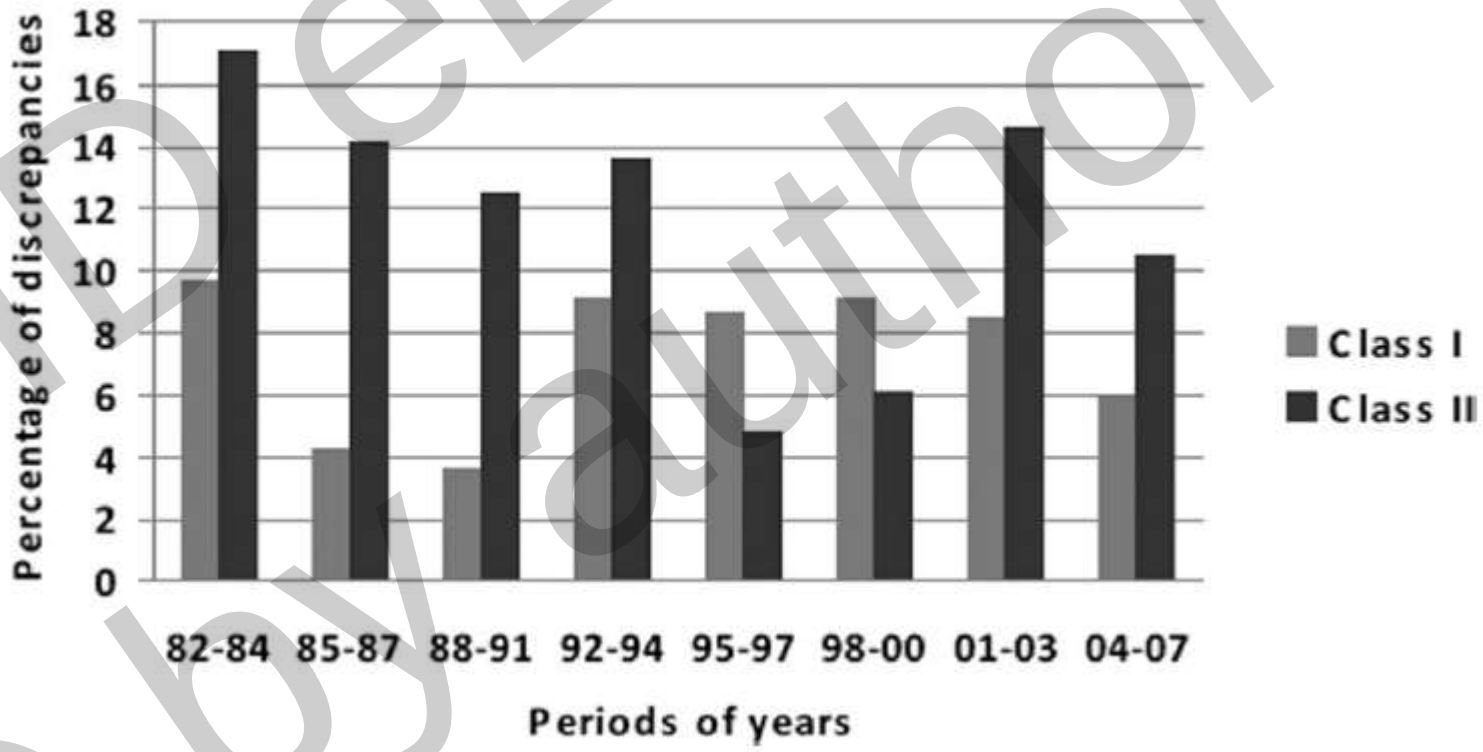
Winters B et al:. BMJ Qual Saf 2012 (n=31 articles)

Roosen J et al:. Mayo Clin Proc 2000 (n=100 patients from 1996, autopsy rate 93%)

Prospective autopsy study in the ICU

Table 3. Major discrepancies between clinical diagnoses and autopsy findings

Discrepant Autopsy Findings (127 = 15%)	N
Infectious disorders N=53 (42%)	
Pneumonia	23
Secondary peritonitis	12
Invasive aspergillosis	8
Pulmonary tuberculosis	3
Intra-abdominal abscess	3
Mediastinitis	2
Meningoencephalitis	2
Cardiovascular disorders N=21	
Endocarditis	8
Myocardial infarction	8
Aortic dissection	3
Cardiac tamponade	2
Pulmonary disorders N=26	
Pulmonary embolism	24
Aspiration pneumonitis	2
Gastrointestinal disorders N=18	
Gastrointestinal hemorrhage	7
Mesenteric ischemia	6
Acute pancreatitis	5
Oncologic disorders	
Lymphangitis carcinomatosa	3
Lung cancer	2
Other	4



Tejerina E et al. Crit Care Med 2012, n = 834 patients with autopsy (autopsy rate 30%), median ICU LOS before death = 4d

Autopsy studies in the ICU: particular patient groups: surgical patients with septic shock

relevance of persistent septic focus

77% of the patients had a continuous septic focus at autopsy!

32% had more than one focus!

Even in those treated for more than 7 days = 89% had a septic focus!

Most frequent septic foci at autopsy:

Pneumonia	41%
Tracheobronchitis	29%
Peritonitis	23%
IA abscesses	9%
Pyelonephritis	6%

Torgersen C et al. Crit Care and Trauma 2009 , n = 235 dead SICU patients with sepsis/septic shock that underwent autopsy (autopsy rate 92,4%)

Autopsy studies in the ICU: particular patient groups: cancer patients (1)

			N
Class I discrepancies ($n = 15$)	Opportunistic infections ($n = 10$)	VRE pneumonia	2
		Legionella pneumonia	1
		PCP pneumonia	1
		Invasive aspergillosis	1
		Candida empyema	1
		VZV meningoencephalitis	1
		HSV esophagitis	1
		CMV pneumonia	1
		Disseminated necrotizing toxoplasmosis	1
	Cardiac complications ($n = 5$)	Ischemic cardiomyopathy	2
		Thrombotic endocarditis	2
		Congestive heart failure	1
Class II discrepancies ($n = 10$)	Cardiopulmonary complications ($n = 7$)	Pulmonary embolism	4
		Thrombotic endocarditis	2
		Pulmonary hemorrhage	1
	Opportunistic infections ($n = 3$)	Candidemia	1
		VRE meningitis	1
		CMV proctitis	1

Pastores S et al. Crit Care 2007 (n=658 deaths, 86 (13%) underwent autopsy)

Autopsy studies in the ICU: particular patient groups: cancer patients (2)

Table 2: Goldman class I and II discrepancies in various subgroups

Major missed postmortem diagnoses	All patients (*n*=70)	HSCT (*n*=26)	Hematologic malignancies (*n*=21)	Solid malignancies (*n*=23)
Invasive aspergillosis	5	3	1	1
Pulmonary embolism	4	1	1	2
Cancer recurrence	2	0	1	1
Bacterial pneumonia	1	0	0	1
Diffuse alveolar hemorrhage	1	1	0	0
Diffuse alveolar damage	1	0	1	0
Subarachnoid hemorrhage	1	1	0	0
Totals	15	6	4	5

HSCT: Hematopoietic stem cell transplantation

Table 3: Characteristics of patients in various sub groups with major discrepancies

Patient #	Cancer diagnosis	Clinical diagnosis	Autopsy findings
1.	Leukemia/HSCT	Pneumonia/CNS bleed	Aspergillosis
2.	Leukemia/HSCT	Pneumonia	Subarachnoid hemorrhage
3.	Leukemia/HSCT	Pneumonia	Aspergillosis
4.	Renal cell carcinoma/HSCT	Pneumonia	Aspergillosis
5.	Lymphoma/HSCT	CMV pneumonia	Pulmonary embolism
6.	Lymphoma	Septic Shock	Diffuse alveolar hemorrhage
7.	Lymphoma	Diffuse alveolar hemorrhage	Aspergillosis
8.	Lymphoma	Diffuse alveolar hemorrhage	Diffuse alveolar damage
9.	Lymphoma	Acute respiratory distress syndrome	Pulmonary embolism
10.	Lymphoma	Septic shock	Central nervous lymphoma
11.	Lung cancer (Small cell)	Pneumonia	Aspergillosis
12.	Endometrial cancer	Septic shock	Pulmonary embolism
13.	Colon cancer	Pneumonia	Diffuse pulmonary metastasis
14.	Breast cancer	Septic shock	Pulmonary embolism
15.	Glioblastoma	Gastrointestinal bleeding	Pneumonia

HSCT: Hematopoietic stem cell transplantation, CNS: Central nervous system, CMV: Cytomegalovirus

Khawaja O et al. Avicenna J Med 2013 (n=70 patients with autopsy over 6 years)

Autopsy studies in the ICU: particular patient groups: cirrhosis

Class I n=11 (13%)	Class II n=3 (3%)
1. Metastatic linitis plastica	1. Acute pancreatitis
2. Oesophageal variceal bleeding	2. Necrotizing Mucor Mycosis pneumonia
3. Disseminated Mucor Mycosis	3. Focal aspergillosis (myocardial)
4. Disseminated HCC	
5. Invasive candidiasis	
6. Herpes simplex pneumonia	
7. Gastric Rupture	
8. Pneumocystis pneumonia	
9-11. Invasive aspergillosis	

Class I infectious = 7
Class I vascular or mechanical = 2
Class I malignancy = 2

De Mey N et al. Abstract, ISICEM 2015, n = 581 patients with cirrhosis admitted to the MICU, 142 died, 83 (58%) underwent autopsy

Autopsy studies in the ICU: aspergillus in patients without malignancy

TABLE 1. CHARACTERISTICS OF ALL OBSERVED CASES

	All (*n* = 127)	Proven IA (*n* = 56)	Probable IA (*n* = 49)	Possible IA (*n* = 2)	Colonization (*n* = 20)
Age, yr, mean	61	59	63	61	64
Sex, male, n	84	39	35	2	8
Patients with hematologic malignancy, n	38	26	12	0	0
Patients without hematologic malignancy, n	89	30	37	2	20
COPD, n	35	12	21	2	0
Solid organ transplants, n	9	4	5	0	0
Systemic disease, n	17	6	8	0	3
Cirrhosis, n	6	3	0	0	3
Other, n	22	5	3	0	14
SAPS II, mean	54	57	52	43	54
Predicted mortality, %	53	58	49	31	51
Observed mortality, %	86	98	90	0	50
ICU length of stay, d	20	14	23	32	28
Hemodialysis in ICU, n	54	27	20	0	7
Mechanical ventilation, n	123	56	47	2	18
Neutropenia, n	19	12	6	0	1
Autopsy, n	76	52	19	0	5

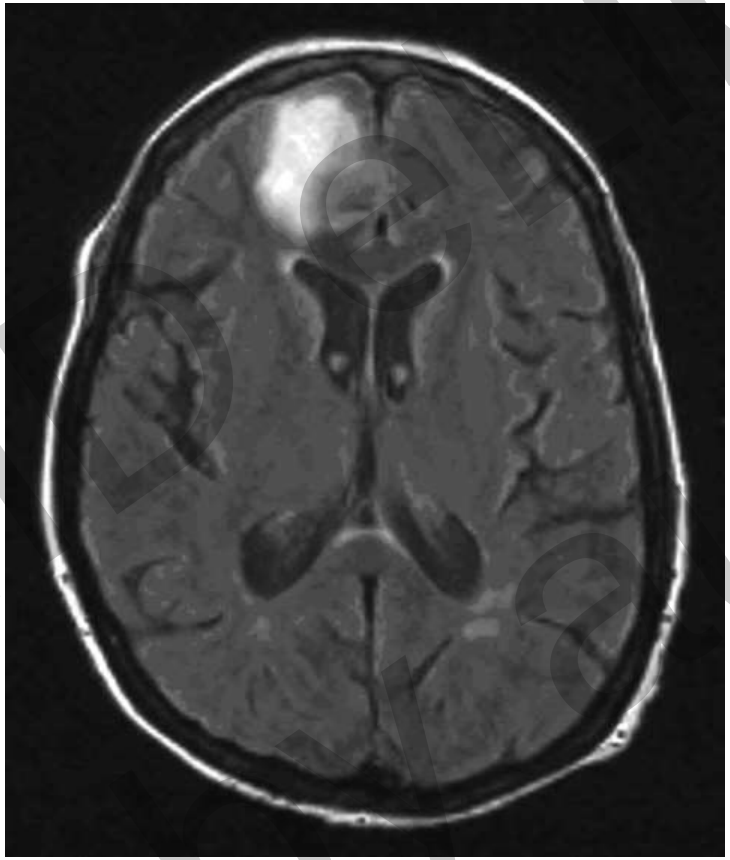
Meersseman W et al. Am J Resp Crit Care Med 2004, 1850 admissions, excluding patients with heamtological malignancies or cancer: 3,7% had proven or probable IA

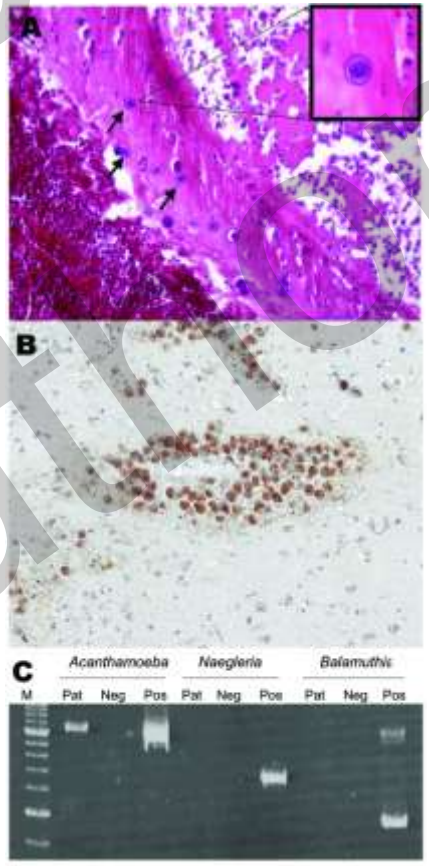
Autopsy in the ICU and misdiagnosis: not necessarily an error

66 yr old female
PMH: hepatitis C with cryoglobulinemic vasculitis treated with prednisolone and plasmapheresis and later with rituximab

Admission MICU for status epilepticus

Postmortem histologic diagnosis: Necrotizing hemorrhagic meningoencephalitis due to infection with Acanthamoeba spp. (granulomatous amebic enecephalitis)





A) Cysts in a vessel wall (arrows) of the patient (hematoxylin and eosin stain, magnification ×250). Inset shows a cyst at higher magnification (hematoxylin and eosin stain, magnification ×800). B) Immunohistochemical staining with antibody to *Acanthamoeba* cysts within vessel walls (magnification ×250). C) Polyacrylamide gel electrophoresis of PCR products for *Acanthamoeba* spp

Meersseman W et al. Emerging Infectious Dis 2007

Cause of death in the ICU – autopsy findings: take home

- In ± 20-25% of patients dying in the ICU autopsy reveals a major missed diagnosis
- In ± 9% of cases this diagnosis would likely have impacted outcome
- Cardiac or vascular problems + abdominal bleeding are the most frequently missed diagnoses at autopsy in the general ICU population
- In immunocompromised patients opportunistic infections rank first among major missed diagnoses
- Aspergillus is the most frequently missed infectious cause of death