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Nutritional markers in patients with diabetes and pancreatic exocrine failure

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Abstract

Aims: Altered pancreatic exocrine function can be observed in patients with type 1 or type 2 diabetes. In the present study, we evaluated the potential nutritional consequences of this dysfunction.

Methods: Serum concentrations of nutritional markers, including albumin, cholesterol, triacylglycerol, vitamins A, D, and E, were assessed in a cohort of 468 patients (137 with type 1 diabetes and 331 with type 2 diabetes), after exclusion of the patients with a CRP > 10 mg/l. These patients were compared with 47 patients with diseases of the exocrine pancreas and diabetes (type 3c diabetes or pancreatogenic diabetes). Fecal elastase-1 and chymotrypsin concentrations were measured and patients with type 1 and type 2 diabetes were divided into three groups according to whether zero (group NN), one (group LN), or both (group LL) concentrations were decreased.

Results: Several markers differed significantly between the groups of patients, including BMI, albumin, phosphorus, and fat-soluble vitamins. Patients with pancreatogenic diabetes had markedly more profound alterations than patients with type 1 or type 2 diabetes and altered exocrine function. However, patients with type 1 or type 2 diabetes and decreased concentrations of both elastase-1 and chymotrypsin had lower albumin, phosphorus, and vitamin A than patients with normal pancreatic exocrine function.

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Conclusions: Modest nutritional alterations were found in patients with type 1 or type 2 diabetes and altered exocrine function. Patients with type 1 or type 2 diabetes and altered exocrine function may thus deserve to be screened for nutritional deficiencies.

Keywords: Diabetes, Nutrition, Pancreatic exocrine dysfunction, Fat-soluble vitamins, Fecal elastase

Introduction

Pancreatic exocrine function can be altered in patients with diabetes [1–6]: it has been recently rediscovered that the size of the pancreas is decreased in patients with type 1 diabetes (T1D) [7–12], including in patients with recent-onset diabetes [8, 11, 12]. This seems to indicate that the exocrine pancreas could be damaged early in T1D natural history [13], given that the exocrine pancreas represents more than 95% of the pancreatic mass. Moreover, it has recently been shown that a leucocytic infiltration can be observed in the exocrine pancreas of patients with T1D [14–16], suggesting that the exocrine dysfunction can also be a consequence of an immune-mediated destruction of the exocrine pancreas. Likewise, T2D is associated with low-grade inflammation: macrophages can be observed in islets [17] and chronic pancreatitis has been frequently observed at autopsy since the seminal work of R. Cecil [18].

In patients with T1D, pancreatic exocrine failure is associated with diabetes of long duration [1, 19–21], whereas in patients with T2D, we showed that it is also associated with vascular diseases [1].

Malabsorption of fat-soluble vitamins is a well-established consequence of chronic pancreatitis and other diabetes-associated diseases of the pancreas. However, outside the context of chronic pancreatitis, pancreatectomy and other well-defined diseases of the exocrine pancreas, nutritional consequences of pancreatic exocrine failure have seldom been described [22, 23], in part, because the exocrine deficiency is deemed to be mild in the context of T1D or T2D, and often occurs without steatorrhea [5, 24–27]. However, we and others [1, 21, 25] have shown that the BMI of patients with pancreatic exocrine dysfunction in the context of T2D is lower than that of patients with normal pancreatic exocrine function, and this observation raises the question of the nutritional consequences of this pancreatic exocrine failure. In the present study, we investigated several nutritional markers, including the serum concentrations of vitamins A, D, and E in relation with pancreatic exocrine status in patients with diabetes. The results were compared with those of patients with overt exocrine diseases of the pancreas and pancreatogenic diabetes (PD).

Materials and methods

Patients

From our cohort of 667 patients [1] who had an investigation of pancreatic exocrine function, 537 patients were assessed for vitamins A, D, and E, in addition to serum albumin. These

patients were compared to 55 patients with PD. From this new cohort, we excluded all patients with a C-reactive protein > 10 mg/l, because inflammation can alter the serum concentration of several markers such as vitamin A [28], thus leaving 515 patients: 137 with T1D, 331 with T2D and 47 with PD. Among the 137 patients with T1D, plain abdominal radiography or CT scan was normal in all of the 101 patients in whom they were performed. Among the 331 patients with T2D, plain abdominal radiography or CT scan was normal in all of the 289 patients in whom they were performed.

The PD group included 37 patients with alcohol-induced pancreatitis, three with total or subtotal pancreatectomy (1 nesidioblastosis, 1 intraductal papillary mucinous neoplasm of the pancreas, and 1 unknown), three with genetic chronic pancreatitis including 1 fibro calculous diabetes, and four with idiopathic chronic pancreatitis. Diabetes was confirmed in all patients. All of the patients with alcohol-induced chronic pancreatitis had pancreatic calcifications on CT scan.

Pancreatic function assessment

Exocrine function of the pancreas was assessed by the measurement of fecal elastase-1 concentration and chymotrypsin activity performed on a sample of feces obtained in non-diarrheic patients. Samples were stored at −20 °C until analysis. Pancreatic fecal elastase-1 concentration was determined using a "sandwich"-type enzyme immunoassay (Schebo-Biotech, Germany) and results were expressed as µg/g of stool. The normal cut-off value was defined as > 200 µg/g. Fecal chymotrypsin activity was measured using a colorimetric method using Succ–Ala–Ala–Pro–Phe-*p*-nitroanilin as substrate (Immundiagnostik, Germany). Results were expressed as U/g of stool at 25 °C and activity values > 6 U/g were considered normal.

Nutritional assessment included measurements of serum vitamin 25OH-D2 + D3, vitamin A and vitamin E, albumin, calcium, phosphorus, and serum lipids.

Vitamin A (retinol) and vitamin E (alpha-tocopherol) were assayed by HPLC as previously described in [29], with excellent intra and inter-assay reproducibility at all levels of retinol and for higher levels of alpha-tocopherol, but with lower precision when alpha-tocopherol was < 7.5 µmol/l. As this low level of alpha-tocopherol was only found in four patients in our whole cohort, we consider our method to be satisfactory.

Vitamin A deficiency was defined as a vitamin A concentration < 0.7 µmol/l and vitamin E deficiency was defined as a vitamin E concentration < 12 µmol/l. Vitamin D concentration was assayed as the sum of 25-hydroxy vitamin (D2 + D3) (Immunodiagnosticsystems, Paris, France). Vitamin D deficiency was defined as a vitamin D concentration < 75 nmol/l, severe vitamin D deficiency was defined as a vitamin D concentration < 25 nmol/l [30].

Statistical analysis

We classified the patients into three groups as previously described [1]:

- Group LL: patients with a fecal elastase-1 < 200 µg/g AND a fecal chymotrypsin activity < 6 U/g (both parameters decreased).

- Group LN: patients with a fecal elastase-1 < 200 μg/g OR a fecal chymotrypsin activity < 6 U/g (only one decreased parameter).
- Group NN: patients with NORMAL fecal elastase-1 AND fecal chymotrypsin activity.

We have previously shown that the patients of the LL group display more severe decreases in both fecal elastase-1 concentration and fecal chymotrypsin activity than those of the LN group [1]. Comparisons of groups were performed using non-parametric tests, i.e., ANOVA using the Kruskal–Wallis test. When the test was significant, three pairs of data, PD vs LL, LN vs LL, and NN vs LL were compared using the Tukey post-hoc test. Categorical parameters were compared using the Pearson's Chi-square test. Correlations between continuous parameters were assessed with the non-parametric Pearson's test. Independent parameters that correlated significantly with serum concentration of fat-soluble vitamins were analyzed in a multivariate analysis with adjustment for gender, age, BMI, duration of diabetes, HbA1c, serum cholesterol concentration, serum triacylglycerol concentration, eGFR, and either fecal elastase-1 or fecal chymotrypsin concentrations.

Statistical analyses were performed using Sigmastat version 3.5. Results are expressed as median and interquartile range. *P* values were considered significant if < 0.05.

Results

Clinical characteristics of the patients

The clinical characteristics of the patients are presented in Table 1. Patients of the different groups were of similar age. The patients included in the present study are a subpart of those described in a previous publication [1]. As previously reported in this former publication, the patients were divided with regard to the results of fecal elastase-1 and chymotrypsin into LL (78 patients), LN (94 patients), and NN (296 patients) groups, as described in "Methods".

As shown before in this cohort, altered pancreatic exocrine function was more frequent in patients with T1D than in patients with T2D (24% of patients with T1D belonged to the LL group, vs only 13% of patients with T2D). In patients with T1D, pancreatic exocrine dysfunction was associated with a longer median duration of diabetes (19 years in the LL group vs 13 years in the NN group), this was not observed in patients with T2D. In patients with T2D, altered pancreatic exocrine function was associated with insulin use, as we already described [1].

Nutritional markers in patients with diabetes

BMI was significantly lower in the PD group than in the LL group, and in the LL group than in the NN group. Lower BMI in the LL subjects as compared to NN subjects was, however, only observed in patients with T2D, not in those with T1D (Table 1). Mean serum albumin and phosphorus concentrations were lower in the LL group (36.4 g/l and 1.15 mmol/l, respectively) as compared to the NN group (38 g/l and 1.22 mmol/l, respectively) (Fig. 1).

Although cholesterol and calcium concentrations differed significantly under ANOVA analysis, no significant difference was found between the LL group and the LN and NN groups.

Table 1. Clinical characteristics of the patients.

	PD ($n=47$)	Type 1 or 2 diabetes ($n=468$)	LL ($n=78$)	LN ($n=94$)	NN ($n=296$)	Name of test, P value
Age (years, median [IQR])	55 [46–63]	58 [49–66]	57 [45–68]	58 [50–65]	57 [51–65]	Kruskal, $P=0.62$
Males (n, %)	42 (89%)	272 (58%)	48 (61%)	51 (54%)	173 (58%)	Pearson, $P=0.0003$
Type 1 Diabetes (n, %)[a]	–	137 (29%)	33 (42%)	40 (42%)	64 (22%)	Pearson, $P<10^{-6}$[b]
Known duration of diabetes (years, median [IQR])	6 [1–14]	12 [6–20]	15 [5–25]	12 [7–21]	11 [6–19]	Kruskal, $P=0.0021$ Post-hoc: PD vs LL**
Known duration of diabetes in patients with T1D (years, median [IQR])	–	15 [6–27]	19 [8–35]	18 [9–30]	13 [2–22]	Kruskal, $P=0.042$
Known duration of diabetes in patients with T2D (years, median [IQR])	–	11 [6–19]	14 [4–22]	9 [5–19]	11 [6–19]	Kruskal, $P=0.52$
HbA1c (%, median [IQR])	8.2 [7.2–10]	8.8 [7.7–10.2]	8.8 [7.9–10.3]	8.9 [7.6–9.9]	8.9 [7.6–10.3]	Kruskal, $P=0.62$
HbA1c (mmol/mmol)	66	73	73	74	74	
BMI (kg/m^2, median [IQR])	22.6 [20.1–25.4]	27.7 [24.5–32.4]	26.0 [23.8–28.6]	27.2 [24.4–32.1]	28.7 [24.8–33.7]	Kruskal $P<10^{-6}$ Post-hoc: PD vs LL and NN vs LL**
BMI in patients with T1D (kg/m^2, median [IQR])	–	24.9 [22.6–27.9]	24.7 [23.1–26.4]	25.8 [22.7–28.5]	24.8 [21.9–28.3]	Kruskal, $P=0.64$[b]
BMI in patients with T2D (kg/m^2, median [IQR])	–	29.1 [25.9–33.9]	27.1 [24.6–29.7]	29.2 [24.5–33.7]	30.1 [26.0-34.2]	Kruskal, $P=0.0064$[b] Post-hoc: NN vs LL**
Insulin use (n, %)[c]	42 (89%)	196 (59%)	35 (78%)	25 (46%)	136 (58%)	Pearson, $P=0.0061$

The P values indicated in the last column are the overall P values of the Kruskal–Wallis or Pearson Chi-square tests performed for each parameter. For the Kruskal–Wallis tests, if the P value was <0.05, LL was compared to PD, LN and NN groups: *$P<0.05$, **$P<0.01$

[a]Only in patients with T1D or T2D

[b]Comparison of LL, LN and NN only

[c]Only in patients with PD and T2D

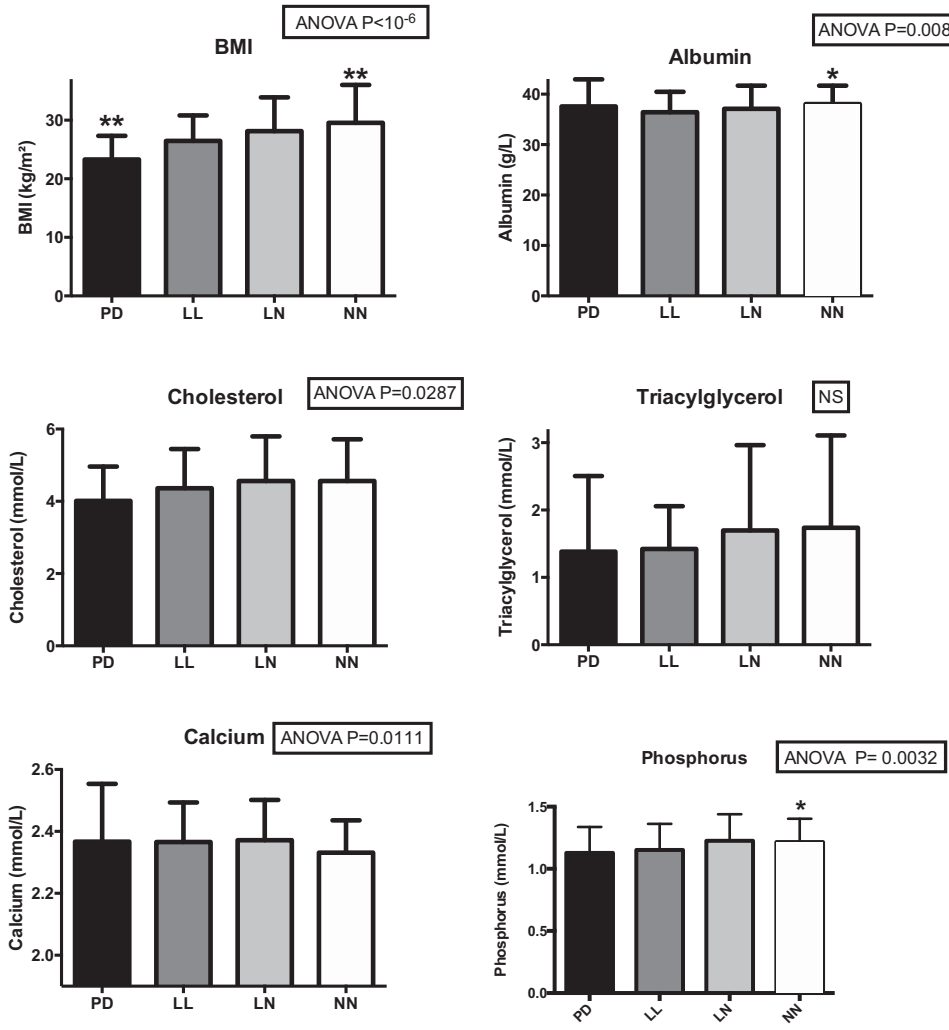

Fig. 1. BMI, albumin, cholesterol, triacylglycerol, calcium, and phosphorus concentrations in the PD, LL, LN, and NN groups. If the *P* value of ANOVA was < 0.05, LL group was compared to PD, LN, and NN groups: **P* < 0.05, ***P* < 0.01

Serum concentration of fat-soluble vitamins in patients with diabetes

As shown in Fig. 2, the serum concentrations of vitamins A, D, and E differed significantly between groups. Post-hoc analyses showed that vitamin D and vitamin E were lower in the PD group as compared to the LL group. Vitamin A was lower in the LL group than in the LN and NN groups.

The prevalence of vitamin D deficiency was extremely high in the whole study cohort: vitamin D concentration was < 75 nmol/l in 94% of the patients and was < 25 nmol/l (severe vitamin D deficiency) in 20% of the patients. In contrast, the prevalence of vitamin A and E deficiencies,

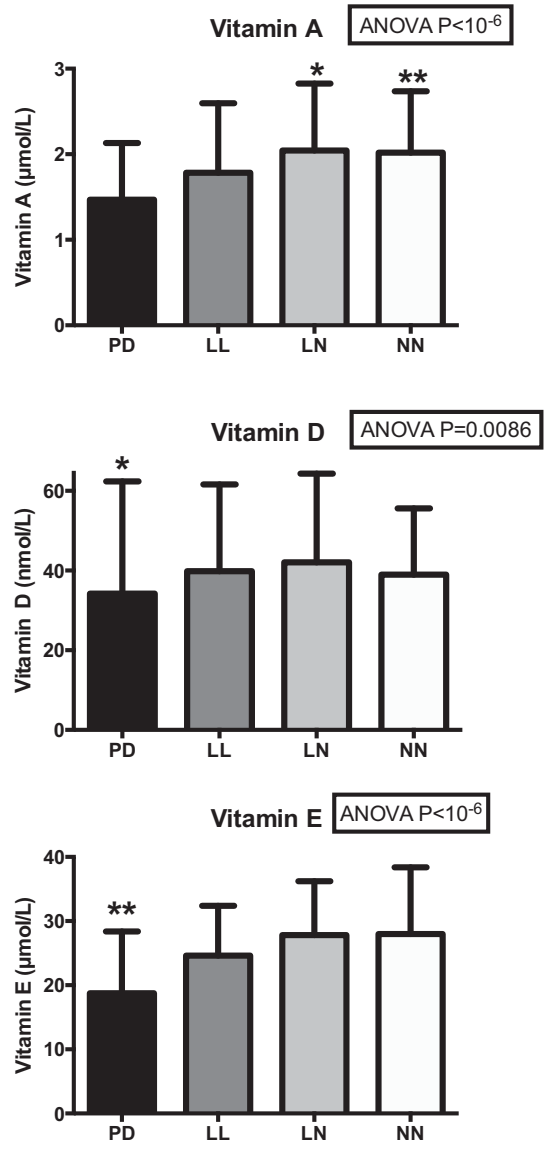

Fig. 2. Vitamins A, D, and E concentrations in the PD, LL, LN, and NN groups. If the *P* value of ANOVA was < 0.05, LL group was compared to PD, LN, and NN groups: **P* < 0.05, ***P* < 0.01

defined, respectively, as a value below 0.7 µmol/l and 12 µmol/l, were very low, 1.2% and 4.4%, respectively. However, vitamins A and E deficiencies and severe vitamin D deficiency were more common in patients of the PD group (6.7%, 22%, and 38.8%, respectively) and in patients of the LL group (2.6%, 9.2%, and 24.7%, respectively), than in patients of the LN (0%, 2.2%, and 20.2%, respectively) and NN groups (0.3%, 1.4%, and 16.6%, respectively) (Table 2).

Serum concentrations of fat-soluble vitamins were affected by several parameters. Multivariate analysis with adjustment for gender, age, BMI, duration of diabetes, HbA1c, serum cholesterol concentration, serum triacylglycerol concentration, Egfr, and either fecal elastase-1 or fecal

Table 2. Prevalence of fat-soluble vitamins deficiencies in patients with diabetes.

	PD	LL	LN	NN	*P* value
Vitamin D deficiency[a] (*n*, %)	42 (95.5%) *N* = 44	71 (92.2%) *N* = 77	79 (88.8%) *N* = 89	276 (95.2%) *N* = 290	0.16
Severe vitamin D deficiency[b] (*n*, %)	17 (38.6%) *N* = 44	19 (24.7%) *N* = 77	18 (20.2%) *N* = 89	48 (16.6%) *N* = 290	0.0058
Vitamin A deficiency[c] (*n*, %)	3 (6.7%) *N* = 45	2 (2.6%) *N* = 78	0 (0%) *N* = 94	1 (0.33%) *N* = 295	N/A
Vitamin E deficiency[d] (*n*, %)	9 (22%) *N* = 41	7 (9.2%) *N* = 76	2 (2.2%) *N* = 92	4 (1.4%) *N* = 291	0.0001

The *P* values indicated in the last column are the overall *P* values of the Chi-square tests. The test was not applicable for vitamin A deficiency, because the number of patients with deficiency was too small
[a]As defined by a vitamin D concentration < 75 nmol/l
[b]As defined by a vitamin D concentration < 25 nmol/l
[c]As defined by a vitamin A concentration < 0.7 µmol/l
[d]As defined by a vitamin E concentration < 12 µmol/l

chymotrypsin concentrations showed that serum lipids concentrations and BMI were independently associated with serum concentrations of vitamins A and E, whereas only serum cholesterol concentration was associated with vitamin D concentration. When the analysis was performed after exclusion of the PD patients, fecal elastase-1 concentration remained a significant independent determinant of vitamin E concentration, but not of vitamin A (data not shown).

Discussion

In the present study, we have investigated the nutritional consequences of impaired exocrine function in patients with diabetes. Patients with varying degrees of impairment of exocrine function tests and either T1D or T2D were compared with patients with PD. In patients with PD, nutritional defects were quite mild, with a median BMI of 22.6 kg/m^2 and a serum albumin concentration of 37.6 g/l, owing to the fact that 27 patients out of 47 (60%) already received pancreatic enzyme therapy at the time of study. In the patients with type 1 and type 2 diabetes, the patients in whom both fecal elastase concentration and fecal chymotrypsin activity were decreased (LL group) had an intermediate nutritional status between that of patients with PD and patients with normal exocrine function. BMI, phosphorus, and vitamin A were lower in patients of the LL group as compared to patients of the NN group. Fecal elastase concentration was positively associated with serum vitamin A and serum vitamin E in a multivariate analysis that also revealed a correlation between the serum concentration of vitamins A and E on one hand and BMI, GFR, and serum lipids concentration on the other hand. With regard to vitamin D concentration, the deficit was quasi-universal in all groups of patients, but severe deficiency was more frequent in patients of the LL group as compared to patients of the NN group. In patients with T1D or T2D and altered exocrine function, serum phosphorus concentration was lower in the LL group, suggesting that these patients might have lower phosphate intestinal absorption and secondary hyperparathyroidism as a consequence of more severe vitamin D deficiency, but serum PTH concentration was not measured in this study. However, it must be noted that patients with severe vitamin D deficiency

did not have a significantly lower serum phosphorus concentration than the other subjects, even though diabetes is known to alter the parathormone increase in face of vitamin deficiency due to decreased magnesium concentration in patients with diabetes [31].

The patients with T2D and altered exocrine function tests had a lower BMI than the patients with normal exocrine function tests. It has already been observed that the weight of the patients with low fecal elastase is lower than that of patients with normal exocrine function tests [2, 20, 21]. We have shown that the weight gain after initiation of insulin was similar in patients with or without exocrine failure, suggesting that weight loss in these patients was mostly due to more severe insulin deficiency, not to malabsorption secondary to exocrine failure [1]. We have, however, also shown that pancreatic exocrine deficiency is associated with lower insulin secretion [13]. This concurs with the higher prevalence of insulin use observed in patients with T2D and altered exocrine function.

In this study, only serum concentration of vitamin A was assessed, not the concentrations of retinol-binding protein (RBP) or transthyretin (TTR). We verified in a subset of this cohort that vitamin A was highly correlated with RBP and TTR (n = 65, correlation coefficient > 0.95, $P < 10^{-6}$, data not shown) and we confirmed that in patients with diabetes the relation of serum retinol, RBP and TTR are unchanged and occur in a 1:1:1 complex, as already described [32, 33]. Thus, in these patients, assessment of RBP and TTR gives no further information than that of retinol alone. Serum retinol reflects an individual's vitamin A status, particularly when the body's reserves are limited [34]. Serum retinol < 0.7 μmol/l is considered diagnostic of vitamin A deficiency [35]. In the present study, serum concentration of vitamin A correlated with multiple parameters, including gender, BMI, serum lipid concentration, and eGFR. Except for lipids [36], these parameters were not yet known to be associated with vitamin A concentration in patients with diabetes. Inflammation is known to influence serum concentration of vitamin A as is malnutrition. We excluded patients with a CRP > 10 mg/l from the present study.

To our knowledge, only a few studies have analyzed the nutritional consequences of altered exocrine function in patients with diabetes [22, 27]. In the study by Ewald *et al.*, 80 patients with fecal elastase-1 concentration < 100 μg/g were randomized to either 40,000 U pancreatin per meal or to placebo for 16 weeks. At baseline, serum concentration of vitamins A, D, and E was normal in both groups and remained unchanged during the trial. However, the serum concentration of vitamins in these patients was not compared to reference values [22]. On the other hand, Lindkvist *et al.* showed that in patients with T2D, fecal elastase-1 concentration positively correlated with 25-hydroxy vitamin D [27]. Finally, one important point of discussion relates to the threshold of fecal elastase-1 concentration that defines pancreatic exocrine insufficiency. Traditionally, a concentration < 100 μg/g is said to be diagnostic of exocrine failure and values > 200 μg/g are considered normal [37, 38]. More recently, due to the lack of sensitivity and specificity of the test in certain conditions [39–41], the American guidelines have suggested that a concentration < 50 μg/g should be considered diagnostic of exocrine insufficiency [42], and a threshold of < 15 μg/g has even been suggested [43]. If these different thresholds were applied to our population, between 0.2

Table 3. Percentage of patients with fecal elastase-1 concentration below several thresholds.

	Pancreatogenic diabetes (*n* = 27) (%)	Type 1 or -2 diabetes (*n* = 467) (%)
Elastase-1 concentration		
< 200 µg/g	93	25
< 100 µg/g	81	15
< 50 µg/g	74	9
< 15 µg/g	67	0.2

and 25% would be considered to have exocrine insufficiency, as compared to 67–93% of the patients with PD (Table 3). This may explain the relatively mild pattern of nutritional deficits in the patients with T1D or T2D and low elastase concentration. If a criterion of Elastase-1 < 50 µg/g is applied, about 10% of patients with diabetes would be considered to have exocrine insufficiency. This may be important to consider not only in the context of fat-soluble vitamin deficiency, but also with regard to hypoglycaemia [22].

Conclusion

In patients with type 1 or type 2 diabetes and exocrine dysfunction, modest nutritional alterations can be observed. Indeed, BMI was lower in patients presenting with type 2 diabetes, low fecal elastase-1 concentration, and low fecal chymotrypsin activity than in patients with type 2 diabetes and normal pancreatic exocrine function. Moreover, patients with diabetes and exocrine dysfunction presented more frequent vitamin A and E deficiencies and severe vitamin D deficiency than patients without pancreatic exocrine dysfunction. Hence, patients with type 1 or type 2 diabetes and altered pancreatic exocrine function should be screened for nutritional deficiencies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. All investigations were performed in the context of routine patient's care.

Ethical standard statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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2

Treatment options for covert hepatic encephalopathy

Sahaj Rathi, Radha K. Dhiman

Abbreviations

AASLD	American Association for the Study of Liver Diseases
BCAA	Branched-chain amino acids
CFF	Critical flicker frequency
CHE	Covert hepatic encephalopathy
EASL	European Association for the Study of the Liver
HE	Hepatic encephalopathy
LOLA	L-Ornithine L-aspartate
MELD	Model for end-stage liver disease
MMSE	Mini-mental state examination
OHE	Overt hepatic encephalopathy
PHES	Psychometric hepatic encephalopathy score
PSS	Portosystemic shunt
SBP	Spontaneous bacterial peritonitis

Clinical vignette

Case 1

A 45-year-old male with a history of ethanol-related cirrhosis for the past 3 years presented for routine follow-up. He was doing well on medical management and had no episodes of overt encephalopathy, ascites, jaundice, or variceal bleeding. His only complaint was a feeling of fatigue. Upon questioning he admitted being "a little careless" lately. He had been in a minor traffic accident last month due to inattention. Family members reported him to be a "very careful" driver in the past. Clinical examination was unremarkable except a palpable spleen. His

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mini-mental state examination (MMSE) was normal, and he could perform simple calculations. His Child-Pugh score was 6/15 (Child class A), and MELD score was 8. A psychometric hepatic encephalopathy score (PHES) battery and critical flicker frequency(CFF) test were done under a study protocol, which revealed evidence of covert hepatic encephalopathy (CHE) (PHES −8; CFF 34/s).

Case 2

A 64-year-old lady with cryptogenic cirrhosis for the past 2 years, which has been well compensated, was admitted for Colles' fracture. She had history of another fall a couple of weeks back which led to a knee bruise. There was no history of behavioral changes or disorientation. A detailed neurological examination including MMSE was unremarkable. Her Sickness Impact Profile-Covert Hepatic Encephalopathy (SIP-CHE) score was 2, indicating covert HE. She also performed poorly on the animal naming test (10 in 1 min). Covert HE was confirmed by administering PHES battery.

Hepatic encephalopathy (HE) is one of the most troublesome complications of cirrhosis. It affects a majority of patients at some point during the course of disease. The spectrum of neurological involvement is diverse, ranging from subtle cognitive changes to deep coma. Based upon the severity of neurological deficit, HE has been subdivided into overt and covert. Overt HE is when the encephalopathy is evident on a physician evaluation. Patients with more subtle cognitive changes inapparent on a routine clinical examination are categorized as covert HE—a term which includes both minimal HE and Grade I HE of the West Haven scale.

Covert HE (CHE) may be seen in 30–84% patients with cirrhosis [1]. Cognitive defects in these patients include inattention, impaired visuomotor coordination, and impaired working memory. These changes result in poor quality of life, driving difficulties, accident proneness, and workspace problems [1]. Patients with CHE are more likely to develop progression of cirrhosis, episodes of overt HE, and mortality [2, 3]. The implications are not limited to the patient, as CHE is also associated with an increased burden on the caregivers [4]. However, this condition is highly under-recognized and undertreated due to the paucity of evident symptoms and absence of standard definitions. The diagnosis of covert HE is based upon specialized neurocognitive testing.

Treatment of CHE predominantly revolves around lowering ammonia levels, even though neuroinflammation and oxidative stress too contribute to CHE. Agents that reduce ammonia include nonabsorbable disaccharides, antibiotics, ammonia scavengers, nutritional modulation, and probiotics. However, unlike overt HE, trials in covert HE are relatively limited.

Nonabsorbable disaccharides

Nonabsorbable disaccharides like lactulose and lactitol have been the mainstay of therapy in patients with hepatic encephalopathy for decades. They lead to reversal of CHE as evidenced by

improvement in psychometric scores, thereby improving health-related quality of life. They also prevent development of overt episodes of hepatic encephalopathy [5–7]. In a placebo-controlled trial, treatment with lactulose for 3 months led to reduction in the number of abnormal neurophysiological tests and improvement in quality of life [6]. The use of lactulose has been considered cost effective in preventing motor vehicle accidents in the United States [8]. However, the existing evidence does not yet support improvement in driving performance with lactulose.

The major side effects of this drug include diarrhea, bloating, and nausea. Most studies from the Eastern parts of the world report very low rates of drug discontinuation due to side effects, while these numbers may be up to 28% in the West [9, 10]. These side effects are usually dose dependent, and can be minimized by titrating doses to achieve two three soft stools per day. We have recently shown that sociocultural factors play a major role in patient acceptance of lactulose and perception of its side effects. We projected risk-benefit scenarios of chances of developing OHE against expected side effects of lactulose to two cohorts of patients, one each from India and the United States. Indian patients were much more likely to accept lactulose even if the risk of OHE was low, probably as twice-a-day stool frequency is considered acceptable in India [11].

Antibiotics

Rifaximin has replaced metronidazole and neomycin as the antibiotic of choice in the management of HE. It is a nonabsorbable antibiotic which modulates gut flora and improves dysbiosis. Moreover, rifaximin has not been shown to induce resistance in the intestinal flora, and has very rarely been associated with *Clostridium difficile*-associated diarrhea [12].

Rifaximin has been effective in the improvement of psychometric scores, thereby reversing CHE. It also improves quality of life and driving performance in patients with CHE. It is usually well tolerated, and drug discontinuation is rarely required [13, 14].

Probiotics

The ratio of autochthonous to non-autochthonous flora significantly affect ammoniagenesis. Probiotics have been shown to improve HE by reducing gut dysbiosis. Both pharmaceutical probiotic preparations and commercially available probiotic yogurt have been studied in this regard [15, 16]. These have been successful in reversing CHE and improving quality of life while being well tolerated by most. A recent meta-analysis suggested that probiotics led to improvement in CHE and reduced recurrence of OHE [17].

Ammonia scavengers

L-Ornithine-L-aspartate stimulates urea cycle and glutamine synthesis in the periportal hepatocytes and skeletal muscles, consuming ammonia in the process. It has been effective in reversal of CHE, improving quality of life, as well as prevention of OHE [7, 18].

Nutrition

Cirrhosis is a state of accelerated starvation as a consequence of depleted hepatic glycogen stores, deficient muscle stores due to sarcopenia, and systemic inflammation. As a result, a majority of patients exhibit features of malnutrition [19]. Protein restriction in patients with encephalopathy is not recommended anymore. Cirrhotic patients seem to have better cognitive function in a fed state as opposed to a fasting state despite higher ammonia levels in the latter [20]. A recent trial demonstrated that patients compliant with a diet of 30–35 kcal/kg/day energy and 1.0–1.5 g/kg/day vegetable protein intake showed reversal of CHE and improvement in quality of life. This effect was more pronounced in patients with early cirrhosis [21]. The use of branched-chain amino acids as dietary supplements has also been associated with CHE reversal and increased muscle mass [22].

Shunt closure

Presence of spontaneous portosystemic shunts may predispose cirrhotic as well as noncirrhotic patients for CHE. This has been demonstrated in patients with extrahepatic portal venous obstruction and noncirrhotic portal fibrosis where evidence of cognitive deficit is present despite normal hepatocellular synthetic function [23, 24]. However, currently there is neither evidence nor recommendation to suggest occlusion of these shunts in such situations for CHE.

Fecal microbiota transplantation (FMT)

Gut microbiota modulation with antibiotics and pre/probiotics has long been used for treatment of HE. An attempt to modulate gut microbiome with FMT made in a patient with CHE who was unable to afford standard therapy showed improvement in cognition with FMT [25]. Thereafter, a randomized controlled trial showed lower rates of HE recurrence and improved cognition in patients who received FMT, while there was no change in the overall MELD score. Moreover, the FMT group had lower frequency of severe adverse events. However, larger, well-controlled trials are needed to establish safety and efficacy before FMT can be recommended as a treatment option [26].

Approach considerations

A paucity of studies in general, and well-controlled head-to-head trials in particular, limit informed decision-making when choosing the appropriate agent and duration of therapy in patients with CHE. Considering this, we recently conducted a network meta-analysis to compare the efficacies of all available agents. Such analysis can give meaningful comparisons between pharmaceutical agents which have not been compared head to head, with the help of appropriate statistical tools. In this study, rifaximin and lactulose were found to be the most effective agents for reversal of CHE [27].

Whether all patients with CHE need treatment is a matter of debate among the experts. Whereas many studies support treating CHE by demonstrating improvement in quality of life, cognitive function, and driving performance, the heterogeneity in the diagnostic criteria used, short follow-up, and lack of clinically relevant endpoints limit the significance of this evidence. The 2014 EASL-AASLD guidelines do not recommend treatment of CHE routinely due to a paucity of robust evidence of benefit. This conclusion was derived largely based on studies about MHE. Nevertheless, the negative implications of CHE on the quality of life, work performance, driving, and caregiver burden are well described. While patients categorized as grade I HE may be treated routinely, the decision of treating those with minimal HE is better taken on a case-to-case basis after a thorough discussion with the patient. The anticipated benefits have to be carefully weighed against the adverse effects of medications and cost of therapy. Patients who drive for a living, operate heavy machinery, have a history of accidents/falls which can be ascribed to inattention, or complain of reduced work productivity may be routinely treated.

No recommendations exist on the duration of treatment in these patients. Most studies have continued treatment for 3–6 months. However, follow-up data is not available for these patients. A recently published research followed up patients for 6 months after 3 months of lactulose or rifaximin therapy. They found that over half of the patients, who initially had resolution of CHE, had an episode of OHE or developed CHE again after discontinuation [28]. As the underlying disease persists, it may thus be prudent to continue the therapy indefinitely or until tolerated in order to maintain the non-encephalopathic state (Fig. 1).

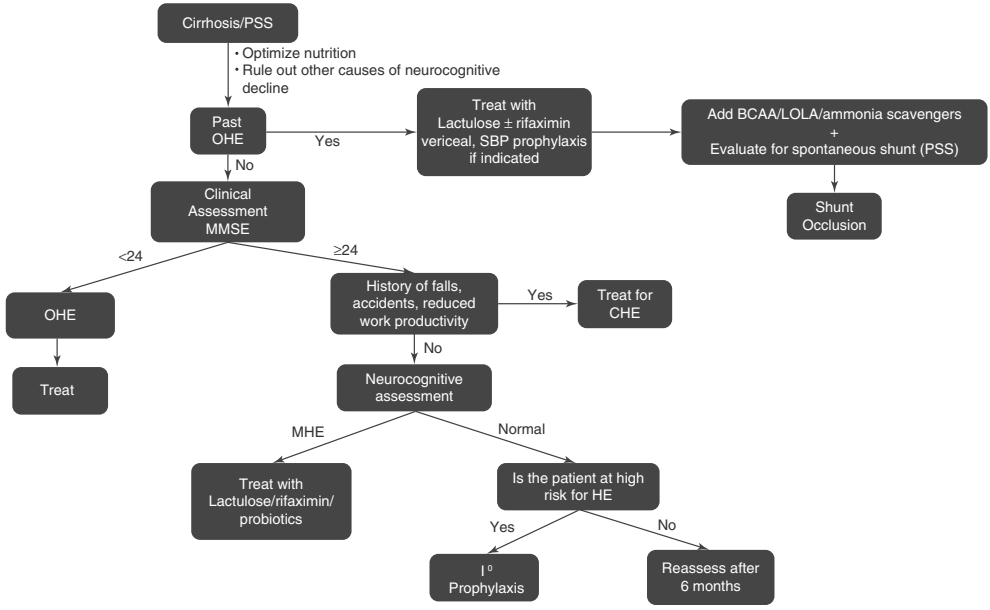

Fig. 1. Algorithm for outpatient management of hepatic encephalopathy. *BCAA* branched-chain amino acids, *LOLA* L-ornithine L-aspartate, *MMSE* mini-mental state examination, *PSS* portosystemic shunting, *SBP* spontaneous bacterial peritonitis. Source: From Ref. [29]

Clinical vignette: follow-up

Case 1

The patient was started on appropriate nutritional therapy with high-protein (vegetable and casein based) diet ~1 g/kg/day, and energy intake of ~35 kcal/kg/day. Rifaximin 550 mg twice daily was started as the patient was unwilling for lactulose therapy. The patient was reassessed 3 months later. He reported feeling more energetic. His psychometric scores and quality-of-life parameters improved. However, there was no change in the Child-Pugh or MELD scores. He has not had any further accidents since the beginning of therapy, and is tolerating the therapy well.

Case 2

The patient underwent surgical fixation of the fracture. After the surgery, her nutrition was optimized with a high-protein and high-calorie diet (as in Case 1). In addition, branched-chain amino acids were supplemented. On follow-up 3 months later, she had no further falls, reported subjective improvement in well-being, and showed an improvement in her PHES score.

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3

Management of hepatic encephalopathy not responsive to first-line treatments

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Keywords: Hepatic encephalopathy, Spontaneous portal-systemic shunts, Precipitating factors

Abbreviations *HE* hepatic encephalopathy, *TIPS* transjugular intrahepatic porto-systemic shunt, *SPSS* spontaneous portal-systemic shunt

Abstract

Purpose of review: Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that occurs in up to 30% of patients with cirrhosis. HE may be a consequence of pure liver failure, as in patients with fulminant hepatitis, or of the combination of liver failure and portal-systemic shunting, as in patients with liver cirrhosis. Episodes of HE are usually related to precipitating events, such as infections or gastrointestinal bleeding; a minority of cirrhotic patients experienced a chronic HE, refractory to standard medical treatment. The prevention of HE recurrence, after the first episode of HE, could be obtained by the administration of prophylactic therapy with lactulose, rifaximin or a combination of both. The aim of this review is to clarify some key points in the management of cirrhotic patients with HE, not responsive to first line treatment.

Recent findings: Recent studies investigated the role of fecal microbiota transplantation in the treatment of HE with promising results, but further investigations are needed.

Summary: In a cirrhotic patient with acute cognitive impairment, the correct diagnosis of HE, after excluding other causes of neurological diseases, is mandatory for the correct management

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of the precipitating factors and for the treatment. In patients not responsive to standard treatment, the probable precipitating factors have not been correctly identified, multiple precipitating events are coexisting or a new precipitating event is superimposed.

In some patients with recurrent HE, characterized by persistent alterations in neurological symptoms, without specific precipitants events, the presence of spontaneous or iatrogenic shunts should be investigated.

Introduction

Hepatic encephalopathy (HE) is a neurological syndrome, frequent in patients with liver cirrhosis, characterized by a complex spectrum of nonspecific neurological and psychiatric manifestations severely affecting the life of patients and caregivers. The prevalence of overt HE fluctuates between 10% in compensated cirrhosis and 50% in patients with a transjugular intrahepatic portosystemic shunt (TIPS) [1, 2••]. According to the recent guidelines [2••], HE could be *episodic*, reversible in a few days, *recurrent* with two or more episodes over a period of 6 months, and *persistent* with a chronic alteration in mental status. Another relevant distinction is between *spontaneous* and *precipitated HE*, the latter induced by a specific event (bleeding, infections, constipation, etc.); in these patients, the rapid identification of the precipitant and its correction is essential for the regression of HE [1, 2••]. Concerning the *pharmacological treatment*, as suggested by International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) guidelines [1], lactulose represents the first choice for treatment of episodic HE, whereas rifaximin is considered and suggested as an effective add-on therapy to lactulose for prevention of HE recurrence. Oral branched-chain amino acids and L-ornithine L-aspartate (LOLA) can be used as an alternative for patients nonresponsive to standard therapy. Moreover, support *nutritional intake* should be preserved as further explained.

Thus, from a practical point of view, a patient with overt HE should be promptly treated to induce the resolution of the symptoms. Once it has been achieved, the clinical goal should be the effective prevention of further episodes. As a consequence, patients could be non-responders to the treatment of the HE episode or non-responder to the prophylactic treatment aimed at avoiding the occurrence of further HE episodes.

Management of unresponsive episodic HE

The strategies for the management of episodic HE are summarized in Table 1. In patients not responding promptly to this approach, three possible hypotheses can be made: 1) the diagnosis of HE is not correct and a differential diagnosis should be reconsidered to take into consideration other causes of cognitive impairment; 2) the precipitating factors have not correctly identified; 3) multiple precipitating events coexist in the same patient or a new precipitating event is superimposed.

Table 1. Treatment strategies in cirrhotic patients with episodic HE.

General supportive care
Prevent falls or body harm in disorientated patients
Take care of bladder and bowel function
Take care of intravenous lines
Monitor fluid balance
Monitor blood glucose and electrolytes
Monitor arterial blood gases
Correct acid/base disturbances
Monitor blood pressure
Avoid aspiration pneumonia
Prevent causes of sepsis
Support nutritional needs
Energy intake of 35–40 kcal/kg body weight/day and protein intake of 1.2–1.5 g /kg body weight/day are recommended [1, 2••].
In patients with severe hepatic encephalopathy (grades III–IV), solutions with an increased content of branched-chain amino acids and reduced amount of aromatic amino acids can ameliorate neurological symptoms, ensuring adequate protein intake.

The algorithm to exclude neurological disease other than HE has been previously reported [3•] and should be carried out in all patients with HE and repeated in non-responders. Moreover, of great importance is also the identification of the precipitating events.

Management of HE not responsive to first-line treatment

The search of a precipitating event, both new or superimposed, should be carefully evaluated in case of patients with recurrent bouts of overt HE, even assuming secondary prophylaxis. In some cases, multiple precipitating events may coexist in the same patient and the failure to identify and correct all the precipitating factors can lead to a difficult management of HE. Recently, Pantham *et al.* identified different concurrent precipitating factors in patients with overt HE requiring hospitalization [4].

Table 2 summarizes the prevalence of precipitating events reported in published randomized controlled trials (RCTs) on episodic HE treatment. *Infections* represent the most common precipitating event; thus, in all patients with non-responsive HE, it is mandatory to perform a bacteriological screening to exclude infections. In some cases, infections, such as spontaneous bacterial peritonitis (SBP), may be asymptomatic and require specific procedures to be detected, as further explained. *Gastrointestinal (GI) bleeding* should be considered in case of ongoing anemia at serial hemoglobin measurements and/or in the presence of overt GI. *Dehydration* can occur in patients with cirrhosis and overt HE because of multiple events, including reduced fluid intake, diuretic use, and lactulose-related diarrhea. In addition to dehydration, *hypokalemia* and/or *hyponatremia* are common electrolyte disturbances

Table 2. Published randomized controlled trials on episodic hepatic encephalopathy treatment.

Precipitant(s)	Simon-Talero [5]	Sharma [6]	Sharma [7]	Rahimi [8]	Sidhu [9]	Bajaj [10••]	Total
Diuretics/dehydration (case n)	36	-	-	29	39	-	104
Constipation (case n)	22	23	19	8	94	1	167
Electrolyte disturbance (case n)	-	12	10	4	39	1	66
Gastrointestinal haemorrhage (case n)	-	28	27	6	12	1	74
Infections (case n)	25	40	43	10	57	1	176
Total preceding events/total points	83/56	103/120	99/120	57/50	241/193	4/20	587/559

and should be corrected appropriately. Use of *psychoactive medicines* such as opioids and benzodiazepines should be searched and discontinued, and a urine toxic screen should be considered in all patients. *Alcohol withdrawal* is identified by the presence of a series of typical clinical manifestations such as rhythmic tremor, excitability, and autonomic disturbances such as tachycardia and hypertension associated with diaphoresis. In patients with severe overt HE who are unresponsive to treatment, the *possibility of underlying traumatic brain injury must* be excluded by a careful history, neurologic examination, and brain imaging. For example, alcohol use and chronic liver disease can increase the risk of subdural hematoma [11, 12] mimicking overt HE and often accompanied by focal neurologic signs that may be difficult to detect in severe HE. Brain imaging should be considered in patients with severe overt HE; imaging is mandatory if lateralizing signs are present. Finally, *meningitis* and *encephalitis* should be included in the differential diagnosis for patients who do not respond to conventional treatment.

Following the identification of new or superimposed precipitant(s), the best treatment strategy is therefore represented as follows:

General supportive care and *nutritional intake* should be preserved, as reported in Table 1.

Treatment of the precipitating event: a) Stop GI bleeding with drugs, endoscopic therapy or TIPS, correcting severe anemia with blood transfusion; b) treat infections (urinary tract, blood, lung or SBP) with specific antibiotic therapy; c) discontinue exogenous sedatives; d) discontinue diuretics in case of electrolyte abnormalities or deterioration of renal function and correct electrolytes and dehydration if necessary; e) perform a bowel enema in case of constipation; f) discontinue nephrotoxic drugs; g) treat alcohol abstinence syndrome. In case of concomitant brain injury, cooperation of the neurologist/neurosurgeon is recommended.

Management of patients not responsive to prophylactic treatments

After the resolution of the HE episode, the clinical problem is how to prevent its recurrence. Recent RCTs showed that this target could be obtained by the administration of lactulose [13], rifaximin or a combination of both [14].

Patients with recurrent or persistent HE are characterized by chronic neurological symptoms, often without a precipitating event [2••], high levels of ammonia and electrophysiological abnormalities. Paradoxically, these patients may have a relatively mild hepatocellular disease without signs of portal hypertension (absence of ascites and varices) that contrasts with the severity of the mental status. In these patients, the persistence of HE may be sustained by the presence of large spontaneous portal-systemic shunts (SPSSs) [15•,16] that increase the bioavailability of intestinal ammonium, increasing the risk of HE. A recent retrospective study identified SPSSs in 60% of 1729 cirrhotic patients that underwent radiological screening [17] and our group demonstrated the presence of SPSSs in 71% of cirrhotic patients with chronic HE, non-responsive to lactulose and rifaximin [15•]. In these patients, the embolization of SPSSs usually improved neurological symptoms and reduced the incidence of HE after the procedure.

Another group of patients at high risk to develop recurrent or persistent HE refractory to standard treatment is represented by cirrhotic patients submitted to a TIPS. TIPSs have been used for more than 25 years to treat complications of portal hypertension [18]; the main problem in the management of patients submitted to this procedure is the development of overt HE [19, 20]. Persistent HE refractory to standard treatment occurs in 5–10% of patients submitted for a TIPS. In these cases, the occurrence of HE may need several hospitalizations and can be treated by reducing the diameter or by occluding the stent [21, 22], unfortunately reducing the patient's quality of life. A TIPS should be revised when a causal relationship between the shunt and HE is suspected, when HE occurs within a few weeks or months after the TIPS, or when the procedure leads to a significant reduction of portal-systemic gradient. This supports the hypothesis that excessive portal blood diversion is responsible for HE and, on the contrary, a TIPS should not be revised in patients with persistent HE due to liver failure. The complications of portal hypertension, such as ascites or varices, may recur as a consequence of shunt reduction; so, the decision to revise the stent requires caution.

As already said, TIPS reduction or shunt occlusion is not always successful in controlling HE; in non-responsive patients, liver transplantation remains the ultimate treatment. The main studies reporting the effect of spontaneous shunt occlusion or TIPS revision in patients with chronic/recurrent refractory HE are reported in Table 3.

Another therapeutic option in patients with recurrent HE not associated with TIPS or shunts may be fecal microbiota transplantation (FMT); patients with HE have, in fact, disrupted gut microbiota, partly driven by frequent antibiotic and lactulose use, which results in further HE recurrence [32]. To support this hypothesis, Bajaj *et al.* conducted an RCT to compare FMT to standard of care (SOC) treatments (lactulose and rifaximin) in safety, neurocognitive, microbiota and metabolomic changes [10••]. In the FMT arm, compared to the SOC arm, there was a lower incidence of serious adverse events and of HE episodes and there was also a significant improvement in neurocognitive tests, not observed in the SOC arm. These promising results need to be confirmed in further larger cohorts of patients.

Table 3. Main studies reporting the effect of spontaneous shunt occlusion and TIPS revision in patients with chronic/recurrent refractory HE.

Studies	Type of radiological intervention	Number of points with refractory HE/ treated with shunt occlusion/revision	Child-Pugh class	Number of points improved	Adverse events after shunt occlusion
Laleman W 2013 [23]	Shunt embolization	37/37	B/C	29	Varices 19 (de novo 2), ascites 15 (de novo 6), bleeding 1
An J 2014 [24]	Shunt embolization	17/17	B/C	10	Ascites 3, varices 8, bleeding 0
Gwon D 2015 [25]	Shunt embolization	16/73	B:13 C: 3	16	Ascites 5, varices 4, bleeding 0
Mukund A 2017 [26]	Shunt embolization	17/22	B/C	16	Ascites 16, varices 5, bleeding 1
Bureau C 2017 [27]	TIPS revision	1/29	C:1	1	–
De Santis A 2016 [28]	TIPS revision	2/38	B:1 C:1	2	Ascites 1, bleeding 1
Nardelli S 2016 [29]	TIPS revision	3/82	B:1 C:2	3	–
Cookson DT 2011 [30]	TIPS revision	8/NR	B:3 C:5	5	Bleeding 3, deaths 2
Fanelli F 2009 [31]	TIPS revision	12/189	A:1 B:5 C:6	12	Ascites 1, OLT 1, deaths 4

Compliance with ethical standards

Conflict of interest
Silvia Nardelli, Lorenzo Ridola, Stefanie Gioia, and Oliviero Riggio declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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Future of leadership in healthcare business: a global perspective

Nicolas M. Casati, Kartik Kesavabhotla, George R. Cybulski

Concentrated are my senses with the joy I feel—Humming Horizons.
by Dr. Bharat S. Thakkar

Introduction

The human factor

Unlike a corporate manager looking at a company from top to bottom out of necessity, a leader leaves the 99 others in safety while searching for the lost one, endlessly trying to solve this inequation. Note that the manager title is not in question here, but that the manager should be a good leader. An example of a good leader is Bob Chapman. Chief Executive Bob has a mandatory furlough program: no layoffs went into effect during a corporate crisis, because talent was a priority over profits and they had hired the right people from the start. Dr. Kolenda further illustrated this with inspirational leadership to describe making the choice of both conviction and open-mindedness. That choice leads to the causality of open-mindedness ending in good judgement, which employees perceive as a leader's purpose. A leader precedes the team towards risk and takes the first and hardest hit, while the old-style manager runs away from risk, letting the team face risk first (Fig. 1). The old-style manager acts by adding or subtracting the human factor as needed (Fig. 1). The leader-manager antagonism is a question of semantics, meaning it is not because one is a manager that they are not a leader and conversely. It is not the title, but the leading with purpose that counts, i.e. inspirational leadership.

Continuing education

The necessity to be financially prepared for any situation with inspirational leadership is why leadership in Continuing Education and an Employee Emergency Fund is necessary. This fund is

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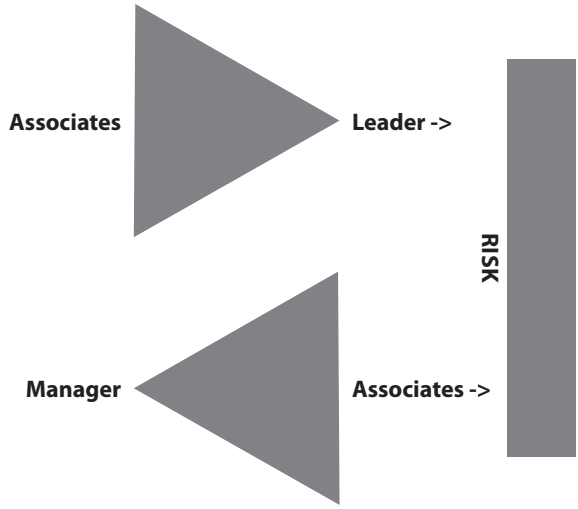
Fig. 1. Facing risk differently



available to all levels of the organization (a $4 million fund for a $953 million operation). Every Continuing Education project, every employee suggestion should be implemented, after careful deliberation. Below are three ideas which should be considered. The remanufacture of surgical instruments made of plastic within the hospital itself, because plastic keeps the integrity of the sterile field but ends up in landfills. This plastic could be remanufactured using a model-20a plastic injection machine (this would need FDA 510k premarket notification, AAMI, OSHA…, etc., approval). Knowledge tested with S.T.R.E.A.M. (science, technology, robotics, engineering, art, and mathematics) will demonstrate viability of the idea. Most centers use inordinate amounts of plastic and just dispose of it. The only wastes typically separated on site are bio-hazard, chemical, sharps, and pharmaceutical wastes.

A second area, which needs heavy continuing education investments, especially in the medical field due to Health Insurance Portability and Accountability Act contingencies (HIPAA), is training of personnel in computer use. Anti-virus, anti-spyware, firewall, intrusion detection systems, intrusion prevention systems, and other tools will prevent hundreds of thousands of dollars in technical repair costs, and these extra costs are not factored into the typical corporate balance sheet. Companies need to protect themselves from malware, adware, spyware, ransomware, Trojan horses, logic bombs, and worm viruses, but also from rootkit, bootsector, executable, macro- and polymorphic viruses. This is why the Computer & Telecommunications budget line item for a neurosurgery outpatient clinic should have at least a 1.5 million dollar budget for a 953 million dollar operation. At the risk of being pleonastical and dithyrambic, formal and informal leadership skills to protect the company are important in all organizations and at all levels.

A third area which needs the assistance of an Employee Emergency and Continuing Education Fund is teaching employees about finance, beyond their retirement plan. Global finance leaders are faced with competitors who have seemingly boundless appetites for future growth, often aided by Federal Reserve mandated quantitative easing (QE). Growth accompanied quantitative easing, Kashyap, Berner, and Goodhart (2011) posit has no real effect on the economy domestically:

"benefits of more QE now seems small" (Kashyap *et al.*, 2011). Economists like Kashyap have shown that crisis can be caused by "Firesales" in an era where every business is about growth (Kashyap *et al.*, 2011).

Some things should be decided using wisdom. Wisdom like the proposed "Basel III reforms" (Kashyap *et al.*, 2011). A Firesale is a "forced sale of an asset at a dislocated price" and in the case of a hospital, it is better to be good financial stewards than face a situation where everything must be sold (Kashyap *et al.*, 2011).

Healthcare leaders know that, in the face of these crises described in the previous paragraph, "value in health care has been defined as health outcomes for the patient per dollar spent" and as we will see later on, Dr. Shetty is a gold standard for this (Smith, Rambachan, Cote, Cybulski, & Laws, 2015). Future value in healthcare is contingent upon value based medicine, reimbursement and patient satisfaction according to several senior managers informally interviewed. According to other healthcare finance leaders, preventative medicine, could keep patients from entering a health system emergently in the first place. Nothing is simple in healthcare, which is highly regulated by the government, much like launching rockets to the international space station.

Management style

The insightful CEO of SpaceX and Tesla Elon Musk, for example, has an unorthodox management style, which implies a disdain for ritual or orthopraxy (Fig. 2). Musk is admired for his ipseity. He finds partners who share this selfhood. This selfhood becomes a corporation, and Musk's partners, who know how to obtain him government funds, end up creating exposure and viability to what was just a dream (a dream like launching Falcon Heavy with Space X). Most importantly, he personally delegates ideas—a leader of leaders if you will (e.g., the Hyperloop whitepaper, which Richard Branson picked up by founding Virgin Hyperloop 1). The Process Improvement budget and Continuing Education budgets often overlap, because their common goal is to help employees self-improve. In Fig. 2, there can only be one dreamer (Lead Engineer) per project and similarly, there can only be one contract (Venture Capitalist or Angel Investor) funding each project. If the project is complex, then subcontracting comes into play.

A equalitarian business plan

Ideas are presented in this chapter using Musk's First Principles approach to problem solving. Ideas for the chapter were inspired by a Midwestern Academic Medical System with 28 specialties and

Fig. 2. Elon Musk's problem-solving approach

7 subspecialties in neurosurgery with a 153% calculated increase in assets and liabilities between 2014 and 2015. The average rate of 153% growth was extrapolated. This 153% growth rate excludes property, which according to market analysis for 2017 grows in value nationally by an average of 4% per annum. A typical building costs $225 million to erect according to estimated cost in 2014 (or year 1 of the budget). According to Phillips (2012), 4–5% of the budget should be reserved for Process Improvement (Phillips, 2012). Phillips posits that a "comprehensive measurement and evaluation process, including ROI, can be implemented for about 4 or 5% of the direct program budget" (Phillips, 2012). Process Improvement projects are now ubiquitous, as we saw earlier with A+ certification training, finance and working with remanufactured plastic (Adrianzen, 2014). Process improvement will be funded out of the "salaries, benefits and other costs" budget of 28 million dollars. An estimated 4 to 5 percent of 28 million dollars is 1.5 million dollars. This is in addition to the computers and telecommunications budget of 1.5 million dollars and the continuing education and employee emergency fund of 4 million dollars, for a $953 million operation. Increasing expenditure for plastic equipment from ten thousand dollars (knowing a single robot arm approximately costs $1,000) to two hundred thousand dollars per year in year 8 and that robot maintenance fee is $100,000 (out of the general budget of $225 million). Plastic acquired should be reused in its entirety (at the end of 8 year growth plan). An illustration of the surgical process of an outpatient neurosurgical unit is shown in Fig. 3. This is the patient experience once scheduled for surgery using software called EPIC OpTime.

Figure 3 is linear to illustrate a daily routine, however, this daily routine repeats itself and inscribed into other multiple steps (e.g., Surgeons make incisions for the robot arms to fit through and Scrub Technicians insert and retrieve Mazor Robotic arms before and after surgery). In regards to the sterile reprocessing steps it is suggested to use a Model 20a plastic injection machine to remold Mazor Robotic arms in-house and then to put them through a decontamination and sterilization cycle. The reason for multiple steps missing from this diagram is that the current job description of a Sterile Processing Technician is to decontaminate, assemble trays and sterilize. Decontamination, tray assembly and sterilization could be done using Kiva® robots which would move trays across the department floor. Kawasaki MC004N robot arms could be used to assemble surgical trays and then take them in and out of a sterilizer. Sterile Processing Technicians would then have available time to remanufacture a selection of Mazor Robotic arms with variable distal tips such as, needle holders, retractors, forceps using plastic and polypropylene—for metal like properties. Metal scissors, cauterizing tools and telescopes for example, are part of a selection of

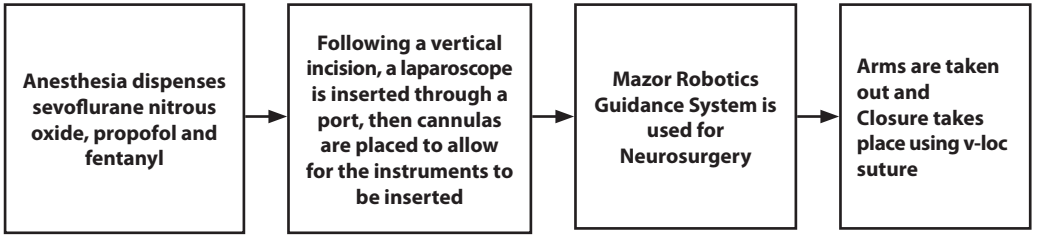


Fig. 3. Robot surgery flowchart

items which cannot be remanufactured by simply remolding. Purchasing even a single Mazor Robotics Renaissance® Guidance System at a ticket price of $849,000.00 needs planned ROI before putting in for a requisition. In this case, it might be a good option to consider leasing capital equipment with a short-term lease agreement. Looking at the numbers in Table 1, it is possible to see that there is close to statistically significant data with close to 7% of unsuccessful screw placement attempts according to Hu, Ohnmeiss, and Lieberman (2013) showing that robotic surgery can be unsuccessful in only 7 cases in this large study. 110 screws still had to be placed manually, so a surgeon will still have to be present. This is very statistically significant, but improvements can be made towards making never events not statistically significant.

Table 1. Screw placement statistics according to Hu *et al.* (2013).

Number of patients with robotic guided arm successful screw placements	*Number of patients with robotic guided arm unsuccessful screw placements*	*Total number of screws placed*	*Number of screws not placed correctly using robotic guided arm screw placements*	*Robotic guided arm screw placement aborted, screws placed manually*
95 patients	7 patients	949	11	110

It would be ideal from a business standpoint to invest in retraining humans *and* buy robots which both together grow corporate equity versus a layoff and buying government low-risk bonds with the proceeds from the layoff. While human resources and equities increase exposure to risk, they grow the economy if used wisely. The operative word is *wisely* because if [a company is] unwisely managed, Kashyap *et al.* (2011) predicts "Firesales". Global leaders of the future will have to face the challenge of staying in command of the derivatives market (since the derivatives market is the largest market estimated in the quadrillion dollar range). It is important to create technology overrides (technologies like FinBots or other automations in pursuit of capital gains are dystopic when compared with bank employees' job description in the 1990s, according to one of the co-author's experience). In the case of Mazor Robotics Renaissance® Guidance System, the consequences, if the robot were to receive instructions from another computer than the one intended, would be dire. No matter how much automation, there will still be a need for human leadership (e.g., a Neurodiagnostic Technologist). The budget, for a $953 million operation in year 1 at $28 million, accounts for forecasted personnel, call-off costs, but other human resources costs as well (see Table 2). This table is not exhaustive.

Table 2. Staffing for an outpatient neurosurgery center.

Scrub tech/circulating nurse	Sales representative
Attending neurosurgeon	Radiologist
Attending anesthesiologist	Engineer
Pharmacist	Risk management
Sterile processing technician	Neuro-diagnostic technologist
Inventory technician	Information technologist
Safety officer	Quality leader
Process improvement leader	Analytics leader

Economic externalities

Leadership deals with non-traditional economics, i.e., externalities. Leadership teams have to adapt to the challenge of business synergies often involving economic externalities, such as controlling future, quality outliers, but also some hard sciences like S.T.R.E.A.M and controlling safety of care, effectiveness of care, decreasing mortality, decreasing readmissions, timeliness of care, improved radiological imaging (qure.ai) and cost of providing this care. The rate of change is directly proportional to how fast futuristic ideas are available, unfettered by patents (Intellectual Property should still be considered as a commodity). Externalities are in effect an unchosen cost to a corporation and the categories of unchosen costs are always increasing. To succeed, an endeavor has to have multi-team contingency theories to reach the common corporate objective, without being deleterious to the bottom line, basically an externality with a tolerable margin of risk.

Leaders track costs, multi-disciplinary teams, exponential rates of changes in technology as well as externalities. All of these factors pale in comparison with the global leader's primary challenge of creating a better patient experience in the future of healthcare. Global healthcare leaders are bringing lean leadership into the hospitals by challenging leaders to go lean and go green (the 5S of Sort, Straighten, Shine, Standardize, Sustain). In short: more work, less staff.

Leaders track costs: the end goal of the 5S. From the perspective of leadership in the next decade and beyond, leaders track costs and one of the leading costs is real estate. A solution to real estate is 3-D printing Dahir Insaat-type buildings (this idea is still at the concept stage, but it would surely put a dent into the estimated $225 million initial investment to build an urban outpatient pavilion). The alternative is leasing. Real estate is not the only big-ticket cost in healthcare. The fight for reimbursement is in the five digits per person in healthcare cost in the USA alone, compared to European countries with healthcare costs per person per year in four digits. With 11 options available for healthcare in the USA and a few international plans (see Appendix A), healthcare challenges presented to the global leaders of the future in regard to reimbursement can represent hundreds of billions in unnecessary costs.

Reimbursement

Reimbursement is partially a problem due to an outdated procurement cycle dependent on clearing of checks and availability of deposits. In the future, Blockchain (Bitcoin, Litecoin, Ethereum…, etc.) will simplify the procurement cycle by using blockchain without use of an FDIC bank, because blockchain is tamperproof (Umeh, 2016). The world market itself is simplifying with the advent of Canadian-European agreements such as CETA, Asian-European agreements such as JEFTA (EU-Japan) and EVFTA (EU-Vietnam) as well as TTIP (Transatlantic trade and investment partnership). The banking system is still old fashion, due to cyber security and batching. Cybersecurity and batching slow down the banking system.

Politics, preventative care and Dr. Shetty's model

Future healthcare leadership deals with economic externalities in terms of preventative care challenges, as a future unchosen cost, but a necessary one to prevent unnecessary Emergency Room walk-ins in a growing economy with growing demand. This is done more and more by opening walk-in clinics to treat minor injuries instead of crowding the Emergency Room. New smartphone applications simplify the ER visit nowadays with patient being triaged selecting options on their phone for fractures, fever, or other. This simplifies the budget and regroups physicians with multiple specialties. Modern medicine has continued to exist in a growth economy by continuing to increase demand in natural resources to supply outpatient surgery, gene therapy, a wellness program, etc.; however, the most efficient way to cut healthcare costs is with preventive measures. Exercise, the National Institute of Health All of Us research, good nutrition, DNA screening, DNA telomere extensions, therapeutics and staying intellectually sharp, are some examples of preventative measures. In the future, global leadership challenges will include how to deliver preventative medicine. Answering the challenge of preventative care will save resources in the long run. For example, the OECD estimate of $10,000+ per person spent in the USA alone, and according to Neff *et al.* (2008) can reach as high as $50,000. Preventative care can potentially stop economic crashes on a global scale due to the over-extended economy bound by insurmountable debt toward its healthcare system. With the advent of the internet, it is now possible for individuals to help complete strangers. A company called Lending Club, for example, allows citizens with large savings to finance other citizens who need financing.

Technology

According to Fig. 4, metrics are necessary, and a cadre of leaders need to hold associates accountable, by using the tools of Servant Leadership, acting as a prosumer, limiting waste. Waste, in the past, was difficult to avoid, but with metrics, it becomes possible to monitor (e.g., the Enterprise Data Warehouse—EDW). These same tools which brought us descriptive statistics about productivity also created time guzzling software, which primarily comes from "the Four", which include Amazon, Apple, Facebook and Google, but in China, there is Baidu, Alibaba, Tencent, and Xiaomi.

Fig. 4. Metrics and leadership

Basically an efficient waste of time. Japanese populations have demonstrated that unlike their western counterparts, productivity at all costs is sometimes placed above employee pride in work well done, saving time, but impacting employee morale. What is worse is that these companies advertise they save you time with their services, which is true only if these business models did not end up guzzling so many people's precious hours getting distracted. Used wisely, Amazon automates purchasing and soon will deliver prescription drugs, Apple platforms function faster because often virus free, Facebook provides inexpensive advertising and Google is an encyclopedia.

Global leaders in the future will be able to use much more powerful computers than today to handle a more challenging number of economic externalities. A system like an EDW, Online Analytical Processing (OLAP), and Online Transaction Processing (OLTP) helps global leadership face the challenge of storing future productivity (Kemper & Neumann, 2011). EDW is a tool that can assist the analytics team decisions on which hourly wage associate has the most potential. In a dissertation by Casati (2012), this was calculated by Erlang-C, and Erlang-C can also be used in conjunction with quality of service: QoS software (Casati, 2012). This is all happening within the confines of the FDA's Digital Health Innovation Action Plan (DHIAP), which will provide care on time, with better quality and safety.

If IBM buying Merge Healthcare, Inc. is any sign, future global systems are being geared toward making medical doctor leaders at ease with challenging hospital monitoring systems—Watson computer interpreted medical imaging can now be ubiquitous. Another significant advancement is vital sign monitoring systems that can now use special kinds of tattoos and work off of Wi-Fi, possibly in the future with Quantum Experiment at Space Scale (QUESS) or White-Fi. It will soon become ubiquitous to precisely compare millions of patients' charts to find small geographically isolated groups with similar medical conditions and find the best care for that group, without scrupulosity (using EDW). Unfortunately, the internet age is uncertain with ICANN giving up net neutrality.

Overview

The body of this chapter is going to look at 10 leaders. The first leader is Elon Musk, who streamlined environmentally friendly transportation (whether it is automobiles, hyperloop, or space travel). The second set of leaders is Valentina Rognoli, Jakus, and Shah, specializing in reprinting plastic and tissue in three dimensions. The third leader is Stephanie Leffler who started crowdsourcing, which changed the labor force. The fourth leader is Sol Cates, who specializes in CloudIoT, which would potentially allow Mazor Robotics Renaissance® Guidance System to do spine surgery in the operating room over the Internet wirelessly and potentially assisted by anesthesia robot Sedasys. The fifth leader is Elizabeth Holmes, who started Theranos, which tried to make clinical diagnostic tests cheap. The sixth leader is Philippe Horvath who initiated reparatory medicine. The seventh leader is Wigginton who had the idea of plastic-eating bacterium which could potentially recycle all of the plastic coverings used to keep instruments sterile (the amount of waste generated to guarantee sterility assurance is staggering). The eighth leader is Bill Inmon (father of the EDW). The ninth leader is Dr. Shetty, who started 3 dollars per year health insurance, and finally, Jennifer Neff from Allvivo Vascular, Inc. antimicrobial constructs.

The challenge of future global healthcare leadership can be approached in 2 ways. The first approach to global healthcare leadership is from the moral education standpoint of business, and due to the change in the way business is managed, business schools need to teach how to adapt to change in a moral way, not only in a law abiding ethical way (Kierkegaard's aesthetic, the ethical and the religious). Second, in addition to acting with morality, there is practical usefulness in following moral conscience at work and the phronesic question is no longer "can we?", but "should we?". As a foreword to the visions that follow, this chapter is not meant to be a business plan, a life cycle costing analysis-LCCA- (LCCA is able to show that GDP percentage used on healthcare can be directly proportional to plastic pollution), a sales representative pitch for surgical instrumentation or 3D construction, a sterile processing consultation, a financial analysis, a seminar on information technology, a survey of international affairs, nor a macro-economic report, but it is however meant to bring awareness to all of these aspects of life and suggest improved tools for outpatient center operations.

All while keeping ethics standards high, future healthcare global leaders in Surgical Services will have to deal with how to keep outpatient operating rooms sterile at a low cost, while following a "queuing process" (Casati, 2012).

Leadership visions

Visions

(a) Vision of the future of global healthcare leadership includes behavioral analysis of leaders past and present. The population at large has greater and greater needs, and healthcare needs to increase supply in the era of ever-increasing demand.
The Harvard Grant Study simply states that happiness comes from relationships in life and at work. Another large study is the Global Leadership and Organizational Behavior Effectiveness (GLOBE) study and shows the difference between cultural leadership. Depending on the country, leadership behaves in different ways.

(b) A vision on attempted cost cutting in global healthcare leadership for the future by Theranos' Elizabeth Holmes. The population at large has greater and greater needs, and healthcare needs to increase supply.
As a head-on challenger-healthcare global leader, Elizabeth Holmes had a good concept for the future. This leader's idea to cut diagnostic testing costs in the future was not without challenge, especially in a global environment where Walgreens Boots Alliance is a major player. As a global leader in her industry, she is in principle correct in asking the future market to decrease the challenge of obtaining diagnostic testing. This would in turn decrease the challenge of the future population that can afford to get their medical testing from a global industry leader. For this to happen, the device had to work, and the device called "Edison" produced test results which were voided. The idea of an economy of scale was brilliant, but even if the packaging is immaculate, the customer will still hold the company accountable for the QoS rendered. Bridgewater CEO Ray Dalio with his Dot Collector delivered the desired

service with his device, which was used successfully unlike Holmes, who had a device which did not take off. Devices like Holmes', if it had worked are what would have allowed healthcare to be accessible at home and make a trip to the clinic or hospital a rare occasion due to health issues.

This futuristic trend is visible today since people try to take care of as much as possible of their healthcare challenges through their device (cell phone) ordering over-the-counter medication and if needed, go to a walk-in global clinic leader run by Walgreens Boots Alliance or a local hospital. Traditional US hospitals are becoming large academic medical systems with peripheral outpatient clinics and use their devices more and more for their care.

(c) Vision of future global healthcare leadership's technology in a Crowdsource company like Stephanie Leffler's Vormetric's Chief Security Officer (CSO), Sol Cates. The population at large has greater and greater needs, and healthcare needs to increase supply. Stephanie Leffler, leader of Crowdsource, saw the need for distributing work to employees who are not necessarily local, which is in contrast to crowdfunding, the principle of raising cash. Futuristic technology is developing so quickly that traditional high-school graduate blue-collar employment will be replaced with Crowdsource technology which is good news, because instead of unemployment, it would be a job market displacement accompanied by job retention. Some proposed crowdsourcing projects work, and others do not, but hopefully, Sterile Processing Technicians in the future will not face unemployment because even though robots could potentially replace current job responsibilities, other job responsibilities will be created, like plastic instruments remolding. Crowdsource allows flexibility to both the global healthcare associate who can work on multiple large-scale projects and to the global healthcare employer, to keep overhead low. Crowdsource enterprises are not all the same, some are proprietary, and some are open-source. The avenues for open-source will only expand as Moore's Law accelerates towards Rose's Law (the theory here is that proprietary computing will become more and more complex to encrypt).

Vormetric Chief Security Officer (CSO), Sol Cates is in the forefront of the revolution we are now involved in regarding Cloud Internet of Things. The reason why some technological progress is not lightning fast is that important security measures have to be put in place before everyone connects their kitchen, their self-driving cars, and their home to their cell phone. Many services are available on the Internet, but they are not yet ubiquitous. As CSO, Cates, a global leader is bringing his company into the future by continuously challenging the security of the network built.

In the healthcare space, Vormetric technology could connect hardware such as the Mazor Robotics Renaissance machine to telemedicine, but internal hardware, firmware and network security remain fragile (not to mention nurses are needed to connect robot arms and a surgeon is needed for robot arm insertion incisions). When network security is no longer a concern, Vormetric could also potentially connect to nanotechnology which can "cure" the body from inside (Bhat, 2014). Experiments and treatments can now be measured in pico-moles in reference to Lee Cronin's Chemputer. This type of pico-therapy will need high-powered computing, and these computers will need highly efficient

network security. This Chemputer would "print" prescriptions from inside the body if the Chemputer were miniaturized enough. The medication would only be delivered to the site of need, bypassing the liver and the kidneys (the liver and kidneys experience long-term damage from prescription drugs). These pico-mole amounts also directly protect the environment from large amounts of drugs ingested by patient, then metabolized and sent into the sewage systems which can cause harm to aquatic life. The logical step, after nanotechnology research takes off, is the industrial level. Climeworks Inc. is using technology to suck pico-particles out of the atmosphere. Climeworks, Inc. can suck out 900 tons of CO_2 from the air per year and sell it as fertilizer. Microscopic pico-particles therefore become a commodity and future research can be financed, from the sale of the fertilizer produced from this Carbon Dioxide.

Even if the chance is small that a project works at the industrial level, Dan Schulman famously says: "I want to see that you failed somewhere and then I want to see what you're made of and how you came back from that." Like the unsuccessful Theranos, Thomas Edison "failed" 1000 times before inventing the light bulb. All of these technologies could use the Internet and the future of CloudIoT. Technology can only result in "a number of applications" which "are gaining momentum" (Botta, de Donato, Persico, & Pescapé, 2016). The combined use of "Big Data, Cloud Computing, Internet of Things and Virtual Reality" is becoming mainstream to increase access to healthcare (Lytras, Al-Halabi, Zhang, Haraty, & Masud, 2015).

Granted that there is sufficient cybersecurity, the ambition of this chapter is to plan a business model for global healthcare leaders of the future to use Mazor technology and democratize this process to the most challenged areas of the planet.

The greatest challenge for any area on the planet is the appreciation of real estate over time for something as simple as housing private servers off-site with Network Address Translation and a fixed cost of cooling the server, which makes it a barrier to entry for smaller players (3-D printing Dahir Insaat building could be useful here, but still in the experimental stage).

(d) Vision of future of global healthcare leadership in patient transportation and environmentally friendly power generation using ideas from Elon Musk is funding a Peter Diamandis, MD global learning X-Prize for literacy in Africa. The population at large has greater and greater needs, and healthcare needs to increase supply. Elon Musk is an innovative leader in the sense that he encourages many players in different industries to advance the global economy in different directions, even up into space. Elon Musk, a South African native from the common wealth, unlike some of his fellow billionaires, has been known to work alongside his fellow Engineers. The global economy often is equated with the US Dollar, but the Common Wealth of Nations has a Common Wealth of Nations Currency Union, with its 2.4 billion members and 52 nations who do not share a common currency, but are quite large as well. One of the inspirations which could be extrapolated from Musk is to use Tesla's asynchronous motor inside emergency vehicles to transport patients (the electric motors could be based on a fuel cell which harnesses the energy of hydrogene and oxygene to produce electricity). Elon Musk's electricity theoretically would come from a Solar City, but solutions

need to be found to make the majority of photovoltaic cells without zinc sulfide, cadmium sulfide and silicone tetrachloride. Some researchers have started to study near infrared harvesting transparent luminescent solar concentrators such as the one studied by Zhao, Meek, Levine, and Lunt (2014). Elon Musk founded OpenAI, Solar City, Space X, PayPal, Tesla, Hyperloop, the Boring Company, and Neuralink. All of these projects are just the beginning of a new generation of researchers who will eventually find even better ways to improve tools that leaders use. Researchers are building Hydrogen Internal Combustion engines, build artificial intelligence (reminiscent of Yamakawa, Osawa, and Matsuo (2016) research), harvest energy (like Bristol Cabot Institute's diamond battery), go to space, and recycle (which in part inspired this chapter). Another area of interest is wireless communication. QUESS—a completely secure communication channel for connected devices and appliances or White-Fi could be used in less developed countries, which is an unoccupied space in global healthcare corporations' intellectual property hunt for maximizing profits only when wireless Mazor Robotics can finally function without a nurse inserting and retrieving robot arms and when surgeons no longer need to be present for the initial arm insertion incisions, could this become a possibility.

(e) Vision of future of global healthcare leadership in reprintable surgical instruments and prosthetics and the idea of Valentina Rognoli as well as Jakus and Shah. The population at large has greater and greater needs, and healthcare needs to increase supply. Valentina Rognoli is a leader who contributes to facing the challenges of global future healthcare leadership. She has taken plastic and recycled it into other objects, which is the concept of prosumers and extrapolated to recycling plastic material (Rognoli *et al.*, 2015). This is the concept of being a prosumer and using plastic to remanufacture Mazor Robotics Renaissance® Guidance System arms (Ritzer, Dean, & Jurgenson, 2012). An inexpensive solution, until stocks are depleted, is using the model-20a plastic injector priced at $595.00 (the drill press, a mold clamp, a mold for the specific surgical instrument and unlimited plastic pellets are not included in this price), to remold plastic Mazor Robotics Renaissance® Guidance System arms in the outpatient unit.

Jakus and Shah (2016) took it a step further by developing "3D-printing (3DP) as a vital tool in tissue engineering and medicine" with bone which is "hyper-elastic" composed of "90% hydroxyapatite, and 10% polymer" printed at a rate of "272 to 550 cubic centimeters per hour," which allows for a "mandibular to be printed in 3 hours" (Jakus & Shah, 2016). Printing entire organs has been considered with the help of stem cells. Three-dimensional printed prosthetics are another option for reprints of plastic objects. Intelligent elastomers, mostly based on silicium and using nanotechnology, will provide efficient prosthetics, such as bones, nerves, muscles, and skin artifacts. This use of 3-D printing is an alternate to printing arms with a Model 20a plastic injection machine for a Mazor Robotics Renaissance® Guidance System. Model 20a plastic injection machine might seem like a more attractive proposition at a $595.00 price tag, but this does not include the drill press, a mold clamp, a mold for the specific surgical instrument and unlimited plastic pellets.

(f) Vision of the future of global healthcare leadership in waste management using Nicholas S. Wigginton's discovery of plastic-eating bacterium. The population at large has greater and greater needs, and healthcare needs to increase supply.
A global leader, Nicholas Wigginton, faced the challenge of plastic waste using plastic-eating bacterium, in contrast with Rognoli who recycles for future use. This creates endless entrepreneurial opportunities and jobs, because the population at large will always consume plastic. As the demand for more healthcare facilities increases, there is also an increase in waste generation from these facilities. This situation requires an organized system of healthcare waste management to curb public health risks as well as occupational hazards among healthcare workers as a result of poor plastic materials waste management (our health is definitely affected by the great Pacific patch of plastic the size of Mexico). Wigginton (2016) has some hope for the future of waste management, especially the fact that plastics can be digested by microbes, because there is currently research on a bacterium called Ideonella sakaiensis, which is a bacterium that breaks down one type of plastic.

(g) Vision of the future of global healthcare leadership advances in EDW.
Bill Inmon published a book on EDW in 1992. This book has been a key tool in future global healthcare leadership's hands to meet challenges, just like the thermometer was first used as one of many tools to advance science in the eighteenth century (Casati, 1997).

(h) Vision of an economy of scale according to Dr. Shetty. The population at large has greater and greater needs, and healthcare needs to increase supply (Fig. 5).

(i) Vision of antimicrobial constructs by Allvivo Vascular, Inc. The population at large has greater and greater needs, and healthcare needs to increase supply.
The global leader's vision of the future is such that the coating containing nisin will eliminate all types of ICU infections challenges. Allvivo Vascular, Inc. is the company which owns the patent and "Nisin can be made to form a long lasting antimicrobial compound […] that may be coated onto a substrate, a medical device" (Neff, McGuire, & Joshi, 2008). These "medical devices may be coated with this antibacterial coating, including drug delivery pumps, vascular access devices, transcutaneous devices, neural simulation devices, neural intervention devices, intubation tubes, sutures, shunts, drainage tubes, feeding tubes, orthopedic devices" (Neff *et al.*, 2008). This is not an exhaustive list because there

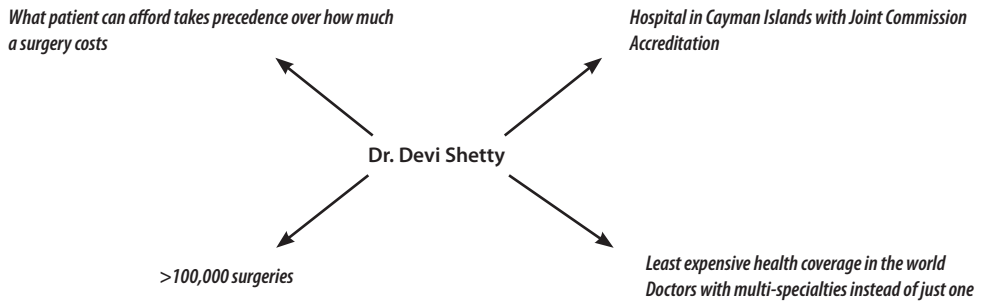


Fig. 5. Dr. Devi Shetty (Anand, 2009)

are "other medical devices which are inserted into the patient's body or which comes into contact with the body or body fluids" (Neff *et al.*, 2008). Neff's present "invention is based on the recognition that known antimicrobial compounds, such as Nisin or other antimicrobials, can be made to form a long lasting antimicrobial surface coating" (Neff *et al.*, 2008). This is done "by linking the peptide with a block polymer" (Neff *et al.*, 2008). The novelty here is that "antimicrobial product formed by the present invention […] may be coated/absorbed onto a substrate" (Neff *et al.*, 2008). Any instrument inserted inside the body can benefit from this "including catheters and the like" (Neff *et al.*, 2008). The invention has antimicrobial properties preventing central line-associated bloodstream infections (CLABSI) and catheter-associated urinary tract infections (CAUTI) and "catheters are routinely implanted in the bloodstream, urinary tract, chest, abdomen, leg and spinal cord" (Neff *et al.*, 2008). A significant portion of patients who get these infections are admitted to a hospital for illnesses related to diabetes (diabetics represents 8.3% of the world population and worldwide addiction through our food supply to sugar induced dopamine release in the brain does not help).

This is important because patients with CLABSI or CAUTI "are particularly susceptible to microbial infection, blood clotting and occlusion that can begin within hours of implantation" (Neff *et al.*, 2008). In conclusion, "the cost of ICU infections alone is USD 296 million to USD 2.3 billion with between 2,400 and 20,000 deaths per year" (Neff *et al.*, 2008). This is staggering because a "single episode of central venous catheter-related bacteremia has been estimated to cost between USD 3,700 and USD 50,000." Furthermore, "an attributable mortality rate between 4 and 35%" (Neff *et al.*, 2008).

(j) Vision of the future of global healthcare leadership in reparatory medicine using Philippe Horvath's leadership. The population at large has greater and greater needs, and healthcare needs to increase supply.

Scientists collaborate persevere, motivate, take risks testing a fundamental hypothesis and then deliver results sometimes find extraordinary ways to improve the possibility for new ventures and therefore new leaders through global healthcare challenges. Philippe Horvath and his four partners discovered these genetic "scissors" which can help "repair" the body in the future. Other possibilities include using Clustered Regularly Interspaced Short Palindromic Repeats—CRISPR to "repair" the body (Chylinski, Makarova, Charpentier, & Koonin, 2014). Yehuda *et al.* (2009) discovered, "alterations from stress" are all that you need to repair the body (Yehuda *et al.*, 2009). At the macro-physiological level, Katz (2015), found a way to stop bleeding without manual compression gauze. In the beginning of the twenty-first century, one of the most innovative discoveries in surgery, after the advent of laparoscopic surgery in the last quarter of the twentieth century, was Mazor Robotics Renaissance® Guidance System robotic surgery and other robots which assist surgeons, such as the DaVinci robot and Smart Tissue Autonomous Robot (STAR). Now we are poised for yet one more step forward in the next decade and beyond: "surgical nanobots will be ready for human trials by 2020" (Bhat, 2014). Nanobots have a bright future in the surgical field, but will need all the brightest minds on Earth to bring them into the operating suite after passing trials.

The futurist view that these minds, these leaders could actually tap into all of the human resources at their disposal because the person with the solution to the problem at hand could be in a small remote village. One individual among many, who has a revolutionary cost-cutting idea that can change the world and cannot or does not share it (Fuller, 1975). Daniel Keith Ludwig came to the same conclusion when asked about his ability to build a billion-dollar fortune with a $5000 loan at age 19 by saying all of us have the talent, but few of us act on it.

Author experience

Dr. Cybulski, is an expert neurosurgeon. Dr. Cybulski posits that leadership in neurological surgery will face several challenges in the twenty-first century. These challenges include defining the framework for incorporating rapid technological innovation such as robotic-enhanced surgery into patient care along with creating concomitant ways to improve the value of safety, efficiency, and cost of providing this care. The effectiveness of the Mazor Robotic Spine Surgery System will be measured against these criteria as will other technological innovations. In addition, the leadership of neurological surgery will be faced with the challenge of creating an environment that stimulates recruitment of the brightest minds to the specialty and continuously improves their training.

Dr. Casati, a decontamination expert, uses aseptic technique and standard precautions daily. The current practices pose a challenge to the future where it may be possible to remanufacture plastic surgical instruments onsite and expand globally afterwards.

It is the future of a department like Central Sterile Supply to challenge the reuse of everything possible especially plastic, by taking leadership in helping the globe.

Partial thermoplastic remanufactured within the confines of manufacturer's instructions for use limits refurbishing (Eriksen *et al.*, 2013). In the future, healthcare industry leaders can manage this challenge instead of the onsite repair specialist services used today. It would just be a new role of Sterile Processing Technician, since much time would be freed up by automation.

Current sterile processing machines already have the capability of being connected to the Internet. Instead of having an online connection for information technology diagnostic purposes like today's washers and sterilizers, Cloud IoT will physically move surgical trays with robotic arms through the Sterile Processing Department (trays may no longer be necessary since individual instruments can now be inventoried reliably using RFID). Moving merchandise across the factory floor can be done with Kawasaki's RD80N robot. Tray assembly can be done with a robotic arm such as the Kawasaki MC004N robot. Quality assurance will still be done by humans (Casati, 2012).

This means the global healthcare system leaders need to challenge the way that plastic is being disposed of and not currently using ISO 14040:2006 on Life Cycle Costing (LCC). A health system should aim to live in close autarky.

International Organization for Standardization (ISO) rules are enforced by many different global agency leaders since these rules touch a vast share of the future total domestic commerce

(e.g., the Food and Drug Administration, the Federal Trade Commission, US Department of Agriculture). What we covered are consumer products, which should be "measured" for recycling unlike water for instance, because water is a vital necessity, which should be free.

A recent invention called WaterSeer™ condenses drinking water from the air. Another option than condensation is water purification using "vertically Aligned MoS2 Nanofilms and Visible Light" (Liu *et al.*, 2016). This would be a leap forward for global access to clean water. Skipping Rock Lab, which produces water-filled balls of a material, which look, and acts impermeable, like plastic, but are edible, hence subtracting the challenge for recycling plastic for drinking water storage in the future, because the plastic is biodegradable in the body and most importantly, the water stays sterile. Based on direct experience, it is challenging for future leaders to consume single-use plastic in a Central American and other challenged global Sterile Processing Departments. In the experience of the co-author, sterilization wrapping paper such as Kimberly-Clark™ and Medline™ sterile plastic peel packs, for example, if used by future Central American leaders, could be remanufactured by melting and remolding, because sterilization wrapping paper is a rare commodity in the developing world. Global healthcare leaders need to face the challenge of creating the perception of a leadership system where all plastic is reused in a decontaminated and sterile way, so that access to global high-quality sterile processing and consequently surgery may become a reality.

Ideas for the future

The population at large has greater and greater needs, and healthcare needs to increase supply. Below the authors will deliberate whether the future can be sustainable by comparing GDP per capita with Accounts Receivables and Assets of a futuristic neurosurgery center using robot surgery. The hypothesis testing below is based off of a large amount of data, which for the sake of space could not fit here, but the authors can make it available if requested.

If healthcare industry growth can be similar in a statistically significant way to GDP per capita growth, then building outpatient centers such as the one described below is financially sound.

H0 There is no significant difference between USA per capita Gross Domestic Product costs and independent variables Account Receivables and Assets of Neurosurgery Unit.

H1 There is a significant difference between per capita Gross Domestic Product costs and independent variables Account Receivables and Assets of Neurosurgery Unit.

To appreciate a predictive model of healthcare leadership challenges, historical data are analyzed using statistical software (through SaaS—Software as a Service) to determine trends that might prolong into the future (Vielmetter & Sell, 2014). The researcher will be using public data from a Midwest Academic Medical System surgical services neurosurgery department. The datasets include three variables (2 degrees of freedom). There are two independent variables (Account Receivables, Total Assets) and one dependent variable (per capita GDP). The equation plotting an exponential increase in Total Assets of 153% per annum, against a weak 3% increase in per capita GDP per annum is demonstrated in the following equation (the equation would be more predictive if more data were available):

$$y = e^{0.0003x}$$

Data should be heteroskedastic in order for the multiple regression, to obtain reliable analytics (another useful tool for this would have been Monte Carlo simulation—MCS). Beyond MCS, if using factor analysis there would theoretically be equally heavy loading on accounts receivables, total assets and GDP per capita since the null hypothesis is not rejected. Factor analysis specifically looks at unobserved factors, which might not have been considered in this study. This can be debated since real wages, an unobserved factor, which has not been considered in this study has not moved significantly in comparison to inflation.

In a separate study, according to McKinsey Credit Swiss, going back to 1960 to the present, there is a growing gap between the GDP curve and healthcare expenditures. Using the Big Mac index, the Swiss Franc is 27.2% overvalued compared to the dollar, but the gaps should still be statistically significant for the McKinsey study. This is observed when measuring purchasing power parity, which has diminished due to inflation with unmatched increase in salaries. Furthermore, the derivatives market has grown out of control, absorbing the fruits of economic growth (i.e., productivity). The Aggregate of Demand or GDP includes consumer spending, investment banking, and government expenditures.

The "aggregate per capita GDP is assumed to advance at the same pace as in 1990–2003" when innovation was booming with the dotcoms (Maddison, 2008). This chapter projects trends in revenue sources for a period from 2014 to 2021. It was observed that there is a 153% growth from 2014 to 2015 and therefore a 153% growth trend was applied every year from 2016 to 2021. The data for 2014 and 2015 are based off of historical numbers from a Midwestern Academic Medical System. The predicted growth of approximately 153% was estimated based on observed historical growth from 2014 to 2015. This local Academic medical system growth was observed within a US economy with per capital GDP growing at an average in 2014 at 0.76%, in 2015 at 0.73%, in 2016 at 2.07%, but a 3% long-run inflation rate was adopted. It was decided to run a multiple regression analysis to compare account receivables with total assets because Levy (2010) used this method in a dissertation: "to control for the levels of Accounts Receivable each of the regressions includes the variable Accounts Receivable /Assets" (Levy, 2010). The ratio of Accounts Receivables to Assets is between 0.001 (2014) and 0.006 (2021). Proportionality between 0.001 and 0.006 is within the 0.05 acceptable range. The number 0.05 represents a normal curve tail. When statistics is applied to assets, it is important to hedge intelligently, because the high risk of great gains at the 0.05 tail also inversely has a 0.05 tail for great losses. In Taleb's book, The Black Swan, the discussion regarding fat tail shows this concept of risk of high gains and high losses. If Taleb's principles and Dodd-Frank are kept in mind, risks of extreme market fluctuations should not be a concern.

Conventional ways of looking at Gaussian statistics always concluded with rejecting or not rejecting the null hypothesis. Taleb posits that trying to dismiss the alternative hypothesis of the normal curve, calling it just a type II error when it should have been accepted, can actually lead to a Black Swan. The authors of this chapter see the data with optimism, unlike Noam Chomsky, who predicts doomsday scenarios. Another option to consider is Stephen Hawking's goldfish in a curved bowl analogy whereby our principal tool of observation, our eyes, distort reality. The current data in Table 3 has good validity because it is representative. These numbers represent

process improvement, salaries, benefits, computers and continuing education. Process improvement will be funded out of the "salaries, benefits and other costs" budget of 28 million dollars of which an estimated 4 to 5 percent is approximately 1.5 million. This is in addition to the existing computers and telecommunications budget of 1.5 million dollars and the continuing education and employee emergency fund of 4 million dollars. The reliability of the data from the Academic Medical System is consistent trustworthy numbers.

Table 4 shows the R-squared value of 0.723, which shows that the independent variables (account receivables and total assets trends of the Midwestern Academic medical system) are good predictors of the dependent variable (per capita GDP trends).

Table 5 shows that there is not a significant difference between the datasets and that the p-value is above 0.05, which means the null hypothesis is not rejected. This means that unless there is a type II error (incorrectly retaining of a false Null), US GDP per capita trends into the future accurately predict trends in account receivables and total assets of the Midwestern Academic Medical System. US GDP per capita trends into the future are good predictors for account receivables and total assets trends.

Table 3. Aggregate per capita GDP growth trends.

	Account receivables (M)	***Total assets (M)***	***Per capita GDP +3%/yr***
2014	$0.31	$255.94	$0.05
2015	$0.52	$282.67	$0.06
2016	$0.79	$319.22	$0.06
2017	$1.22	$370.6	$0.06
2018	$1.65	$444.51	$0.06
2019	$2.54	$552.7	$0.06
2020	$3.68	$713.12	$0.07
2021	$5.43	$953.26	$0.07

Table 4. Regression statistics R-squared calculation.

Regression statistics	
Multiple *R*	0.850
R Square	0.723
Adjusted *R S*	0.612
Standard err	39898
Observation	8

Table 5. *P*-value

	***P*-value**
Per capital GDP	0.470
Account Receivables	0.903
Total Assets	0.949

Discussion

In summary, this chapter studied the perception of leadership and in some sections focused on global healthcare leadership's role in the future to make wise use of partially plastic instruments in medicine, which still need decontamination and sterilization, but will be safer for the environment, if remanufactured. It is doubtful that all plastic could be replaced with Skipping Rock Lab-type plastic, which is completely biodegradable.

Technicians will do quality assurance on the cleanliness and sterility of the product, as well as remanufacture plastic instruments using Model-20a plastic injection machines or other machines.

Facing challenges in global healthcare leadership is the key to the sustained development of the healthcare industry and even though companies like Theranos have had a challenging path, they are the way to proceed if breakthroughs in future global healthcare leadership are to be attained.

In the case study we saw, there is no significant difference between GDP per capita versus Total Assets and Account Receivables which means that the null hypothesis is not rejected because p-value is above 0.05. The rate of growth of total assets and Account Receivables is similar to the rate of growth of per capita GDP. This means that domestic growth over the years studied has matched the industry's growth, which is likely to continue into the future (the Credit Suisse study seen earlier does pose some questions on equality of GDP per capita growth). An outpatient neurosurgery center using robotic technology should seek financial support from better reimbursement, help from a charitable foundation, or a good process improvement team that can capture costs. Minimally invasive neurosurgery pavilions using Mazor Robotics Renaissance® Guidance System technologies will necessitate a $255 million initial investment reimbursable through donations for the actual building (or if using sole revenue from net patient receivables, $95 million in net patient receivables per annum). The entire initial investment should be reimbursed by year 10, assuming process improvement project creates exponential growth in productivity (produces growth in general).

The vision of this chapter is that future global leadership will be inspired to use practical wisdom and simultaneously be flexible in the face of challenge. The construction of an outpatient neurosurgery centered around robotic technology and recyclable plastic arms is the proposed vision. This should improve patient comfort and increase confidence level, reduce costs, and eliminate waste. The benefit will outweigh the risk in a Nash equilibrium scenario where doing nothing is worse than trying and failing. If plastic consumption were under control, the great Pacific garbage patch would cease to exist. Reusable plastics could benefit from something similar to the HR 5632—Plastic Recycling Assistance Act of 1990. Even while taking into consideration the limits of reuse of plastic it should be made possible with a model-20a plastic injection machine, but also with biodegradable Skipping Rock Lab plastic (Caleffi & Cacciapuoti, 2016).

In a not too far-off future, the neurosurgery department and other surgical units across the globe will exist in a world of technological singularity. Global leadership challenges will increase exponentially in this world where the singularity has been achieved. At a micro-level, the singularity has happened—at the level of a worm genome (the Openworm project has uploaded a *C. elegans*' brain). Human-assisted robotics will be ubiquitous, and non-invasive treatments with laser beams, magnetic fields, or nanotechnology introduced in blood vessels will be household terms.

In future research, to do a significant Factor Analysis or a Monte Carlo simulation—MCS a plethora of data would be necessary, more than is accessible here, but could spawn another study with the information present as a basis for reproducibility. A GLOBE study, which takes up many resources, more than available here, could show that the outpatient neurosurgery clinics could be implemented differently from country to country. Research on decontamination practices in less developed countries needs further financing. In OECD countries, even before the instrument is handled, a $400 per gallon bottle of Klenzyme is used at the sink and a $50 single-use HumiPak plastic bag is used to humidify body fluids before it reaches the Sterile Processing Department (this is unaffordable to less industrialized countries). If solar panels like Zhao *et al.* (2014) were installed worldwide, energy inequality would certainly not be what it is today. Finally, water should be ubiquitous, if apparatus like the Liu *et al.* (2016) WaterSeer™ were readily available.

Entrepreneurship and good relationships, according to the Harvard Grant Study: the necessary instruments for a change in direction of an enterprise. Healthcare corporations are faced with a high barrier to entry in the healthcare market, reminiscent of Elizabeth Holmes' Theranos unicorn failure, from $1 billion to bankruptcy. The leadership challenge in healthcare is to create innovation at low costs, collaborate with venture capitalists and angel investors with high liquidity or partner with healthcare institutions with high profit margins. All that is needed is a little perseverance, a lot of motivation, long-term collaboration, and not being afraid to take risks testing models before a "go-live" event.

Conclusion

Whether it be equal opportunity afforded to individuals to fairly compete against multinationals and nationalism, whether it be informatics advancements, whether it be CRISPR, printing drugs, printing buildings or printing prosthetics, whether it be environmental protection, whether it be Dr. Shetty's affordable healthcare, Kierkegaard's ethics and aesthetics create a sense of moral deontology versus a climate of utilitarianism, sidestepping current society's aboulia, which prevents de facto equality.

Appendix A

List of healthcare reimbursement systems

1. The Veteran's Healthcare Administration.
2. Planned Parenthood (James Grisson's cancer treatment).
3. Military programs.
4. Medicare.
5. Medicaid.
6. State's Children Health Insurance Program.
7. Department of Defense Tricare.
8. The Indian Health Services.
9. The Affordable Care Act/American Health Care Act.
10. The Walgreens walk-in clinics.

11. Non-profit Academic medical systems.
12. Outside the USA, there are programs like French Social Security.
13. National Health Service in the UK.
14. MD leaders like Dr. Shetty's clinics in India.
15. Executive Health.

Appendix B

Keyword map categories: Information Systems, Organizational Behavior Studies, Trade Agreements, Finance, and Plastic Recycling

	Central Sterile Supply	Logic bombs	Externalities
	Safety	Worm viruses	
Virtual Reality	Mazor Robotics Renaissance	Rootkit	
	Sedasys	Bootsector executable	
Cybersecurity		Macro- and polymorphic viruses	
Epic's Optime		HIPAA	Firesale
	Multi-disciplinary team	Ethics	Prosumer
Diamond battery	Specialists	Morality	CETA
	Generalists	Phronesis	JEFTA
			VEFTA
Zinc sulfide	Rentier capitalist	Inspirational leadership	TTIP
Cadmium sulfide	S.T.R.E.A.M.	Myer–Briggs	OECD
Silicon tetrachloride	Blockchain	GLOBE	
	Bitcoin		
	Litecoin		
	Ethereum		Crowdsource
			Crowdfund
90% hydroxyapatite, 10% polymer bone	Intellectual Property		Moore's Law
Plastic-eating Ideonella sakaiensis	Singularity		
OLAP			
OLTP	CloudIoT	Kierkegaard- aesthetic, ethical, religious	Refurbish
Nisin			Remanufacture
CRISPR	EDW		Process improvement
Anti-virus	QUESS	Autarky	
Anti-spyware	White-Fi	Life Cycle Costing	Productivity/Quality tracking
Firewall			
Intrusion detection systems		Account Receivables	Lean
Intrusion prevention systems	Telemedicine	Total Assets	5S of Sort, Straighten, Shine, Standardize, Sustain
Malware	WaterSeer	Per capital GDP	HR 5632—Plastic Recycling Assistance Act of 1990
Adware, Trojan horses	Nanotechnology		Capital gains
Spyware, Ransomware	Big data	Reimbursement	

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5

The ethical foundations of medical scientific writing

Michael Hanna

Introduction

Striving to be a better person, who lives more ethically today than you did yesterday, is the first and most essential step for writing better scientific papers. If you give only superficial thought and lip-service to the ethics of scientific research – i.e. if you simply think "yeah, yeah, yeah, I already know all this ethics stuff; let's move along to the 'real' science" – then you will not know the *right* way to conduct and report medical research. And if you do not know the right way to conduct and report medical research, you will do it in ways that are wrong. Conducting and reporting research involves making dozens, or even hundreds, of little choices per day – most of them without much conscious realization that another little choice is actually being made. Even if one does stop to notice them, most of these choices seem to be only technical choices about methods or grammar or whatever else, but they are not only that. Viewed in another light, they are also moral choices about what to do and say, or not do and say, why, and how. If you do not recognize this deeper moral dimension of scientific research, or if you fail to respond to it appropriately, then you risk making choices that will seem appropriate for reaching your practical goals, but which may often run counter to the greater purposes of scientific medical research. When you spend time reading the ethical guidelines and earnestly reflecting on how they apply to your research, the quality of your research and reporting will improve. You will find yourself making subtle but important changes in your work. And you will find yourself prepared to make better decisions going forward.

Unfortunately, following all the ethical guidelines and expectations for scientific research and writing does not in any way guarantee that you will publish good scientific papers. You might lack access to interesting and strong data; you might lack enough practice writing and rewriting; you might simply be a mediocre scientist; you might just have bad luck. But if you do not make conscience efforts to always follow all the ethical guidelines and expectations, then you will be stuck circulating lousy manuscripts not worth reading. Indeed, there would even be a real risk that you would write junk science worthy of retraction if it ever did get published. If you lack the proper

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moral motivation and ethical guidance, your scientific work and writing will stagger off track at every step, without your awareness, like a drunk trying to walk home in the dark. And like most drunks, you will probably deny there is any shortcoming or fault in what you are doing. If you want to perform and publish high-quality research, the first and most essential step is to improve the ethical foundation of your work, so you will be able to run fast in a straight line.

This chapter here addresses only the deeper ethical issues that serve as the foundation for excellent science across all phases of research, analysis, writing, and publishing.

Most unethical behavior arises when researchers are acting primarily for their own gain (advancing their careers, getting more money for themselves, etc.). If making more money or advancing your career are really your main goals, there are many other not disreputable fields where that is accepted or even expected, and where one has much higher chances of reaching those goals. The goal of medicine and science by contrast is to improve the health and knowledge of humanity. That can only be achieved if everyone contributing does so honestly and for the right humanitarian reasons. Most ethical rules in scientific publishing revolve around honest communication, because dishonest communication winds up wasting other people's time and resources and demoralizes them. Adhering to high ethical standards also improves the scientific quality of research and reporting and puts authors in a stronger moral position to defend their work.

Moral vices and virtues

Although there are many different kinds of ethical violations in research and reporting, they can all be explained, at bottom, by just three root causes: ignorance, laziness, and/or greed. Of these three, ignorance is surely the most widespread and forgivable cause of unethical conduct in research and reporting. Many people contributing to medical research and reporting are either relatively new and inexperienced in this field (i.e. junior researchers and trainees) or are only sporadically or tangentially involved in the work (e.g. healthcare professionals not working primarily in research). Such people often have inadequate education and training specifically about the ethics of research and scientific reporting. Because they are not thoroughly familiar with the ethical guidelines and expectations, they sometimes violate them, unknowingly. In other words, ignorance can result in unethical conduct. Second, somewhat less forgivable but still not quite reprehensible in most cases is laziness. Sometime people know or sense that what they are doing is not really the right way that research or reporting should be done, but doing things the right way would require more time and effort (often unpaid). Because they do not want to expend more time and effort to do things the right way, some people simply try to slip by with the work done in ways they know are not right or at least have been told are not right. In some cases one might be able to argue that the root problem is not simply laziness but instead that the researchers have not been provided sufficient resources to do the work any better. In most cases though, authors of papers know that they could correct or improve something in their paper that is not right ethically (or not right scientifically and therefore also ethically), but they simply do not want to be bothered. In other words, laziness is the bottom line explanation for the ethical problems, not merely insufficient resources. Finally, and most reprehensibly, many ethics problems – including nearly

all of the most unbelievable scandals – can be explained entirely by the greed of the researchers for more money, either directly or indirectly. Greed for money also usually explains most misconduct of people who are well-established in research and know (or surely should know) how unethical their misconduct really is. Whenever someone is caught falsifying their data or reports, or stealing other people's work (through plagiarism or otherwise), or even "merely" falsifying authorship lists, the explanation almost always is that the culprits expected to obtain more money than they otherwise would have, through commercial profits, obtaining research grants, increased clinical activity through "fame" of research, advancing their career, etc. So greed for money and other personal gains is almost always the root cause of the worst ethical violations in medical research in the current era. The explanation is not something else.

Thus almost all ethical problems in research and reporting have the root causes of ignorance, laziness, or greed. In other words, unethical conduct in medical research is ultimately due to character flaws or vices of the researchers themselves (and not really to some other external or systemic factors).

It is important for all medical researchers to realize that these vices – ignorance, laziness, and greed – are the root causes of nearly all unethical misconduct in medical research, because that realization points the way toward better prevention of unethical misconduct. Because these vices are the root causes of unethical misconduct, researchers must make efforts to cultivate the opposite moral virtues, in order to reduce their own risk of acting unethically. And because the vices are specifically ignorance, laziness, and greed, the specific virtues that researchers should make efforts to cultivate are their opposites: ethical knowledge, "extra-mile" diligence (or "extra-kilometer" diligence), and disinterest of money and personal/career gains. Gaining ethical knowledge is the first and easiest virtue to cultivate. It starts by reading the relevant ethical guidelines. Most of them are only a page or two in length, so it is odd that they are not all routinely read and discussed by the medical research community. Because they are so brief, it is helpful to reread them at the start of every new study and paper and reflect on how they apply to your ongoing work. Cultivating the virtue of diligence is a bit more elusive. But most people who gain some experience in research and reporting will quickly notice that many little situations arise, where they know (or have been told) that something they are doing is not really right (ethically, or scientifically and therefore also ethically), but they do not want to bother doing more work to fix it, because "extra" work seems tedious and time-consuming. Cases where this would be financially difficult (e.g. additional data collection is needed) are different, but in most cases, the only barrier is the researcher's willingness to expend more time and effort doing the work. The amount of extra work required is often not much (a few hours to a couple days), especially considering the bigger picture of how much work a person can do in a year, but strangely many people still put up quite a fuss at the thought of having to do even a small amount of "extra" work. People often rationalize their laziness with phrases such as "it's good enough", "no one will notice", "it doesn't really matter", and so on. When researchers find themselves in those situations, where a choice must be made between either leaving things as they are, despite knowing that something is wrong or suboptimal, or being *diligent* and going the extra mile to do things the right way, researchers should make that choice of going the extra mile, for the mere sake of doing better quality work and

being a better researcher. Finally, researchers should cultivate disinterest in financial or personal/career gains. Of course mostly everyone in medical research will say that they do not give much thought to money and that it does not affect their decisions in their research and reporting. To a large degree, that is indeed true. But it is quite rare that this is completely true. Most people in medical research still hope to obtain better positions, more salary, more research funding, more fame and recognition, more everything. Understandably so. But not really. It is very rare to find anyone who comprehends that money is actually a noxious system of artificial rewards (like food pellets for lab rats) that can distort their judgments and behaviors and therefore is better to avoid and give away than to want and pursue. True scientific curiosity, objectivity, and judgment begins just a little bit beyond the point where all interest in money, praise, and career advancement truly ends. So researchers must make a choice. Just ask Dr. Faust.

Responding to ethical misconduct

Regrettably, there is one more major reason why you need to know all the ethical guidelines and expectations really well. One might assume that people working in medical research have above average moral character and high ethical standards. And most of them do. But unethical conduct, especially in minor forms, is also not uncommon in the world of medical research [1]. A meta-analysis of 18 surveys found that 12.3% of respondents had observed data fabrication or falsification by their colleagues, an unweighted median of about 40% of respondents from a subsample of 10 studies knew of cases of fraudulent reporting more broadly defined, and overall "misconduct was reported more frequently by medical/pharmacological researchers than others" [2]. These were conservative estimates that excluded plagiarism and several other forms of misconduct unrelated to changing study results. So if you spend at least a year in medical research, there is a substantial likelihood that you will notice at least some minor forms of unethical conduct. Indeed, you might even find yourself being negatively affected by that misconduct. Therefore, you need to thoroughly learn the research ethics ahead of time, so you are able to clearly identify misconduct as such when you encounter it, and so you are ready to report it, if it is not simply an unintended mistake. Fortunately, most unethical misconduct in medical research is unintentional and is quickly corrected by the people involved when someone else makes them aware of it.

But if you observe unethical misconduct that appears conscious/deliberate or that does not get fully corrected when pointed out, you have an ethical obligation to report it [3], even if it seems that doing so will have negative repercussions for you. Start by documenting everything (including conversations) very well. People who knowingly engage in misconduct may also destroy evidence, and they will certainly deny or reframe anything that lacks undeniable evidence. Next, contact lawyers to discuss the situation and get their advice. Always follow your lawyer's advice; if you are not satisfied with your lawyer's advice, find a new lawyer, and follow his or her advice. Never report cases of research misconduct to the institution where it is occurring, (unless your lawyer advises you do to so). Regardless of whether the institution is a university, a company, a government agency, or whatever else, it is not an independent and neutral institution of justice, and you should not expect neutrality or justice from them [3, 4]. Instead, these institutions all have their

own self-interests [5]. Any internal committees they have set up to field such complaints about misconduct exist primarily to protect the self-interests of the institution, not to administer justice and promote ethics. The one and only goal of institutions is to protect themselves from lawsuits and/or bad press, because those consume their finances and damage their reputation (and thus their future revenues). Cases of misconduct will only receive a fair and objective review from courts of law or other external commissions with absolute nothing to lose by reaching a guilty verdict and proclaiming it publicly in full detail.

So never make a report or complain to your university or other institution, neither in writing nor orally, unless your lawyer advises you to do so and writes it for you. Anything you report to your institution will be used by their legal team to protect the institution and possibly to attack you. Do not be fooled by their pretenses to neutrality, whistleblower policies, and so on. If there is a problem, let your law firm handle it for you. Because of the potential legal issues, no university ethics board will ever provide feedback on anything you tell them, unless the university's legal team has assured themselves that there is no basis for your claims and wants you to stop complaining. If you bring research misconduct to light, it is probably a good idea to start looking for another job elsewhere. Even if you are entirely innocent, the institution will probably try to get rid of you, because your complaints are potentially damaging to their reputation. Moreover, it is usually easier for them to shoot the messenger than to address any real problems reported to them. Finally, whatever the situation is or however much it is harming you, do not take it personally or get too upset. Just follow your lawyer's advice and move forward. There is always some other better research paper you could be writing somewhere else instead.

Conclusion

The purpose of medical scientific research is to improve the health of humanity, by increasing our collective knowledge on how best to prevent, identify, and treat illnesses. People who want to do better medical research should commit themselves to serving that deeper purpose of medical research. Ethical guidelines on the performing and reporting of research serve as an initial explanation of how researchers are expected to behave. Ethical guidelines tell researchers what they should and should not do, but the guidelines are generally unable to provide guidance about why. Although researchers should always follow the explicitly recommended behaviors of the ethical guidelines, it is even more important to recognize the underlying, unspoken moral foundation of the guidelines, and then adopt that spirit in everything you do. Primarily that means recognizing that the only purpose of medical scientific research is to improve the health of humanity, by increasing our collective knowledge on how best to prevent, identify, and treat illnesses. Researchers who dedicate themselves to this intrinsic purpose of medical research will find that it goes a long way toward ensuring ethical conduct more reliably and robustly, right down into little detail choices that ethical guidelines often fail to consider. Dedication to this purpose of medical research has a further advantage besides ensuring better ethical conduct. People dedicated to this deeper intrinsic purpose of medical research will also find that it leads them toward accomplishing research with greater relevance and impact. Without this proper

deeper moral orientation, researchers inevitably drift down toward narrow technical studies on obscure topics. Their work then achieves their petty practical goals of career advancement and so on, but it has limited real impact on human health and knowledge. You should of course always read and follow the ethical guidelines. Yet ideally you should also honestly assess your motivations for doing medical research (rather than clinical care, non-medical research, or whatever else). And you should assess how well your motivations are aligned with the deeper inherent purpose of medical research – to improve the health of humanity, by increasing our collective knowledge on how best to prevent, identify, and treat illnesses.

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A practical guide to writing (and understanding) a scientific paper: clinical studies

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Fact Box 1

To become a medical writer, it is necessary to understand medical concepts and terminology, be familiar with relevant guidelines and the structure and content of specific documents, and, finally, have a good set of writing skills. A topic of interest, supported by current literature, should be identified and the work planned in an accurate way before starting the enrollment of the patients.

Introduction

Writing a scientific paper is a relevant part of the activities of medical doctors. Publishing and reviewing is becoming increasingly important for the progress of medical knowledge, offering the opportunity to share the results of the work that has been done or studying the work of other researchers. This is critical for the evolution of modern science, considering that the work of one scientist is based upon the results of others. Clinical outcomes can only be improved through

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research, education, and patient care. All these experiences are shared with the global community, primarily through peer-reviewed research papers and review articles [11, 15].

Two aspects are the most challenging. First the long time needed to obtain a paper of good quality and second the style of writing, generally regarded as less attractive when compared with surgical procedures. Some studies have attempted to analyze the most challenging topic at the beginning, identifying the cognitive burden, group support, and mentoring, the difficulty involved in distinguishing between content and structure, and the backward design of manuscripts as the most relevant [18]. When a medical doctor starts to write a paper, the motivation is crucial; however, the time that is needed to write without taking too much time from everyday clinical activities requires commitment. To become a medical writer, it is necessary to understand medical concepts and terminology, be familiar with relevant guidelines and the structure and content of specific documents, and, finally, have a good set of writing skills [19].

The aim of this paper is to provide tips acquired from authors attempting to help to write good-quality clinical papers without wasting their time and how to publish them in the appropriate journals. We have selected specific topics, which are analyzed in dedicated paragraphs. The different selections are how to choose the topic, find the current literature, analyze the data, structure the paper, write the paper, and handle references and some final tips on how to manage the submission process.

How to choose the topic of your work

Before beginning to enroll patients, to collect data, or to research the literature, the first step is to choose a topic of interest for your work [17, 23]. To do this, the best way is to ask your leader what is of interest, considering the trends in surgical procedures or the introduction of innovative techniques [21]. Once a topic has been identified, an accurate search of the literature, using the most common databases, can help the researcher to identify the actual "hot" topic in that specific field of research. It is necessary to know the timelines to follow, the data that should be collected, and the review/approval process to be followed.

Find current literature

Medical science is based on data available in the literature. The widespread availability of information due to the use of the Internet has given clinicians an opportunity to access the literature well. The most used database in which life sciences and biomedical papers are collected is MEDLINE (Medical Literature Analysis and Retrieval System Online, MEDLARS Online). PubMed is a free search engine primarily accessing the MEDLINE database of references and abstracts on life sciences and biomedical topics [8].

It is important to remember that PubMed should not be confused with PubMed Central, a free digital archive of articles, accessible to anyone from anywhere via a basic web browser. The full text of all PubMed Central articles is free to read, with varying provisions for reuse.

To obtain more effective results, there are some tips to take into consideration in terms of using PubMed. The home page has a link to some tutorials, which will help the researcher to use the search engine correctly. MeSH (Medical Subject Headings) is the NLM (National Library of Medicine)-controlled vocabulary thesaurus used for indexing articles for PubMed. This vocabulary helps to identify the correct words that should be used in medical research and helps the authors to find the correct subject headings. It is very important to remember that, in MeSH, the subject headings are arranged in a hierarchy and a search for a descriptor will include all the descriptors in the hierarchy below the given one [8].

Regional health and medical databases have been compiled by the WHO (World Health Organization) to complement the internationally known bibliographic indices such as MEDLINE.

The regional medical indexes, published by or under the auspices of WHO Regional Offices, provide access to bibliographic information about the health material published locally. They thus add a further dimension to the retrieval of information from developed country-oriented databases [10].

The Cochrane Library is a collection of databases in medicine and other health-care specialties provided by Cochrane and other organizations. At its core is the collection of Cochrane Reviews, a database of systematic reviews and meta-analyses that summarize and interpret the results of medical research. The Cochrane Library aims to make the results of well-conducted controlled trials readily available and is a key resource in evidence-based medicine [6, 9].

How to decide on the kind of clinical paper

There are different types of scientific article, some of which require original research (primary literature) and some that are based on other published work (secondary literature). It is important to have a clear idea about the different types of article that you can publish in a specific journal. Original research comprises studies based on clinical activities and is classified as primary literature. This group includes original treatment studies or observational studies. Treatment studies are mainly randomized, controlled, clinical trials (RCT) or adaptive controlled trials. Observational studies are cohort studies that are prospective, retrospective, case control, and cross-sectional and finally case reports. A review article surveys and summarizes previously published studies, rather than reporting new facts or analysis, and is for this reason called secondary literature.

One important step is to determine the level of evidence, i.e., a ranking system used to describe the strength of the results measured in a clinical trial or research study. The levels of evidence are an important component of evidence-based medicine (EBM), and understanding the levels and why they are assigned to publications and abstracts helps the reader to prioritize the available information. Many different ways of grading the level of evidence are described, and many journals assign a level to papers that they publish. Randomized, controlled trials are generally defined as level 1 of evidence, but some aspects have to be considered to assess the quality of the paper, including randomization, blinding, a description of the randomization and blinding process, and a description of the number of subjects who withdraw or drop out of the study; the confidence intervals relating to study estimates; and a description of the sample size calculation [5].

Although the goal is to improve the overall level of evidence in medical practice, this does not mean that all lower-level evidence should be discarded. Case series and case reports are important for hypothesis generation and can form the basis of more relevant studies [5, 13].

How to write the paper

Many techniques for writing a scientific paper in an effective way have been described [12, 16]. The formal Introduction, Methods, Results, and Discussion (IMRAD) structure of scientific papers was adopted in the 1980s. Nowadays, IMRAD is the format encouraged for the text of observational and experimental studies by the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," which has become the most important, widely accepted guide to writing, publishing, and editing in international biomedical publications [4]. The Uniform Requirements are released by the International Committee of Medical Journal Editors (ICMJE). Some types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or even unstructured formats [15]. Detailed suggestions on how to write the specific parts of the paper are available online at the ICMJE website. The UK National Knowledge Service provided funding to start the EQUATOR (Enhancing the Quality and Transparency of Health Research) project. This initiative seeks to improve the reliability of medical publications by promoting the transparent, accurate reporting of health research [1]. In the present article, the techniques most used by the authors are reported. If writers have a specific journal in mind in which to publish their work, it is crucial to read the instructions to authors and remember that many journals have open access instructions for reviewers. This is very useful, because it lets the researchers know which reviewer is going to check their work. The language must be correct and, if researchers do not write fluent English, it is suggested that they should use online services or mother tongue colleagues/copy editors. There are limits to word count, usually 3000–4000 words (different for different journals), and many papers are too long and may be rejected for that reason alone.

The following section will provide some tips for the correct writing of the different sections of a manuscript.

Fact Box 2

Clinical studies are written following the IMRAD structure since the 1980s (Introduction, Methods, Results, and Discussion). The abstract section should emphasize new and important aspects of the study or observations, without overinterpreting findings. The introduction should describe the background of the study and should finish with a statement of the clear aim of the study. Methods should explain the structure of the study, the way in which the results were obtained, and all the steps relating to patient management, from enrollment to final evaluation.

Abstract

The usual sections defined in a structured abstract are background/purpose, methods, results, and conclusions. The abstract should provide the background to the study and should state the aim, the basic procedures/methods (selection of study participants, settings, measurements, and analytical methods), the main findings (giving specific effect sizes and their statistical and clinical significance—but not repeat which statistical methods were used), and principal conclusions. The results section is the most important part of the abstract, and nothing should compromise its range and quality. It should emphasize new and important aspects of the study or observations, without overinterpreting findings. Most journals require abstracts that conform to a formal structure within a word count of 200–250 words. Even if the abstract is the first part of any article and the only section freely available in the most used search engine, it should be written after the paper is finished.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract [3, 7]. Level of Evidence is also frequently added at the end of the abstract.

Introduction

The scope of the introduction is to show what is already known on the subject of the paper and—more important—to introduce what is unknown to justify the structure of the study and what is intended to be examined.

Many reviewers regard the introduction as a section of little interest and general—and lengthy—considerations about the topic or common knowledge should be avoided.

The introduction should finish with a statement of the clear aim of the study, with primary and secondary outcomes considered, and the hypothesis of the investigation, at least for clinical studies.

Methods

The methods section is an exact description of the work done by researchers involved in the study and should explain the structure of the study, the way in which the results were obtained, and all the steps relating to patient management, from enrollment to final evaluation.

The first statements have to describe the research design, the clinical diagnosis of the patients recruited, and in most cases the setting of the study.

If the study compares the results of the treatment in different groups, these groups have to be described carefully. Randomization is of central importance in clinical trials because it reduces bias and represents a basis for ensuring the validity of data analysis using statistical testing. The generation of an unpredictable allocation sequence represents the first crucial element of randomization in a randomized, controlled trial [20]. The two fundamental characteristics of randomization are that researchers must be unable to predict the group to which a patient will be assigned until the patient is unambiguously registered in the study and that researchers are unable to change a patient's allocation once he/she has been randomized. Remember that randomization with a low-quality allocation sequence can result in a biased estimation of the treatment effect [14, 22].

The treatment given to patients has to be described in a detailed manner. The length of the study from enrollment to conclusion has to be reported. Outcome measurements using instruments or scoring systems should be described and explained. Care should be taken to select the appropriate outcomes for the specific disease or intervention; the outcome should have good reliability, validity, and sensitivity. When patient-reported questionnaires are used, it is important to report whether patients were blinded to the treatment received in the event of a randomized trial, in order to minimize the bias. It is also important to report whether the investigators that are dedicated to objective evaluations (e.g., clinical findings, radiographic measurements) were blinded to patient treatment. The primary and secondary outcomes must be clearly specified.

A crucial and often neglected section in a scientific manuscript is the statistical section. The software used for the statistical computation should be reported. Before performing the statistical analysis, the data should be tested for normality (e.g., using the Kolmogorov-Smirnov test), since the normal or non-normal distribution influences both the way measurements are reported (mean ± standard deviation for normal, median, and interquartile ranges for non-normal distribution) and the choice of statistical tests. When comparing two independent groups, the "independent sample *t*-test" and the "Mann-Whitney test" should be used for normally or non-normally distributed continuous measurements, respectively. When similar comparisons relate to the same group (e.g., pre- vs. post-treatment), the "dependent sample *t*-test" or the "Wilcoxon test" should be used analogously. If categorical variables (e.g., IKDC grade) are compared, the "chisquare test" should be used. If three or more groups are being compared, the "ANOVA" or "Kruskal-Wallis test" should be used in the event of normal or non-normal distribution, respectively. For correlation analysis, the Pearson or Spearman tests should be used when the distribution of the variables is normal or not normal.

In the case of RCTs, a sample size calculation is mandatory to establish the sample size, since there is a great risk that an underpowered study will suffer from a so-called beta error (type-2 error), thereby possibly missing the chance to show a statistically significant finding. The sample size calculation must be performed prior to the start of the study; there are commercially available programs that can easily be used for this purpose.

Fact Box 3

If there is a large volume of data, it is suggested that results should be reported in tables, while repetition in the text section must be avoided. The aim of the discussion section is to interpret and describe the significance of the study findings in the light of what was already known about the research problem being investigated and to explain the impact of the results on that specific topic.

Results

The results section is the most important and is often the only section that is of interest to a stressed reader. All data must be reported carefully, like the number of patients that completed the study, the dropout rates in the different groups, and eventually the dropout rate associated

with the specific treatment. It must be remembered that most quality score questionnaires regard a dropout rate exceeding 20% as an indicator of a low-quality study. The primary outcome results have to be expressed with statistical data. Any negative findings or unexpected collateral effects have to be reported. Based on normal or non-normal distribution, the standard deviations and the interquartile ranges should always accompany the mean and median value, respectively. If the number of patients included in the study is limited, individual patient data can be reported in a table.

If there is a large volume of data, it is suggested that they should be reported in tables, while repetition in the text section must be avoided. However, a summary of the main and most relevant findings is useful to the reader in order to focus on the results. All details can be given in tables and repetitions must be avoided.

Discussion

The purpose of the discussion section is to explain what your results mean and what contribution your paper makes to the field of study [22]. The aim of the discussion section is to interpret and describe the significance of the study findings in the light of what was already known about the research problem being investigated and to explain the impact of the results on that specific topic. Each of the main results of the study should be analyzed and discussed, possibly in the same order as they are reported in the results section. The discussion section is based on interpretation, which is a subjective exercise. For this reason, the author must avoid overinterpreting the results of the study, one of the most frequent errors made. On the other hand, the discussion section is not a repetition of the introduction or methods sections. The discussion section has to acknowledge any limitations of the study, especially in terms of the methodology, and any alternative explanations of the findings [2]. A concluding take-home message can restate the answer one last time and/or indicate the importance of the work by stating implications, applications, or recommendations [24].

References

Authors should provide direct references to original research sources whenever possible. Secondary references should be avoided. Science is based on the results produced by the scientific community, and the method the community uses to share results is publication in scientific journals. This database of information has become larger in recent years, thanks to the use of the Internet. This is an important opportunity for researchers who can access a great deal of information about a specific topic. Every published paper cites previous articles supporting the statements and background of the research, and these articles are cited at the end of the paper. References should not be used by authors, editors, or peer reviewers to promote self-interest. One suggestion for researchers is to use only references useful for the article, supporting specific purposes. Considering that science is always evolving and the impact of journals is different, references must be updated and, if possible, they should attempt to cite articles in the most relevant journals [15].

It is not superfluous to mention that references should be formatted and ordered according to the specific journal guidelines. All too often this is not adhered to.

How to manage the submission process

The submission process is the last step in the preparation of the article. This step is often complex, due to the different submission manager platforms at different journals. One suggestion to help researchers to make it easier is to prepare all the materials before starting the submission, also collecting information on ethics committees and clinical trial registration. More and more journals nowadays require a disclosure of financial conflicts of interest, which should be collected from every author, possibly before submission, especially in the case of multicenter studies. Sometimes, minor mistakes such as line numbering or line spacing determine the need for revision and time loss.

One useful tip is to check the PDF generated by the submission system to check for errors or mistakes.

Conclusion

Becoming a good scientific writer requires a long learning curve. The authors of this short guide feel that, to obtain good results in writing, a passion for clinical practice and being interested in analyzing the results of the clinical work are crucial. Writing and sharing the results of clinical work with others means taking part in something greater, whose aim is to obtain better results in the treatment of the patients.

Good luck!

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7

Ethics of scientific writing

Michael Hanna

Introduction

Scientific writing is the process of putting information and thinking into a final permanent report, so it can be read and used by other people. For any given research study, there are innumerable various ways to legitimately write that report (depending on what exactly the authors want to say and how). But readers expect that each journal paper corresponds appropriately to the research reported. The amount of writing published about a research study should correspond appropriately to the amount and value of the actual research performed, and the writing about that research should be original, scientific, and truthful. Ethical problems arise whenever there is a gross disconnection between the writing activity of the authors and the actual research they have done. So ethical scientific writing involves several issues: 1) avoiding plagiarism – the copying of someone else's expressions or ideas, 2) writing a report that is accurate and unbiased, 3) maintaining patient confidentiality, 4) not writing too many papers from a research study – so-called "salami publication", and 5) not failing to actually write-up and publish a peer-reviewed journal paper about a completed study.

No plagiarism

Plagiarism is the copying of someone else's expressions. Traditionally, it has been considered, along with fabrication and falsification, as one of the three major forms of research misconduct [1–3]. (Recent scholarship on research misconduct has displaced that traditional triplet with more useful taxonomies [3–6], but plagiarism is still viewed as serious misconduct.) Plagiarism usually refers to copying texts written by someone else or "borrowing" their underlying ideas, but it can also refer to copying their graphs, images, or other forms of expression. Plagiarism is a serious offense, and it can be sufficient grounds for retracting a published article [1, 7, 8]. Indeed, it seems that a much greater portion of journals are explicitly concerned about plagiarism or duplicate publication than about data fabrication or falsification [9], perhaps because the publishers of the journals view plagiarism and duplicate publication as infringing directly on their business interests.

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It was asserted that all research misconduct has one of three vices as its root cause: ignorance, laziness, or greed. This explanation is clearly applicable to plagiarism. Some people (mostly students) plagiarize because they do not know it is serious misconduct or because they do not fully understand how to properly cite other works or otherwise avoid it [10]. Other people (mostly early career researchers with poor motivations for being in research) are aware that they should not plagiarize but do it anyway, in order to reduce the amount of work they do to generate publications. And finally some people (mostly well-established researchers) plagiarize other people's work (especially unpublished cutting-edge ideas) to try to grab more resources (especially grants) for themselves. Whatever the cause of plagiarism, the consequence is that whenever someone is plagiarizing, he or she is failing to contribute anything new and instead is just taking credit for someone else's contributions. Plagiarism is essentially a form of theft of intellectual property – and the social recognition and material rewards that are received for that intellectual property [10, 11, 12]. Interestingly, disdain for plagiarists appears to be deeply rooted in human beings' way of viewing the world; it is not something artificial first learned in the university. Clever studies have shown that children as young as 6 years old express less approval of "copy-cats" [13, 14].

It has sometimes been asserted that researchers who are not native speakers of English need to copy other people's papers in order to express themselves in good English [15, 16]. That argument is pathetic rubbish [17]. Although it does usually require more time and effort to write in a foreign language than one's native language, that is no excuse for stealing someone else's work. And there is no validity to anyone's claims that they are less capable of originally expressing their own ideas and/or less capable of upholding high ethical standards, simply because they grew up speaking some language other than English. *Au contraire*, people who speak English as a second (or third or fourth or fifth) language are oftentimes *more* capable of expressing their own thoughts in their own words than are native speakers of English, because people who learn a second language become consciously aware of the medium of language that we all use to communicate our thoughts. (And for that reason among many others, everyone should learn at least one other non-native language.) Several people who were not native speakers of English became famous for literary works they wrote in English – Joseph Conrad, Joseph Brodsky, Jack Kerouac, Chinua Achebe, V.S. Naipaul, Arthur Koestler, Salman Rushdie, Kahlil Gibran, Vladimir Nabakov, and many others.

Never copy phrases or sentences from another source without citing that source. It is equally illegitimate to copy a sentence while replacing words with other synonyms to try to hide the copying. In that scenario, the plagiarist is still copying something that someone else wrote, and stealing credit for that person's thoughts behind the specific word choices. When you are drafting your papers, look inside your own head, and figure out what it is you want to say. If you need to, talk aloud to yourself or to someone else, to help you figure out what you want to say. When you think you know what you want to say, type it – in your own words. If you find yourself getting stuck at the keyboard, make an audio recording of yourself talking (either to yourself or to someone else), and then type it later from the audio recording. Don't worry about how good it is. It is only a first draft. You can revise and edit it later.

If you can speak your own thoughts in English, you can also write your own thoughts in English, without plagiarizing someone else's text. But if you find it difficult to express yourself in English as a foreign language, just write the first draft of your paper in your own native language. Then you can also publish it in a journal of your own native language. Or if you really want to publish your paper in English, you can translate it into English (or have someone else translate it for you). Indeed, you can even do both: publish your paper first in your own native language, and then publish a translation in English. Just be sure to tell the journal Editors when you submit the manuscripts about the other version in the other language.

When you do finally have something written down, if you know someone else has already said something similar, put a citation to their work at the end of your sentence. However, there is probably no need to try to cite multiple "sources", if you are writing something generic (e.g. "The study was designed as a randomized controlled trial") or if you are writing something that has already been said so many times that it has become common knowledge (e.g. "The limbic system regulates emotions"). But even in these cases, do not copy anything from a specific source; write what you want to say in your own words without using someone else's text as a model.

If you need to use material from another work, charges of plagiarism can be avoided by citing the source that you are summarizing. If you are quoting the exact words that were written by someone else, you should put their copied words inside quotation marks and cite your sources in the references. Yet the use of such direct quotations is rare in medical science. Direct quotations are usually only used in medical science if: A) the source quoted is a higher authority (e.g. a government report or an official document from a professional society) and consequently it is important to use their exact wording, or B) the source text is being quoted in order to emphasize and discuss the way those original authors worded their ideas (e.g. disputing their way of talking about the topic). Otherwise, the preferred standard approach in medical science to cite someone else's text is to summarize (or at least paraphrase) their text, without quotation marks, and cite the reference. Typically this means writing just one sentence to summarize an entire paper.

Completeness and balance

Research reports must be accurate, complete, and reasonably balanced [18]. In other words, errors, omissions, or bias are not merely low-quality work, they are viewed as unethical, just as carelessly providing sub-standard care to patients would also be viewed as unethical, not merely as low-quality medical services [19]. If you feel unable to write a research report that is accurate, complete, and reasonably balanced, seek out further education and/or training before continuing with research. Accuracy can usually be achieved almost completely by double checking and triple-checking every detail of everything you do, and then checking it again a few more times, and then asking a few other people to do the same. Completeness is much easier to achieve – just do not intentionally exclude anything that could be considered important. Writing a paper that is reasonably balanced can be somewhat more difficult to judge. It does not require writing something

that is neutral or agnostic about the topic. Researchers often have viewpoints about their topics, and these are a valuable component of scientific progress. But writing reasonably balanced reports requires thinking seriously about other competing interpretations of your results and other viewpoints and arguments about the topic.

Patient confidentiality

Your research report must maintain the confidentiality of the patients' identities and/or obtain their permission to publish the information, depending on the details of the content. Any photographs of a patient that might enable someone to identify him or her must be masked to the extent possible and require the patient's written permission to publish. Published radiographic images should not contain the patient's name or date of birth on them, as they often do in routine clinical practice. Case reports or other narrative accounts of a patient's medical condition or treatment history usually also require the patient's written consent to publish.

Avoid salami

Researchers are encouraged to avoid so-called "salami publication", which evokes the image of slicing a stick of salami into thin layers. "Salami publication" refers to the practice of unnecessarily dividing up the results of a study into two or more papers, for the main purpose of publishing more papers from a fixed amount of results [20, 21]. The consequence is that each paper contains less substantial content and readers have less information if they do not obtain and read the other papers. There may often be legitimate reasons to publish more than one paper from a study [21, 22], especially for major studies or if the target audiences are very different: for example, a multinational randomized controlled trial on a new treatment might yield one paper on the clinical outcomes for care-providers and another on the economic aspects for policy-makers. If instead the papers could be sensibly published all together but the investigators simply want to get more publications out of the study, then they are engaging in salami publication. Salami publication is not inherently unethical, but it is discouraged as a self-interested low-quality approach to reporting research [23, 24]. Journals usually also view it as wasteful of their resources [20, 24, 25]. And if readers and journal Editors are not clearly informed about the related papers, then salami publication is deceptive and unethical [25]. If researchers report substantially overlapping data in two or more manuscripts or papers, then what they are doing is not "salami publication", but "redundant publication" – a more unethical issue. Although the term "salami publication" refers to publishing, the problem actually arises during the writing of a study (or even earlier during the planning of the writing). So whenever you are writing a first draft of your research, it is preferable to pack as much of the results as sensible into just one paper. Do not try to divide up your results from the outset, unless there are clear justifications inherent in the contents. Always inform the readers and journal Editors of any other related publications or manuscripts in preparation.

The ethical obligation to write and publish

Finally, if you conduct research, you have an ethical obligation to write it up and publish it. The ethical obligation to write up and publish the research is usually incurred because most researchers say they will conduct the research according to ethical guidelines and those guidelines usually state that the researchers are obliged to publish the research [18]. But in any case, the ethical obligation to write up and publish the research is essentially an implicit obligation or debt to the people (or the animals) that participated in the research and to the people who paid the costs of the research. Unless there is a scientifically legitimate explanation, failure to write up and publish a research study means that the efforts and risks of the participants (or the lives of animal subjects) and the funders' financial resources have gone to waste [26–28]. Failure to publish the research would be a betrayal of their trust and support.

It does not matter if the results were negative or inconclusive. All research should be published, regardless of the results or conclusions, to prevent publication bias from distorting the overall sum of evidence available in the literature [29–32]. The only exception is when the research had problems that were sufficiently substantial to render the results not publishable, from a scientific viewpoint.

"Publication" here means some kind of peer-reviewed report in an indexed journal, (or in some special cases in a book). The obligation to publish research is not fulfilled by publishing a conference abstract, self-posting a webpage or other internet document, or publishing in a periodical that is not peer-reviewed and indexed. (Nonetheless, some of those actions might preclude subsequent publication at many peer-reviewed journals – especially if the copyright has already been transferred to a third party.) It is generally accepted that research conducted for an academic degree need not be published beyond whatever the university requires, (though it remains questionable why not).

Unfortunately, many studies are never published, simply because the investigators run out of time, budget, and/or interest [33–36]. But those are not really ethically legitimate reasons to not write up and publish a study; they are more akin to poor excuses for leaving debts unpaid. Such researchers should not undertake any new research, until they have published all the valid data that they already have.

Conclusion

The ethical issues that arise during the writing phase – plagiarism, incomplete or biased reporting, failure to maintain patient confidentiality, "salami" publication, and non-publication are quite different from each other. Yet what they all have in common is disregard for the community of readers and failure to understand writing as a social service for that community. Think of it this way. Non-publication is a like a party guest who sits silently in a corner refusing to talk with anyone else. "Salami" publication is like someone who hogs the conversation by talking endlessly in detail about one small event. Incomplete or biased reporting is like someone who spins fisherman's tales that lead people astray about what actually happened. And plagiarism is like someone

who, instead of adding something new to the dinner conversation, merely repeats what someone else just said ten minutes ago. So when writing your papers, try to keep an image in mind of the readers for whom you are writing. Then remember that writing is a social service you are performing for those readers, to share your new knowledge with them. They want you to be a good conversationalist. Writing is not merely the task of typing words on a computer to finish an assignment. Writing serves to communicate truthfully and socially with other human beings.

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Notes:

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BCAA support recommended by

AASLD[1] EASL[2] ESPEN[3] ISHEN[4]

- Helps restore BCAA:AAA ratio[5,6]
- Helps improve Hepatic Encephalopathy[6,7]
- Helps prevent progression of hepatic failure[6]
- Helps improve muscle mass[6]

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AASLD: American Association for the Study of Liver Diseases, **EASL:** The European Association for the Study of the Liver, **ESPEN:** European Society for Clinical Nutrition and Metabolism, **ISHEN:** International Society for HE and Nitrogen Metabolism.

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