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Diagnostic Indices for Vertiginous Diseases

Otmar Bayer[1*†], Jan-Christian Warninghoff[2†], Andreas Straube[3]

Abstract

Background: Vertigo and dizziness are symptoms which are reported frequently in clinical practice. We aimed to develop diagnostic indices for four prevalent vertiginous diseases: benign paroxysmal positional vertigo (BPPV), Menière's disease (MD), vestibular migraine (VM), and phobic postural vertigo (PPV).

Methods: Based on a detailed questionnaire handed out to consecutive patients presenting for the first time in our dizziness clinic, we preselected a set of seven questions with desirable diagnostic properties when compared with the final diagnosis after medical workup. Using exact logistic regression analysis diagnostic scores, each comprising of four to six items that can simply be added up, were built for each of the four diagnoses.

Results: Of 193 patients 131 questionnaires were left after excluding those with missing consent or data. Applying the suggested cut-off points, sensitivity and specificity were 87.5 and 93.5% for BPPV, 100 and 87.4% for MD, 92.3 and 83.7% for VM, 73.7 and 84.1% for PPV, respectively. By changing the cut-off points sensitivity and specificity can be adjusted to meet diagnostic needs.

Conclusions: The diagnostic indices showed promising diagnostic properties. Once further validated, they could provide an ease to use and yet flexible tool for screening vertigo in clinical practice and epidemiological research.

Background

Vertigo and dizziness are, like headache, very prevalent symptoms in daily clinical practice. The life time prevalence is estimated to be 20 - 30% [1]. For the symptom headache it was shown that a very simple screener with only three questions are able to differentiate headaches with a sensitivity of 0.81 (95% CI 0.77 to 0.85), a specificity of 0.75 (95% CI 0.64 to 0.84), and a positive predictive value of 0.93 (95% CI, 89.9 to 95.8) to predict a migraine [2]. Therefore we investigated whether such a screener which can be easily filled out by the patients during the time in the waiting room can be also developed for patients suffering from vertigo or dizziness. We focused our efforts on the differentiation of the most prevalent diagnoses benign paroxysmal positional vertigo (BPPV), Meniere's disease (MD), vestibular migraine (VM) and phobic postural vertigo (PPV) since these four diagnoses cover about 54% of all patients in a dizziness out patient unit [1]. The screener was developed by analysing a larger questionnaire, which was administered to patients presenting in a dizziness clinic at the neurology department of Munich university, a tertiary center for vertigo disorders.

Methods

We conceived a short questionnaire by analysing and subsequently condensing a detailed questionnaire designed for patients suffering from vertiginous diseases. The detailed questionnaire with specific questions about vertiginous diseases evolved on the basis of the pain questionnaire of the German Society for the Study of Pain http://www.dgss.org, chapter of the IASP. Data collection was done between 2003 and 2007. In order to get detailed and structured information about the history of the patients and

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the signs of the actual clinical symptoms we asked the patients to fill in the questionnaire. Since this data collection was introduced as a pilot, the questionnaire was handed out on predefined dates (usually once a week) to all patients presenting for the first time in the dizziness clinic on that day to obtain an unbiased sample. All patients gave their written informed consent to this procedure. Since the study was not experimental, and the data were gained in clinical routine, the approval of an ethics committee was not necessary. All data were anonymised. All patients were seen by two experienced neurologists who were blinded to the answers given in the questionnaire and received a complete medical work up with patients undergoing a clinical neurological examination, orthoptic examination, eye movement recording, and, if necessary, Doppler sonography of the cranial vessels, evoked potentials, cranial imaging and consultations of other specialities (e.g. ENT, ophthalmology, and psychiatry); for further details see [3].

The analyses were based on clinical diagnoses rather than on restrictive inclusion criteria, such as used e. g. in clinical trials. Although the latter approach has the advantage of high diagnostic accuracy, it restricts the study sample to typical patients with clear syndromes, which does not always match with clinical reality. Diagnostic criteria applied in the clinic were: for PPV as described by Brandt [4]. BPPV was diagnosed if reproducable by positioning maneuvers, or in case of a distinctive history with other causes ruled out. MD according to the AAO-HNS [5, 6] criteria, if hearing loss was not audiologically documented before or in the ENT department, anamnestic hearing loss was accepted. VM patients fulfilled the criteria of definite or probable migrainous vertigo [7].

We developed diagnostic indices for the four most frequent diagnoses: PPV (n = 53), BPPV (n = 19), VM (n = 14) and MD (n = 11). First we screened the detailed questionnaire for items potentially useful for diagnostic indices:

- The kind of vertigo (rotational vertigo, unsteadiness, feeling of being in a lift, lightheadedness)
- Perception of the environment (like on a roundabout, like on a boat, very blurred)
- The occurence of vertigo (in attacks, persistent, persistent with attacks)
- Duration of attacks (seconds, minutes, hours, days, more than one week)
- Intensity of vertigo attacks and intensity of persistent vertigo (intensity scale from no vertigo "0" to the most intense possible vertigo "10")
- Trigger with pre-formulated answers: "alleviating", "no influence" or "amplifying" (physical load, psychological load, darkness or bad sight, turning while staying in bed, head inclination, bending down, raise, relaxing itself, shaking the head, cough, large heights)
- Concomitant symptoms with pre-formulated answers: "always", "frequently", "occasionally", "never" (vision disorders, diplopic images, speech disorder or dysphagia, paraesthesia, paralysis, sweating, drop seizure, headache, defective hearing, ear noises, nausea, vomiting, impaired consciousness)

After screening of the larger questionnaire the following items were chosen for further investigation: The kind of vertigo (rotational vertigo, unsteadiness, feeling of being in a lift, lightheadedness), perception of the environment (like on a roundabout, like on a boat, very blurred), and the concomitant symptoms defective hearing, ear noises, nausea, vomiting, sweating, drop seizures with pre-formulated answers "always", "frequently", "occasionally", "never".

Sensitivity, specificity, positive and negative predictive value with respect to the four main diagnoses were calculated for these questions (Table 1). Based on the positive likelihood ratio (i. e. sensitivity/(1 - specificity), primary criterion) and the other test measures mentioned above, variables were built and preselected as candidates to be included in the diagnostic score. To build the diagnostic score multivariate logistic regression modelling was applied using a backward elimination strategy for variable selection. The full model included all preselected variables. The effect estimates with the highest p-values were identified and the corresponding variables were removed successively until only effects significantly differing from 0 with $p < 0.20$ were left in the model. The linear predictor of the resulting final model was used as the diagnostic score, and calculated for each patient with sufficient data. Finally, receiver operating characteristics (ROC) curves were drawn, where the area under the curve (AUC) served as a measure of the diagnostic index's test power. An AUC of 1 indicates a perfect test.

The whole selection and modeling procedure was done separately for the four diagnoses. To address the problem of collinearity in multivariate modelling, we computed Spearman's rank correlation coefficients supplemented by a priori knowledge to identify prediction variables of similar content (rho >= 0.5). Whenever two such variables (e.g. rotational vertigo and like on a roundabout) appear in a model, the effect estimates are likely to become insignificant. In these situations we tried replacing the variables by one indicating, if at least one of the underlying questions was answered positively; in case of the example rotational vertigo or like on a roundabout. In cases of doubt we favoured the model resulting in the better AUC. A useful side effect is that this approach also increases the proportion of evaluable scores in case of incompletely filled in questionnaires.

Due to a limited number of cases for some diagnoses, some cells in the contingency tables happened to be empty (e. g. none of the MD patients indicated having persistent vertigo). This

Table 1: Sensitivity and specificity of the items included in the diagnostic indices.

	PPV		BPPV		MD		VM	
	sens.	spec.	sens.	spec.	sens.	spec.	sens.	spec.
occurrence of vertigo								
in attacks	0.32	0.28	0.74	0.47	0.91	0.48	0.79	0.47
as persistent v~	0.38	0.91	0.00	0.76	0.00	0.78	0.00	0.77
kind of vertigo								
rotatory vertigo	0.21	0.25	0.79	0.62	0.64	0.57	0.79	0.60
unsteadiness	0.64	0.68	0.16	0.43	0.46	0.51	0.43	0.50
lift feeling	0.15	1.00	0.00	0.89	0.00	0.91	0.00	0.90
lightheadedness	0.40	0.79	0.11	0.64	0.09	0.66	0.43	0.71
perception of environment								
like on a roundabout	0.26	0.26	0.79	0.58	0.64	0.51	0.77	0.54
like on a boat	0.64	0.65	0.32	0.46	0.46	0.50	0.31	0.47
very blurred	0.21	0.98	0.00	0.85	0.00	0.87	0.08	0.88
ear noises								
never - occasionally	0.70	0.33	0.88	0.35	0.10	0.23	0.86	0.34
frequently - always	0.30	0.68	0.12	0.66	0.90	0.75	0.14	0.62
defective hearing								
never - occasionally	0.89	0.30	0.94	0.23	0.10	0.11	0.86	0.21
frequently - always	0.11	0.68	0.06	0.77	0.90	0.89	0.14	0.65
nausea/vomiting/sweating								
never - occasionally	0.65	0.59	0.78	0.52	0.20	0.41	0.07	0.38
frequent - always	0.35	0.40	0.22	0.48	0.80	0.58	0.93	0.62
drop seizure								
never - occasionally	0.80	0.24	1.00	0.27	0.50	0.23	0.64	0.19
frequently - always	0.20	0.76	0.00	0.73	0.50	0.82	0.36	0.81

Note that the cut-off points for the ordinal variables ear noises, defective hearing, nausea/vomiting/sweating, and drop seizures were chosen arbitrarily and do not necessarily match those of the diagnostic indices.

causes the problem of quasi-complete separation of the data, which corrupts the corresponding maximum likelihood estimates in the usual logistic regression. This problem is commonly circumvented by excluding the respective variables. However, when building diagnostic indices, such a procedure could lead to the exclusion of variables with high sensitivity or specificity. We therefore applied exact logistic regression using Firth's 2nd order bias correction [8–10], a method, which is now available in major statistical software packages, that has been demonstrated to give proper results in the situation just described [11].

Results

Of 193 patients 131 (74 female and 57 male, mean age 54, ranging from 16 to 90 years) were included, while the remaining 62 patients were excluded because of missing data or missing consent for this observational study.

Diagnostic Index for PPV

After the selection process described in methods, the calculation of the diagnostic score for PPV was reduced to five items as detailed in Table 2. When a cut-off point of 0.31 is used, this diagnostic index had a sensitivity of 73.7% and a specificity of 84.1%. The ROC curve in Fig. 1 depicts other sensitivities/specificities that can be obtained by using other cut-off points. If, for example, a very high sensitivity of 0.97 is desired, the specificity would be lowered to 1 - 0.48 = 0.52. The area under the curve was 0.845.

Diagnostic Index for BPPV

The diagnostic index for BPPV used two more items; the AUC of the ROC was 0.943. Using -1.22 as the cut-off point resulted in a sensitivity of 87.5%, specificity of 93.5% and a positive predictive value of 73.7% (Fig. 1).

Diagnostic Index for MD

The diagnosis of MD was predicted by vertigo appearing in attacks, the kind of vertigo, the perception of the environment as well as the concomitant symptoms: ear noises and nausea, sweating, vomiting. The odds of the outcome MD were associated with an increasing frequency of these vegetative symptoms in a quite log-linear fashion. At a cut-off point of 6.70 a sensitivity of 100% and a specificity of 87.4% were computed for this diagnostic index, while the AUC was 0.988 (Fig. 1).

Diagnostic Index for VM

The diagnostic index for VM contained persistent vertigo, rotational vertigo or perception of the environment like on a roundabout, defective hearing or ear noises, and sweating/nausea/vomiting. Using a cut-off point of 2.81 resulted in a sensitivity of 92.3% and specificity of 83.7%, the AUC was 0.894 (Fig. 1).

Discussion

The diagnostic indices were developed as an instrument to preselect patients with vertiginous diseases using a simple screener on the basis of self reporting. Such a screener can never completely replace a medical consultation and a clinical examination of the patient. This is especially true for patients suffering from vertigo of multiple causes, e. g. PPV following organic vestibular disorders, or complicated BPPV. However, it can help to save time by allowing the examination to focus directly on the main symptoms. Furthermore, it may be a useful tool in epidemiological studies.

In the progress of building the diagnostic indices we noticed that in some cases characteristics individually had a relatively low sensitivity and specificity but that the sensitivity and specificity increased in combination with other characteristics.

PPV

As expected, the construction of the diagnostic index for PPV turned out to be intricate, since the characteristics hardly had a sufficient sensitivity and specificity. In some cases an earlier specific vertigo disease (e.g. vestibular neuritis) can form the base of PPV [12], so the diagnostic index ought to include modified symptoms of the initial organic vertigo disease with the aid of variable combinations of characteristics.

BPPV

While the clinical diagnosis of BPPV is quite straight forward, the symptoms of BPPV may be caused by different vertiginous diseases. Vestibular migraine imitates the symptoms of BPPV in some patients [13]. Furthermore, there seems to be a statistical connection between BPPV, MD and VM, without sufficient knowledge about the underlying pathophysiology [14]. Since they are typical BPPV symptoms, rotational vertigo and feeling "like on a roundabout" not surprisingly met the preselection criteria described in methods. Both were tested independently and combined as a composite variable (rotational vertigo OR roundabout) to resolve potential collinearity issues. Interestingly, including unsteadiness - which is a negative predictor of BPPV as can be seen from the negative sign in Table 2 - turned out to have better predictive power, than including rotational vertigo or feeling "like on a roundabout". Although the items used in our questionnaire were not specifically designed for BPPV, the sensitivity (0.875) and specificity (0.935) of the diagnostic index fit well with another study which reported a sensitivity of 0.88 and a specificity of 0.92 for recurrent attacks that lasted less than one minute and typical head movement that activates vertigo [15]. This combination of characteristics had a sensitivity of 0.38 in patients with BPPV in our study, since the sensitivity for vertigo attacks that lasted only seconds had a sensitivity of 0.38. Furthermore typical head movement as a trigger for vertigo had an equal sensitivity in patients with BPPV, PPV, MD and VM. The prevalence of rotational vertigo in BPPV patients was very similar (0.86 compared to 0.79 in our study).

MD

Amongst other variables, the initial prediction model for MD contained the well-established triad rotational vertigo (sensitivity 0.64), ear noises and defective hearing. However, defective hearing was dropped during the selection process and thus does not appear in the final diagnostic index. Being aware of the triad, we tried a composite variable (defective hearing OR ear noises). However, omitting ear noises finally led to the better model. In comparison, a structured questionnaire on vertigo tested in a sample of 100 vertigo patients with a MD prevalence of 5% revealed a sensitivity, specificity and positive predictive value of 0.80, 0.97, and 0.57, respectively[16].

VM

The combinations of symptoms appeared heterogeneous in patients with VM. Rotational vertigo had the highest sensitivity (0.79) but showed the same sensitivity in patients with BPPV and MD. This was already noticed in a former study [13]. According to the findings of Neuhauser and colleagues, the typical duration of attacks varies among patients and thus is not sufficiently specific [7]. The concomitant symptoms sweating/nausea/vomiting, which can also be found in the IHS criteria for migraine elevated the sensitivity and specificity of the diagnostic index. VM has already been characterized as "the chameleon of vertiginous diseases" due to the extreme variations of symptoms which may last from minutes to hours [17]. Nevertheless, the diagnostic index achieved a good sensitivity and specificity. In the ID migraine validation study, among patients presenting for routine primary care appointments and reporting headaches in the past three months, a subset of three questions was identified that revealed a sensitivity, specificity, and positive predictive value of 0.81, 0.75, and 0.93, respectively [2]. The much higher positive predictive value can be attributed to a higher prevalence of VM patients in this setting.

There are only a small number of other studies which have tried to establish a diagnostic questionnaire for vertigo. Most other studies have focused on the impact of vertigo on the quality of life or tried to estimate the subjective severity of vertigo. As there are established vertigo questionnaires designed for the

Table 2: Calculation of the diagnostic scores for PPV, BPPV, MD, and VM.

Question - Item/answer	PPV	BPPV	MD	VM
How does your vertigo occur?				
in attacks	0		3.77	
as persistent vertigo	2.22	-2.35		-1.79
as persistent vertigo with attacks	1.65			
What kind of your vertigo do you have?				
rotational vertigo	-1.48[1]			1.55[1]
unsteadiness		-3.26		
feeling of being in a lift	1.79	-3.06		
lightheadedness			-2.54	
How do you perceive the environment during vertigo?				
like on a roundabout	-1.48[1]			1.55[1]
like on a boat				
blurred		-3.42	-3.74	
How often do you have defective hearing?				
never				
occasionally				-1.14[2]
frequently				-1.14[2]
always				-1.14[2]
How often do you have ear noises?				
never				
occasionally				-1.14[2]
frequently				-1.14[2]
always		-3.03	5.42	-1.14[2]
How often do you have sweating/nausea/vomiting?				
never			0 = 0 · 0.98	
occasionally			0.98 = 1 · 0.98	
frequently		-1.21[1]	1.95 = 2 · 0.98	2.82
always		-1.21[1]	2.93 = 3 · 0.98	
How often do you have drop seizures?				
never				
occasionally				
frequently	1.70	-2.95[2]		
always		-2.95[2]		

For answers marked in the questionnaire, the corresponding numbers are added up. Items marked with the same superscript number within one diagnosis are scored only once. E. g. the score for PPV of a patient reporting "rotational vertigo" or "perception of the environment like on a roundabout" (both marked by 1) will be diminished by 1.48 no matter whether this patient reports both or only one of these two symptoms. Patients are allowed to check only one answer per question, except for the 2nd and 3rd question.

purposes just described, it may be effective to extract diagnostic information from these tools. A study identified a subset of items from the dizziness handicap inventory (DHI) to detect BPPV in 373 patients referred to a tertiary center [18]. The resulting score was reported to have a maximum positive likelihood ratio of 2.29 as compared to 13.5 in the present study.

A study about the role of open-ended questionnaires conducted in 54 patients [19] suffering from vertigo, supported our

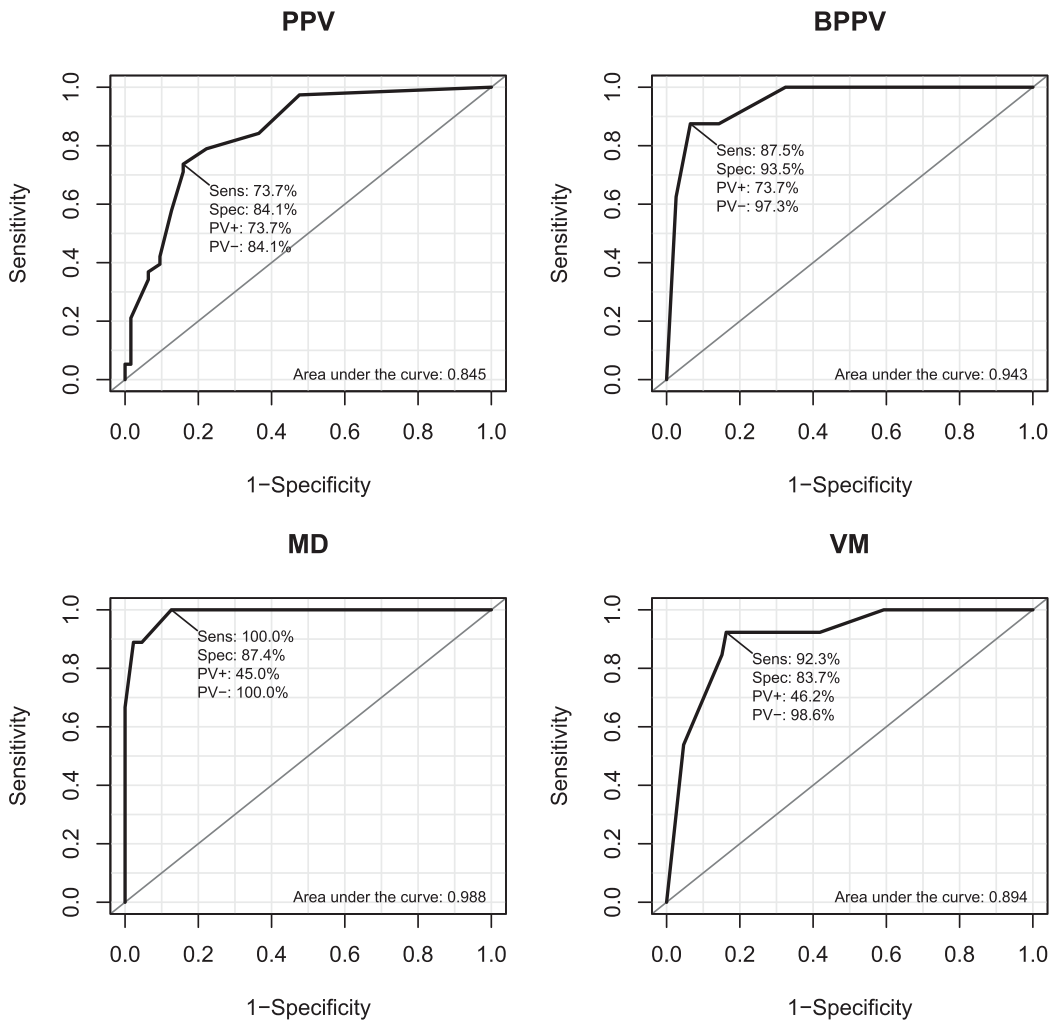

Fig. 1: ROC curves of the diagnostic score for phobic postural vertigo (PPV), benign paroxysmal positional vertigo (BPPV), Menières disease (MD), and vestibular migraine (VM). Abbreviations used in the figure: Sensitivity (Sens), Specificity (Spec), positive predictive value (PV+), negative predictive value (PV-).

methods: When questions had a number of possible answers, patients were more likely to report their symptoms in full.

Another study in 57 patients used a matrix classification based on type, episodic vs. persistent vertigo, and hearing loss to assign one of the diagnoses BPPV, MD, vestibular neuritis or labyrinthitis [20]. By comparison, the sensitivity and specificity of this tool were 0.50, 0.89 for BPPV, and 0.73, 0.81 for MD, respectively.

It should be noted, that we did not confine the patients to those given one of the four diagnoses investigated; 26% had other diagnoses. This reflects the clinical situation, where a patient complaining of vertigo is presented to the doctor, rather than a patient which is a priori known to have either PPV, BPPV, MD, or VM with the doctor only having to pick one out four possible diagnoses.

62 (32%) of the eligible patients could not be included in the analysis, most of them because of not returning the questionnaire. Keeping in mind, that the original questionnaire where the items for the diagnostic indices were embedded was 16 pages long, it is very likely to obtain better participation in future studies by shortening the questionnaire. A summary of the patients excluded has been published before ([3]http://www.biomedcentral.com/1471-2377/9/29, Table five). An overrepresentation of one of the four diagnoses of interest among these patients could give rise to concern that the questionnaire is not suitable to a specific group of patients. Compared to the patients included (PPV 53 (40.5%), BPPV 19 (14.5%), MD 11 (8.4%), VM 14 (10.7%)) such overrepresentation was not found, except for MD (12.9 vs. 8.4%, p = 0.43).

The limitations of our study include the small number of patients with MD (n = 11) and VM (n = 14), and the findings should therefore be considered preliminary. A test with a larger number of patients could help to prove whether the sensitivity and specificity of the screener hold importance. The diagnostic

index was developed in patients referred to our outpatient clinic, which is a tertiary center for patients with vertigo and dizziness. In the majority of cases these patients suffer from chronic vertigo and were referred to our outpatient clinic after several consultations with medical specialists. This probably results in an overrepresentation of patients who were less easy to diagnose. The calculated sensitivity and specificity values may therefore be even better in unselected patients e. g. in a general practitioner's practice.

The advantage of our diagnostic indices is the development of one screening questionnaire with identical questions for four vertiginous diseases.

Conclusions

We proposed a short screener, from which diagnostic scores for four prevalent vertiginous diseases can easily be calculated. Although cut-off points were provided, the clinician or researcher may vary them to achieve better sensitivity or specificity as needed in the particular setting. The scores can also easily be converted to odds ratios (OR = e^{score}) if desired. The test properties are promising and further validation in other populations is warranted.

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Authors' contributions: OB did the statistical analysis, drafted the manuscript, and recruited patients. JW drafted the manuscript, and was responsible for the data management. AS conceived the study, contributed to the manuscript. All authors read and approved the final manuscript.

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Back into the Wild: How Resistant Pathogens Become Susceptible Again?

Solen Kernéis[1,2,3*], Sandrine Valade[4], Paul-Louis Woerther[5,6]

Historically, every large-scale antibiotic use was followed by the emergence and selection of resistant strains. This dogma was already true at the time of Fleming, since first description of a penicillin-resistant *Staphylococcus aureus* isolate in the 40s. Despite the large panel of antibiotics made available since that time, this sequence has thereafter never been denied. In certain species, emergence of resistance is linked to the great plasticity of bacterial genomes, which enables occurrence of mutations secondarily selected by antibiotic pressure. In other species, resistance results from the acquisition of pre-existing genes through mobile genetic elements, which generally originate from environmental bacteria progenitors.

Reversion of resistance can occur either at the strain-level, through mutations or loss of resistance genes that restore the antibiotic-susceptible phenotype [1]; or at the population-level, basically relying on a temporal change in the equilibrium between susceptible and resistant strains within a bacterial population (Fig. 1). These dynamic trends are relatively easily captured by surveillance of phenotypic in vitro susceptibility or ad hoc epidemiological studies. Underlying mechanisms involve multiple and complex factors, which remain mostly unexplained and unpredictable, as illustrated for the three following microorganisms associated with significant burden in Intensive Care Unit (ICU) patients.

Methicillin-resistant *Staphylococcus aureus*

Staphylococcus aureus is a leading cause of severe community and hospital-acquired infections (device-related bacteremia, infective endocarditis). A rapid spread of Methicillin-resistant *Staphylococcus aureus* (MRSA) in the 90s led to implement infection control programs (based on active surveillance, barrier precautions and alcohol-based hand-rub solutions) in ICUs worldwide. Although MRSA-related invasive infections subsequently decreased in the UK, the US, Australia and France [2], similar trends were observed in settings without prevention programs [3]. Today, MRSA is still circulating in geographical areas where these programs were implemented (i.e., most of the US states). This paradoxical evolution can partly be explained by the shift in circulation of epidemic clones. Indeed, since the 2000s, the epidemiology was marked by the emergence of Community Associated-MRSA clones that rapidly spread and even replaced hospital acquired-MRSA clones [4]. These clones (i.e., USA300 lineage) differ by smaller SCCmec types (the cassette encoding methicillin resistance), less co-resistance and the presence of different virulence factors profiles, that may be involved in their success and fitness. Reasons for rise and fall of specific clones, including the USA300, and the respective role of infection control protocols and antibiotic use still remain obscure.

Streptococcus pneumoniae

Streptoccus pneumoniae (*Sp*) is a leading cause of community-acquired life-threatening invasive infections (pneumonia, meningitis and bacteremia). Since the 2000s, a continuous decrease of the incidence of penicillin-non susceptible invasive pneumococcal disease was reported in several countries [5]. Nasopharyngeal carriage of *Sp* is frequent, therefore exposing to bystander selection, i.e., inadvertent pressure imposed by antibiotics on commensal bacteria, other than the targeted pathogen [6]. Countries with high antibiotic consumption have higher rates of non-susceptible Sp. Moreover, reduction of antibiotic pressure significantly reduces colonization with resistant Sp strains [7]. Both 7-valent (PCV7) and 13-valent (PCV13) pneumococcal conjugate vaccines target serotypes associated with high virulence and

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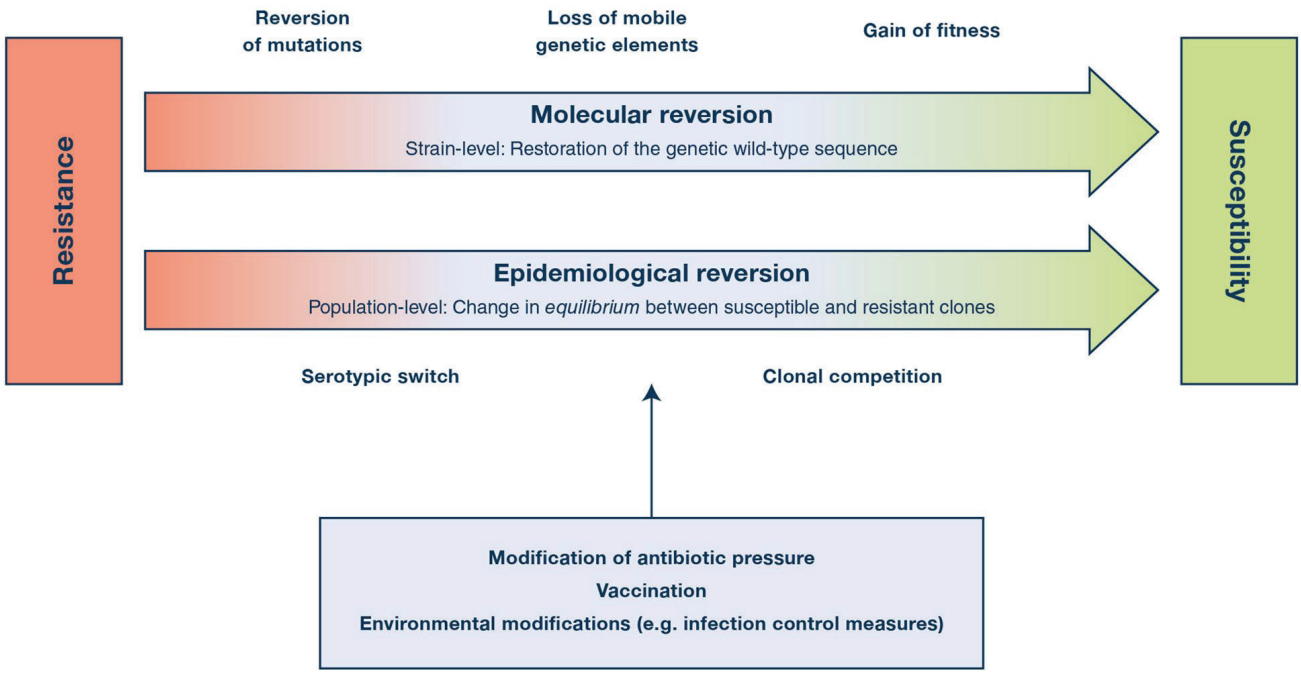

Fig. 1: Overall representation of the forces that drive reversion of bacterial resistance. Reversion of resistance can occur at the strain-level through mutations or loss of resistance genes that restore the antibiotic-susceptible phenotype, or at the population-level, basically relying on a temporal change in the equilibrium between susceptible and resistant strains within a bacterial population. Intrinsic biological determinants involved in the success of high-risk clones (e.g., virulence factors, plasmid compatibility, co-resistance to other antibiotics, etc.) are not represented on this figure.

antibiotic resistance. In France, after successive implementation of a national plan for decreasing antibiotic use and two vaccination campaigns (PCV7 and PCV13 in 2003 and 2010, respectively), an overall reduction of resistance in Sp was reported [5]. This reduction was largely driven by a decrease of penicillin non-susceptible serotypes included in vaccines. Interestingly, introduction of PCV7 was initially followed by an overall, though moderate, increase of pneumococcal meningitis. One hypothesis is that reduction of antibiotic use resulted in a positive selection of penicillin-susceptible strains that show higher transmissibility and invasiveness [8]. This illustrates both the key role of antibiotic pressure and the competition between susceptible and resistant strains in modulating the effects of vaccines.

Pseudomonas aeruginosa

Pseudomonas aeruginosa (*Pa*) is mainly involved in healthcare-associated infections, particularly in ICUs. Emergence of resistance in Pa mostly relies on chromosomal genes regulations or mutations and, to a lesser extent, transferable enzymes [9]. Between 2014 and 2017, a small but significant decreasing trend of resistance to piperacillin/tazobactam, aminoglycosides and carbapenems was reported in Pa strains collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net, https://www.ecdc.europa.eu). Previous exposure to antibiotics is a well-known risk factor for infections caused by resistant Pa strains. However, the reverse effect—that is, reduced consumption of antibiotics bringing Pa back to susceptibility is unclear. Retrospective studies showed that antimicrobial stewardship programs were associated to a slight decrease of imipenem-resistant Pa in ICUs [10], with heterogeneous results [11]. And interestingly, multi-drug resistant strains belong to specific clones with enhanced capacity of biofilm formation and higher spontaneous mutation rates [9].

The above examples illustrate how forces shaping the epidemiology of resistance are complex. In the ICU, where antibiotic pressure is high, other factors such as clonal dissemination, serotypic switch induced by vaccination, infection control strategies, as well as potential confounding factors (i.e., changes in sample collection strategies, setting and patient populations, revisions of clinical breakpoints for particular species) likely play a central role. To date, the impact of resistance reversion on mortality, length of stay and costs is still marginal in the ICU, compared to the considerable burden of multidrug-resistant Gram negative bacteria (GNB) [12]. Moreover, these dynamic trends must be confirmed before considering revising antibiotic protocols in critical patients.

Multidrug resistance in GNB is now the most urgent threat in the ICU. This trend however reflects more complex realities, as illustrated by several recent reports: the concomitant emergence of both susceptible and resistant *E. coli* clones in blood stream infections in England [13], the restoration of carbapenem susceptibility after acquisition of resistance to ceftazidime-avibactam in KPC-producing *Klebsiella* [14], and the significant fitness cost that potentially disadvantages polymyxin-resistant *Klebsiella* strains carrying the mcr-1-plasmid [15]. These examples illustrate that antimicrobial resistance should not be regarded as fate. In this light, specific surveillance protocols including both susceptible and resistant clones could provide valuable information to anticipate future emergencies and determinate the most appropriate actions. The complex mechanisms underlying reversion to susceptibility are currently largely unexplored and constitute an outstanding issue for future research.

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Iron Replacement in Inflammatory Bowel Diseases: An Evolving Scenario

Fabiana Busti[1], Giacomo Marchi[1], Domenico Girelli[1]

Iron deficiency anemia (IDA) represents the most common extra-intestinal complication in patients with chronic inflammatory bowel diseases (IBD) [1, 2]. Iron deficiency (ID), even without anemia, negatively impacts on patients' quality of life, and is associated with the development of various comorbidities and an increased risk of hospitalization [3]. Thus, timely correction of ID, before anemia develops, is a major goal in IBD patients.

Historically, oral iron salts (typically ferrous sulfate) have been generally considered the standard first-line therapy for IDA, especially when anemia is mild and/or paucisymptomatic. The recommended daily dose for adults with ID is 100 to 200 mg of elemental iron. Although oral iron salts are safe, relatively inexpensive and widely accessible, their use is associated with several gastrointestinal adverse effects (AEs), such as nausea, constipation, diarrhea, and abdominal pain that can arise in up to 30–70% of patients [4]. Such AEs are particularly relevant in IBD patients, as they already have a damaged intestinal mucosa [5] and lead to premature discontinuation of oral iron in more than half of the subjects [6]. This compromises efficacy, since only a small amount (10–20%) of traditional oral iron formulations is absorbed in the duodenum, and consequently a prolonged intake (at least 3–6 months) is needed to normalize hematopoietic status and replenish iron stores, which in turn is essential to prevent short-term recurrence of ID/IDA. As a matter of fact, a number of reasons may argue against the use of oral iron in IBD. First, non-absorbed iron (near 80% of ingested doses) may further damage the intestinal mucosa through a direct toxic effect due to the production of reactive oxygen species [ROS] [7]. The residual iron has also been demonstrated to be able to modify the gut microbiome, thereby promoting local inflammation [8, 9]. Moreover, recent experiments in anemic mice have shown that a 2-week treatment with low doses of ferrous sulfate induced an increased expression of several inflammatory markers, including C-reactive protein and Interleukin-6 [10]. Local and systemic inflammation may further hamper intestinal iron absorption via the up-regulation of hepcidin, the key regulator of iron homeostasis [11-13]. Indeed, some studies have reported a worsening of disease activity scores in IBD patients treated with oral iron [5].

In recent years, iron replacement therapy has been revolutionized by the introduction of novel intravenous (IV) iron preparations (e.g., ferric carboxymaltose) [14]. These "third-generation" formulations allow the rapid correction of ID with few administrations (e.g., just one or two infusions 1-week apart) and have a reassuring safety profile [14]. However, at least for the moment, they can be administered only in hospital setting, causing patients' discomfort and loss of working days. Of note, despite optimal correction of ID, anemia tends to recur in more than 50% of IBD patients within 10–12 months [15], resulting in the need of repeated infusions. While the long-term safety of repeated high-dose IV iron infusions in terms of susceptibility to infections or ROS generation remains to be fully evaluated, this approach has become increasingly popular and implemented in clinical guidelines [16].

Nevertheless, the development of newer oral iron preparations designed to increase absorption and decrease gastrointestinal AEs has led to reconsider the use of oral iron in IBD patients. One of these innovative preparations is "sucrosomial" iron (SI), which is a source of ferric pyrophosphate protected by a phospholipid bilayer membrane plus a sucrester matrix [17]. Based on in vitro experiments, it has been postulated that SI absorption takes place through a yet not fully elucidated mechanism based on the formation of vesicle-like structures able to bypass the conventional iron absorption pathway mediated by divalent metal transporter-1 (DMT-1) [18]. Moreover, SI administration in a mouse model of IDA did not induce hepcidin increase or any inflammatory response [10].

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In the issue of Internal and Emergency Medicine, Abbati and co-workers investigated the effects of low-dose SI (30 mg/day for 12 weeks) in 30 uncomplicated IBD patients with mild anemia and ID (Hb levels 11.0–11.9 g/dl in females and 11.0–12.5 g/dl in males; transferrin saturation <20%) [19]. At the end of treatment, patients had a mean Hb increase of 0.7 g/dl, while in about 30% the mean Hb increase was>1 g/dl. Although the hematological response was mild, it was statistically significant and could be considered relevant in view of the low dose and the very low frequency of gastrointestinal AEs. Indeed, more than 80% of patients completed the scheduled treatment. SI treatment was also associated with a significant increase of transferrin saturation (from 11 to 17%). While this study is limited by the small sample size, the results are in accordance with other published case series [17]. Besides SI, other novel oral compounds (e.g. ferric maltol) have been proven effective in IBD patients unresponsive or intolerant to traditional oral iron salts [3, 20]. The use of the latter compounds is also under critical revaluation, in light of the impressive advance in our knowledge of pathophysiology of iron deficiency [14]. Indeed, recent elegant studies in non-anemic ID women have shown that low doses of ferrous sulfate given on alternate days were as effective as the classical daily schedule and much better tolerated [21] [22]. While daily iron doses increased hepcidin for up to 24 h[21], the alternate day regimen allowed sufficient time for hepcidin return to baseline, hence optimizing fractional iron absorption and reducing gastrointestinal exposure to unabsorbed iron, ultimately leading to improved tolerance [22].

In summary, iron replacement therapy with oral compounds is facing a new era after decades of stagnation. Regarding IBD, larger trials, including patients with clinical features less selected as compared to the trial by Abbati *et al.*, are needed to clarify whether or not new preparations and regimens will be actually viable alternative to current protocols. If the benefits suggested by the study of Abbati *et al.* will be confirmed, the future approach to mild IDA could change in several areas beyond gastroenterology.

Compliance with ethical standards

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Professional Development

Feedback Redefined: Principles and Practice

Subha Ramani[1], Karen D. Könings[2], Shiphra Ginsburg[3], Cees PM. van der Vleuten[2]

Feedback is defined as a regulatory mechanism where the effect of an action is fed back to modify and improve future action. In medical education, newer conceptualizations of feedback place the learner at the center of the feedback loop and emphasize learner engagement in the entire process. But, learners reject feedback if they doubt its credibility or it conflicts with their self-assessment. Therefore, attention has turned to sociocultural factors that influence feedback-seeking, acceptance, and incorporation into performance. Understanding and application of specific aspects of psychosocial theories could help in designing initiatives that enhance the effect of feedback on learning and growth. In the end, the quality and impact of feedback should be measured by its influence on recipient behavior change, professional growth, and quality of patient care and not the skills of the feedback provider. Our objective is to compare and contrast older and newer definitions of feedback, explore existing feedback models, and highlight principles of relevant psychosocial theories applicable to feedback initiatives. Finally, we aim to apply principles from patient safety initiatives to emphasize a safe and just culture within which feedback conversations occur so that weaknesses are as readily acknowledged and addressed as strengths.

Keywords: Feedback; Residency education; Feedback culture; Sociocultural theory; Feedback credibility.

The term "feedback" has its origin in mechanical environments and refers to an auto-regulatory mechanism where the effect of an action is fed back to modify future action. Based on whether the gap between actual and desired performance is narrowing or widening, the type of feedback is referred to as positive or negative feedback respectively. The term is now used in various professions in the context of performance appraisal and practice improvement. Once dominated by expert opinions and recommendations [1, 2], feedback in medical education has shifted its attention to feedback provider-recipient relationships and factors that promote acceptance and incorporation [3–5]. In this perspective, we compare and contrast older and newer definitions of feedback, explore feedback practices and models used in medical education, and review tenets of relevant psychosocial theories applicable to the design of impact-enhancing feedback initiatives.

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Feedback: A Vital Cog in the Wheel of Competency-based Medical Education

In the era of competency-based medical education, formative performance-based feedback is essential for learners to calibrate their performance and formulate action plans to narrow the gap between their current and expected performance [6–10]. In several studies, medical students and residents report that faculty feedback is infrequently provided and vague language has little impact on their performance [4, 11–13]. Clinical teachers report several barriers including lack of time and space for direct

observation and feedback, lack of feedback skills, and concerns that "negative" feedback would damage teacher-learner relationships [14–17]. Tackling complex barriers related to interpersonal relationships or institutional culture demands understanding of these factors [18–20].

Traditional Definitions and Models

Older definitions of feedback emphasize teachers' skills in providing feedback, a mostly unidirectional model for feedback conversations. Ende defined feedback in medical education as "information describing students or house officers' performance in a given activity that is intended to guide their future performance in the same activity" [1]. The "feedback sandwich" model, which recommends starting and ending with positive feedback, interposed by negative feedback [21], has not been shown to improve learner performance [22]. The Pendleton model features four key steps: learner self-assessment of strengths, teacher agreement/disagreement, learner assessment of deficiencies, and teacher agreement/disagreement [23]. However, most older definitions and models have not adequately showcased learner engagement in the conversation or their role in creating a road map for performance improvement. It had been assumed that improving teachers' feedback skills would somehow lead learners to change practice and improve performance (Fig. 1).

Recent research suggests that teachers' perceptions of effective feedback may not be shared by learners, and teachers are largely unaware of when and why learners reject feedback [24–27]. In Graduate Medical Education settings, residents are the first-line providers of patient care and it is important to preserve their self-esteem and autonomy during feedback conversations. Such settings warrant a learner-focused model with learners as active seekers of feedback and contributors to the conversation rather than passive recipients [4, 28]. Short working relationships pose an additional barrier to learner-centered feedback approaches, yet, such approaches may be needed to promote behavior change. Therefore, the landscape of feedback needs to shift from teachers' feedback techniques to learners' goals, acceptance, and assimilation of feedback, regardless of the duration of working and learning relationships. To do this effectively, key factors that influence feedback acceptance need to be analyzed and understood.

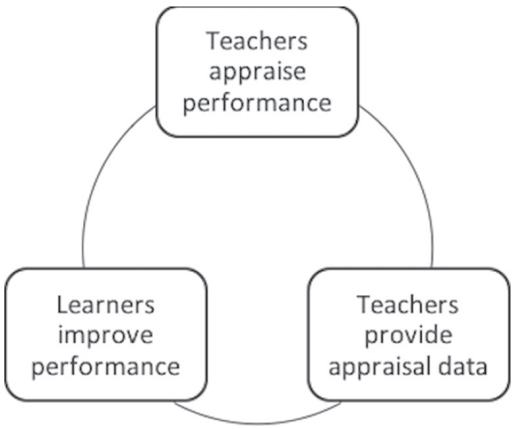

Fig. 1: Older definitions and models of feedback in medical education are unidirectional with the direction of flow from teachers to learners. Learners' performance improvement is assumed, and learning opportunities are not consistently created to allow for or document behavior change.

Feedback Through a Sociocultural Lens

Newer definitions of feedback emphasize its impact on recipients; until learners act on feedback, the feedback loop remains incomplete [3, 8, 9, 29, 30]. However, learners reject constructive feedback, namely feedback on deficiencies or areas for improvement, if the process or provider lack credibility in their eyes [16, 31–33]. Credibility is influenced by factors such as learner-teacher relationships, the manner of delivery, perceived intentions of feedback providers, direct observation of performance, congruence of data with self-assessment, and perceived threat to self-esteem or autonomy [17, 27, 30, 34–37]. Two recent feedback models, the R2C2 model (relationships, reaction, content, and coaching) and the educational alliance model, place learners at the center of a feedback conversation and prioritize learner-teacher relationships as precursors to feedback conversations that target change in learner behavior and practice [38–42]. Institutions need to promote trusting teacher-trainee relationships within a safe learning environment and facilitate regular direct observation of performance to enable meaningful feedback exchanges [4, 19].

The feedback encounter is a complex exchange of information influenced by many factors such as the stress of the clinical environment, time pressures, emotional reactions, interpersonal tensions, and the learning culture [15, 16, 18]. Although clinical supervisors are aware that feedback is intended to improve trainee performance, many struggle to provide constructive feedback as they do not wish to be seen as unkind, and wish to preserve self-esteem of and their relationship with trainees [16, 17, 19]. Sociocultural factors that influence feedback can be examined through different viewpoints: the recipient, the provider, and the context. Figure 2 is a depiction of a central role for learners' performance improvement in the feedback loop,

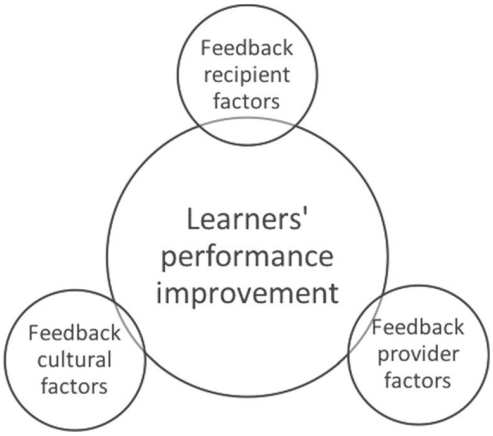

Fig. 2: Sociocultural influences of feedback can be feedback provider related (teachers), feedback recipient related (learners), and feedback culture related (institutional). Learner-centered models of feedback emphasize the central position of learners in the feedback conversation with performance improvement as the end goal.

influenced by factors related to feedback providers, recipients, and the institutional context.

Feedback Recipients

Feedback models which cast learners as passive recipients are likely to be ineffective in graduate medical education; advanced trainees need to actively engage in appraisal of their practice [43]. Feedback acceptance is influenced by feedback-seeking behaviors, ability to self-assess, and perceptions of threat to self-esteem [30, 44, 45]. Goal-orientation of learners may also have a strong impact on feedback-seeking and acceptance [4, 43, 46, 47]. Individuals with a performance goal-orientation seek feedback to showcase excellence and receive positive judgements; [48, 49] they tend to reject feedback perceived as negative or threatening to their self-esteem [19, 37]. Those with a learning goal-orientation focus on mastery of tasks and professional growth [48, 49]. Institutions and teachers can promote a learning goal-orientation by emphasizing mastery of new knowledge and skills rather than appearance of excellence, normalizing areas for improvement, and communicating explicit messages that constructive feedback is necessary for performance improvement.

Feedback Providers

Medical education has historically focused on teachers' skills in "providing" feedback to learners [1, 2, 50, 51]. Its impact on learner behavior will likely be enhanced if feedback initiatives enhance teachers' skills in promoting a positive learning climate, establishing rapport with learners, focusing on goal-directed feedback and action plans for performance improvement [30, 34, 52]. It is essential that clinical teachers observe segments of their learners' performance in a variety of domains, debrief observations in a timely manner, and provide opportunities for learners to implement action plans. Finally, it is important for teachers to encourage learner self-assessment and reflection to discuss both strengths and areas that need improvement.

Feedback Culture

A strong feedback culture promotes ongoing formal and informal feedback targeting continuous performance improvement [53, 54]. Educational institutions can establish such a culture by facilitating trusting relationships between teachers and learners, building in time and space for feedback even in busy clinical settings and creating a shared understanding between teachers and learners about the process and content of feedback [16, 19, 55–57]. More research is needed to explore how institutional culture can influence the quality and impact of feedback, feedback-seeking, acceptance, and performance improvement [5, 39, 41, 42]. Understanding sociocultural factors in various learning and work environments is essential before designing initiatives to promote meaningful feedback exchanges and enhance its impact on behavior change and professional development.

Theoretical Principles Relevant to Enhancing the Impact of Feedback

Since recent research has described feedback as a complex interpersonal encounter with relationships playing an important role in learner acceptance and behavior change [4, 12, 18], it would be useful to explore sociocultural factors that impact feedback [3, 8, 15, 19, 27, 41]. Specifically, concepts from three psychosocial theories are relevant to the sociocultural aspects of feedback: (1) sociocultural theory [58], (2) politeness theory [59], and (3) self-determination theory (Table 1) [60]. The theories highlight core principles that can guide development of new models and enhance techniques for effective feedback conversations, especially in clinical settings where learning occurs on teams. These principles include relatedness/relationships, self-efficacy, autonomy, and intrinsic motivation for continuous performance improvement and are described in more detail below.

Sociocultural theory, which proposes that humans learn largely through social interactions influenced by cultural beliefs and attitudes, grew from the work of Vygotksy [61]. Drawing upon this theory, Lave and Wenger describe that individuals transform through participation in communities of practice [58]. As learners assume increasing responsibility for their

activities, they move from the periphery to the center of a community. Since clinical learning occurs through team interactions and collaboration, institutions should attend to the broader community in which learning is occurring as well as development of individual learners within these communities. Applying these principles to feedback, educators need to (a) identify learner abilities using a developmental approach, (b) calibrate gaps in learners' current versus expected performance, and (c) provide formative feedback to guide independent practice.

Concepts from Brown and Levinson's politeness theory are relevant to feedback conversations. This theory, from the field of linguistic pragmatics, proposes that two types of "face," positive and negative, play a role in most social interactions [59, 62]. The positive face reflects an individual's need to be appreciated by others, and the negative face reflects an individual's need for freedom of action. The clinical environment is characterized by interpersonal relationships between teachers and learners, and multiple team members. In such settings, constructive feedback may be perceived as "negative" and thus a breach of the norms of expected politeness. Honest constructive feedback is essential for longitudinal growth as self-affirmation alone is not the path to professional improvement. However, clinical teachers tend to

Table 1. Three relevant psychosocial theories, core principles that could enhance the impact of feedback, and corresponding strategies to address those principles.

Relevant psychosocial theory	Core principles	Implications for feedback strategies
Sociocultural theory	Learning through social interactions Transformation through communities of practice Community influenced by cultural beliefs and assumptions	Educators: - Identify learner abilities using a developmental approach - Calibrate gaps in learners' current versus expected performance - Provide formative feedback to guide independent practice - Use coaching skills for learner growth Institutions: - Provide a safe and just team culture - Establish trusting teacher-learner working relationships - Encourage communities of practice on clinical teams and in training programs
Politeness theory	Self-efficacy/self-image Autonomy/ freedom from imposition by others	Educators: - Initiate feedback conversations with previous examples of excellence - Obtain learner goals and engage in goal-directed feedback - Facilitate learner reflections to calibrate gap between current performance and expected performance - Co-create action plans for improvement and future learning opportunities - Focus on professional growth and patient care outcomes Institutions: - Facilitate teacher-learner relationships - Encourage direct observation of performance - Train teachers to provide constructive feedback based on observed behaviors - Orient learners to seek feedback and train them to accept feedback and incorporate into performance - Establish an environment of gradual, increasing, and appropriate autonomy for learners - Shift from performance to learning goal-orientation
Social determinant theory	Autonomy Relatedness Intrinsic motivation	Educators: - Shift the focus from the individual to the context - Shift from instructional messages to self-regulation - Shift the focus from the perspective of feedback providers to recipients - Direct observation of performance - Encourage self-reflection and self-assessment - Challenge learners in a supportive environment Institutions: - Establish a safe and just culture - Set expectations for ongoing formative feedback - Encourage continuous improvement mindset - Stimulate learning goal-orientation - Emphasize excellence and safety in patient care

emphasize positive performance during feedback exchanges to avoid damaging teacher-learner relationships and learner self-esteem [15, 31]. Thus, a polite or face-saving learning culture may have a negative impact on feedback conversations, an area that warrants further research [63].

Self-determination theory, described by Ryan and Deci, states that human beings tend to regulate behaviors autonomously, take on challenges, and learn through intrinsic rather than extrinsic motivation [60]. Extrinsic motivation is driven by external factors with the goal of achieving defined outcomes [60]. Intrinsically motivated individuals take on activities for inherent satisfaction rather than to achieve a given result [60]. We propose that intrinsic motivation would positively influence feedback-seeking, acceptance, and assimilation, therefore performance improvement. Ten Cate *et al*. suggest approaches to boost intrinsic motivation during feedback conversations: shifting the focus from the individual to the context; shifting from instructional messages to self-regulation; and shifting the focus from the perspective of feedback providers to recipients [64].

Where Do We Go From Here?

Based on evolving acknowledgement that feedback is a learner-centered and sociocultural phenomenon, it is important to swing the pendulum of feedback research and faculty development from teacher techniques to learner outcomes. Medical educators should examine what institutional cultural factors influence the quality and impact of feedback conversations at their own institutions from multiple perspectives. Observational studies are necessary to examine teacher and learner behaviors during feedback conversations and explore whether intentions of speakers match the perceptions of receivers. Co-construction of feedback conversations, action plans for improvement, and new learning opportunities by teachers and learners are more likely to result in professional growth [39, 42]. Finally, the most credible feedback on clinical performance might be from patients to fulfill the ultimate goal of high-quality and safe patient care. Integration of patient feedback into performance assessment is fraught with challenges, but if implemented effectively, it could trigger meaningful behavior change and enhance safety and quality in patient care [65]. More research is needed in this important area.

Applying principles from patient safety initiatives, we propose that educational institutions adopt a fair and just culture within which feedback is exchanged. Such an organizational culture ensures learning and continuous improvement through acknowledgement of areas of weaknesses as well as areas of excellence, willingness to seek help, focus on humanism and accountability to excellent care [66–68]. Institutions have a major role in establishing this culture to mitigate the effects of the hierarchical clinical environment, empower learners to take ownership of their professional growth, and enable collaborative bidirectional feedback. This empowerment can be driven by explicit expectations for collaborative calibration of performance against expected goals and clear messages that all professionals have strengths and areas for improvement. Focus on reflective practice, lifelong learning, and continuous improvement is essential for safe and high-quality patient care.

Relationships, not recipes, are more likely to promote feedback that has an impact on learner performance and ultimately patient care [69]. After all, why should feedback conversations be any different than skilled physician-patient communications, with a focus on rapport, learner self-reflection, and shared decision-making?

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Description: Stugeron® Plus consists of 20 mg cinnarizine and 40 mg dimenhydrinate as a fixed dose combination. Therapeutic Indication: For the treatment of vertigo. Contraindications: Severe renal impairment, severe hepatic impairment, patients with known hypersensitivity to the active substances, diphenhydramine or other antihistamines of similar structure or to any of the excipients. Warnings and Precautions: Should be taken after meals to minimize any gastric irritation; Should be used with caution in patients with conditions that might be aggravated by anticholinergic therapy; Should be used with caution in hypotensive patients; When administering patients with Parkinson's disease, caution should be exercised. Interaction: Concurrent use of Alcohol/CNS depressants/Tricyclic Antidepressants may potentiate the sedative effects of either of these medications or of Stugeron® Plus. Stugeron® Plus may mask ototoxic symptoms associated with amino glycosidic antibiotics and mask the response of the skin to allergic skin tests. The concomitant administration of medicines that prolong the QT interval of the ECG (such as Class Ia and Class III antiarrhythmics) should be avoided. Pregnancy and lactation: Stugeron® Plus should not be used during pregnancy and usage should be discouraged in nursing women. Effects on Ability to Drive and Use Machines: Stugeron® Plus may cause drowsiness, especially at the start of treatment, therefore, should not drive or operate machinery. Posology and Method of Administration: Adults and Elderly: 1 tablet three times daily, to be taken unchewed with some liquid after meals. Children and adolescents under the age of 18 years: Stugeron® Plus is not recommended. Undesirable Effects: Commonly observed adverse reactions include somnolence and dry mouth. Other adverse reactions include constipation, weight gain, tightness of the chest, worsening of an existing angle-closure glaucoma, reversible agranulocytosis and extrapyramidal symptoms. Overdose: Drowsiness and ataxia with anticholinergic effects are usually seen. Convulsions, respiratory depression and coma may occur in cases of massive overdosage. General supportive measures and gastric lavage with isotonic sodium chloride solution are recommended. Short-acting barbiturate and physostigmine (after physostigmine test) can also be used in case of marked symptoms. ® - Registered trademark of Johnson & Johnson, USA. Version of API: CCDS dated 05 Jan 2016

Stugeron® / Stugeron Forte®

Description: Stugeron® and Stugeron Forte® are available as oral tablets containing 25 mg and 75 mg of cinnarizine respectively. **Indications:** 1. Prophylaxis of migraine. 2. Disorders of balance - maintenance therapy for symptoms of labyrinthine disorders, including vertigo, dizziness, tinnitus, nystagmus, nausea and vomiting. 3. Prophylaxis of motion sickness. **Contraindications:** Stugeron®/ Stugeron Forte® is contraindicated in patients with known hypersensitivity to the drug. Warnings and precautions: Stugeron®/ Stugeron Forte® may cause epigastric distress; taking it after meals may diminish gastric irritation. In patients with Parkinson's disease, Stugeron® should only be given if the advantages outweigh the possible risk of aggravating this disease. **Interactions:** The sedative effects of Stugeron® / Stugeron Forte® may be potentiated when used concomitantly with alcohol, CNS depressants, or tricyclic antidepressants. Because of its antihistamine effect, Stugeron®/ Stugeron Forte® may prevent otherwise positive reactions to dermal reactivity indicators if used up to 4 days prior to skin testing. **Pregnancy and lactation:** Stugeron®/ Stugeron Forte® should be used during pregnancy only if the therapeutic benefits justify the potential risks for the fetus. Nursing should be discouraged in women using Stugeron®/ Stugeron Forte®. Since somnolence may occur, especially at the start of treatment, caution should be taken during activities such as driving or operating machinery. **Interactions.** Alcohol/CNS depressants/ and tricyclic antidepressants: The sedative effects of Stugeron® / Stugeron Forte® and of any of the following may be potentiated when used concomitantly: alcohol, CNS depressants, or tricyclic antidepressants. **Diagnostic interference:** Because of its antihistamine effect, Stugeron®/ Stugeron Forte® may prevent otherwise positive reactions to dermal reactivity indicators if used up to 4 days prior to skin testing. **Dosage and administration:** Prophylaxis of migraine: Adults:1 tablet of 25 mg three times a day, 1 tablet of 75 mg daily. Disorders of balance: Adults: 1 tablet of 25 mg three times a day, 1 tablet of 75 mg daily. Prophylaxis of motion sickness: Adults and adolescents (13 years and above): 1 tablet of 25 mg at least half an hour before travelling, to be repeated every 6 hours. Stugeron®/ Stugeron Forte® should preferably be taken after meals. **Adverse reactions:** Commonly observed adverse reactions include somnolence, nausea and weight increase. The post marketing studies have reported extrapyramidal disorder, parkinsonism and cholestatic jaundice and lichen planus in the frequency of <1/10000 patients (very rare). **Overdose:** The most commonly reported signs and symptoms associated with overdose of cinnarizine include alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms, and hypotonia. For any overdose, the treatment is symptomatic and supportive care. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. ® - Registered trademark of Johnson & Johnson, USA. Version of API: CCDS dated 31 May 2019

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