Differential diagnosis and proper treatment of acute rhinosinusitis: Guidance based on historical data analysis

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ABSTRACT

Background: *The time course of rhinovirus positive and negative rhinosinusitis has not been quantified yet, which aggravates proper selection and justification of the optimum treatment for this illness. Such quantitative information would facilitate an early and proper identification of the disease and its differentiation from acute bacterial rhinosinusitis, and could diminish harmful overuse of antibiotics, arguably driven by patients' want for attention and the treating physicians' inability to offer an adequate verbal comfort in its stead.*

Objective: *Extraction of the quantitative information needed to identify rhinovirus positive or negative rhinosinusitis and to allow selection of the most appropriate treatment from the published time dependence of individual clinical symptoms of the disease.*

Methods: *Scrutiny (and modeling) of temporal evolution of all noteworthy symptoms of rhinosinusitis with a simple mathematical expression that relies on two adjustable parameters per symptom (and potentially a general time offset as an extra adjustable parameter).*

Results: *Adverse effects of rhinosinusitis can be grouped according to the sequence of their exponential appearance and ~2.6 times slower exponential disappearance, rhinovirus negative rhinosinusitis generally improving ~25% faster and being ~40% less severe. The major early local symptoms (throat soreness and scratchiness, headache) vanish with a half-life of ~1.8 days, whereas further local symptoms take ~1.6 times longer to disappear. At least 50–60% improvement of two prominent early symptoms, sore throat and sneezing (but not of nasal discharge, cough, and hoarseness) by day 5 of the disease implies a nonbacterial origin of rhinitis and should exclude use of antibiotics.*

Conclusion: *Temporal evolution of all rhinosinusitis symptoms is qualitatively similar, which makes the early symptom decay a good proxy for, and predictor of, the disease perspective. Knowing a symptom intensity at just three to four time points suffices for reconstructing its entire time course and total intensity or gravity. This permits an easy and early identification of rhinosinusitis, and its plausible differentiation from acute bacterial rhinosinusitis, disease treatment optimization, and corresponding clinical trials simplification and/or shortening.*

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The average adult experiences two to three common cold (acute rhinitis or, more precisely, rhinosinusitis) attacks annually, mostly due to rhinovirus infections; the rate in children is four times higher.[1] By definition, the disease resolves within 4 weeks and is typically easily differentiable from allergic rhinitis.[2] Conversely, many patients and some physicians cannot easily separate viral from bacterial infection, although ≤2% of acute rhinitis cases in primary care are reportedly due to bacteria.[3] The predominantly viral origin[4] of rhinitis can also explain the high rate and swiftness of spontaneous remission in the placebo groups of antibiotic trials of the disease, in which 70%[5] to 75%[6] of patients experienced the main symptoms diminution within 7–10 days.

All this notwithstanding, and despite a drop in such treatment propensities from 80–90% at the end of previous century,[7] too many patients with acute rhinosinusitis still receive antibiotic prescriptions in the United States. To date, nearly 40% of patients expect such a treatment, and 45% of primary care physicians in an ambulatory care setting would chose to administer an antibiotic to a patient with 5 days of acute rhinosinusitis symptoms.[8]

All noteworthy symptoms of rhinovirus positive and negative rhinosinusitis are listed in an early, data-rich article.[9] In sequence of their highest occurrence frequency, the symptoms are, *e.g.*, nasal discharge, sneezing, sore throat, nasal obstruction, hoarseness, scratchy throat.[9] The individual symptoms time dependences over a 9 (for some symptoms 15) day period are also illustrated in the article, which, however, does not

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quantify their specific characteristics, overall duration, and gravity. This leaves patients and physicians unaware of the most likely progression and remission times of the disease. Likewise, the pertinent U.S. Food and Drug Administration Guideline does not break down the condition's duration to the individual symptom level, despite proposing some other criteria for assessing or quantifying an acute viral rhinosinusitis.[10]

Characterization and a reliable description of the noteworthy clinical symptoms of rhinosinusitis as a function of time are as yet unmet desires. Such information would facilitate the differentiation between viral and bacterial rhinosinusitis, could ameliorate the disease treatment, and further therapeutic developments. For example, an official guideline specifies the improved time to clearance of symptoms and a clinical cure rate as the two most preferred therapeutic success measures,[11] notwithstanding that the typical onset and clearance time of rhinosinusitis symptoms are not yet published.

This article aims to fill the above-mentioned gaps by quantifying the typical onset and clearance time of rhinosinusitis symptoms and to offer specific guidance for viral rhinosinusitis identification, and thus for a proper treatment of acute rhinosinusitis. A key finding is that each clinically relevant symptom of viral rhinosinusitis increases exponentially toward an unreachable intensity maximum. The reason is concomitant, slower, but ultimately prevailing, suppression of rhinosinusitis, which causes an exponential amelioration and, therefore, final decay of the disease. The time course of each rhinosinusitis symptom, consequently, is biexponential.

Herein I exploited the most-extensive published clinical data set on rhinosinusitis[9] to model quantitatively the illness development. The resulting model parameters characterize each clinically important symptom of rhinosinusitis, its temporal development, and gravity, which are clues to differentiating between the viral and bacterial type of the disease. The generally good and robust calculatory reproduction of clinical observations, moreover, justifies the model use in future clinical studies and for making clinical decisions.

METHODS

Clinical Background and Institutional Review Board Approval

The *post hoc* analysis described herein relies on 50-year-old clinical observations set,[9] which remain unsurpassed in terms of temporal characterization of clinical symptoms of rhinovirus infections but lack specific confirmation of an IRB approval.[11] Its old age notwithstanding, the set was consequently canonized by partial inclusion into the current clinical practice guideline for adult sinusitis.[12] The underlying population was young (83% were age <35 years), mixed (59% women, 41% men), and experienced 3314 respiratory illnesses during observation of 468 working adults over 3 years. A total of 1025 of such illnesses were sampled; this revealed rhinoviruses in 239 of the samples (23%), which is quite typical.[13] The study subjects averaged 2.3 respiratory illnesses and 0.5 rhinovirus illnesses per year. Epidemics of respiratory illness recurred chiefly in early fall (affording a 43% rhinovirus isolation rate, on average). The late spring outbreaks were fewer.

Methodological Background

The symptoms caused by a local, external trigger, such as a local infection, depend on the infectant's local activity and its consequences' onset time ($t_{o,1/2}$) and decay time ($t_{d,1/2}$). The activity is typically a product of the infectant's potency and concentration. Because the potency is normally nearly constant, one may assume proportionality of the infectant's local activity and concentration, whereby the latter changes with the infectant's progeny, distribution, and a body's response to them. Time dependence of an infectant concentration, therefore, influences temporal evolution of the resulting illness during a monocausal infection. Some symptoms of such local infection then appear and disappear rapidly, depending on their individual nature, whereas other symptoms appear and disappear more slowly. Because of their common and originally single cause, all symptoms of rhinosinusitis evolve with time as described by the following, simple biexponential function[14,15]:

$$Symptom\ (t) = S_{\max,B}\,[-e^{-0.693\,(t\ -\ t_0)/t_{0,1/2}} + e^{-0.693(t\ -\ t_0)/t_{d,1/2}}],$$

with the symptom specific parameters $t_{o,1/2}$, $t_{d,1/2}$, $S_{max.B}$, which are derivable from each individual experimental data set with, *e.g.*, the Solver function of Excel (Microsoft Seatle, WA) or StarOffice Calc. A pluri-causal infection, due first to virus and then to bacteria, *e.g.*, has more complexity, *e.g.*, a tetra- or even multiexponential time dependence. $S_{max.B}$ specifies the highest modeled ("observed") individual symptom value and $t_{o,1/2}$, $t_{d,1/2}$ the symptom-characterizing onset and decay half-lives, respectively; t_0 is the potential time difference between an infection and the first recorded observation of a symptom, common to all symptoms. Further symptom characteristics derivable from the equation are the following: $t_{max.B}$, which describes a symptom's maximum position in time, and AUC_B, which gives the area under the individually optimized biexponential function curve up to $t \sim 8\ t_{d,1/2}$. (The result of the corresponding original data integration with the trapezoidal formula is the AUC

Table 1 **Parameterization of rhinosinusitis or rhinosinusitis symptoms vs time data* for subjects with rhinovirus, RV^+, and subjects without rhinovirus, RV^-, ranked in the sequence of decreasing gravity, *i.e.*, of AUC_B**

	S %	$t_{o,1/2}$ Day	$t_{d,1/2}$ Day	$t_{max.B}$ Day	$S_{max.B}$ %	AUC_B % Day	AUC % Day	AUC/ AUC_B	$\Sigma \mid Error \mid / n\ S_{max.B}$#
Nasal discharge									
RV^+	100	0.72	4.32	2.2	58.2	517	444	0.86	0.0079
RV^-	100	0.89	3.29	2.3	45.0	345	166	0.48	0.0502
Cough									
RV^+	100	1.74	5.30	4.2	38.9	510	408	0.80	0.0072
RV^-	100	1.55	3.48	3.3	28.9	276	124	0.45	0.0909
Nasal obstruction									
RV^+	100	1.11	3.23	2.6	37.6	304	250	0.82	0.0051
RV^-	100	1.45	2.54	2.7	20.3	155	68	0.43	0.1224
Sneezing, RV^+	100	0.41	2.39	1.3	57.1	279	244	0.88	0.0154
Hoarseness									
RV^+	104	1.83	3.59	3.6	24.8	254	186	0.73	0.0439
RV^-	100	1.46	2.59	2.8	20.8	161	69	0.43	0.2336
Sore throat, RV^+	100	0.45	1.95	1.2	50.0	217	195	0.90	0.0174
Scratchy throat, RV^+	100§	0.79	1.77	1.7	28.8	140	130	0.93	0.0212
Headache, RV^+	100	0.73	1.70	1.5	30.7	139	129	0.93	0.0431
Sputum, RV^+	96	1.76	2.47	3.0	11.9	97	77	0.79	0.0488
Malaise, RV^+	100	1.02	1.42	1.7	12.0	57	53	0.93	0.0558
Feverishness, RV^+	100	0.85	1.25	1.5	14.0	57	53	0.93	0.0225
Myalgia, RV^+	100	1.05	1.43	1.8	11.3	54	47	0.88	0.0662
Chills, RV^+	99	1.07	1.32	1.7	7.6	35	34	0.97	0.0569

**From Ref. 9.*

AUC_B = Area under the individually optimized biexponential function describing the symptom; S = the symptom's nominal maximum intensity; $t_{o,1/2}$ = the symptom's onset half-life; $t_{d,1/2}$ = the symptom's decay half-life; $t_{max.B}$ = the symptom's maximum position in time; $S_{max.B}$ = the highest modelled ('observed') individual symptom value; AUC = the symptom's area under the 'curve' joining experimental data; n = the number of data points (deducible from the data in Fig. 1); RV^+ = positive for rhinovirus; RV^- = negative for rhinovirus.

#$\Sigma \mid Error \mid$ gives the sum of the absolute differences between each measured and corresponding Symptom(t) set, i.e., the square root of χ^2, optimized with the Löwenberg-Marquardt nonlinear regression algorithm (0.67 ± 0.33, on average), which identifies the relative error of each fit.

§Fixed paramenter value; if this parameter value set free, the consecutive results are 61, 0.57, 2.24, 1.5, 28.7, 147, 130, 0.88, 0.0167.

(area under the curve). Because the observation period is normally shorter than the disease duration, at least for some symptoms, the ratio of the two integral values is always <1; in the present study, it is AUC:AUC_B = 0.87 ± 0.07, on average.) For the analyzed data set, no time offset was needed and the individually determined maximum occurrence frequency was always (approximately) 100%. Hence: t_0 = 0 days and $S_{max.B}$ = 100% in this study; for more details see Table 1 and Online Supplemental Material.

RESULTS

Figure 1 compares the clinically observable rhinosinusitis symptoms occurrence with their modeling results. The nearly perfect match confirms that an individually optimized biexponential function fully captured the time dependence of each noteworthy symptom of rhinosinusitis in the explored canonical data set. Excluded are the potential symptoms "vomiting," "diarrhea," and "staying home," which are too weak to reveal any obvious time dependence.[9] Such symptoms, therefore, have no predictive power for rhinosinusitis and should not be given any practical attention. The temporal characteristics of all clinically relevant rhinosinusitis symptoms and the corresponding full AUC_B are quantified in Table 1. For comparison, also included in Table 1 are the corresponding AUCs gained by directly integrating the published data and the normalized, *i.e.*, relative, fit errors. The smallness of the latter (Table 1, column

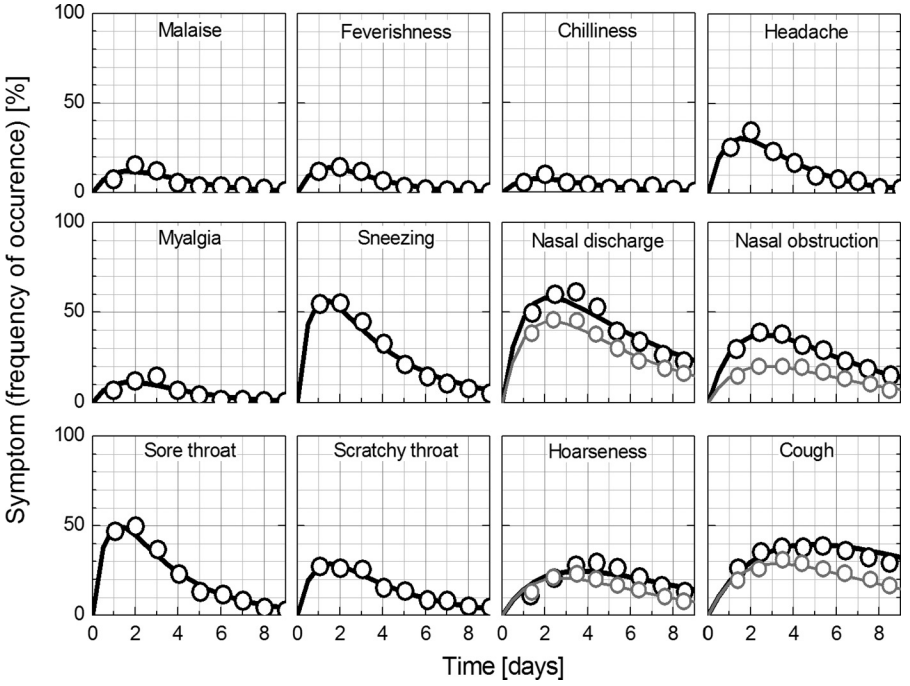

Figure 1. *Time dependence of occurrence frequency of clinical symptoms of rhinovirus (RV) positive (RV^+, ○, 139 patients) and negative (RV^-, ○, 326 patients) rhinosinusitis (from Ref. 9). Each curve illustrates the biexponential function specified in the text that best fits the underlying data set. If no data are shown for patients with RV^-, then no corresponding time-resolved data are provided for such patients in the original publication from Ref. 9). The corresponding parameter values are provided in Table 1.*

$\Sigma\ |Error|/n\ S_{max.B}$) corroborates the data description and analysis advocated in this article. (Specifically, the relative error is typically 1–2% for the major and 5–7% for the minor, and hence relatively "noisier," symptoms.)

The clinical aspects of rhinosinusitis are highlighted from a different, statistical, angle by using nasal discharge as a representative example in Fig. 2. This focusses on information density variation, generated herein by eliminating every second (top right), every third (top left), or the second and the third of each three consecutive experimental data points (bottom left). In the bottom right panel, the data set from the bottom left panel, moreover, is truncated after the third considered data point. The small effect of the observation period shortening on the calculated half-lives of rhinosinusitis symptoms (here exemplified by nasal discharge, sneezing and nasal discharge, as *partes pro toto*) are specified in Tables 2–4. Fig. 2 and Tables 2–4 validate the conclusion that even a short observation period can highlight rhinosinusitis. As long as the last observation day fulfills the condition $t_{final} \geq 2.5\ t_{max,B}$ the half-life extracted by modeling a limited data set is quite similar. If $t_{final} \geq 3\ t_{max,B}$, then all model-derived $t_{.,1/2}$ values are nearly identical. This confirms that the proposed extrapolation procedure is robust, if it relies on the individually optimized biexponential model described in the Table 1 footnote.

More explicitly, during viral rhinosinusitis, nasal discharge and sneezing, scratchy and sore throat, and headache all evolve rapidly, with $t_{o,1/2} = 0.6 \pm 0.2$ days (Table 1). Nasal obstruction, malaise, myalgia, and chills have nearly a twice-longer onset time, $t_{o,1/2} = 1.1$ days, whereas cough and sputum appear three times more slowly ($t_{o,1/2} \sim 1.75$ days). Thus grouped, the temporal sequence of its symptoms highlights three stages of rhinosinusitis. First, rhinosinusitis signs are observable at the primary infection site (nasal cavity surface) and its drainage goal (throat); second, the deeper local tissue gets involved and the body rest reacts to infection; third, the affected tissues start clearing.

The time course of rhinosinusitis symptoms recorded by patients without rhinovirus is qualitatively similar. However, quantitative data analysis exposed ~25% shorter diminution half-time of such patient symptoms. The corresponding maximum intensity of symptoms was hence ~25% weaker, and the disease gravity on average was 40% lower, which could explain the practical insignificance of the minor symptoms of the patients who were RH^- (AUC < 200% day). Furthermore, the onset half-time of cough and hoarseness was ~15% shorter in the patients without rhinovirus, whereas nasal obstruction and discharge had ~25% longer onset times (see Table 1 for further details).

DISCUSSION

Despite its apparent "triviality," rhinosinusitis is more than a quickly passing nuisance. Experts reckon that the total direct health care costs attributable to primary medical diagnosis of the condition were U.S. $3 billion in 1996,[16] which, at present, corresponds to ~U.S. $6 billion annually. Such a diagnosis too often triggers an antibiotic prescription, which fosters building resistance.[7] One reason for the overprescription is patients' desire to receive a pharmacologic treatment. Another reason is that some

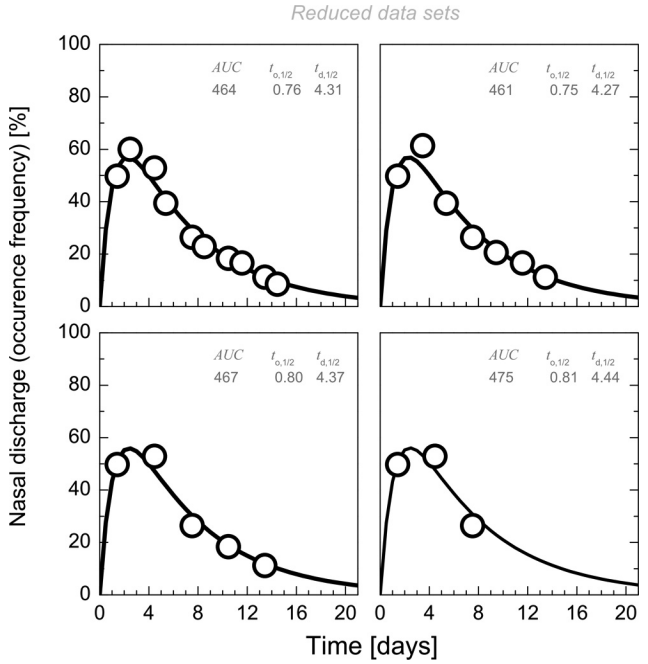

Figure 2. *Nasal discharge versus time, measured (o) (from Ref. 9) and modeled with the biexponential function (curves) having the specified parameters. See the text and the Online Supplemental Material for further details; for parameterization of the full early data set, see Tables 2–4.*

physicians have difficulty in differentiating between a viral upper respiratory infection and an acute bacterial rhinosinusitis.[17] A lack of ready information about relative intensity and duration of rhinosinusitis' main symptoms contributes to the difficulty.

To facilitate physicians discussing rhinosinusitis with patients and to mitigate antibiotics overuse problem, I mathematically scrutinized each well-documented clinical symptom of the disease noted in a large historical study. (The underlying equation is popular in pharmacokinetic studies and later called the Bateman equation.[15]) This clarified the typical progression and remission of the disease and, hence, the likely evolution of an untreated individual's rhinosinusitis, its purely viral origin presuming. From now on, a physician who addresses rhinosinusitis with a patient can, therefore, better form an educated opinion about the disease cause and also decide more rationally for or against a pharmacologic treatment. For example, if, and only if, rhinosinusitis symptoms will not recede quasiexponentially and approximately with the characteristic decay times listed in Table 1, then a physician will have good cause for treating the condition with an antibiotic drug because up to one-third of such adult patients with persistent symptoms have an acute bacterial rhinosinusitis, with arguably different detailed time characteristics. In any event, a physician who is treating rhinosinusitis will be able to assure his or her patients with validated, quantitative information about each individual symptom time course and, even more importantly, its resolution outlook. Just gazing at the published illustrations of the rhinosinusitis time course would not enable such a discussion and therapeutic decision-making.

Patient recovery characteristics, quantified by symptom diminution half-lives, form three broad and understandable groups. The early indicators, sore and scratchy throat; the general symptoms, headache, malaise, feverishness, myalgia; and chills all fade with a half-life of 1.5 ± 0.3 days (for the strongest among them, ~1.8 days). The essentially local and more-intense symptoms (nasal obstruction and sneezing, hoarseness, sputum) have a twice-as-long half-life, ~3 days ($t_{d,1/2}$ = 2.9 ± 0.6 days). Nasal discharge and cough persist longer still, and both disappear with a half-life of ~5 days. On average, rhinosinusitis symptoms thus vanish 2.6 ± 0.1 times more slowly than they appear. Each rhinosinusitis symptom, therefore, peaks approximately on the second day after the original infection, $<t_{\max.B}>$ = 2.1 ± 0.9 days, or more precisely at $<t_{\max.B}/t_{o,1/2}>$ = 2.2 ± 0.5 days (Table 1). (Neglecting cough and hoarseness yields $<t_{\max.B}>$ = 1.8 ± 0.5 days; neglecting nasal discharge and focusing on the next four strongest symptoms gives $<t_{\max.B}/t_{o,1/2}>$ = 2.3 ± 0.3 days.) To comfort a patient, his or her treating physician could point at a quick disappearance of headache and announce that nasal obstruction and sneezing, hoarseness, and sputum will all wane at approximately half the pace. At least 50–60% ameliorations of sneezing (65–75%) and throat scratchiness by day 5 (6) of rhinosinusitis, moreover, indicates a purely viral origin of the disease.

The analyzed historical data set offers no information about any concomitant bacterial infection.[9] However, such an infection is rare in acute rhinosinusitis[3] and/or during the early stage of the illness, and is also incompatible with the simple biexponential time course of the disease described herein. It, therefore, is unlikely that overlooked bacterial infections affected this work's conclusions. On the contrary, the excellent agreement between results of the models used and clinical observations implies that the investigated patients did not have a bacterial rhinosinusitis.

Some people repeatedly experience rhinosinusitis[13] and are then especially prone to complications, *e.g.*, a bacterial co- or postinfection.[18] Such people should ideally be instructed to record their main symptoms (Table 1) as a function of time, *e.g.*, on a visual analog scale. (A free template is available on request.) The advising physician could then analyze his or her records with the formula (*) or by relying on Fig. 1 (exploiting its grids) to spot a bacterial

Table 2 **Parameterization of truncated information on published symptoms of rhinosinusitis or rhinosinusitis with the biexponential (Bateman) equation: Nasal discharge*#**

Nr. of Data	t_{final}, Day	$S_{max.B}$, %	$t_{o,1/2}$, Day	$t_{d,1/2}$, Day	$\Sigma \mid Error \mid$	$< \mid Error \mid > / n\ S_{max.B}$
15	14.5	100	0.72	4.32	11.92	0.0079
14	13.5	100	0.72	4.33	11.84	0.0085
13	12.5	100	0.72	4.34	11.83	0.0091
12	11.5	100	0.72	4.33	11.81	0.0098
11	10.5	100	0.72	4.31	11.77	0.0107
10	9.5	100	0.72	4.32	11.76	0.0118
9	8.5	100	0.73	4.34	11.68	0.0130
8	7.5	100	0.74	4.42	11.23	0.0140
7	6.5	100	0.76	4.59	10.11	0.0144
6	5.5	100	0.80	4.85	8.90	0.0148
5	4.5	100	0.90	5.72	3.63	0.0073
4	3.5	100	0.99	6.78	0.05	0.0001

t_{final} = Last day in the test data series considered in the analysis; $S_{max.B}$ = ; $t_{o,1/2}$ = onset time; $t_{d,1/2}$ = decay time.
**See Table 1 footnote.*
#From Ref. 9.
$t_{max.B}$ = 2.2 days and AUC = 514 × (1 ± 0.01) days %.

Table 3 **Parameterization of truncated information on published symptoms of rhinosinusitis or rhinosinusitis with the biexponential (Bateman) equation: Sneezing*#**

Nr. of Data	t_{final}, Day	$S_{max.B}$, %	$t_{o,1/2}$, Day	$t_{d,1/2}$, Day	$\Sigma \mid Error \mid$	$< \mid Error \mid > / n\ S_{max.B}$
9	9.02	100	0.418	2.38	59.651	0.066
8	8.03	100	0.421	2.40	54.231	0.068
7	7.01	100	0.425	2.42	49.083	0.070
6	6.10	100	0.432	2.46	39.551	0.066
5	5.05	100	0.444	2.52	24.837	0.050
4	4.06	100	0.465	2.64	5.518	0.012
3	3.06	100	0.484	2.75	0.387	0.001

t_{final} = Last day in the test data series considered in the analysis; $S_{max.B}$ = ; $t_{o,1/2}$ = onset time; $t_{d,1/2}$ = decay time.
**See Table 1 footnote.*
#From Ref. 9.

infection early. The latter would be indicated by deviations from the expected or illustrated temporal profile of viral infection symptoms. Insightful modeling can overcome some lack or loss of clinical observations in the process (Fig. 2 and Tables 2–4). The proviso is that at least one datum is available for the ascending and at least one datum is available for the descending part of the curve. (The third required datum should ideally, but not necessarily, be near the symptom's maximum.) To yield results with a <10% error, the last considered time point should fulfill the condition, $t/t_{o,1/2} > 9$. Low variability of the model-derived disease descriptors, caused by data density reduction (Fig. 2) or time axis truncation (Tables 2–4), vindicates this conclusion.

It stands to reason that the approach advocated herein is useful for analyzing and modeling most, if not all, symptoms' evolution caused by a local perturbation or such an infection. (A biexponential expression similar to the mathematical formula specified Table 1 footnote, *e.g.*, well describes local effects of botulinum neurotoxin injections.[19]) One, therefore, should also scrutinize other local diseases, including bacterial rhinosinusitis, by using clinical symptoms modeling; however, a lack of suitably detailed clinical information on such rhinosinusitis precludes this to date. For this purpose, one could use the equations with proven value in pharmacokinetic studies analysis or any other convenient mathematical formula(s), by using Excel (Microsoft) or the open source StarOffice Calc and then analyze with the in-built Solver routine.

Table 4 **Parameterization of truncated information on published symptoms of rhinosinusitis or rhinosinusitis with the biexponential (Bateman) equation: Scratchy throat*#**

Nr. of Data	t_{final}, Day	$S_{max.B}$, %	$t_{o,1/2}$, Day	$t_{d,1/2}$, Day	$\Sigma \lvert Error \rvert$	$< \lvert Error \rvert > / n\ S_{max.B}$
9	9.02	100	0.453	1.98	66.982	0.074
8	8.03	100	0.455	1.99	64.265	0.080
7	7.01	100	0.459	2.00	60.184	0.086
6	6.10	100	0.461	2.01	59.588	0.099
5	5.05	100	0.444	2.02	58.947	0.118
4	4.06	100	0.491	2.13	29.68	0.074
3	3.06	100	0.535	2.32	8.006	0.027

t_{final} = Last day in the test data series considered in the analysis; $S_{max.B}$ = ; $t_{o,1/2}$ = onset time; $t_{d,1/2}$ = decay time.
**See Table 1 footnote.*
#From Ref. 9.

CONCLUSION

One can model rhinosinusitis with pairs of onset and decay times as the key temporal characteristics of each individual symptom of the condition. The earliest symptoms (sneezing and sore throat, followed by nasal discharge, scratchy throat, and headache) have 0.6 ± 0.2 days onset half-life, on average. The latest symptoms (cough and sputum) have onset half-lives of ~1.75 days. Any symptom of rhinosinusitis generally disappears ~2.6 times more slowly than it appears. It, moreover, evolves and devolves ~25% faster in subjects without rhinovirus. Among the noteworthy symptoms, throat soreness and scratchiness as well as headache vanish first, with a half-life of ~1.8 days. Comforting patients with such quantitative information about the symptoms' progressive diminution might obliterate their desire for superfluous antibiotic prescriptions and/or may encourage use of less harmful treatments. When asking a patient to describe his or her symptoms' evolution until the presentation day, likely to coincide with the symptoms peak on the second day of an infection, could help in the further development of prediction of rhinosinusitis. The latter is prone to resemble the time course evaluated and described herein.

All symptoms of rhinosinusitis appear and disappear exponentially. This recognition allows a shortened observation time and can lower the necessary number of observations in a clinical study of the condition. The proposed biexponential formula, which describes the time course of rhinosinusitis, has merely two individually adjustable parameters (and, potentially, a common, originally unknown, infection time offset). The formula, hence, is suitable for robust inter- and extrapolations in any available data set. One, consequently, could use the formula for optimizing future clinical studies of rhinosinusitis and statistical evaluation of their results. Mathematical scrutiny of clinical symptoms advocated herein could prove useful for analyzing localized diseases other than rhinosinusitis. Based on different mathematical formulas, different nonlocal diseases would also be analyzable.

REFERENCES

1. Winther B, Gwaltney JM Jr, Mygind N, et al. Viral-induced rhinitis. Am J Rhinol 12:17–20, 1998.
2. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. Otolaryngol Head Neck Surg 152(suppl.): S1–S43, 2015.
3. Puhakka T, Mäkelä MJ, Alanen A, et al. Sinusitis in the common cold. J Allergy Clin Immunol 102:403–408, 1998.
4. Gwaltney JM Jr, Scheld WM, Sande MA, et al. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 90(pt. 2):457–461; discussion 462, 1992.
5. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 54:e72–e112, 2012.
6. de Bock GH, Dekker FW, Stolk J, et al. Antimicrobial treatment in acute maxillary sinusitis: A meta-analysis. J Clin Epidemiol 50:881–890, 1997.
7. Sharp HJ, Denman D, Puumala S, et al. Treatment of acute and chronic rhinosinusitis in the United States, 1999–2002. Arch Otolaryngol Head Neck Surg 133:260–265, 2007.
8. Mohan S, Sisler K, Christopher K, et al. Societal and physician perspectives on sinonasal diagnosis and treatment. Am J Rhinol Allergy 28:487–492, 2014.
9. Gwaltney JM Jr, Hendley JO, Simon G, and Jordan WS Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. JAMA 202:494–500, 1967.
10. FDA 2012. Guidance for Industry Acute Bacterial Rhinosinusitis: Developing Drugs for Treatment. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. CDER. Available online at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070939.pdf; accessed August 15, 2016.
11. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: Establishing definitions for clinical research and patient care. Otolaryngol Head Neck Surg 131(suppl.):S1–S62, 2004.
12. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: Adult sinusitis. Otolaryngol Head Neck Surg 137(suppl.):S1–S35, 2007.

13. Lima JT, Paula FE, Proença-Modena JL, et al. The seasonality of respiratory viruses in patients with chronic rhinosinusitis. Am J Rhinol Allergy 29:19–22, 2015.
14. Bateman H. The solution of a system of differential equations occurring in the theory of radioactive transformations. Proc Cambridge Phil Soc 15:423–427, 1910.
15. Garrett ER. The Bateman function revisited: A critical reevaluation of the quantitative expressions to characterize concentrations in the one compartment body model as a function of time with first-order invasion and first-order elimination. J Pharmacokinet Biopharm 22:103–128, 1994.
16. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: Contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol 103:408–414, 1999.
17. Mahoney MC, and Rosenfeld RM. Clinical diagnosis and evaluation of sinusitis in adults. Am Fam Physician 76:1620–1624, 2007.
18. Carr TF. Complications of sinusitis. Am J Rhinol Allergy 30: 241–245, 2016.
19. Cevc G. Improved bioassays using a local effect, such as muscle paralysis, as an endpoint. Toxicon 99:89–94, 2015. □