

Risk comparison of beta-lactam-induced anaphylaxis: Therapeutic stratification analysis in a Vietnamese pharmacovigilance database

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Abstract

What is known and objective: There is limited data on the specific risks of anaphylaxis induced by beta-lactam drugs. The aim of this study was to compare the risks of reporting beta-lactam-induced anaphylaxis using the national pharmacovigilance database of Vietnam (NPDV).

Methods: The multivariate generalised linear regression model was applied for signal generation and comparison of beta-lactams.

Results: Between 2010 and 2016, there were 2,921 reports of anaphylaxis (19.93%) from 14,655 spontaneous reports of beta-lactam use in the NDPV. Anaphylaxis signal generation was also found for the subgroup J01D (cephalosporins and carbapenems) (ROR = 1.27 [1.16-1.39]) and beta-lactamase-sensitive penicillins (ROR = 1.74 [1.27-2.35]). In the third generation cephalosporin subgroup, different risks were identified for the following combinations of beta-lactams: 1) cefotaxime with cefoperazone+sulbactam; 2) cefixime/cefpodoxime/cefdinir with cefoperazone+sulbactam or ceftizoxime/cefoperazone/ceftazidime/ceftriaxone/cefotaxime. For the second generation cephalosporin subgroup, different risks were found for cefotiam compared to cefmetazole, cefaclor, cefamandole and cefuroxime.

What is new and conclusion: These findings identified and highlighted the different anaphylactic risks caused by various beta-lactams in the main subgroups.

KEYWORDS

beta-lactam, developing countries, drug-induced anaphylaxis

1 | WHAT IS KNOWN AND OBJECTIVE

As first-line treatment for many bacterial infections, beta-lactams are the most commonly used antibiotics in clinical practice

worldwide. However, beta-lactams can cause many hypersensitivity reactions, including anaphylaxis: a life-threatening adverse drug reaction (ADR). The immunological mechanism of anaphylaxis induced by beta-lactam is mediated by IgE antibodies

acting through FcεRI.¹ There is still not enough known about beta-lactam-induced anaphylaxis, and there is a lack of quantitative data in developing regions. To our knowledge, anaphylaxis induced by the third generation of cephalosporins is relatively rare in western countries,^{2,3} but it remains a common cause of anaphylaxis in developing countries.^{4,5} The growing use of these drugs in recent decades means that an up-to-date and comprehensive assessment of the benefit/risk ratio is required. Therefore, the purpose of this research was to propose, for the first time, a preliminary approach for comparing the anaphylactic signals of risks related to different beta-lactams.

2 | METHODS

The pharmacovigilance network in Vietnam comprises two pharmacovigilance centres: the National Drug Information and Adverse Drug Reaction Monitoring Centre (NDIADRM) established in Hanoi in 2009, and the Regional Drug Information and Adverse Drug Reaction Monitoring Centre established in Ho Chi Minh City in 2011. Healthcare workers (HCWs) across the country can contribute to the NPDV by spontaneously sending ADR reports to the two centres. Each ADR report submitted to the pharmacovigilance centres are required to be written on an official ADR form, including at least the following information: patient's characteristics (age, sex), suspect drug(s), description of the ADR and the reporter's information.⁶

The coding of ADR terminology and suspected drugs were classified according to the WHO Adverse Reaction Terms and the WHO Anatomical Therapeutic Chemical classification system accordingly.⁷ ADR causality was assessed (using the WHO-Uppsala Monitoring Centre Causality Assessment) by trained NDIADRM personnel and/or one or two members of the Technical Expert Committee, depending on the severity of the ADR.^{8,9} The aforementioned activities are regularly performed for all ADRs reported to the NDIADRM within a set time limit (from several weeks to several months, depending on the severity of the ADRs).⁸ Then, all the ADRs in the NPDV that met the following criteria were included in this study: 1) spontaneously reported by HCWs; 2) recorded in the NPDV between 1st January 2010 and 31st December 2016; 3) no missing data in terms of patient characteristics (age and sex), suspected drugs and ADR description; 4) ADR causality for suspected drugs with a "certain," "probable" or "possible" assessment and 5) patient using only one beta-lactam drug (the information was validated by reviewing the original paper reports).

A case/non-case analysis was carried out to calculate the signals for different beta-lactams in beta-lactam subgroups.^{10,11} In this study, we use the definition proposed by the Second Symposium on the Definition and Management of Anaphylaxis to identify anaphylaxis reports (cases).¹² According to this definition, anaphylaxis is an acute serious systemic reaction that meets at least one of the following three clinical criteria:

What we already know about this subject

- Signal generation and the different risks of a specific drug can be estimated by using disproportionality analysis (case/non-case method)
- Not a lot is known about the risk of beta-lactam-induced anaphylaxis caused by different drugs in the same therapeutic area.

New information obtained during this study

- In Vietnam, cephalosporin is the most common cause of beta-lactam-induced anaphylaxis, particularly third-generation cephalosporins.
- This study suggests a new approach that identifies the different risks of reporting anaphylaxis in beta-lactam users, rather than traditional case/non-case method.

1. Rapid skin manifestation with either cardiovascular or respiratory system involvement
2. At least two cutaneous, respiratory, gastrointestinal or cardiovascular symptoms shortly after exposure to a likely allergen
3. Reduced systolic blood pressure (<90 mmHg or >30% decrease) after exposure to known allergen.

Adverse drug reaction reports other than those being studied were deemed as non-cases in case/non-case study design. The calculation of Reporting Odds Ratio (ROR) together with its 95% CI is similar to the calculation of an odds ratio from a case-controlled study, using the multivariate logistic regression model (Table 1). For the direct signal comparison between drugs in same pharmacotherapeutic category, we chose the approach of the generalized logistic regression model to compute the ROR value of each combination of drugs.^{13–16} In that case, we could calculate RORs, which vary from drug to drug in a subgroup. Statistical analyses were completed using R statistical software (version 3.4.0, issued 21 April 2017).¹⁷

3 | RESULTS AND DISCUSSION

Between 2010 and 2016, the NPDV received a total of 14,656 ADR reports with one beta-lactam as a suspected drug. From this total, 2,921 reports (19.93%) were about anaphylaxis. Among beta-lactam use, we found that cephalosporins were the most commonly reported group, especially the third-generation cephalosporins J01DD (C3G, $n = 1,947$), followed by the first-generation cephalosporins J01DB ($n = 210$) and the penicillin combinations J01R ($n = 204$). We identified the signals generated only for the cephalosporins and carbapenems subgroup (J01D, ROR = 1.27 [1.16–1.39]) and beta-lactamase-sensitive penicillins group (J01CE, ROR = 1.74 [1.27–2.35]) (Figure 1).

TABLE 1 Traditional of case/non-case method and new approach

	Generalized logistic regression model for signal generation	Generalized logistic regression model for signal comparison
Model equation	$\text{Log}(p/(1-p)) = \beta_0 + \beta_1 * \text{Age} + \beta_2 * \text{Sex} + \beta_3 * \text{Year} + \beta_4 * \text{Drug}_i + \varepsilon_i$	
Patient characteristics as covariates	• Age is continuous variable, corresponding to the age of patient • Sex is factorial variable, corresponding to the gender of patient • Year is factorial variable, corresponding to the reporting year	
Properties of drug use as covariate	• Drug_i is binomial variable corresponding with the use and not using the specific drug	• Drug_i is factorial variable corresponding with the alternative use of drugs in the same therapeutic subgroup of Drug_i
Output	Calculation of different signals between the use of drug X and the no use of drug X.	Calculation of different signals of risk of the use of drug X compared with the others in the same therapeutic subgroup.

After a stratified analysis of four generations of cephalosporin, we found no signal with any cephalosporin, except for cefoperazone+sulbactam (ROR=1.40 [1.02–1.90]) (Figure 2).

The preliminary results of the new approach of the case/non-case method were chosen and further analysed for C3G and second-generation cephalosporins (C2G). The analysis of risk comparison among C3G drugs showed significantly different risks between the following combinations (Table 2):

1. Cefotaxime with cefoperazone+sulbactam
2. Cefixime/cefepodoxime/cefepidur with cefoperazone+sulbactam or ceftizoxime/cefoperazone/ ceftazidime/ceftriaxone or cefotaxime.

Despite the fact that there was no signal generated for the C2G subgroup, different risks were found for cefotiam compared with cefmetazole, cefaclor, cefamandole and cefuroxime (RORs were

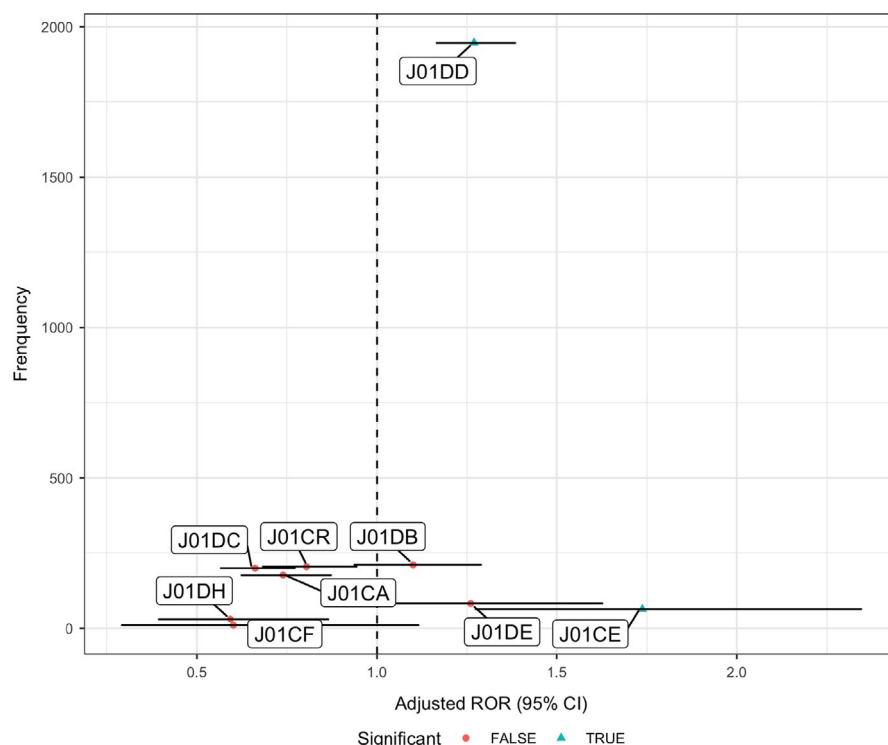
4.77 [1.24–31.51], 6.97 [1.86–45.54], 4.86 [1.35–31.12] and 4.22 [1.27–26.12], respectively) (Table 3). (For other beta-lactams not being discussed here, see the Appendix S1).

4 | DISCUSSION

4.1 | The use of beta-lactams in developing countries

In Vietnam, beta-lactams, one of the most commonly-used antibiotics,¹⁸ were the main cause of ADRs according to NPDV data during the period 2010–2016.⁵ The data on serious ADRs triggered by beta-lactams (for example, anaphylaxis in this case) remain limited because drug use and prescription practices are different between countries. The appropriate use of antibiotics seems well controlled

FIGURE 1 Signal generation of beta-lactam subgroups by traditional case/non-case method. J01DB first-generation cephalosporins, J01DC second-generation cephalosporins, J01DD third-generation cephalosporins, J01DE, fourth-generation cephalosporins; J01DH, carbapenems; J01CA, penicillins with extended spectrum; J01CE, beta-lactamase sensitive penicillins; J01CF, beta-lactamase resistant penicillins; J01CR, combinations of penicillins, incl. beta-lactamase inhibitors



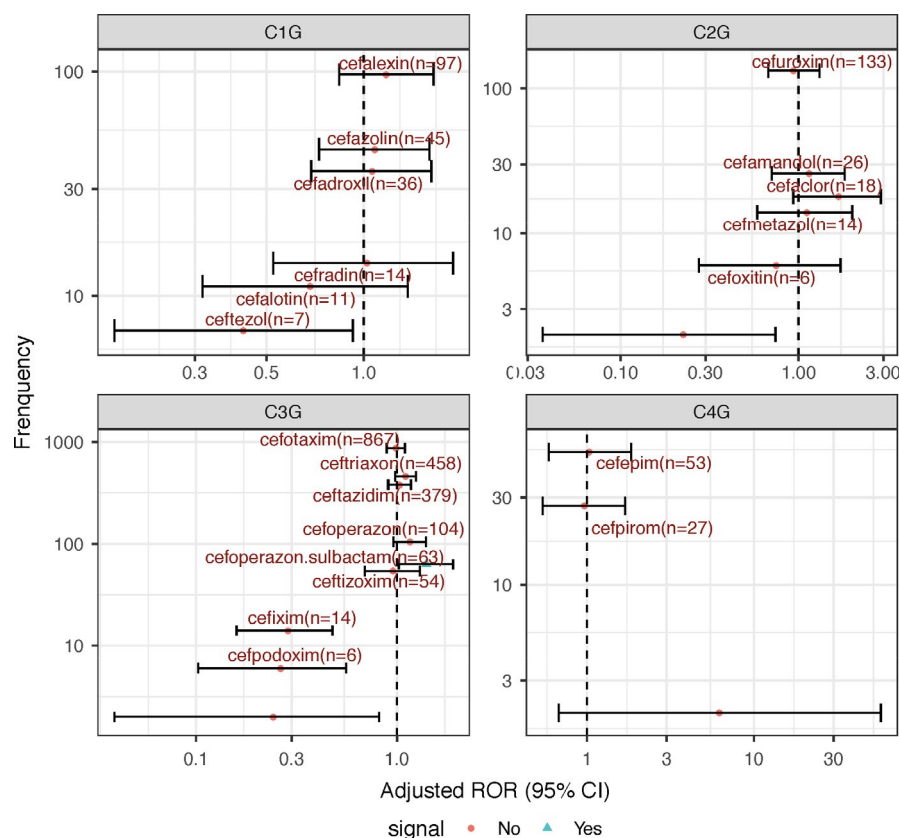


FIGURE 2 Signal generation within strata of the cephalosporins by traditional case/non-case method. C1G, first-generation cephalosporins; C2G, second-generation cephalosporins; C3G, third-generation cephalosporins; C4G, fourth-generation cephalosporin

TABLE 2 Different anaphylactic risks of the third-generation cephalosporins (ROR [95%CI])

Reference	Cefotaxime	Ceftriaxone	Ceftazidime	Cefoperazone	Ceftizoxime	Cefixime	Cefoperazone +sulbactam	Cefpodoxime	Cefdinir
Cefdinir	0.25[0.04-0.83]	0.23[0.04-0.76]	0.24[0.04-0.80]	0.23[0.04-0.81]	0.25[0.04-0.89]	0.84[0.13-3.24]	0.18[0.03-0.62]	0.92[0.13-4.28]	-
Cefpodoxime	0.27[0.10-0.57]	0.25[0.10-0.53]	0.26[0.10-0.55]	0.26[0.10-0.56]	0.28[0.10-0.63]	0.91[0.31-2.37]	0.19[0.07-0.43]	-	1.09[0.23-7.77]
Cefoperazone +sulbactam	1.40[1.02-1.92]	1.29[0.93-1.78]	1.36[0.97-1.87]	1.33[0.91-1.95]	1.45[0.94-2.23]	4.76[2.62-9.21]	-	5.22[2.31-14.04]	5.69[1.62-36.10]
Cefixime	0.30[0.16-0.49]	0.27[0.15-0.45]	0.28[0.16-0.48]	0.28[0.15-0.49]	0.30[0.16-0.55]	-	0.21[0.11-0.38]	1.10[0.42-3.20]	1.20[0.31-7.90]
Ceftizoxime	0.97[0.70-1.32]	0.89[0.64-1.23]	0.94[0.67-1.29]	0.92[0.63-1.34]	-	3.29[1.81-6.37]	0.69[0.45-1.06]	3.61[1.60-9.71]	3.93[1.12-24.97]
Cefoperazone	1.05[0.83-1.33]	0.97[0.75-1.23]	1.02[0.79-1.30]	-	1.08[0.74-1.59]	3.57[2.05-6.68]	0.75[0.51-1.10]	3.91[1.79-10.31]	4.26[1.24-26.80]
Ceftazidime	1.04[0.90-1.19]	0.95[0.81-1.11]	-	0.98[0.77-1.27]	1.07[0.77-1.49]	3.51[2.09-6.41]	0.74[0.53-1.03]	3.85[1.81-9.99]	4.20[1.24-26.19]
Ceftriaxone	1.09[0.96-1.24]	-	1.05[0.90-1.23]	1.04[0.81-1.33]	1.12[0.82-1.57]	3.69[2.20-6.72]	0.78[0.56-1.08]	4.05[1.90-10.49]	4.41[1.31-27.52]
Cefotaxime	-	0.92[0.81-1.05]	0.96[0.84-1.11]	0.95[0.75-1.21]	1.03[0.76-1.43]	3.39[2.03-6.14]	0.71[0.52-0.98]	3.72[1.75-9.60]	4.05[1.20-25.23]

Values in bold indicate significant difference.

TABLE 3 Different anaphylactic risks of the second-generation cephalosporin (ROR [95%CI])

Reference	Cefuroxime	Cefamandole	Cefaclor	Cefmetazole	Cefotiam	Cefoxitin
Cefoxitin	0.78[0.28-1.80]	0.68[0.23-1.71]	0.47[0.15-1.28]	0.69[0.22-1.92]	3.28[0.69-23.62]	-
Cefotiam	0.24[0.04-0.79]	0.21[0.03-0.74]	0.14[0.02-0.54]	0.21[0.03-0.81]	-	0.30[0.04-1.44]
Cefmetazole	1.13[0.59-2.04]	0.98[0.46-2.02]	0.68[0.30-1.52]	-	4.77[1.24-31.51]	1.45[0.52-4.49]
Cefaclor	1.65[0.91-2.87]	1.43[0.71-2.88]	-	1.46[0.66-3.30]	6.97[1.86-45.54]	2.12[0.78-6.46]
Cefamandole	1.15[0.70-1.84]	-	0.70[0.35-1.42]	1.02[0.49-2.17]	4.86[1.35-31.12]	1.48[0.58-4.30]
Cefuroxime	-	0.87[0.54-1.43]	0.61[0.35-1.10]	0.88[0.49-1.70]	4.22[1.27-26.12]	1.29[0.56-3.51]

Values in bold indicate significant difference.

among western countries (US, Europe, etc.), whereas the problem of irrational use and resistance of antibiotics is as a major public health concern in developing countries. Other socio-economic factors (for example, limited public health infrastructure or health insurance coverage) could also have a large influence on these differences.¹⁸

The high rate of ADR reporting for beta-lactams could reflect the overuse/over-prescription of these drugs. In Vietnam, the high consumption of beta-lactams, especially C3G, could easily lead to therapeutic failure and antibiotic resistance.¹⁸ Our finding also shared a similar situation that C3G was the most common cause of anaphylaxis

and all ADRs in Vietnam. Furthermore, our study also estimated, for the first time, the specific risk of C3G which is less commonly used in western countries.^{3,19} Our research presents a further analysis of these drugs that could fill the current research gap and contribute to international knowledge on the specific risks of this type of drug.

4.2 | Methodology

Compared with our previous findings using the original case/non-case method for the entire Vietnamese pharmacovigilance database,⁵ the results of this study reinforced the major contribution of C3G subgroup to anaphylaxis and also evaluated the different risks of each drug in the same therapeutic subgroup. In fact, the lack of credibility in the risk assessment of the case/non-case method originates from the challenge of choosing suitable non-cases, which is similar to the controls in the case/control method. As far as we know, the output of traditional case/non-case method was the increased signal (via ROR) of the risk related to drug X compared with the risk related to no use of drug X.^{14,16,20} And due to their nature, these ROR values did not allow for a comparison between drugs. Regarding the preliminary results by using our approach (the multivariate generalized linear regression model), we proposed a complementary method that allows us to directly compare the risks of each drug. From a clinical perspective, the risk comparison could help us to generate a hypothesis for ranking the specific signals of risk of these drugs with the same or similar therapeutic area.

4.3 | The different anaphylactic risks between beta-lactams

Cephalosporins accounted for the majority of beta-lactam-induced anaphylaxis cases ($n = 2438$, 83.46%) in our study. Three C3G drugs (cefotaxime, ceftriaxone and ceftazidime) were the beta-lactams that were most frequently reported to the NPDV ($n = 1722$, 58.95%). This finding was different to that of the Korean study conducted by Yang et al. which found that the cephalosporin with the highest signal of risk was ceftizoxime (13.0 cases per 100,000 exposures), followed by cefepime, cefotaxime, ceftizoxime, ceftriaxone and cefuroxime (9.3 per 100,000).²¹ The aforementioned study also indicated that there was no case of anaphylaxis induced by cefoxitin, cefmetazole or cefotiam, whereas these drugs triggered a lot of cases in our study.

We found that C3G use was the main cause of drug-induced anaphylaxis in Vietnam, with signal generation. This finding is consistent with results recorded in China, confirming the higher risks related to these drugs.²² Among the C3G drugs, our finding also indicated a significant increase of anaphylactic risks related to parenteral drug when directly compared with oral ones despite that fact that administration of any drug by any route can potentially cause anaphylaxis.^{23,24} This could be partly explained that ADR reports were mainly come from hospitals in Vietnam.

In the analysis on four cephalosporin subgroups, the majority of anaphylactic signals of these drugs were not generated. The finding could be partially explained by the theory of cross-reactivity of beta-lactam drugs. However, not all beta-lactams have the same risks, even when they belong to the same pharmaco-therapeutic category. For example, our results raised the hypothesis that the anaphylactic risk of cefotaxime was higher than cefoperazone+sulbactam among C3Gs.

In the risk comparison results within the C3G subgroup, we pointed out the importance of updating the benefit-harm balance of some antibiotics with a similar indication in order to ensure the drug safety in clinical use.²⁵ A hypothesis of lower "anaphylactic affinity" of cefpodoxime, cefixime and cefdinir, when compared with other C3Gs, has been raised,²⁶ and this should be further investigated to be taken into account in treatment. In the C2G subgroup, we found a significant difference in the risk of cefotiam use despite no signal generation with this subgroup or its specific drugs.

The limit of this study is based on spontaneous reporting of ADRs, for example underreporting, missing data, selective notification, selection bias, competition bias, etc.¹¹ The signal generation and signal comparison that only allow us to draw a hypothesis on the risks. According to recent European Medicines Agency recommendation, the estimation of disproportionality analysis with a $ROR > 2$ should be taken into account for further investigation of signal generation.²⁷ In addition, the stratified or subgroup analysis reduces the number of cases and non-cases that could potentially influence the reliability of results, especially when the number of cases is low.^{16,28,29} In the study, when stratified by therapeutic area, the case numbers are well maintained. This approach also improves the "diluting" effect (over-reporting of a specific group and/or under-reporting of others) due to the high consumption of antibiotics (predominantly C3Gs) in Vietnam,⁵ and it becomes closer to a case/control study. In addition, the population-based exposure data of cephalosporins are not available to be included in the analysis. Hence, the calculation of different risks could be greatly influenced by the variation of drug exposure, especially when extrapolate to a greater population. The calculation of "different risks" in our study did not aimed to estimate the "true risks" due to the limits of disproportional analysis approach using spontaneous reporting database. They were only the "signals of risk," requiring further research to confirm. Despite significant limitations and many biases, the methods allow for the early generation of drug safety signals. In some cases, they are the only tools available, particularly for the study of rare events (such as anaphylaxis) or uncommonly used drugs.

5 | WHAT IS NEW AND CONCLUSION

To conclude, we have introduced an approach to estimate the different risks between beta-lactam drugs and pointed out that the signals of risk were increased with some drugs in the same therapeutic group. Investigating beta-lactam-induced anaphylaxis could

contribute to the appropriate use of antibiotics in clinical practice. Our findings are grounds for better communication between health-care practitioners in developing countries where antibiotic resistance is a major national public health issue. Further validation and research are required to fully understand the risk of beta-lactam-induced anaphylaxis in resource-limited contexts.

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CONFLICT OF INTEREST

Khac-Dung Nguyen, Hoang-Anh Nguyen, Dinh-Hoa Vu, Van-Tu Dao, Jean-Louis Montastruc and Haleh Bagheri have no conflicts of interest that are directly relevant to the content of this manuscript.

AUTHOR CONTRIBUTION

Hoang-Anh Nguyen and Khac-Dung Nguyen designed the study. Khac-Dung Nguyen, Hoang-Anh Nguyen and Dinh-Hoa Vu involved in research. Khac-Dung Nguyen and Dinh-Hoa Vu analysed the data. Khac-Dung Nguyen, Van-Tu Dao, Haleh Bagheri and Dinh-Hoa Vu involved in new models and methods. Khac-Dung Nguyen, Dinh-Hoa Vu, Van-Tu Dao, Jean-Louis Montastruc and Haleh Bagheri wrote the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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