



פרופ' פרוכטר אורן

מחלות ריאה חוות דעת רפואיות משפטיות

מומחה למחלות ריאה ולרפואה פנימית
מנהל מחלקת ריאות וטיפול נמרץ נשימתי
מרכז רפואי וולפסון בית הספר לרפואה אוניברסיטת תל אביב
נייד 054-2518445
פקס 03-6354174
prof.fruchter@gmail.com
www.prof-fruchter.co.il

תל אביב, יום ראשון 28 יולי 2024

חוות דעת רפואית

צינקולקר ערן ת.ז. 038423679

אני החתום מטה, פרופ' אורן פרוכטר, מרח' אליהו ברלין 1 תל אביב נותן בזאת את חוות דעתי
המקצועית בעניין **צינקולקר ערן ת.ז. 038423679**

ואלה פרטי השכלתי וניסיוני המקצועי

תואר בוגר במדעי הרפואה, האוניברסיטה העברית ו"הדסה" ירושלים (1990)
לימודי רפואה, האוניברסיטה העברית ו"הדסה" ירושלים מספר רישיון: 26306 (1994)
חבר סגל בדרגת פרופ' חבר קליני, בית הספר לרפואה של אוניברסיטת תל אביב (2015-נוכחי)
מומחה לרפואה פנימית (בהצטיינות) מספר רישיון מומחה: 20770 (2004)
מומחה ברפואת ריאות (בהצטיינות) מספר רישיון מומחה: 25688 (2008)
רופא בכיר, המחלקה לרפואה פנימית "ג" מרכז רפואי רמב"ם (2004-2006)
רופא בכיר, המכון למחלות ריאה, מרכז רפואי רמב"ם (2008-2009)
מנהל השירות לרפואת ריאות פולשנית מרכז רפואי "רבין" קמפוס "בילינסון" (2009-2014)
ס.מנהל המכון למחלות ריאה מרכז רפואי "רבין" קמפוס "בילינסון" (2014-2015)
מנהל מחלקת ריאות וטיפול נמרץ נשימתי, מרכז רפואי וולפסון (2015-נוכחי)
מרצה למשפטנים בתחום רשלנות רפואית, בית הספר ללימודי המשך, הפקולטה לרפואה תל אביב

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prof.fruchter@gmail.com

- 1 לימודי תעודה "משפט רפואי" הפקולטה למשפטים אוניברסיטת תל אביב 2023
- 2 חבר האיגוד הישראלי לרפואת ריאות, החברה האירופאית למחלות מערכת הנשימה, החברה
3 האמריקאית למחלות ריאה.
- 4 חבר בוועדת הבוחנים למומחיות ברפואת ריאות מטעם המועצה המדעית של ההסתדרות הרפואית
- 5

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1 נתבקשתי על ידי משרד עו"ד פרייברג-רסקין לחוות דעתי לעניין המחלה הריאתית של מר
2 צינקולקר (להלן גם "החולה" או "התובע"), לעניין נכויות רפואיות הנגזרות מהמצב הרפואי,
3 ולעניין קשר סיבתי אפשרי, ככל שקיים, בין הנכות, לבין תאונת עבודה שהתרחשה במהלך
4 עבודתו כטכנאי מיזוג אוויר בתאריך 29.4.21.

5 לצורך כתיבת חוות הדעת, בהסתמך על ניסיוני המקצועי שפורט לעיל, בדקתי את החולה במרפאתי
6 ביום 23.7.24, עיינתי בספרות הרפואית הרלבנטית כפי שתפורט בהמשך, ונעזרתי בחומר הרפואי
7 הרלבנטי לתחום התמחותי שהועמד לרשותי כדלקמן:

- 8 • סיכומי ביקור רופא משפחה ורופאים מקצועיים "שירותי בריאות כללית"
- 9 • סיכומי ביקור רופא ריאות "שירותי בריאות כללית"
- 10 • בדיקת רופא משפחה מתאריך 4.5.21
- 11 • סיכום מידע רפואי "שירותי בריאות כללית" 17.10.23
- 12 • פענוח צילום חזה 4.5.21
- 13 • תפקודי נשימה 27.2.23
- 14 • חשבונית מס מתאריך 29.4.21

15 להלן סיפור המקרה

16 התובע יליד 1976 (בן 48 במועד עריכת חוות הדעת).

17 טכנאי מיזוג אוויר בהכשרתו ומקצועו. בעבר שוטר יחידת סיור בריא פרופיל 97.

18 שולל תחלואה נשימתית קודמת שולל אסטמה או מחלות ריאה אחרות בעברו.

19 עישון מגיל 17 ועד גיל 48 עד חפיסה ליום.

20 עובד כטכנאי מיזוג אוויר משנת 2009.

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- בתאריך 29.4.21 בעת עבודה באיזור "אבן יהודה" הלחים חלק מזגן עם התפרצות של גז מסוג Freon 22. מתאר שחש תחושה חזקה מאוד של מחנק ונאלץ לצאת החוצה מהאיזור הסגור בו היה ולאחר מכן המשיך לחוש בקוצר נשימה עם תחושת מחנק.
- נבדק על ידי רופא משפחה בתאריך 4.5.21

שלום רב,

תאריך ביקור: 04/05/2021

סוג ביקור: 0 ביקור רגיל

מהות הביקור: רגיל

תלונות/סיבת הפניה: לפני שבוע נשם גז רעיל. FREON 22
עכשיו יש לו קוצר נשימה.

ממצאים: קולות הלב תקינים.
כניסת אוויר תקינה בשני הצדדים.
אין קולות נשימה נוספים

אבחנות בביקור

קוד	אפיין	אבחנה
7860		DYSPNEA
		FREON 22 INHALATION

הפניות בביקור

הפניות	פרטי ההפניה	קוד	התחייבות	סטטוס
הפניה לדימות	78060-צילום חזה	H3		הודפס

תרופות בביקור

תדירות												
P	n	ק	נ	OP	סה"כ	משך	D	פ	יחידה	הגשה	מנה	תרופה
1	W	0	0	N	יחידה	1	1	0	זריקה	INJ		METHYPREDNISOLONE INJ 125 MG 2
12												
תאונה												
תאונה	גר"ן	ת. אישור	טיפול מחזורי				עין	תרופה				
								METHYPREDNISOLONE INJ 125 MG 2				

- לפי הכתוב טופל על ידי סטרואידים במתן תוך ורידי .
- פענוח צילום חזה 4.5.21

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סיבת ההפניה:

קיימת הפניה ממוחשבת / סרוקה

ביצע:

צילום חזה בתאריך 04/05/2021 15:20 מ.ג. 1125002117866 מבצע: הצב נמר;
צילום חזה;

ממצאים:

לא נצפה תסנין תפליט פלאורלי או גודש
נצפה ניפוח יתר ללא שינוי משמעותי בהשוואה ל-9.6.2016
צל הלב לא מוגדל

סיכום:

כמפורט בפענוח לעיל.

- 1
- 2 החולה מתאר שמאז האירוע קוצר נשימה במאמץ קל מתקשה בביצוע של עבודות פיזיות מתקשה
- 3 בעת מאמץ.
- 4 מרגיש שמאז אותו אירוע "לא חזר לעצמו". מתאר שכחודש לאחר התאונה היה באירוע משפחתי
- 5 ובו נאלץ להפסיק לרקוד בשל תחושת קוצר נשימה.
- 6 נבדק על ידי רופא ריאות בתאריך 31.12.22

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תאריך: 30/12/2022

סיכום יעוץ

פרטי המטופל:		שם משפחה ופרטי:	צינזולקר ערן	מס זהות:	00038423679	גיל:	46.08	מין:	ז
ת.לידה:		30/04/1976	ישוב:	ניצני עוז	רחוב:	הפרחים			
מס בית:		30	טלפון:	50-5674647	טלפון מסך:	77-3453494			

לכבוד: ד"ר זסלבסקי גלינה

תלונות: בן 46.

מעשן כבד.

ללא מחלות ברקע.

רק תלונות על קוצר נשימה בעונות מעבר. ומקבל טיפול בסרטייד. !!

לאחרונה תלונות על קוצר נשימה ומחנק במאמץ חזק.

עבר בדיקת קרדילוג - נשללה בעיה לבבית.

ממצאים: במצב כללי יציב

נינוח

ללא מצוקה נשימתית

סטורציה - 96% על אויר חדר

מעל לריאות כניסת אויר שווה וטובה דו"צ.

אבחנות

מועד גילוי	איפיון	אבחנה
		DYSPNEA

תוכנית אבחנתית

הפניות	פרטי ההפניה	קוד	סטטוס
הפניה לדימות	78060-צילום חזה		H3 הודפס
טופס הפניה כללי	78065-ספירומטריה עם מרחיבי		H4 הודפס

פעולות ביעוץ

פעולות	קוד	כמות	בוצע בתאריך
654 פתיחת תיק	654	1	30/12/2022

סיכום והמלצות: מעקב רופא משפחה

מופנה לספירומטריה עם מרחיבי סימפונות

צילום חזה

הפסקת עישון

ביקור חוזר לאחר הבדיקות.

1

2

להלן בדיקת רופא ריאות 30.12.22

חוות דעת צינזולקר ערן ת.ז. 038423679

עמוד - 6 - מתוך 12

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תלונות:

30/12/2022

בן 46

מעשן כבד

ללא מחלות ברקע

רק תלונות על קוצר נשימה בעונות מעבר. ומקבל טיפול בסרטייד !!

לאחרונה תלונות על קוצר נשימה ומחנק במאמץ חזק.

עבר בדיקת קרדילוג - משללה בעיה לבבית.

18/07/2023

עדיין מעשן.

תלונות על קוצר נשימה במאמצים ובעליית מדרגות.

תפקודי ריאה - FVC-73-79

FEV1-62-68

FEV1/FVC-70-70

TLC-85

DLCO-77

הפרעה חסימתית בינונית וירידה קלה בדיפוזיה

התמונה מתאינה ל COPD בחולה מעשן !!!!

ממצאים: 30/12/2022

במצב כללי יציב

נימוח

ללא מצוקה נשימתית

סטורציה - 96% על אויר חדר

מעל לריאות כניסת אויר שווה וטובה דו"צ.

18/07/2023

אבחנות

מועד גילוי	איפיון	אבחנה
		COPD
		DYS-PNEA
		SMOKER

1

2

כאמור סוכם כ COPD. הוחל טיפול במשאפים מסוג Incruse + foster

3

להלן סיכום מידע רפואי מתאריך 17.10.23

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תאריך: 1/10/2023

סיכום מידע רפואי

פרטי המטופל:			
שם משפחה ופרטי:		צינולקר ערן	
ת. לידה:	30/04/1976	ישוב:	יציני עוז
מס בית:	30	טלפון:	50 - 5674647
מס זהות:		00038423679	
גיל:		47.05	
מין:		ז	
רחוב:		הפרחים	
טלפון נספח:		77 - 3453494	

מיועד ל- כל המעוניין

נרשם על סמך הרשום בתיק משקל 86kg גובה 176cm לחץ דם 91 / 132 B.P. מעשן כעת 27.76 bmi

אבחנה -מצב בריאותי

Current Diagnoses

בעיות פעילות

ת. גילוי	אפיין	בעיה
01/01/1992		SMOKER

Past Diagnoses

בעיות עבר

ת. סיום	ת. גילוי	אפיין	בעיה
17/10/2023	00/02/1999		DISLOCATION SHOULDER RECURRENT LT

Medications

תרופות קבועות

...	פעמים	א. הגשה	כמות	תרופה
ביום	1	שאיפות	1	INCRUSE ELLIPTA<>INH 55MCG 55MCG
ביום	2	שאיפות	1	FOSTER INH 100MCG/6MCG 100MCG/6MCG

תלונות החולה ומצב נוכחי

קוצר נשימה במאמץ קל . מתקשה מאד בעבודות פיזיות. מתקשה בביצוע של פעולות יום יומיות.
בעוד אשר בעבר במהלך עבודתו היה מסוגל להרים משאות כבדים כעת אינו מסוגל ומתקשה בעלייה של מדרגות

בבדיקה

מספר נשימות 12 סטורציה 97% . חזה : התפשטות שווה סימטרית

ריאות : בניקוש הדיות יתר . אקספיריום מוארך.

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1 תפקודי נשימה (% מערך חזוי לפי גיל, מין וגובה)

תאריך	FEV1	FEV1/FVC	FVC	TLC	RV/TLC	DLCO
27.2.23	62-68	0.88	73-79	85	130	77

2

Name: צינצולקר, ערן

ID: 03842367-9

Sex: Male

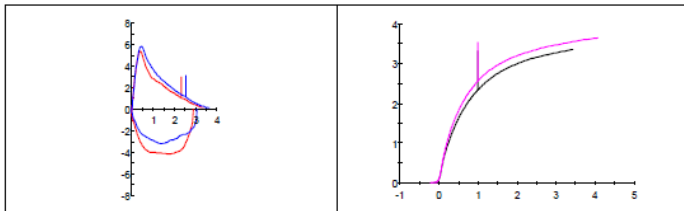
Date: 27/02/2023

Age: 46

Height: 176.00

Weight: 84.00

	Pre-Bronch			Post-Bronch		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----						
FVC (L)	3.35	4.58	73	3.65	79	+8
FEV1 (L)	2.34	3.72	62	2.56	68	+9
FEV1/FVC (%)	70	79	88	70	88	+0
FEF 25-75% (L/sec)	1.68	4.10	40	2.10	51	+25
FEF Max (L/sec)	5.37	8.94	60	5.80	64	+7
FEF 25% (L/sec)	3.18	7.78	40	4.18	53	+31
FEF 50% (L/sec)	1.88	4.87	38	2.30	47	+22
FEF 75% (L/sec)	0.91	2.04	44	1.20	58	+31
---- LUNG VOLUMES ----						
SVC (L)	3.49	4.58	76			
TGV (L)	2.88	3.45	83			
RV (Pleth) (L)	2.51	2.11	118			
TLC (Pleth) (L)	6.00	6.98	85			
RV/TLC (Pleth) (%)	42	32	130			
---- DIFFUSION ----						
DLCOunc (ml/min/mmHg)	24.01	31.14	77			
DL/VA (ml/min/mmHg/L)	4.45	4.46	99			



Post-Test Comments:

נפחי הריאות: ירידה בנפח הריאות הכללי כעדות להפרעה רסטורטיבית קלה
דינמיקת הנשימה: ירידה בינונית בזרימות הנשימתיות, שיפור קל אחר מרחיבי סמפונות
סיכום: הפרעה מעורבת רסטורטיבית (קלה) וחסימתית (בינונית) עם מרכיב הפיך חלקי
בדיקת דיפוזיה - ירידה קלה בדיפוזיה הכוללת, תקינה אחר תיקון לנפח אלביאולרי
ריווי המצץ - 98%

3

חוות דעת צינצולקר ערן ת.ז. 038423679
עמוד - 9 - מתוך 12

פרופ' אורן פרוכטר

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דיון

1

2 מדובר בגבר כבן 48 עם עישון ברקע ללא תחלואה נשימתית בעברו וללא אבחנה קודמת של COPD
3 או אסטמה. בתאריך 29.4.21 נחשף במהלך עבודתו כטכנאי מיוזג אוויר לגז מזגנים מסוג Freon
4 22. מדובר בחומר hydrochlorofluorocarbon (HFFC). מדובר בחומר המכיל תערובת של
5 hydrogen, fluorine and carbons, הידוע כחומר מגרה דרכי אוויר שעלול להביא בעת חשיפה בעת
6 תאונה ל acute inhalational injury עם התפתחות של chemical pneumonitis (דלקת ריאות
7 כימית), ברונכיוליטיס (דלקת סימפונות קטנים), ובצקת ריאות. (מקור 1).

8 במקרה הנוכחי התמונה הקלינית של קוצר נשימה שהופיע לראשונה בחייו לאחר האירוע יחד
9 עם תמונה קלינית שהצריכה מתן סטרואידים – גם ללא ממצא האזנתי או ממצא בצילום החזה ,
10 הינה בסבירות גבוהה משקפת נזק נשימתי שנגרם בשל אותה חשיפה וזאת בשל סמיכות הזמנים
11 בין החשיפה לקליניקה והיעדרה של קליניקה דומה קודמת.

12 חומרים מגרים כאשר הם נשאפים לריאותיו של אדם המצוי בקרבתם עלולים להביא להתפתחות
13 של אסטמה במנגנון של RADS (כלומר reactive airway disorder syndrome). כלומר מתפתחת
14 תוך זמן קצר ביותר (כמו במקרה זה) רגישות יתר של דרכי האוויר המביאה לתסמינים בלתי
15 חולפים של אסטמה (ראה מבואות 2-4). תסמינים אלה מתבטאים בקוצר נשימה מלווה בשיעול
16 וקליניקה של צפצופים בדרכי הנשימה הדורשת טיפול קבוע בתכשירים מרחיבי דרכי אוויר וכן
17 סטרואידים בשאיפה.

18 התמונה הקלינית בהמשך של מחלת ריאות חסימתית שלא הייתה ידועה קודם לכן (בהינתן עישון
19 קודם ממושך) מהווה קרוב לוודאי שילוב בין נזקי אותה חשיפה תעסוקתית תאונתית חדה והשפעת
20 העישון.

21 יש להניח כי החלק היחסי של תרומת אותו אירוע תאונתי של שאיפת חומר מגרה דרכי אוויר
22 להתפתחות מחלתו הנשימתית עומד על כ 2/3 כאשר החלק היחסי של העישון עומד על 1/3 .

פרופ' אורן פרוכטר

מנהל מחלקת ריאות וטיפול נמרץ נשימתי
מרכז רפואי וולפסון והפקולטה לרפואה אוניברסיטת תל אביב
prof.fruchter@gmail.com

I. קיימת סבירות של מעל 50% כי תנאי העבודה השפיעו על התפתחות הליקוי כלומר סביר יותר לקבוע כי תנאי העבודה והחשיפה לחומרים שפורטו לעיל השפיעו על הופעת הליקוי הנשימתי או החמרתו לעומת המצב ההפוך.

II. לתנאי העבודה של התובע הייתה השפעה משמעותית ביותר על הליקוי במידה שעולה באורח וודאי על סף של 20%. במקרה זה אני קובע כי לתנאי העבודה מגיעים לסף של 2/3.

קביעת דרגת נכות

על בסיס הנכתב לעיל, ועל יסוד תקנות הביטוח הלאומי " קביעת דרגת נכות לנפגעי עבודה"- תשט"ז 1956 (תיקון 2019) ולפי "תדריך לרופא נפגעי עבודה 2013 המוסד לביטוח לאומי " אני קובע את נכות החולה מבחינה ריאתית כמפורט להלן:

מחלת ריאות חסימתית כרונית FEV1 62-68% - נכות של 30% לפי 5 (א-ב סעיף ביניים).

ספרות

1. Hydrofluorocarbons pneumonitis as a complication of inhalation injury following air-conditioning repair. Respirology Case Reports. 2022;10:e0983. wileyonlinelibrary.com/journal/rcr2 1 of 3
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3. Acute Responses to Toxic Exposures in : Murray and Nadel. Textbook of Respiratory Medicine. 7th Edition. Chap 103.
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- 1 הריני מצהיר בזאת, כי ידוע לי עניין החוק הפלילי בדבר מתן עדות שקר בשבועה בבית המשפט,
2 דין חוות דעת זאת כשהיא חתומה על ידי, כדין עדות בשבועה שנתתי בבית משפט.
3 בזאת אני בא על החתום,


המרכז הרפואי וולפסון
פרופ' פרוכטר אורן
מנהל מחלקת ריאות ט.נ. נשימתי
מ.ר. 26306

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6 פרופ' אורן פרוכטר
7 מנהל מחלקת ריאות וטיפול נמרץ נשימתי
8 מרכז רפואי וולפסון ואוניברסיטת תל אביב

CASE REPORT

Hydrofluorocarbons pneumonitis as a complication of inhalation injury following air-conditioning repairs

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Associate Editor: Yet Hong Khor

Abstract

Hydrofluorocarbon (HFC) pneumonitis is an uncommon cause of inhalation injury. HFCs are a group of chemicals predominantly used for refrigeration and cooling. A 19-year-old air-conditioning technician developed acute onset of dyspnoea and chest tightness while servicing an air conditioner in a confined space. We diagnosed him with HFC pneumonitis based on the history of exposure and the high-resolution computed tomography (HRCT) thorax findings. He was treated with steroids and supportive oxygen therapy. He recovered fully after 5 days of hospitalization and was discharged. Review at 2 weeks in the outpatient setting showed significant radiological improvement on HRCT thorax.

KEYWORDS

air conditioning, hydrofluorocarbons, inhalation injury, pneumonitis, systemic steroid

INTRODUCTION

Inhalation injury refers to damage to the respiratory tract or lung tissue from heat, smoke or chemical irritants during inspiration that can cause acute and fatal pneumonitis.¹ Hydrofluorocarbons (HFCs) are synthetic organic compounds that contain fluorine and hydrogen atoms.² They are relatively non-flammable and are used in a wide variety of cooling systems, from refrigerators and freezers to automotive air-conditioning units. We report a unique case of acute HFC pneumonitis in a 19-year-old man following an inhalation injury during air-conditioning service in a confined space.

CASE REPORT

A previously well, non-smoker, 19-year-old part-time air-conditioning service operator presented with an acute onset of dyspnoea after servicing an air conditioner in a confined closed office space. He noted a faint sweetish smell when he started his job but he continued to work. One hour later, he developed shortness of breath with palpitations and a sensation of chest tightness.

Upon arrival to the emergency department, pulse rate was 125/min with a respiratory rate of 22 breaths per

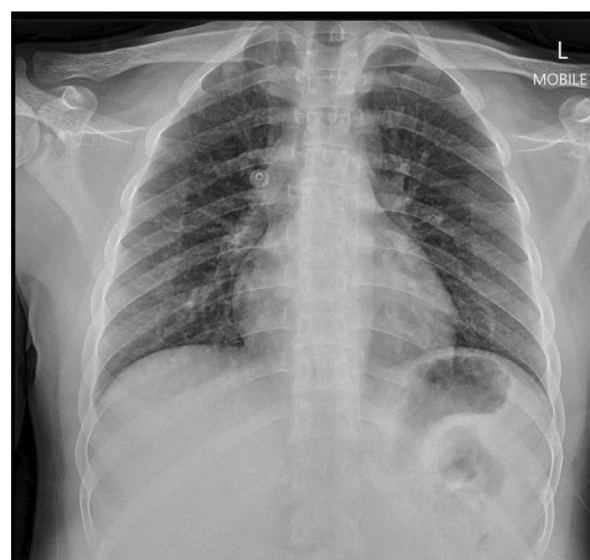


FIGURE 1 Chest radiograph on admission showing bilateral pulmonary infiltrates

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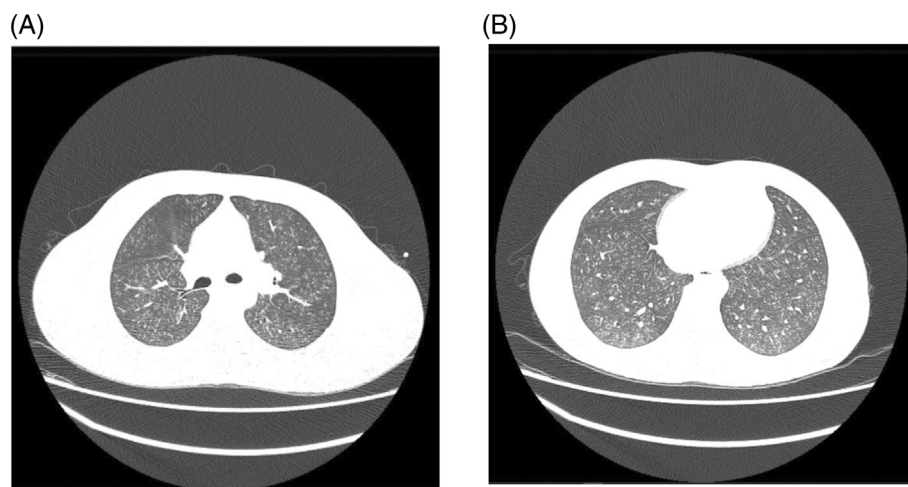


FIGURE 2 (A, B) High-resolution computed tomography thorax (axial view) showed diffuse ground-glass centrilobular nodules with minimal peripheral bronchiole wall thickening.

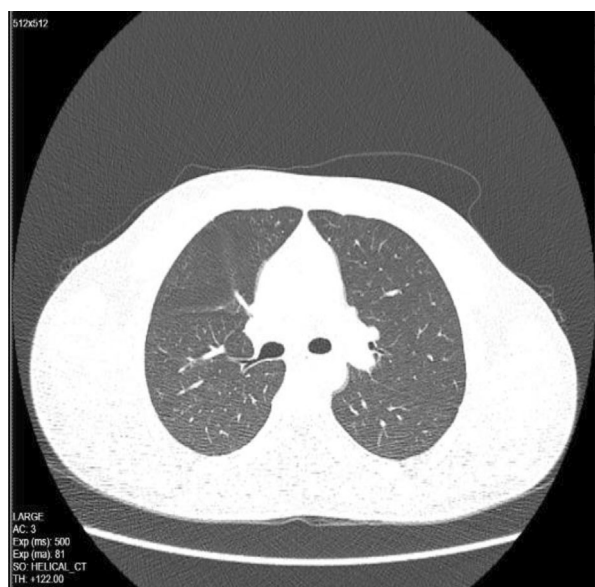


FIGURE 3 Marked improvement in centrilobular nodularity, with residual seen at the right upper and middle lobes

minute (bpm) and oxygen saturation was 90% on room air. Examination of the respiratory system revealed generalized rhonchi with reduced air entry bilaterally. Systems review was unremarkable.

Laboratory results revealed elevated white blood cells (11.6/ μ l) and C-reactive protein was 0.83 mg/L. Serum electrolytes, hepatic and renal function tests were normal. Arterial blood gas on room air demonstrated pH 7.39, partial pressure of carbon dioxide (PaCO_2) 39.7 mmHg, partial pressure of oxygen (PaO_2) 62.5 mmHg and HCO_3^- 23.6 mmol/dl. COVID-19 real-time reverse transcription-polymerase chain reaction test was negative and electrocardiogram was normal.

The chest radiograph showed mild pulmonary infiltrates (Figure 1). We proceeded with a high-resolution computed

tomography (HRCT) of the thorax that showed diffuse ill-defined ground-glass centrilobular densities scattered in both lung fields with no zonal predominance (Figure 2).

Based on the history and investigations, a diagnosis of hydrochlorofluorocarbon (HFC)-induced acute pneumonitis was made. He was treated with 100 mg intravenous hydrocortisone three times per day, nebulized salbutamol and oxygen supplement. He was given intravenous antibiotics (amoxycillin and clavulanic acid) due to mild leucocytosis. Oxygen saturation improved markedly after the administration of intravenous steroid, and subsequently the patient was able to wean off oxygen at day 4 of intravenous steroid administration. He was discharged with oral prednisolone 35 mg daily for a total of 2 weeks. We did not perform spirometry or bronchoscopy.

He was reviewed in clinic at 4 weeks post discharge. A repeat HRCT thorax (Figure 3) showed marked improvement in the degree of ground-glass centrilobular nodules, with residual nodules seen at the right upper and middle lobes.

DISCUSSION

HFCs are synthetic organic compounds that contain hydrogen, fluorine and carbons, which are relatively non-flammable, chemically stable and non-reactive.² HFCs have a wide variety of usage and they are also frequently used in air conditioning and as refrigerants in refrigerators and freezers.³

Acute HFC exposure can cause multi-organ dysfunction.⁴ HFC pneumonitis is an acute pneumonitis caused by aspiration and/or inhalation of HFC compounds with low viscosity and high volatility.⁴ The clinical presentation of hydrocarbon pneumonitis is often non-specific and includes breathlessness, cough, chest pain and haemoptysis.⁵ This usually improves over a few days with supportive measures.⁶ The patient stated that he accidentally inhaled volatile HFCs

during his work in an enclosed space and developed symptoms as described.

Exposure to several irritant substances at high levels may cause bronchiolitis and pulmonary oedema or 'chemical pneumonitis', depending on the solubility and physicochemical properties of the substance. HFCs disrupt surfactants, resulting in the decrease of pulmonary compliance and they can also cause pulmonary injury, with resultant inflammation, oedema and necrosis.⁴ The characteristic thin-section computed tomography (CT) findings are bronchial wall thickening, centrilobular nodular areas of ground-glass attenuation and confluent areas of ground-glass attenuation with peribronchiolar distribution, or extensive ground-glass opacity and consolidation.⁷ Some of these changes were evident in the case described.

A case report describing seven construction workers exposed following an installation of an additional HF (hydrofluoride) gas storage tank showed similar HRCT thorax findings of diffuse patchy ground-glass opacities with centrilobular nodules. Treatment given was similar to our patient. They showed resolution of CT at 3 months.⁸ In this case, the follow-up CT at 1 month showed remarkable improvement. However, no pulmonary function test and bronchoscopy were done for this patient.

Apart from supportive care, treatment with intravenous antibiotics and steroids are common therapies. Additionally, leucocytosis is commonly observed in patients with HFC pneumonitis, which is also a typical laboratory finding in cases of pneumonia.⁹ Differentiating chemical pneumonitis from infective pneumonitis is difficult but not impossible. Clinical history or further investigations, such as bronchoscopy, are useful. Sen et al. reported in their retrospective study that patients with hydrocarbon pneumonitis responded well to steroid therapy.⁹ However, none of these treatments have adequate randomized controlled data to prove their therapeutic effect on patients with hydrocarbon pneumonitis. Therefore, supportive care remains the mainstay of treatment for this condition.

In conclusion, HFC pneumonitis is an important diagnosis to make in a patient with a history of exposure to HFC products. Supportive care remains the mainstay of treatment, and antibiotics and steroids are reasonable therapeutic choices. Patients' clinical improvement precedes the resolution of radiological changes on chest x-ray. The prognosis of patients with HFC pneumonitis appears favourable with accurate diagnosis and appropriate care.

AUTHOR CONTRIBUTION

All authors contributed to the case report, discussion and writing of the manuscript.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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RADS and Its Variants

Asthma by Another Name

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KEYWORDS

- Reactive airways dysfunction syndrome • Work-exacerbated asthma
- Irritant exposures • Irritant asthma

KEY POINTS

- Acute high-level irritant exposures can cause asthma and exacerbate underlying asthma.
- Lower-level irritant exposures can at least exacerbate underlying asthma, although there is emerging consensus that recurrent lower-level exposures may also cause asthma.
- There is overlap between the exposures that have caused acute irritant-induced asthma and work-exacerbated asthma (WEA), many of which are also sensitizers.
- New-onset asthma in workers following lower-level irritant exposures, with no prior history of respiratory symptoms or asthma, may well be limited to a subset of “susceptible” hosts, such as those with asymptomatic airway hyperresponsiveness, atopy, and those who “outgrew” childhood asthma.
- The ATS statement on WEA has identified research needs to better define risk factors, biologic mechanisms, and outcomes in WEA, which should help facilitate necessary interventions in the medical system, as well as to formulate and apply strategies for prevention.

INTRODUCTION

Asthma is a chronic respiratory condition characterized by variable airflow obstruction, airways hyperresponsiveness, and airway inflammation. Approximately 7.7% of US adults of working age have asthma¹ and an estimated 16.3% of all cases of adult asthma have been attributed to asthma caused or exacerbated by workplace exposures.² Many other conditions and factors, such as rhinosinusitis, gastroesophageal reflux disease (GERD), vocal cord dysfunction, and cigarette smoking, may trigger symptoms that mimic asthma but are not, and these are covered elsewhere in this issue. Other, more serious conditions that mimic asthma include hypersensitivity

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pneumonitis, which can be caused by low molecular weight irritants that are also sensitizers,^{3–6} bronchiolitis obliterans,^{7,8} and irritant/odorant-triggered cough.^{9–11} Whereas asthma caused by sensitization is well described and well accepted,^{12–16} it is not the primary focus of this article. On the other hand, reactive airways dysfunction syndrome (RADS) and other variants of irritant-induced or irritant-exacerbated asthma may not always initially appear as asthma, but are, in fact, alternate presentations of asthma. Therefore, occupational and environmental exposures that can cause or exacerbate asthma should be considered as well. Although unique conditions exist in the workplace that more often lead to the type of exposures that can cause or exacerbate asthma, exposure to sensitizers and irritants that exacerbate or cause asthma can also occur in the home, during avocational activities, and following accidental industrial releases into the environment. Thus, although the terms occupational and workplace are used in this article, environmental sources of these exposures should also be considered.

The role of irritants in the causation of asthma is now well established. RADS was originally defined in 1981 by Brooks and Lockey¹⁷ and detailed in case series of new-onset asthma syndrome within 24 hours following a single, high-level irritant exposure.¹⁸ Since that time, modifications to the case definition have been proposed, and more recently the term “acute irritant asthma” has been used, with good consensus that this is not just an asthma syndrome but indeed occupational asthma.^{14,16,19,20} Asthma has been reported after lower-level irritant exposures, with considerable controversy regarding whether or not the lower-level irritant exposure caused the asthma,^{21,22} was a result of concurrent immunologic sensitization,^{16,23} or caused an exacerbation of underlying asthma.^{14–16,24,25} Work-exacerbated asthma (WEA) is defined as “preexisting or concurrent asthma that is worsened by workplace conditions,”²⁵ in which there is a temporal association between asthma exacerbations and work in a place where conditions exist that can exacerbate asthma, but that asthma caused by work (immunologic asthma and acute irritant asthma) is considered unlikely. WEA is often not compensable under workers’ compensation.

This article covers the different clinical variants of irritant-induced asthma, specifically focusing on high level irritant-induced asthma and irritant-induced WEA reviews known causes, addresses the often adverse medical and socioeconomic outcomes of this complex condition, and considers issues of causation from an occupational and environmental medicine perspective.

CLINICAL VIGNETTE 1

John Adams is a 45-year-old city maintenance worker. He is a never-smoker and has no history of asthma or other medical problems. He performs maintenance inside city facilities, including the wastewater treatment plant. On one occasion, a regulator malfunction caused the sudden high-pressure release of 100% chlorine into the very small room where he was working. The sudden release caused him to take in a deep breath, and he experienced immediate cough, burning eyes and nose, chest burning and tightness, and shortness of breath. He was taken to the emergency department and placed on oxygen. He is not sure about what other treatment he received, but after a period of time he felt somewhat better and was discharged. Most of his symptoms continued to improve, but the dry cough persisted. He noted chest tightness and shortness of breath with exertion, such as walking in the mountains. His chest symptoms were also triggered by irritants, such as cigarette smoke, perfume, and dust, which had never bothered him before. He seeks medical attention for these symptoms 3 months later. Could this be asthma?

ACUTE IRRITANT ASTHMA

Yes, asthma should be considered as part of the differential diagnosis, and should be confirmed by methacholine challenge or bronchodilator responsiveness. The presentation is consistent with RADS, defined as asthma caused by a single, high level, irritant exposure hypothesized to cause acute bronchial mucosal damage leading to airways hyperresponsiveness. Whereas allergen exposures are well-documented causes of asthma, the role of irritants in the causation of asthma has been recognized only more recently. RADS was originally described as a “persistent asthma syndrome” after high-level irritant exposure.^{17,18} Brooks noted that although the illness clinically simulated bronchial asthma and was associated with airways hyperreactivity, it differed from typical occupational asthma because of rapid onset (within 24 hours) after a single high-level environmental exposure, and this period of time is too short for the development of sensitization.¹⁸ Although the validity of the syndrome as new-onset asthma was initially debated,^{26,27} numerous case reports have followed,^{9,28–32} and it is now widely accepted that acute high-level irritant exposures not only cause a syndrome that mimics asthma but can cause asthma itself.^{14–16,19,20} Tarlo and Broder introduced the term “irritant-induced asthma” in 1989 to include workers in their case series who had high-level irritant exposure on more than one occasion,³³ which has been subsequently reported by others.³⁰ Other studies included those with onset of symptoms up to 7 days after a well-defined spill; they identified additional cases that otherwise met the case definition.³⁴ The term “acute irritant-induced asthma” was recently proposed,^{16,20} and for workers without any prior history of asthma, the term is an accurate unifying descriptor. A list of some of the exposures reported to have caused acute irritant asthma, termed RADS and asthma after spills or accidental exposures, are shown in **Table 1**. The clinical criteria for RADS described by Brooks¹⁸ and modifications that have been proposed are shown in **Box 1**.

In many cases, the symptoms resolve within months, but they can persist in some.^{9,18,29–32,35,36} The long-term sequelae can be significant. One long-term follow-up study of workers (52% participation) with claims accepted by the workers' compensation agency in Quebec revealed significant ongoing respiratory impairment and psychosocial impact two years after initial symptoms. These patients presented with acute irritant-induced asthma due to a well-defined high-level accidental release (57% chlorine) and had symptoms that developed within 24 hours and persisted beyond 3 months. All subjects still had respiratory symptoms; 68% were on inhaled corticosteroids, there had been no significant improvement in forced expiratory volume in 1 second (FEV1) (mean FEV1 74.5% $\pm$ 19.5% predicted), and most still demonstrated airways hyperresponsiveness based on methacholine challenge or improvement after bronchodilator. There was a negative impact on quality of life, and about one-third had abnormal depression scores.³⁷ The long-term impact was similar to that reported in immunologic asthma.³⁸

CLINICAL VIGNETTE 2

Michael Janvier is a 54-year-old insulator in a large plant. He has a 5-pack-year history and had stopped smoking at age 30. He has no prior history of respiratory symptoms. He has performed installation, repair, and routine maintenance on the pipes in a chrome-plating shop on and off over the past 10 years. Some of the pipes were located 4 to 5 feet above the acid baths. Depending on the job, he could spend several weeks or even months at a time in that shop. He sometimes felt burning in his eyes, nose, and throat, as well as some cough, although these symptoms were fairly mild and typically resolved later that evening or the next day. About a year ago, he began

Table 1 Reported high-level irritant exposures associated with development of acute irritant-induced asthma, along with pH, potential for thermal injury, and sensitizer potential					
Author	Outcome	Reported Chemical	High or Low pH	Potential for Thermal Injury	Potential Sensitizer
Brooks et al, ¹⁸ 1985	RADs after single high-level exposure	Uranium hexafluoride			–
		Floor sealant			?
		Spray paint (3)			?
		35% hydrazine			
		Heated acid	+	+	
		Fumigating fog			?
		Metal coat remover	?		
Tarlo and Broder, ³³ 1989	RADs after 1 or more high-level exposures	Fire/smoke		+	?
		Acids	+		
		Calcium oxide			
		Chlorine, sulfuric acid, sulfur dioxide	+		
		HCl, phosgene	+		
		Calcium oxide, welding fumes			?
		Burnt paint fumes		?	?
		Spray paint no isocyanate			
		Chlorine			
		Toluene diisocyanate			+
Chatkin et al, ⁴⁵ 2007	Asthma after spills or accidental exposures	Diphenyl methane diisocyanate			+
		Isocyanates			+
		Paint			?
		Solvents			
		Chlorine			
		Ammonia	+		
		Calcium oxide	+		
		Acrylates			+
		Amines			+
		Epoxy resins			+
		Dyes			?
		Ozone			?
		Pesticides			
		Wood dust			?
		Methylmercaptan			

The “+” refers to the listed chemical exposures that have one or more of the other properties: high or low pH, potential for thermal injury and/or are potential sensitizers. The “?” refers to those chemical exposures that might have one of those properties, but there is insufficient information about the exposure to determine.

Abbreviation: RADs, reactive airways dysfunction syndrome.

to notice worsening shortness of breath while running and playing soccer. He also started awakening at night with chest tightness about once a week. A cardiac evaluation was negative, including a normal stress echocardiogram. His symptoms continue to worsen and he seeks further medical attention. Could this be this asthma?

ASTHMA FOLLOWING LOWER-LEVEL IRRITANT EXPOSURES

In 2005, Brooks³⁹ introduced the term “not-so-sudden onset” irritant-induced asthma to describe the exposures in a subgroup of subjects who had onset of asthma

Box 1**Clinical criteria for acute irritant-induced asthma^a**

1. A documented absence of preceding respiratory complaints.
2. The onset of symptoms occurred after 1 or more high-level exposures.^b
3. The exposure was to a gas, smoke, fume, or vapor that was present in very high concentrations and had irritant qualities to its nature.
4. The onset of symptoms occurred within 24 hours^c after the exposure and persisted for at least 3 months.
5. Symptoms simulated asthma with cough, wheezing, and dyspnea predominating.
6. Pulmonary function test may show airflow obstruction.
7. Methacholine challenge testing was positive.
8. Other types of pulmonary diseases were ruled out.

^a Clinical criteria for RADs defined by Brooks¹⁸ with minor modification as noted.

^b Exposure to high-level irritant exposure on one or more occasions not confined to a single workplace event.³³

^c Others have used symptom onset up to 7 days after exposure.³⁴

following longer and less intense irritant exposures. In a group of 71 subjects considered to be at moderate to high risk for RADs after repeated exposures to chlorine at a pulp and paper mill, 82% had persisting respiratory symptoms, 22% had evidence of reduced FEV₁, and 41% had nonspecific airways hyperresponsiveness based on methacholine challenge that persisted 18 to 24 months after the end of exposure without clear host predisposition.⁴⁰ In contrast, long-term decline in lung function was seen in a longitudinal study of workers exposed to “puffs” of chlorine at a metal production plant; these exposures caused mild symptoms in those with a smoking history of 20-pack-years or more.⁴¹ Kipen and colleagues²¹ described a series of 10 cases of adult-onset asthma following “low-dose” irritant exposures, as shown in **Table 2**. Four of the cases were reported due to exposure to acid mist, whereas 4 or 5 of the other irritant exposures potentially also could have been sensitizers. In this series, another 5 cases had been excluded because of a history of asthma before the exposure, although 41% of the cases did meet the investigators’ criteria for history of atopy (case history reviewed for seasonal allergy, rhinitis, atopic skin disease, or positive immediate hypersensitivity skin results). Host predisposition was also suggested as a mechanism in the subgroup with “not so sudden” irritant-asthma reported by Brooks and colleagues,²² in which 88% were atopic (defined as allergen skin testing or radioallergosorbent tests positive, personal history of allergic disease, elevated total immunoglobulin E level, or family history of allergy) and 40% had a history of childhood asthma or asthma that had been quiescent at least 1 year.

It is important to recognize that a single, high-level exposure to a sensitizing chemical with irritant properties may also cause irritant asthma, although it may be difficult to exclude concurrent sensitization when that exposure is not confined to a single event.^{18,33} Distinguishing between an immunologic and irritant mechanism can be difficult in the individual patient. This has been handled in a number of different ways: excluding those with exposure to irritants that were also sensitizers,^{39,42} analyzing the chemical composition to exclude the presence of sensitizers to determine irritant mechanism,⁴³ using a specific inhalational challenge (SIC) in the laboratory or workplace to distinguish the two,⁴⁴ or including all high-level exposures regardless of SIC

Table 2 Reported low-dose irritant exposures, associated work-exacerbated asthma, and low-dose RADS, along with pH, potential for thermal injury, and sensitizer potential					
Author	Outcome	Reported Chemical	High or Low pH	Potential for Thermal Injury	Potential Sensitizer
Chiry et al, ⁴⁶ 2007	WEA with negative SIC	Flour			+
		Latex			+
		Isocyanates (3)			+
		Glutaraldehyde			+
		Triethanolamine			+
Lemiere et al, ⁴⁷ 2012	WEA with negative SIC	Ammonia	+		
		Engine exhaust fumes			
		Pyrolysis fumes		?	?
		Metal fumes			?
		Silica			
		Mineral fibers			
		Metal compounds			?
		Animal-derived aerosol			?
		Wood			?
		Flour			+
		Acrylates			+
		Paints, including industrial and motor vehicle			+
		Adhesives			?
		Degreasing stripping agents			
		Hardeners			+
Kipen et al, ²¹ 1994	Low-dose RADS	Isocyanates			+
		Solvents			
		Bisulfite+SO2			
		Chemistry teaching laboratory	?		?
		Acid mist (4)	+		
		Cutting oil			?
		Cleaning agents			?
		Perfume agents			?
		New carpet installation			?

The “+” refers to the listed chemical exposures that have one or more of the other properties: high or low pH, potential for thermal injury and/or are potential sensitizers. The “?” refers to those chemical exposures that might have one of those properties, but there is insufficient information about the exposure to determine.

Abbreviations: RADS, reactive airways dysfunction syndrome; SIC, specific inhalation challenge; WEA, work-exacerbated asthma.

results.⁴⁵ The latter is not inconsistent with the original criteria proposed by Brooks and colleagues.¹⁸ As shown in **Table 1**, many of the irritant exposures reported to cause acute irritant induced asthma are also potential sensitizers. Perhaps more important than establishing mechanism, establishing whether or not there is concurrent immunologic asthma has important implications for the degree of exposure control required for the worker to successfully remain in the workplace.

As described for high-level irritant exposures, lower-level exposures to sensitizing chemicals with irritant properties can also cause asthma either by an irritant or a sensitizing mechanism. Immunologic asthma has been differentiated from irritant-induced

asthma in some studies by results from SIC.^{46,47} As shown in **Table 2**, many of these irritant exposures in which sensitizers were not automatically excluded are very similar to the exposures reported with acute irritant asthma listed in **Table 1**. In a study by Kogevinas and colleagues,⁴⁸ occupations associated with excess risk of occupational asthma included farmers, painters, plastics workers, cleaners, spray painters, and agricultural workers; these are occupations in which there may be concurrent exposures to sensitizers. Overrepresentation of respiratory symptoms and asthma has been reported in workers repeatedly exposed to moderate to low-level irritant exposures that can also be sensitizers, such as cleaning workers^{49–51} and hair dressers.⁵²

CLINICAL VIGNETTE 3

Sandra Dalton is a 26-year-old woman with a prior history of childhood asthma and seasonal allergic rhinitis. Her asthma improved when she was an adolescent, and she used a bronchodilator only before exercise or for chest symptoms associated with an upper respiratory infection (URI). Six months ago she began a job with a company producing experimental semiconductors. She was responsible for loading panels of chips into a holder; this holder was then lowered into a nitric acid bath before the chips were removed and sent down the assembly line. Her job also involved refilling the nitric acid reservoir when levels were low. Although the bath was covered, it was opened to load and remove the computer chips. The room had an unpleasant acrid odor, and after about 3 months at work, she began to develop more frequent episodes of chest tightness that no longer completely resolved after using her bronchodilator. A recent URI triggered profound cough and wheezing, requiring a burst of oral steroids and the addition of a steroid inhaler to control symptoms. Is the patient's asthma exacerbation work related?

WORK-EXACERBATED ASTHMA

Yes, it is now widely accepted that low-level irritant exposures can exacerbate preexisting asthma.^{14–16,24,25} WEA was recently defined by the American Thoracic Society as “preexisting or concurrent asthma that is worsened by workplace conditions,” wherein the asthma either predates the exposure (preexisting) or is determined to have occurred independently, but concurrently with the workplace exposure (concurrent).²⁵ The diagnosis of WEA requires establishment of temporal association between asthma exacerbations and work in a workplace where conditions exist that can exacerbate asthma. WEA is common, reportedly occurring in 23% of adults within a health maintenance organization.⁵³

Temporary Exacerbation Versus Permanent Aggravation of Preexisting or Concurrent Asthma

There is an assortment of irritant workplace exposures that may temporarily increase symptoms due to underlying asthma, or indeed any other chronic lung disease. Such increases in symptoms are often mild, temporary, and respond well to simple measures to decrease or avoid exposure, with the occasional additional use of short-acting bronchodilators. Patients with severe underlying asthma may not be tolerant of low level irritants that are present in many different environments. The problem occurs when there are specific exacerbating conditions that exist in the workplace, but the worker does not have control over mitigating them; such workers are often unable to remain in the workplace. A letter to the editor described the long-term impact of WEA in 10 cases 1 to 4 years after a diagnosis of WEA. None had been able to remain in the workplace because of their respiratory symptoms, and

they also were unable to obtain any financial compensation from the Quebec Worker Compensation Board.⁵⁴ Although it is possible that medical treatment or enhanced ventilation or respiratory protection might have allowed these workers to remain in their jobs, outside of the workers' compensation system, such patients often do not have the authority to effect meaningful decreases in respiratory exposures in the workplace.

As a result, loss of employment, a need to change jobs, and other adverse socioeconomic effects,^{55–58} as well as increased use of health care resources and decreased quality of life,⁵⁹ have been documented by a growing number of studies of workers after a diagnosis of WEA. If the worker does not return to baseline status despite optimized medical therapy, and reasonable exposure control measures have been implemented, such worsening would be considered a permanent aggravation, rather than a temporary exacerbation.

Although there are considerable data on disability and adverse socioeconomic outcomes in WEA, there are few clinical outcome studies.²⁵ There are also no clinical outcome data on workers who receive optimized medication therapy and reasonable workplace exposure controls, and their long-term ability to remain within the workplace (ie, the extent to which such cases of WEA could be limited to temporary exacerbations that are not associated with job loss and other socioeconomic disadvantages).

More concrete consideration of permanent aggravation can be made in the context of an acute irritant injury in a worker with preexisting asthma. The original clinical criteria proposed by Brooks and colleagues¹⁸ excluded persons with preceding history of respiratory complaints. In most cases, it is impossible to verify a preexisting lack of airways hyperresponsiveness or airflow limitation. Multiple cases of high-level irritant exposures resulted in asthma that otherwise met the definition of RADS except for a prior history of mild asthma.^{22,36,60,61} There is nothing about underlying asthma that would be expected to confer immunity from airways injury following such irritant exposures that cause RADS in a worker with normal airways. Indeed, one might postulate that those with preexisting asthma are even more susceptible to airways injury and persistent effects from irritant exposures, as is suggested by the 76% of subjects with a preexisting history of asthma who had accepted claims for asthma by the Ontario Workers' Compensation Board following high-level irritant exposures.⁴⁵ In many cases, with treatment, workers with preexisting asthma will be able to return to their baseline status in the same way as those with no prior history of asthma. In others, the condition does not return to baseline, and there is objective evidence of permanent worsening, such as a change in FEV1, methacholine PC-20, medication requirements, and/or the need for permanent removal from exposure even after optimized medical treatment and implementation of exposure controls. In this setting, the term "acute irritant-aggravated asthma" could be considered to describe the permanent change from the patient's baseline condition.

CHALLENGES IN THE DIAGNOSIS OF IRRITANT-INDUCED VERSUS IRRITANT-AGGRAVATED ASTHMA FROM AN OCCUPATIONAL AND ENVIRONMENTAL MEDICINE PERSPECTIVE DISTINGUISHING WORKERS WITH PREEXISTING OR CONCURRENT ASTHMA FROM NEW-ONSET ASTHMA

There can be difficulty distinguishing between new-onset occupational asthma caused by work, and WEA. For example, in a group of 53 workers with documented reversible airflow limitation or airways hyperresponsiveness and WEA, defined by worsening asthma symptoms at work and a negative SIC, only 20% reported a history

of asthma before the exposure.⁴⁷ The investigators concluded that although it is often not possible to confirm by objective testing, a proportion of these subjects may suffer not from WEA, but from “low-dose irritant asthma” (ie, new-onset asthma). In another study, clinicians were not able to reliably differentiate the peak flow measurement pattern in workers with new-onset occupational asthma versus WEA on visual inspection or computer analysis.⁴⁶ In fact, the US National Institute for Occupational Safety and Health (NIOSH) Sentinel Event Notification Systems for Occupational Risks (SENSOR) program for surveillance of work-related asthma considered new-onset work-related asthma symptoms to be work-initiated asthma, even in the context of preexisting asthma that had been untreated or asymptomatic for at least 2 years before entering the workplace.⁶²

Preexisting asymptomatic airways hyperresponsiveness (AHR) is well described as one of the factors that can predispose to asthma, and some investigators have argued that the existence of preexisting AHR precludes a diagnosis of RADS as new-onset asthma. The prevalence of asymptomatic airways hyperresponsiveness has ranged from 4% to 35% of the population depending on the definition used.⁶³ It is described with⁶⁴ and without⁶⁵ correlation with eosinophilia, which along with atopy can also predispose to asthma. A prior history of asthma, including childhood asthma, is also defined as preexisting asthma. The extent to which these are preexisting conditions, or simply markers of host risk factors for asthma, remains to be determined.⁶⁶

In many of the US workers’ compensation systems, work-related conditions are defined on a medically probable (greater than 50% likely) basis that the need for treatment in a case is the result of a work-related exposure when certain factors are present. These factors include: (1) the work exposure causes a new condition; or (2) the work exposure causes the activation of a previously asymptomatic or latent medical condition to become symptomatic and now require treatment; or (3) the work exposure aggravates a preexisting symptomatic condition that now requires treatment that was not needed before. A helpful approach to determining whether a condition is work-related is recommended by the Colorado Division of Workers’ Compensation: would the patient need the recommended treatment if the work exposure had not taken place? If the answer is “no,” then the condition is most likely work related.⁶⁷ To establish that the worker had preexisting or concurrent asthma, the physician would need to verify an asymptomatic or well-controlled stable asthma pattern that had clearly changed due to a well-defined workplace irritant exposure. It is also incumbent on the physician to rule out the contribution of nonoccupational causes to the asthma exacerbation, such as GERD, infection, or rhinosinusitis.

Defining High-Level Exposure

What constitutes a high-level exposure may or may not be obvious. In cases of very high-level accidental releases where no respiratory protection had been worn, the high-level exposure is obvious. A good example is the massive exposure to airborne alkaline particulates following the World Trade Center collapse in 2001; this led to the development of asthma in many of the first responders.^{68–70} When explored, a dose-response has been noted,²⁸ but in most cases, no industrial hygiene monitoring data or dose reconstruction by an industrial hygienist are available. In less obvious cases, the physician can try to estimate the “dose” that was delivered to the lungs of the individual worker based on the intensity of the irritant exposure, the frequency, and the duration.

Intensity

Intensity is determined by the airborne concentration of the vapor, dust, gas, or fume, as well as the innate irritating properties of the chemical(s). Some chemicals are inherently more irritating than others.⁹ For example, those with very low, or worse, very high pH, are extremely irritating. When heated chemicals are inhaled, thermal injury may compound the damage.

A release may or may not be large. A worker very close to the source of a release may have a high concentration in his or her breathing zone that is not shared by others a little farther away, as the concentration of irritants can be fairly quickly dissipated through dilution with ambient air currents. Airborne concentrations will be much higher within a confined space because there is no such potential for dilution. Chemicals with very low vapor pressure can quickly volatilize in considerable quantity, particularly when heated. The size of the chemical particle and its water solubility will determine deposition within the respiratory tract, with the smallest and most water-insoluble chemicals having the greatest potential to reach the lower airways.

However, there does not need to be a release or other recognized event to signal exposure to high-level irritants. Not all workplaces will have appropriate engineering controls in place, such as enclosures and local exhaust ventilation, which can greatly minimize exposure to vapors, dust, gas, and fumes. Such controls need to have been installed and used correctly to be effective. Unrecognized failures of these control measures may result in unrecognized excess exposures, although such exposures may be limited to only a few individuals who work directly in the area. Air monitoring by an industrial hygienist can determine actual airborne concentrations, although if interim control measures have been implemented, these may not reflect the actual concentration at the time of the release or engineering control failure.

The amount of the vapor, dust, gas, or fume that reaches the lungs of the worker will be considerably decreased if respiratory protection is used, but only if it was used and worn correctly, and the exposure did not exceed the respirator's protective limits. A filtering respirator needs to have the correct cartridges for the exposure. For example, particulate filtering cartridges are highly effective in trapping airborne particulates but do not filter out irritant gases. Combined particulate (P100) and organic vapor cartridges are highly effective protection against many gases and vapors, as well as fumes and particulates. Filtering facepiece respirators are considered protective at concentrations up to 10 times the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL) for half-face respirators and up to 50 times the PEL with full-face respirators. However, the respirator will only have been effective to that level if it was worn properly sealed to the skin without facial hair, and the adequacy of the seal was confirmed by fit testing.

Frequency

The frequency of the exposure is relevant in considering exposures not confined to a single event, and should be considered along with duration.

Duration

The duration of the exposure before moving to fresh air is another important factor in determining "dose" in both high-level and lower-level exposures. Moderate to heavy physical exertion will increase tidal volume and respiratory rate, thus effectively increasing the amount of the irritant delivered to the lungs per unit of time.

SUMMARY

Acute high-level irritant exposures can cause asthma and exacerbate underlying asthma. Lower-level irritant exposures can at least exacerbate underlying asthma, although there is emerging consensus that recurrent lower-level exposures may also cause asthma. There is overlap between the exposures that have caused acute irritant-induced asthma and WEA, many of which are also sensitizers. What constitutes an excessive level enough to cause asthma from acute high-level or recurrent lower-level accidental releases is not currently defined. New-onset asthma in workers following lower-level irritant exposures, with no prior history of respiratory symptoms or asthma, may well be limited to a subset of “susceptible” hosts, such as those with asymptomatic airways hyperresponsiveness, atopy, and those who “outgrew” childhood asthma. But it is reasonable to consider asthma to more likely than not have been caused by such irritant exposures when previously asymptomatic workers develop symptomatic asthma following clearly defined workplace irritant exposures, the asthma is confirmed by objective testing, and other lung diseases and nonoccupational causes of the asthma have been excluded. This attribution of work-relatedness should also apply to workers with prior well-controlled stable asthma who sustain objectively documented changes in the pattern of their asthma.

Workers with irritant-induced and WEA should receive optimized asthma therapy. Equally important is the reduction and control of their exacerbating workplace exposures. Without the ability to receive this combination treatment, it is likely these cases of WEA will not be limited to temporary exacerbations, but will continue to experience the long-term disability and socioeconomic disadvantage that has been repeatedly observed. The ATS statement on WEA has identified research needs to better define risk factors, biologic mechanisms, and outcomes in WEA,²⁵ which should help to facilitate necessary interventions in the medical system, as well as to formulate and apply strategies for prevention.

The informed clinician should be prepared to identify and treat both new-onset and work-exacerbated asthma, and to partner with occupational and environmental medicine clinicians to address the challenges inherent in the diagnosis and treatment of irritant-induced and irritant-aggravated asthma.

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KEY POINTS**INTRODUCTION**

This chapter focuses on the acute effects on the lung after exposure to toxic substances. For most acute toxicant exposures, inhalation is the route of delivery leading to the lung injury. Importantly, *target organ* does not equate with *route of exposure*. In some instances, inhalation may be the route of exposure for the toxicant, and yet the primary target organ is not the lung (e.g., solvent inhalation that causes central nervous system depression). Inhalation exposures leading to nonpulmonary illnesses are not addressed here.

As used in this chapter, *acute* indicates short-term exposures (minutes to hours), with the initial onset of pulmonary responses within a similarly rapid time period. Generally, the relevant toxicant exposures are of high intensity, far in excess of recommended safety limits for population-wide environmental levels.

Because ingestion may also lead to lung injury, paraquat and hydrocarbon, examples of ingested toxins with severe acute target organ effects on the lung, are included in this chapter.

Moreover, this chapter does not address brief exposures, inducing acute responses mediated by anamnestic (i.e., allergic or other immune-mediated) mechanisms. These responses require prior exposures that already have led to sensitization, such as *hypersensitivity pneumonitis* (HP) (see [Chapter 91](#)) or occupational asthma (see [Chapter 100](#)). Although there is overlap with certain specific exposures that at far lower levels are also relevant to ambient air pollution (such as oxides of nitrogen, ozone, and sulfur dioxide), these are addressed at the population level in the chapter on air pollution (see [Chapter 102](#)).

Finally, some toxicants cause unusual pulmonary syndromes after subacute (days to months) exposure. Some of these syndromes have emerged in recent years associated with new technologies or novel toxicants, such as diacetyl-caused popcorn worker's lung and other flavor industry

workers' diseases linked to this chemical,^{1–3} “flock worker's lung” caused by short synthetic textile fibers,^{4–6} and “Ardystil lung,” a dye chemical-induced organizing pneumonia.^{7,8} Some of these syndromes are discussed elsewhere in this text.

PATHOGENESIS OF LUNG INJURY FROM INHALED TOXICANTS**PATTERNS OF RESPONSE TO IRRITANT INHALATION**

Acute lung toxicity results from a variety of exposures but nonetheless is manifest by a narrow repertoire of injury ([Table 103.1](#)). Irritant toxicants can be encountered in various physical states relevant to their inhalational properties. Such states include *gases*, *vapors* (i.e., the gaseous form of a substance that is a liquid or a solid at normal temperatures and pressures), and *fumes* (i.e., solid material, often metals, of small particle size suspended in a gaseous medium [most <1.0 μm and many <0.1 μm in diameter]). *Aerosols* encompass a mix of potential states (i.e., liquid droplets or fine particulates dispersed in a gaseous medium; *smoke* is a subset of aerosols from incomplete combustion).

These various classes of exposures include heterogeneous toxicants capable of causing extensive cell injury throughout the upper and lower respiratory tract. The primary location of respiratory tract injury and the onset of clinical symptoms partly depend on the solubility of the gas, vapor, fume, or aerosol involved and, in the case of fumes or aerosols, on the physical characteristics of the particle or droplet. Other factors that determine the injury pattern following exposure include (1) the amount of the toxicant inhaled, (2) the duration of exposure to the inhalant, (3) the concentration of the inhalant in the ambient air, (4) other physical properties (such as pH or chemical reactivity), and

Table 103.1 Major Clinical Scenarios of Pulmonary Responses Shortly After Acute Toxicant Exposure

Clinical Scenario	Exemplar Exposures	Additional Comments
Mucous membrane and airway irritation (burning eyes, nose, and throat; laryngospasm and bronchospasm) with or without lower lung injury (pulmonary edema, diffuse alveolar damage)	Chlorine, chlorine dioxide, chloramine; bromine; sulfur dioxide; acid aerosols (sulfuric, hydrochloric, hydrofluoric); ammonia; zinc chloride (smoke bombs)	At low exposures, mucous membrane irritation may be the sole effect; with heavy exposure, lower lung injury may be seen
Lower lung injury (pulmonary edema, diffuse alveolar damage) with little or no mucous membrane irritation or airway effects	Nitrogen dioxide, phosgene, ozone, cadmium fume, mercury vapor, nickel carbonyl, fluorocarbon (waterproofing)	Exposure can be inadvertent or occult with presentation delayed 24–48 hr
Self-limited flulike illness with fever and leukocytosis beginning 6–12 hr after a clear exposure history	Zinc oxide fume, heavy organic dust inhalation, polymer fume, endotoxin	The presence of hypoxemia or lung injury indicates another diagnosis
Foreign substance ingestion followed by pneumonitis	Hydrocarbon aspiration, exogenous lipid pneumonia, paraquat fibrosis	Heavy aerosol inhalation can cause lipid pneumonia; paraquat can also be absorbed through the skin

(5) a variety of host factors, such as age, genetics, use of respiratory protection, and comorbid illness. Overwhelming exposures to any irritant inhalant, however, can cause extensive damage throughout the respiratory tract.

Ammonia⁹ and sulfur dioxide¹⁰ are examples of substances that are highly soluble in water. Such highly soluble substances cause immediate irritation of the conjunctival mucosa and upper airways. This immediate onset of irritant effects provides warning symptoms that may prompt the victim to flee, thereby limiting exposure. In contrast, oxides of nitrogen,¹¹ ozone,¹² and phosgene¹³ have relatively low water solubility. For this reason, exposure to one of these agents may *not* be characterized by immediate symptoms of mucous membrane irritation. This may lead to more prolonged exposure and delay in seeking medical attention. Both more-soluble and less-soluble irritant exposures can lead to distal lung injury but, in the case of highly soluble materials, a history of severe upper respiratory symptoms should precede the presentation of distal airway and alveolar damage.¹⁴

Irritants reaching the lower respiratory tract, either because of their inherent physical characteristics or because of exposures that overwhelm the absorptive capacity of the upper airway, can injure both the lung epithelium and its endothelium. Irritant injury at this level leads to a nonspecific pattern of *diffuse alveolar damage* (DAD) similar to that seen from a variety of different causes (see [Chapter 8](#)). The pathologic changes in fatal cases of irritant lung injury include focal and confluent areas of edema with protein-rich fluid in the alveolar spaces, hyaline membrane formation, and denudation of the alveolar epithelium. In addition, mucous membranes of the bronchial and bronchiolar walls may be denuded or destroyed. Pulmonary hemorrhage may be seen in irritant lung injury but is typically not the dominant clinicopathologic manifestation; prominent pulmonary hemorrhage should raise suspicion of other toxicant- or non-toxicant-mediated syndromes¹⁵ (see [Chapter 94](#)).

On the cellular level, respiratory tract injury may be mediated through the deposition or formation of an acid, alkali, free radical, or other reactive chemical species. The precise cellular mechanisms of injury from irritant inhalants have not been fully delineated, even for relatively common irritants such as chlorine or the chemical warfare agent phosgene, substances for which extensive human and experimental animal data exist.^{16–19}

OTHER PATTERNS OF RESPONSE

Acute irritant inhalation injury is the predominant, but not the only, pathophysiologic mechanism underlying acute toxicant-caused lung syndromes. In contrast to the anatomic distribution commonly seen in water-soluble, irritant chemical-related inhalant injury, it may be difficult to delineate a descending, hierarchical pattern from upper airway to lower lung injury following exposure to a diverse group of other agents. Many of these exposures, as with the water-soluble irritants, also lead to acute lung injury through nonimmunologic mechanisms (clinically, *acute respiratory distress syndrome* [ARDS]; pathologically, DAD), as detailed subsequently in this chapter. Other toxicant exposures produce various other syndromes of respiratory tract injury, such as heavy metal pneumonitis,²⁰ hydrocarbon aspiration,²¹ or paraquat lung injury.^{22,23} The inhalation fever syndromes are exceptions in that they do not involve obvious lung injury; the pathophysiology of this group of self-limited acute lung syndromes appears to be cytokine mediated.²⁴

GENERAL MANAGEMENT PRINCIPLES

Symptoms and signs of acute inhalation injury can be delayed in onset. Following removal of the patient from exposure while safeguarding the rescuing personnel, the next most important management decisions include protection of the airway (i.e., preemptive intubation may be required to prevent precipitous airway obstruction from progressive airway edema) and treatment of hypoxemia. The nasopharynx and larynx may manifest injuries earliest because they are exposed to the highest concentrations of inhaled water-soluble toxicants. The upper airway may also be a primary target organ as a result of angioedema in selected toxicant ingestions.²⁵ Within a few hours of exposure, progressive airway edema, mucopurulent sputum production, and bronchorrhea may develop. Bronchoconstriction, peribronchial edema, and bronchial mucosal sloughing may produce atelectasis. In the distal airways and alveoli, epithelial and endothelial injury leads to permeability-induced edema, which can manifest ranging from mild interstitial edema to DAD. Pulmonary edema may be rapid following high-concentration toxicant exposure or may be delayed

up to 24 to 48 hours. Pneumothorax and pneumomediastinum can be acute complications of respiratory tract injury resulting from chemical toxicants.^{26–31}

Acute toxicant lung injury manifest as DAD should be managed consistent with the basic management of acute lung injury from other causes. This includes utilizing lung-protective ventilation strategies for patients with ARDS and avoiding fluid overload.^{32,33} Concomitant airway injury with acute bronchospasm often warrants treatment with bronchodilators because of the airway obstruction.

A beneficial role for systemic corticosteroids in the acute phase of irritant and other chemically mediated forms of acute injury to the lungs has not been established, either by controlled trials in humans or through studies using experimental animal models.^{34,35} Inhaled steroids are more likely to have a better risk-benefit ratio in the therapy of acute inhalation injury (e.g., in the context of bronchospasm and concomitant use of bronchodilators, taking acute smoke inhalation injury as a paradigm).³⁶ Despite the lack of controlled evidence of efficacy, anecdotal reports of benefits of systemic corticosteroid use continue to appear.³⁰ For example, systemic corticosteroids may have a beneficial effect in the treatment of lung injury following zinc chloride inhalation.^{31,37} Prophylactic antibiotic drugs have not proved to be efficacious in toxicant-induced lung injury; antibiotics should be reserved for those patients with clinical evidence of infection, including ventilator-associated pneumonia.^{38,39} To date, convincing data do not support the use of other pharmacologic agents, such as antioxidants, in the generic treatment of toxic chemical lung injury, although this is the subject of experimental research.^{34,40,41}

Certain exposure-specific management issues do occasionally arise. In paraquat-induced lung injury, for example, oxygen toxicity is a particular concern because of the specific mechanism of action of paraquat (i.e., high concentrations of oxygen may lead to more severe lung injury).²² In addition, in paraquat-induced lung injury, immunosuppressive therapy has yielded some promising data but remains to be confirmed in randomized controlled studies.²³ Biologic therapy utilizing an anti-C5a antibody also has demonstrated promise for the treatment of paraquat-induced lung injury and the associated systemic inflammatory response.⁴² In the case of certain metal toxins, chelation may have a therapeutic role, as is addressed later in relation to the specific exposures involved. Inhalation fever is self-limited, so the principal clinical management issue is to exclude other exposures with more serious outcomes.²⁴

Nonspecific treatments for toxic lung injury include interventions to clear the airways of mucus, denuded mucosal tissue, and cellular debris. Such interventions may include chest physiotherapy, intrapulmonary percussive ventilation, inhalation of isotonic saline, aerosolized mucolytic agents such as *N*-acetyl cysteine, and, in some settings, therapeutic bronchoscopy.⁴³ Although a detailed discussion of mass casualty events is beyond the scope of this chapter, large-scale release of toxicant chemicals may result in widespread chaos and confusion that has the potential to overwhelm the public emergency system, including first responders and emergency departments (see also Chapter 59). A surge of highly exposed, acutely ill victims along with lower-exposure risk but anxious patients may present significant challenges to prehospital care and hospital-based emergency care.^{44,45}

Companion animals (e.g., dogs, cats, and birds) often show symptoms and signs in advance of humans. An example of historical interest is that of coal miners bringing canaries into coal mines. This phenomenon may allow the clinician to identify occult exposure, test, and treat while human disease is mild or still subclinical.^{45a}

CHRONIC SEQUELAE AND RESIDUAL EFFECTS

Persons surviving symptomatic exposure to acute irritants may have persistent structural and functional effects. Long-term consequences to the upper airways (nose, pharynx, and larynx) can be sequelae of acute inhalational exposures; upper airway complaints, including chronic rhinitis (reactive upper airway dysfunction syndrome, anosmia, and vocal cord dysfunction), have been reported.^{46–50} Follow-up studies of more homogeneous populations evaluated after inhalation injury (with only a minority experiencing severe injury) suggest that airflow obstruction and nonspecific airway hyperresponsiveness are the most common persistent abnormalities of the conducting airways after irritant injury. Even so, epidemiologic data suggest that only a minority of those exposed will experience these outcomes.^{51–53} The term *reactive airway dysfunction syndrome* has been applied to the persistence of airway reactivity after acute exposure to respiratory irritants.^{54–57} The more general term *irritant-induced asthma* has also been used to describe this condition.^{58,59} Insofar as this can represent a form of work-related asthma, it is addressed in Chapter 100.

Chronic injuries to the lower airways and lung parenchyma are unusual sequelae of acute inhalational exposure. Long-term follow-up evaluation after recovery from ARDS resulting from heterogeneous causes (predominantly associated with sepsis) suggests that residual deficits in lung volumes, airflow, and gas exchange may persist long after recovery.⁶⁰ *Bronchiolitis obliterans* (BO),^{61–69} bronchiectasis,^{9,68,70–73} and organizing pneumonia^{74,75} may all develop, but are rare complications. Irritants, in particular nitrogen oxide and related exposures, have long been known to cause BO.⁷⁶ Yet even with nitrogen dioxide, BO is an infrequent event; for example, only one case was found in a series of 20 moderate to severe exposures.⁶² The histologic manifestations of exposure-related bronchiolitis can include various subtypes.⁶³ Pathologically, acute or subacute irritant-induced bronchiolitis is usually characterized histologically as either proliferative bronchiolitis with organizing pneumonia (that is, a histologic pattern of organizing pneumonia) or constrictive bronchiolitis. The latter appears to be the pathologic correlate of diacetyl-caused popcorn worker's lung² and has been reported in one case of BO following exposure in the World Trade Center disaster,⁷⁷ in a case series of Iraq and Afghanistan military veterans (although no single toxic exposure has been implicated),⁷⁸ and in association with styrene-fiberglass boat construction, presumably with more indolent exposure, rather than acute exposure.⁷⁹ In addition to residual obstructive ventilatory deficits, restrictive deficits may also result from severe irritant inhalation injury.^{70,80} There is also some indication that an isolated reduction in residual volume may be noted in the follow-up of such cases.^{81,82} Finally, nonspecific respiratory signs and symptoms after

Table 103.2 Selected Toxic Agents Causing Pulmonary Responses After Acute Exposure

Agent	Common Exposure Scenarios	References
Acid aerosols	Plating; microelectronics; other manufacturing	123, 149–153
Acrolein	Structural or wildland fires; other combustion	292, 293
Ammonia	Industrial refrigeration leaks; fertilizers	9, 322, 326
Brevetoxin	Aerosolization of “red tide” toxin	311, 313
Bromine	Water treatment; chemical manufacturing	69, 328–331
Cadmium fume	Flame cutting of soldered or sheet metal materials	186–190
Chloramines and nitrogen trichloride	Bleach + ammonia mix; chlorination + ammonia	101–103
Chlorine gas	Gas leak; water treatment; bleach + acid mix	16, 87–96
Chlorine dioxide	Pulp paper bleaching	130, 131
Crowd-control agents (tear gas)	Military and police training and operations	174–177
Dimethyl sulfate	Industrial chemical yielding sulfuric acid	137, 138
Fluorocarbon polymers	Overheating polymers	145, 217, 223
Fluorocarbon sprays	Waterproofing and related aerosol sprays	256–260
Hydrocarbons	Aspiration of low-viscosity materials, “fire eating”	21, 267, 269, 275, 278
Hydrogen sulfide	Sewers and manure pits; fossil fuel and geothermal production	336, 340–342
Mercury vapor	Gold extraction, heating cinnabar	192–199
Methyl bromide	Pesticide fumigant	334, 335
Methyl isocyanate	Pesticide manufacturing	343, 345
Methyl isothiocyanate	Breakdown product of metam sodium fumigant	346, 347
Mustard gas	Chemical warfare agent	70, 155–157
Nickel carbonyl	Nickel processing, metal reclamation	200–204
Nitrogen dioxide	Silage; combustion; explosives; welding; nitric acid mixes	11, 62, 117, 118, 121
Organic dusts or aerosols	Contaminated dust or bioaerosol generation	24, 237, 242, 243
Organophosphates	Pesticide application; chemical warfare	170, 307
Ozone	Bleaching; water treatment; plasma welding	12
Paraquat	Herbicide skin contamination or ingestion	22, 282
Phosgene	Chlorinated solvent breakdown by-product	13, 18
Phosphine	Fumigation with aluminum or zinc phosphide, microelectronics	364–366
Sulfur dioxide	Refrigeration; cement manufacture; mining; pulp paper mills	10, 132–134
Tributyltin (bis[tributyltin] oxide)	Paint additive for mold inhibition	215
Vanadium	Ore processing; fossil fuel by-product, catalyst use	211, 212
Zinc chloride	Smoke bombs (“white smoke”)	179, 183
Zinc oxide fume	Welding galvanized steel; brass casting	218, 219, 236

acute inhalation events can be somatic manifestations of psychological processes and can be further complicated by posttraumatic stress disorder comorbidity.^{83–86}

SPECIFIC EXPOSURES

See [Table 103.2](#) for a list of selected toxic agents causing pulmonary responses after acute exposure.

CHLORINE, CHLORAMINES, HYDROCHLORIC ACID, AND RELATED CHEMICALS

Among toxicants causing pulmonary responses, *chlorine* is a common and potent irritant inhalant accounting for substantial human morbidity.^{17,87,88} Common forms of exposure

include industrial leaks,^{89,90} environmental releases primarily during transport,^{91,92} water purification,⁹³ swimming pool-related events,^{94,95} household cleaning product misadventures,⁹⁶ and even homemade chemical bombs⁹⁷ or intentional terrorist use.⁹⁸

In the form of a yellow-green acrid gas, industrial and environmental releases typically have clear-cut exposure histories. Because the gas is heavier than air, higher contamination can be expected in low-lying areas (hence, its use in trench warfare in World War I).⁹⁹ Other environmental conditions, however, may supervene. Examples include one well-documented case of the gas rising along the heated outside wall of a factory where rooftop workers were exposed.⁸⁹ In another case, chlorine initially collected in a basement but then was sucked up into the central heating system of a dormitory.¹⁰⁰

The history of exposure to chlorine may be less straightforward when the chlorine is generated after de novo generation from chlorine-containing products. Chlorine gas can be generated from liquid bleach containing hypochlorite or from dry powdered bleach containing chlorinated phosphate. In either liquid or powdered bleaches, the chlorine gas is liberated on contact with acids, which can be common in other household products (such as those containing muriatic [i.e., hydrochloric], phosphoric, or hydrofluoric acid⁹⁶) or in industrial settings.⁵³ In contrast, mixing chlorine-containing products with ammonia leads to release of chloramines (monochloramine [NH₂Cl] and dichloramine [NHCl₂]) and related chemicals, especially nitrogen trichloride (NCl₃), chemicals whose irritant effects are attributed to in situ pulmonary reactions releasing chlorine, hypochlorous acid, and ammonia.^{96,101,102} In aquatic venues, including swimming pools, inadvertent mixing of the chlorinated water with nitrogen donors can also happen, with potential irritant effects attributed to nitrogen trichloride in particular.^{101,103} A report of a public aquatic venue mishap found that inadvertent mixing of sodium hypochlorite and hydrochloric acid led to toxic chlorine gas release resulting in a constellation of adverse health effects, including vomiting, coughing, and eye irritation, among several dozen affected bathers.¹⁰⁴ Chloramines evolved from mixing chlorine and ammonia should not be confused with Chloramine-T (sodium-*N*-chlorine-*p*-toluene sulfonamide), a disinfectant that can act as a chemical sensitizer leading to allergic asthma and other anamnestic responses.¹⁰⁵

Irritant effects after inhalation of *hypochlorite* aerosols in confined spaces without a history of combining products (not an uncommon scenario when cleaning bathrooms) can also be associated with irritant effects. Similarly, in certain industrial operations, hydrochloric (hydrogen chloride in water) or hypochlorous acid aerosols are also respiratory irritants.

Chlorine exposure can also take place in specific industrial processes that use inorganic chlorine derivatives. Worthy of particular mention are chlorine dioxide (used in pulp paper processing),¹⁰⁶ chlorinated silanes (gases used in microelectronics),¹⁰⁷ reactive metal halides (e.g., titanium or antimony chlorides),²⁰ and thionyl chloride (which breaks down to yield hydrogen chloride and sulfur dioxide).^{65,108}

For chlorine and related chemicals, there is a dose-dependent exposure-response relationship; that is, lung injury is largely a function of the dose of irritant gas entrained into the respiratory system. For chlorine, as for irritant gases generally, the dose response has been presumed to be equivalent for any given cross-product of concentration and exposure time (Haber's law), although experimental data indicate that this relationship may be more variable.¹⁰⁹

All of these compounds appear to share a final common toxic pathway. As noted in the general discussion of acute toxicant inhalation, water solubility is an important determinant of the dose reaching the lower airways. For chlorine, chlorine dioxide, chloramines, and nitrogen trichloride, their lower solubility favors deeper penetration with a more effective delivered dose compared with an equivalent inhalation of agents with a higher solubility such as acid aerosols. Nonetheless, exposure to any of these compounds is associated with some degree of immediate mucous membrane and upper airway irritation. In fact, the

absence of acute irritant effects is not clinically consistent with chlorine gas or related exposures.

Chlorine inhalation may manifest any of the full spectrum of respiratory tract irritant effects, from minor mucosal responses to upper airway responses to DAD.^{89–99,110,110a} Persistent airway hyperresponsiveness after irritant exposure has been associated particularly with chlorine gas and chlorine-containing products, although this association may have more to do with the frequency of chlorine exposures than with any particular effect of chlorine on the airways.^{16,43,58,59} Human experimental studies have provided inconsistent results about whether persons with underlying airway hyperreactivity may be more responsive to chlorine.^{111,112}

Use of inhaled bronchodilators and inhaled steroids may be indicated for both acute and residual bronchospasm following chlorine inhalation, consistent with the general principles of management addressed previously. Although several case reports and series have touted the potential benefits of nebulized sodium bicarbonate inhalation in the acute treatment of chlorine or chloramine inhalation, the efficacy of this intervention has never been assessed in a controlled trial.^{102,112,113} One small controlled trial administered inhaled bicarbonate 3 months or more after exposure in irritant-induced asthma and described some benefit.¹¹⁴ Other potential therapeutics have been reported on the basis of published animal and human data, including intramuscular sodium nitrite, intramuscular ascorbic acid/deferrioxamine, and sevoflurane (an inhalational anesthetic agent), although the efficacy of such interventions remains to be established.¹¹⁵

OXIDES OF NITROGEN, OZONE, SULFUR DIOXIDE, AND ACID AEROSOLS

These inhalants are major air pollutants; the effects of low-level exposure are discussed in detail in [Chapter 102](#). When inhaled in high concentrations, these irritants can cause acute lung injury. Because of their lower solubility and thus their lower incidence of upper airway symptoms, ozone¹² and, even more commonly, nitrogen dioxide may be associated with a longer exposure with a greater predilection for lung injury.¹¹⁶ With sulfur dioxide and acid aerosols, despite their high solubility, a sufficient intensity of exposure can also lead to DAD.

High-intensity exposure to *oxides of nitrogen* can take place through decomposition of organic matter and other sources. Examples of exposure scenarios include the following: nitrogen dioxide-induced lung injury among farmers (also known as silo filler's disease)^{52,117,118}; use of internal combustion engines in enclosed spaces (with large outbreaks associated with ice resurfacing equipment used in indoor skating rinks)^{11,119–121}; thermal degradation of polymers (e.g., in structural fires)³⁸; toxicant gas produced by the detonation of explosives^{67,122}; the release of gas through reactions of nitric acid breakdown in air or in reaction with metals or organic materials^{123–125}; welding by-products, particularly when “gas-shielded” techniques are used (manual inert gas welding or tungsten inert welding)¹²⁴; and the release of compressed nitrogen dioxide gas.¹²⁶ Historically, the detonation of explosives has been one of the most important sources of exposure to nitrogen oxides.¹²² Work-related exposure to a mixture of nitric acid

and hydrofluoric acid, known as “pickling paste,” used to clean welding joints in welded stainless steel construction, has been reported as a cause of ARDS.¹²⁷ Nitric oxide, an inhalant used therapeutically, breaks down to nitrogen dioxide in the presence of oxygen and thus must be monitored with appropriate delivery devices to avoid exposure to the potentially toxic nitrogen dioxide.¹²⁸

High-intensity occupational ozone exposure is unusual, but it can happen with welding conditions similar to those associated with oxides of nitrogen.¹²⁹ More recently, ozone in water treatment and in pulp paper bleaching has also emerged as a health issue; in the latter industry, there is often concomitant exposure to chlorine dioxide.^{130,131}

Important sources of exposure to high-level sulfur dioxide include mining and ore refining,¹⁰ portland cement manufacturing,¹³² sulfur treatment of fruit,¹³³ and industrial releases.¹³⁴ Sulfur dioxide has been and continues to be important in sulfite process pulp paper processing, where acute gas releases are superimposed on long-term lower-level exposure.^{130,131,135} In the past, sulfur dioxide was also a common refrigerant.¹³⁶

In ambient air pollution, sulfuric acid is an acid aerosol of primary concern; in various occupations, sulfuric acid can also be encountered at high levels. Workers can be exposed to sulfuric acid through both direct use and the breakdown of a highly toxic industrial chemical, dimethyl sulfate.^{137,138} Certain other inorganic and organic acid vapors and aerosols are also important potential causes of acute lung injury, including chromic,¹³⁹ acetic,¹⁴⁰ formic,¹⁴¹ and hydrofluoric acids.^{125,142,143} *Hydrofluoric acid* (hydrogen fluoride) inhalation, in addition to nonspecific irritant effects, can induce clinically significant hypocalcemia, which is thought to result from the formation of insoluble calcium fluoride.¹⁴⁴ Persons can be exposed to hydrofluoric acid in manufacturing of both microelectronics and phosphate fertilizers, in household use of hydrofluoric acid rust removal agents (the mixture of which with hypochlorite bleach can evolve both chlorine and hydrogen fluoride), and in the incomplete combustion (pyrolysis) of fluorinated polymers.¹⁴⁵ Exposure to hydrogen fluoride is a long-term problem in the aluminum smelting industry.¹⁴⁶ Hydrogen fluoride is also released as a breakdown product of sulfur hexafluoride, an electrical insulating liquid chemical used in circuit breakers, cables, capacitors, and transistors.¹⁴⁷

MILITARY AND CROWD-CONTROL AGENTS

Unfortunately, chemical warfare agent exposures are not of mere historical interest.^{99,148,149} Not only can sporadic exposures result from contact with a discarded ordnance,¹⁵⁰ but also, and more importantly, exposure can be widespread through the use of chemical warfare agents in acts of terrorism or in conventional military conflicts. Such risks have raised the specter that the diagnosis and management of such toxicants will again become clinically relevant. Several reviews have addressed general aspects of this question.^{151–153} The goal of this section is to address individual chemical agents, including other military and crowd-control agents that are not warfare chemicals per se, with a focus on their respiratory toxicity. Biologic warfare agents of relevance to the respiratory tract are covered elsewhere (see [Chapter 59](#)).

Sulfur Mustard

Of the major World War I chemical weapons, only sulfur mustard (so called “mustard gas,” although not a true gas in physical state) has subsequently been used in warfare. Classified as a vesicant because of blistering induced by skin contact, mustard gas inhalation causes severe respiratory injury. Largely on the basis of the Iranian experience of their Iraqi war veterans, sulfur mustard survivors can exhibit residual tracheobronchitis, asthma, bronchiectasis, bronchotracheomalacia, BO, and fibrosis.^{70,154–157} Nitrogen mustards were sulfur mustard derivatives originally developed for military purposes but later applied medically; nonetheless, occupationally related acute lung injury has been reported through industrial release.¹⁵⁸

Phosgene

Another World War I toxicant gas, phosgene, currently is encountered as a chemical industry process chemical and as a thermal breakdown product or ultraviolet photoreactant of chlorinated solvents (e.g., methylene chloride).^{13,159} An occult cause of exposure can be inadvertent phosgene production from welding metals “degreased” with solvents.¹²⁹ Phosgene is the prototypical deeply penetrating inhalant exhibiting a delayed onset of symptoms (12 to 24 hours after exposure).^{19,32,160–162} Even victims of phosgene exposure who eventually develop fulminant respiratory failure may exhibit only mild initial symptoms and have a normal chest radiograph in the first 2 hours after exposure.¹⁶³ Methyl chloroformate ($C_2H_3ClO_2$) has chemical and structural similarities to phosgene ($COCl_2$), is used in industrial chemical synthesis, and is also a potent inhalation irritant associated with severe lung injury.¹⁶⁴

Chloropicrin

Chloropicrin, another World War I gas, is a low-threshold irritant currently encountered in chemical manufacturing and as a component of fumigants; it is added to fumigants for its irritant warning properties to deter persons from entering and remaining in structures during or soon after fumigation.^{165–167}

Neurotoxicants

The modern chemical warfare armamentarium is dominated by systemic toxicants developed from organophosphate pesticides (which are discussed later in the section “Pharmacologic Syndromes”); the nerve agent VX is prototypical.^{168,169} These highly lethal neurotoxins have important respiratory effects, including manifestations of both muscarinic receptor stimulation (bronchorrhea and bronchospasm) and nicotinic receptor depolarization blockade (respiratory muscle paralysis); treatment is based on reversing enzyme inhibition and countering the effects of acetyl cholinesterase excess.¹⁷⁰

Chloroacetophenone (Mace), Other Tear Gas Agents, and Zinc Chloride

Crowd-control agents (“tear gases”), as opposed to the war gases, are intended to incapacitate persons through immediate mucous membrane irritation.¹⁷¹ The agents in greatest use worldwide are chloroacetophenone (“mace”) and orthochlorobenzamalonitrile.^{172,173} In addition to their

mucous membrane effects, these agents have also been implicated in lower respiratory injury and even in persistent effects following high-intensity exposures (e.g., in enclosed buildings).^{174–177} Unlike tear gas, exposure to smoke bomb releases (sometimes referred to as “white smoke”) can cause severe lower respiratory injury by exposure to the potent respiratory irritant, zinc chloride fume, created through a pyrotechnic reaction between hexachloroethane and zinc oxide.^{178,179} Military, police, and others who are exposed, often during ill-conceived training exercises, are at risk.^{29,178–183} In an analysis of 15 cases of overexposure to a hexachloroethane–zinc chloride smoke bomb during a military exercise, the serum zinc level correlated with later lung function impairment, a finding suggesting that serum zinc may serve as a biomarker of high exposure that may predict outcomes.¹⁸⁴

TOXIC METALS

Inhalation of certain metal fumes or metal vapors can cause acute pneumonitis.²⁰ Dangerous exposures to toxic metal fumes arise in part because these agents are not immediately irritating, analogous to the delayed symptoms after phosgene or nitrogen oxide gas inhalation. Patients typically present in respiratory distress 12 to 48 hours after exposure. Indeed, the exposure history often remains occult unless aggressively pursued. Metal pneumonitis from these materials also can include fever as a clinical manifestation of this toxic syndrome. However, the term *metal fume fever* should not be used in this context.¹⁸⁵ The toxic mechanism generalizable in heavy metal pneumonitis is presumed to be inhibition of enzymatic and other critical cellular functions.

Cadmium, Mercury, and Nickel

The three metals most important in clinical lung injury are cadmium, mercury, and nickel (nickel in the form of nickel carbonyl). *Cadmium* exposure typically takes place through welding, brazing (high-temperature soldering), or flame-cutting metal, or in working with molten metal under conditions of inadequate ventilation.^{186–189} In welding, brazing, and flame-cutting, the usual source of cadmium is the welding rod, brazing solder, or a metal coating, rather than the base metal itself.¹²⁹ In areas of the world where jewelry is made at a cottage industry level, cadmium use in silver working can present a particular exposure risk.^{190,191}

Mercury is relatively volatile, and high levels can be generated effectively from many nonenclosed operations, most notably through heated metal reclamation processes (e.g., home refining of mercury-gold amalgams or reclaiming of mercury from electronic equipment).^{192–199} Exposure has also been reported after burning mercury sulfide (Chinese red cinnabar) and mercuric oxide for medicinal purposes.¹⁹⁷ Chelation treatment for elevated systemic mercury typically is begun after the onset of pneumonitis, but its efficacy in ameliorating mercury pneumonitis has not been studied.¹⁹⁶

Nickel carbonyl is an organic metal derivative and potent pulmonary toxicant, with exposure described during nickel refining, during manufacturing processes in which it is used as a catalyst or intermediate, and during metal recycling or reclaiming operations.^{200–204} Cases of severe nickel

fume inhalation from metal spraying operations that were nickel carbonyl free suggests that, under certain conditions, inorganic nickel also can cause acute lung injury.^{205,206} The agent dithiocarb (diethyldithiocarbamate) has been used as a chelating antidote for nickel carbonyl pneumonitis, on the basis of supportive animal data, although its benefits are most clear-cut when it is administered soon after exposure (e.g., before the time clinical illness would be manifested); disulfiram has been suggested as a potential alternative treatment, although experimental data to support this practice are also weak.²⁰⁷

Other Metals

Other metals, including antimony, manganese, and beryllium, are sometimes cited as causes of acute lung injury consistent with metal pneumonitis, but there are few reports in the past 50 years providing documentation of such disorders.⁹ A case report implicated copper dust inhalation as a cause of acute lung injury.²⁰⁸ Osmium tetroxide is a potent respiratory irritant with terrorist weapon potential; fortunately, experience with human inhalation exposure has been limited.²⁰⁹ Cerium oxide is another metallic exposure of theoretical concern because of its potential use as a fuel additive and its capacity to cause acute inhalation injury experimentally.²¹⁰

Two other metal compounds are well-documented bronchial irritants in humans. Vanadium (typically as a metal oxide), which is encountered in metal processing and, in lower concentrations, as a fossil fuel by-product, causes acute bronchitis.²¹¹ Among boilermakers, vanadium-rich fuel oil ash is suspected to be a key exposure related to acute respiratory symptoms.²¹² In a single case report, high-intensity exposure to ash from an oil-burning furnace was associated with DAD; although vanadium was detectable in the residue, the toxic mechanism in this case was unclear.²¹³ In another case report, vanadium (as vanadyl pyrophosphate) was linked to pneumonitis.²¹⁴ Tributyltin (bis[tributyltin] oxide) is an organotin compound, which is an organic compound with one or more molecules of tin. Tributyltin, which is used as a mildew and mold retardant, is also an acute airway irritant.²¹⁵

METAL FUME FEVER, POLYMER FUME FEVER, ORGANIC DUST TOXIC SYNDROME, AND OTHER INHALATION FEVERS

Certain febrile flulike pulmonary syndromes reflect similar clinical responses to a diverse group of acute inhalational exposures.^{24,216} Their hallmarks are chills, fever, malaise, and myalgia, with onset 4 to 8 hours after intense inhalation of fumes or organic dusts.^{24,185,217} Common respiratory signs and symptoms include cough or mild dyspnea, but chest radiographic opacities or hypoxemia are not seen and would be inconsistent with this disorder. Peripheral leukocytosis usually accompanies the syndrome; bronchoalveolar lavage shows a marked influx of neutrophils.^{218–220} These syndromes are self-limited, resolving clinically within 12 to 48 hours. Inhalation fevers share a common feature of tachyphylaxis, with a blunted response to daily repeated inhalation (and hence the name “Monday morning fever” among both brass founders and cotton mill workers).^{24,221,222}

Signs or symptoms of pneumonitis should suggest alternative, more serious diagnoses, such as cadmium pneumonitis,^{187,188} HP (see [Chapter 91](#)), active infection (in the case of water-source aerosols), or inhalation of more toxic temperature-dependent fluoropolymer combustion by-products (which include hydrogen fluoride and perfluorobutylene, which is more toxic than phosgene).^{223–225} Toxic pneumonitis caused by fluorocarbon-containing aerosol sprays is an exposure scenario distinct from polymer fume fever resulting from exposure to fluoropolymer combustion by-products or from acute lung injury and is dealt with separately (see the following section).

Metal fume fever is associated with zinc oxide inhalation from welding galvanized metal or brass working.²²⁶ There is only limited clinical evidence that other metals (magnesium and copper) are capable of causing a similar response,^{185,227} and experimental data further discount magnesium as a potential cause of fume fever.²²⁸ Zinc oxide fume rarely has also been purported to cause an acute lung injury pattern in case reports of welding-related illness, but the likelihood of cadmium or nitrogen dioxide coexposures makes this uncommon association questionable.²²⁹ Further, controlled experimental human exposure data do not support this disorder as a zinc oxide inhalation effect.²¹⁹

Polymer fume fever is associated with thermal breakdown products of fluoropolymers (e.g., polytetrafluoroethylene [Teflon] and related materials).^{217,230–232} The pathophysiologic mechanisms underlying the metal and polymer fume fever syndromes have not been established, but research suggests that pulmonary cytokines may play a key role.^{233–236}

Organic dust toxic syndrome (ODTS) is associated with inhalation of materials contaminated with thermophilic bacteria and fungal spores, including wood chips,²³⁷ straw,²³⁸ silage,²³⁹ seeds,²⁴⁰ grains and flour,²⁴¹ and textile raw materials.²²² The increasing industrialization of agricultural processes, especially the use of animal confinement techniques or so-called *concentrated animal feeding operations*, is an additional source of exposure leading to ODTS, although these same settings also can produce irritant gases such as hydrogen sulfide and ammonia.^{242,243} ODTS has gone by various names, including pulmonary mycotoxicosis,²⁴⁴ silo unloader's syndrome,²³⁹ and mill fever.²⁴⁵ One of the best documented historical outbreaks of ODTS was among individuals who worked with contaminated cotton mattresses.²²² Inhalation of aerosols from contaminated water sources produces a self-limited febrile syndrome similar to ODTS. Some of these outbreaks are attributable to inhalation of *Legionella* species without actual infection (i.e., without clinical evidence of pneumonia) and are referred to as "Pontiac fever."^{246–248} Contaminated aerosols causing inhalation fever syndromes can originate from saunas or hot tubs,^{249,250} commercial (industrial) humidifying systems,^{251,252} and metal machining cooling fluids.²⁵³ Along with these heterogeneous exposure scenarios, various different names have been used for these syndromes, including humidifier fever,²⁵² sump bay fever,²⁵⁴ and bath water fever.²⁴⁹ Many of the same occupational and environmental exposures that cause ODTS can cause HP and respiratory tract infections, thus complicating diagnosis and treatment. Certain features help to distinguish ODTS from HP or infection. For one, ODTS is self-limited, typically

resolving spontaneously. For another, ODTS has a relatively high attack rate over a fairly short time period; that is, in contrast to HP in which host susceptibility, including sensitization, plays a role in disease pathogenesis, ODTS does not require sensitization and may develop in a high proportion of all exposed individuals. As with metal fume fever and polymer fume fever, cytokines are presumed to be key mediators of the ODTS and water-borne aerosol-related inhalation fevers, with endotoxin and related factors being key exposure variables.^{24,255}

FLUOROCARBON AEROSOL SPRAY PNEUMONITIS

Acute lung injury following inhalation exposure to commercial fluorocarbon-containing aerosol products is an important emerging syndrome first reported in the early 1990s.²⁵⁶ This syndrome is distinct both from fluoropolymer fume fever, as previously discussed, and from exposure to irritant by-products from higher-temperature thermal breakdown of such polymers. A key feature of fluorocarbon aerosol pneumonitis is the onset of symptoms within several hours after using a spray product containing fluorocarbon polymers. Exposure can take place in an occupational setting (e.g., construction) or, commonly, from home use of over-the-counter products. These exposures can be relatively brief, with varying degrees of ventilation; importantly, exposure need not be in an enclosed space. Victims usually do not recall previous exposure; there is nothing in the condition to suggest a hypersensitivity mechanism. Application of multiple types of fluorocarbon-containing products has been linked to outbreaks; although waterproofing leather and fabric sprays have dominated the reports, other products include floor stain protector, rust-proofing spray, grout sealer, and ski wax.^{256–263} The clinical presentations manifest a range of severity consistent with varying degrees of nonspecific acute lung injury, including ARDS.²⁶⁴ Management is based on standard supportive care. The various descriptive labels for this condition, such as "horse rug lung" and "hill walkers' lung," can obscure the consistent pattern of the syndrome.^{259,265}

HYDROCARBON PNEUMONITIS AND FIRE-EATER'S LUNG

Hydrocarbon pneumonitis can follow oral ingestion of hydrocarbons and associated hydrocarbon aspiration. In the pediatric high-risk age group, aspiration can take place during ingestion from non-tamper-proof containers typically involving mineral spirits, mineral seal oil (common in furniture polish), lamp oil, kerosene (paraffin), turpentine (pine oil), gasoline, and lighter fluid.^{21,266–268} In adults, hydrocarbon aspiration associated with fuel syphoning represents an occupational hazard among diesel-powered heavy equipment and tractor operators.^{269–271} Even though these substances have systemic toxic effects such as central nervous system depression, life-threatening complications of ingestion are predominantly the result of concomitant hydrocarbon aspiration and subsequent pulmonary compromise, making the lung the target organ of concern in hydrocarbon ingestion. Pneumatocele is a recognized complication of hydrocarbon pneumonitis.²⁷² In contrast

to aspiration hydrocarbon pneumonitis, the toxicity of hydrocarbon (solvent) vapor inhalation manifests primarily in either the central nervous system or the heart. Major pulmonary damage associated with acute hydrocarbon exposure by inhalation is unusual but has been reported.²⁷³ Importantly, the lung also appears to be the target organ for the toxicity of intravenously administered hydrocarbons, an unusual but well-documented suicidal scenario.²⁷⁴

Fire-eater's lung is an important variant of hydrocarbon pneumonitis.^{275–277} This syndrome typically involves adolescents or young adults who become exposed through mishap during flame-blowing performances using a variety of different flammable materials. In addition to kerosene and gasoline, the toxicants include jet fuel and, in France, an aromatic hydrocarbon-enriched petroleum-distillate called “kerdan.”^{278,279} There has also been a case of citronella oil aspiration in a fire-eater.²⁷⁵ As with hydrocarbon pneumonitis in children, fire-eater's lung can also be complicated by pneumatocele.²⁸⁰ Although the term *acute lipoid pneumonia* has been used to refer to the fire-eater's lung syndrome, as well as in other acute aspirations, this is a misnomer.²⁸¹

In both childhood and adult pneumonitis, hydrocarbons are aspirated at the time of the initial ingestion or subsequently with vomiting. The low viscosity of an ingested hydrocarbon is considered a major factor promoting aspiration, presumably for mechanical reasons.^{21,267} Although it has been theorized that hydrocarbon toxicity may involve disruption of surfactant, the chemical pneumonitis of the syndrome appears to be nonspecific.

PARAQUAT

Paraquat is a widely used herbicide and a potent toxin. Ingestion, rather than inhalation, is the typical route of exposure associated with human toxicity. There have been systemic reactions following skin exposure after direct exposure to the skin (e.g., soaking of the skin with paraquat) or when the skin integrity has been breached (e.g., preexisting skin lesions or burn). The theoretical risk of smoking contaminated materials has never been established.

Most paraquat deaths result from suicidal intent.^{22,282,283} Paraquat ingestion is a relatively uncommon method of suicide in the United States, but its incidence is greater in a number of other countries, perhaps related to patterns of crop utilization and ease of access.^{282,284} Although paraquat ingestion leads to acute gastrointestinal tract necrosis and multiorgan failure, the lung is the target organ for toxicity among those surviving the immediate postingestion period. Diquat, a related dipyridyl herbicide, does not cause the lung injury associated with paraquat, although poisoning can lead to renal failure and cerebral hemorrhage.²⁸⁵

The pulmonary toxicity of paraquat, in contrast to its gastrointestinal effects, does not reflect caustic irritant injury. The major lung effect of paraquat toxicity is the development of pulmonary edema, usually observed 24 to 48 hours after ingestion. The pulmonary edema may evolve to a condition resembling ARDS, associated with histopathologic findings similar to those of DAD, which may progress to an accelerated, chemically induced pulmonary fibrosis. After stabilization following acute multiorgan toxic effects, disease progression is marked by rapidly worsening

respiratory distress, hypoxemia, and a restrictive ventilatory defect, with decreased lung compliance and diffusing capacity, ending in death from ventilatory failure within days to weeks.^{22,282} Survivors may demonstrate modest and slow improvement in lung function.²⁸⁶

The mechanism of paraquat toxicity is attributed to the generation of superoxide radicals that may be partly iron dependent. Consistent with an oxidant mechanism, supplemental oxygen and radiation therapy may worsen the outcome; there are no known antidotes for paraquat poisoning, and enhanced elimination such as by hemoperfusion has not demonstrated a clear benefit.^{22,282} Plasma paraquat levels can be determined and may have a use in predicting outcome.²⁸⁷ Data suggest a possible therapeutic benefit from immunosuppression, but this awaits confirmation through controlled clinical trials.^{23,282} Death results from multiorgan failure, which usually happens within 1 to 2 weeks but may be observed up to 6 weeks after ingestion.

SMOKE INHALATION

The generic term *smoke inhalation* includes potential exposure to a wide array of substances because of the complex chemistry of heat decomposition and pyrolysis.^{38,288} *Pyrolysis* refers to the thermal decomposition of organic material without the involvement of oxygen and is a common component of burning buildings where oxygen is limited. Pyrolysis produces a variety of gases and a physical product such as charcoal. Although anoxia from carbon monoxide, cyanide, and oxidants represents a major manifestation of toxic insult from acute smoke inhalation, this nonpulmonary target organ effect is not covered here. Nonetheless, some chemical irritants produced as pyrolysis by-products do have significant potential pulmonary toxicity. In contrast to thermal injury to the respiratory tract, which typically is limited to upper airways, with laryngeal edema the major potential medical management problem,^{289,290} inhalation of the smoke from fires can affect the entire respiratory tract through irritant injury.

In certain cases, irritant chemicals are released in fires as preformed substances, but, most commonly, the toxins are formed *de novo*. These irritants are produced by the thermal degradation of both natural and synthetic polymers. The predominant by-products of heat breakdown are determined by the nature of the polymers consumed, the temperature of the fire, and the availability of oxygen.²⁹¹

Generally, polymers do not break down to their monomer precursors, although residual monomers can evolve under certain circumstances. For example, when polyvinyl chloride is burned, hydrogen chloride is released rather than the monomer, vinyl chloride. Many of the specific chemical irritants that can be released as common thermal breakdown by-products are addressed elsewhere in this chapter. These include the following: hydrochloric acid (hydrogen chloride), hydrofluoric acid (hydrogen fluoride), and other acids; ammonia; phosgene; and oxides of nitrogen. The zinc chloride “smoke” of smoke bombs (in contrast to the heterogeneous character of “natural smoke”) was discussed previously.

Aldehydes merit specific attention. They are a common cause of high-intensity irritant lung injury from the smoke from fires. These chemicals include formaldehyde,

acetaldehyde, and acrolein. The most severe irritant, *acrolein* ($\text{CH}_2=\text{CHCHO}$), is least familiar to health care providers. Acrolein, a highly reactive chemical and key toxicant in smoke inhalation injury, is formed as an important pyrolysis product of both synthetic (e.g., acrylic) and natural polymers.^{292,293} In addition to de novo formation as a combustion by-product, acrolein is also intentionally manufactured and used as a pesticide; its use as an aquatic herbicide to facilitate water flow in irrigation canals can lead to human inhalation exposure with irritant effects.²⁹⁴

The general considerations concerning irritant exposure discussed previously, including air concentration and water solubility, come into play in smoke inhalation. These factors are further complicated by the potential interactive effects of multiple simultaneous exposures, as well as the modifying impact of physical cofactors such as airborne respirable particulates (e.g., soot) that may serve as adsorbent carriers facilitating deep lung penetration of toxicants. In practice, detailed exposure data delineating the irritant contents of a specific smoke exposure are rarely available. Information that may help to elucidate exposure conditions include identity of the products involved (e.g., specific synthetic polymers, if known), history of inhalation within an enclosed or confined space, evidence of thermal injury, and carboxyhemoglobin and methemoglobin levels as markers of inhalation severity based on other concomitant exposures (carbon monoxide and oxidants, respectively).

Firefighters (both urban and wildland) and non-occupationally exposed victims of irritant smoke inhalation have proved to be important groups in which to study acute inhalational syndromes. Large-scale conflagrations (e.g., urban “wildland” fires^{295,296}) can expose substantial numbers of persons to irritant combustion by-products, as can smoke drift from intentional burning of agricultural residue. Wildfire health hazards can be expected to increase as climate change creates longer, warmer, and drier seasons. Studies of such populations after smoke inhalation have demonstrated acute and persistent airflow obstruction and increased nonspecific airway hyperresponsiveness.^{297–305} Bronchiectasis and BO have both been associated with combustion by-product exposure.^{66,68} The acute respiratory effects and potential sequelae of exposure to the plume generated by the destruction of the World Trade Center may relate to other factors such as alkaline (high-pH) dust from concrete, gypsum, and glass fibers, rather than to standard smoke particulate.³⁰⁶

PHARMACOLOGIC SYNDROMES

Certain natural and synthetic chemical exposures affect the lung by specific mechanisms consistent with known pharmacologic actions. These chemicals are site specific for key cellular functions leading to adverse respiratory effects. As noted previously, the most potent chemical warfare agents act through acetyl cholinesterase inhibition, with profound impacts on respiratory function.^{168,169} Similar, albeit less potent, agents have widespread uses as agricultural chemicals. Both organophosphate and carbamate pesticides lead to respiratory compromise as a principal toxic effect.

For example, in one case series, a considerable number of poisonings from these pesticides led to respiratory failure, accompanied by a high case-fatality rate; in contrast, all the patients without concomitant respiratory failure survived.³⁰⁷

Inhaled capsaicin, of interest as a research tool to study substance P-mediated effects, is associated with cough in occupational settings (e.g., in chili pepper processing).³⁰⁸ When used as a personal defense spray, respiratory irritation has been reported, although ocular problems are more common.^{309,310}

Brevetoxin is a toxin produced by dinoflagellates associated with “red tides.” Environmental inhalation exposure from airborne aerosols of red tide resulting from wind and surf action causes cough, sneeze, and wheeze.^{311–313} For lifeguards, brevetoxin health effects represent a source of occupational respiratory morbidity, including work loss.³¹⁴ The toxin appears to act by stimulating sodium channels in the lung.

Palytoxin is another natural toxin produced by certain dinoflagellates, as well as by sea anemones and zoanthid corals. Human exposure may result from ingestion, dermal contact, or inhalation. Respiratory illness attributable to palytoxin inhalation has been described among aquarium hobbyists and among individuals in proximity to algal blooms in ocean water.³¹⁵ The palytoxin inhalational toxic syndrome includes dyspnea, cough, fever, and tachycardia.³¹⁶

Respiratory irritation may also be a manifestation of *Pfiesteria* dinoflagellate toxin inhalation (although potential neurotoxicologic effects have been of greater concern).^{317,318}

OTHER INHALANT EXPOSURES

Ammonia

Anhydrous ammonia is a gas at room temperature and ambient pressure, although ammonia is more commonly encountered in aqueous form, as in cleaning solutions. Potential sources of ammonia gas exposure include incidents in the chemical industry and in hazardous transportation, commercial refrigeration systems, and farming (e.g., fertilizer).^{9,318–323} Anhydrous ammonia has also been released from illicit methamphetamine laboratory operations, although such exposures are often in the context of conflagrations with concomitant thermal burns and other coexposures.^{324,325}

Ammonia has prominent irritant properties, such as burning eyes, that warn the exposed individual to escape. It is linked with lung injury chiefly in settings of overwhelming exposure or where immediate escape has not been possible. Both asthma and bronchiectasis have been documented after ammonia exposure.^{9,322} Acute ammonia exposure has also been reported to have residual upper airway effects, including decreased olfactory acuity.⁴⁶ Death may result from laryngeal edema and airway obstruction, acute pulmonary edema, or complications of the pneumonic process (e.g., bacterial superinfection). Lung transplantation following ammonia inhalation has been reported, including in a patient who had severe lung injury following an explosion in a poultry plant.^{326,327}

Bromine and Methyl Bromide

Bromine is an irritant halogen. It is usually handled as a liquid rather than as a gas, but it vaporizes readily. Sources of bromine exposure other than environmental releases include chemical synthesis and water purification.^{69,328–331} Bromine is a more potent irritant than chlorine and is approximately 100 times more irritating than ammonia.³³² In a murine model of bromine-induced lung injury, high heme levels, possibly released from dead inflammatory cells or sloughed epithelial cells, correlated with a spectrum of adverse sequelae, including lung edema, increased airway resistance, and lung inflammation. Therapeutic reduction of heme levels improved lung function and survival, thus suggesting a potential role for heme attenuation as a treatment for victims of bromine inhalation, although this has not been studied in humans.³³³

Methyl bromide is a major industrial fumigant with far-greater potential for public exposure. Methyl bromide is also a potent respiratory irritant, but the central nervous system may represent the more important target organ in typical exposures.^{334,335}

Hydrogen Sulfide

Hydrogen sulfide is a common by-product of petroleum extraction and refining, as well as a potential hazard from the breakdown of organic materials (hence, its common name, “sewer gas”); overexposure can result from work in confined spaces, submersion in manure pits,³³⁶ or proximity to geothermal or volcanic sources.³³⁷ Asphyxial death of several tourists exploring a volcanic crater was attributed to inhalation of mixed gases containing both hydrogen sulfide and carbon dioxide.³³⁸ Hydrogen sulfide is a respiratory irritant, but it is an even more potent cytotoxic asphyxiant, impairing cytochrome oxidase and cellular respiration. Therefore, in cases of severe hydrogen sulfide exposure, rapid cardiovascular collapse and death often overshadow any pulmonary organ effects, although an acute lung injury pattern can be present in persons surviving long enough to receive intensive supportive care; irritant symptoms as a predominant feature may be of greater relevance in lower-intensity exposures.^{337,339–342}

Methyl Isocyanate and Methyl Isothiocyanate

Methyl isocyanate (MIC) use is restricted to a narrow industrial application in the synthesis of pesticides. The mass fatalities at Bhopal, India, make MIC an important toxin for historical reasons. The toxicity of MIC was the result of its severe irritant properties leading to pulmonary edema.^{343–345} No cyanide-mediated mechanism was involved. *Methyl isothiocyanate*, a breakdown product of the soil fumigant metam sodium, is an irritant chemically related to MIC that was also involved in a mass exposure episode, although less severe than the MIC release at Bhopal, and has also been associated with respiratory symptoms following agricultural application.^{346,347} The isocyanates associated with urethane, such as toluene diisocyanate, diphenylmethane diisocyanate, and hexamethylene diisocyanate, are pulmonary irritants but are primarily of concern because of their induced sensitization (see Chapter 100).

MISCELLANEOUS EXPOSURES

Numerous other occupational and environmental agents result in acute pulmonary syndromes. Examples of such exposures include the following: diethylaminoethanol and cyclohexylamine (both anticorrosive boiler additives)^{348,349}; amitrole and glyphosphate (both common herbicides)^{350,351}; thiram (used as a fungicide in agriculture and as a vulcanization accelerator in the rubber industry)^{351a}; sodium azide (used in a variety of chemical applications but important as a potential inhalant through automobile airbag deployment)³⁵²; diazomethane, which is explosive but also highly toxic to the lung, with a delayed onset similar to that of nitrogen dioxide^{353,354}; diborane (an irritant gas used in manufacturing microelectronic equipment)^{355,356}; barium (inhalation can cause bronchospasm and respiratory muscle weakness in addition to life-threatening hypokalemia)³⁵⁷; and hydrogen selenide (an irritant gas used in several industrial processes, as well as being a potential metal processing by-product).^{358,359}

An outbreak of severe lung injury in Korea, particularly among young, peripartum women, was linked to treatment of room humidifier water with two biocides: polyhexamethylene guanidine and oligo(2-(2-ethoxy)ethoxyethyl) guanidinium chloride.^{360,361} The overall mortality rate in what has been labeled “humidifier disinfectant-associated lung injury” is reported to be more than one-third of cases, with three-fourths of those patients requiring mechanical ventilation dying of their injuries.³⁶² After the original offending product was removed from the market, humidifier disinfectant-associated lung injury was described in twin sisters exposed to chloromethylisothiazolinone and methylisothiazolinone, thus broadening the spectrum of disinfectants associated with toxic lung injury.³⁶³

Phosphine is an important agricultural fumigant with pulmonary and systemic toxicity, which is generated on site as a gas given off by moisture coming in contact with solid-form aluminum or zinc phosphide (e.g., in grain storage facilities or railway grain transport cars, where bystanders can be exposed).^{364,365} Ingestion of the parent material by animals can also lead to exposure among treating veterinary personnel.³⁶⁶ Phosphine also has industrial applications, particularly in the production of microelectronics.

Acetic anhydride (used in making epoxy and other resins) has also been associated with acute lung injury following acute inhalation.³⁶⁷ A distinctly different pattern of injury is associated with a related epoxy chemical, trimellitic anhydride, which causes severe pulmonary hemorrhage after subacute exposure.¹⁵

Carbon dioxide, although a bulk asphyxiant and not a respiratory irritant, causes shortness of breath and induces tachypnea; persons can be exposed through natural geologic sources and dry ice sublimation in an enclosed space.^{368–370}

Baby (talcum) powder inhalation can cause pediatric acute pneumonitis within hours of heavy exposure; infant inhalation of nontalcum powders has also led to pneumonitis.^{371–373}

Paraphenylenediamine is a dye used to color hair and can also be admixed with henna as a temporary tattooing agent; its ingestion as an agent of self-harm is common in

TABLE 103.3 Useful Resources for Information About Specific Toxins

- The Household Products Database (<https://healthdata.gov/dataset/household-products-database>) is a consumer guide that provides information on the potential health effects of chemicals contained in more than 7000 common household products used inside and around the home.
- WISER (Wireless Information System for Emergency Responders) (<http://wiser.nlm.nih.gov>) is a system designed to assist first responders in hazardous material incidents.
- The EPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/>) provides access to multiple types of data, including physicochemical properties, environmental fate and transport, exposure, usage, in vivo toxicity, and in vitro bioassay.
- The ECOTOXicology knowledgebase (ECOTOX) (<https://cfpub.epa.gov/ecotox/>) is a comprehensive knowledgebase providing single-chemical environmental toxicity data on aquatic life, terrestrial plants, and wildlife.
- The ATSDR Toxic Substances Portal (<https://www.atsdr.cdc.gov/>) provides information on toxic substances and their health effects.

Asia and Africa. In addition to rhabdomyolysis and renal damage, this chemical has a particular propensity to cause angioedema leading to airway obstruction.²⁵

Naturally occurring sources of exposure can also be associated with acute and subacute lung responses, although these syndromes are poorly characterized. Epidemiologically, *Stachybotrys chartarum* (*atra*) mold growth in water-damaged residential structures was initially linked to a cluster of cases of pulmonary hemorrhage in infants, although the association was later retracted in a follow-up review by the U.S. Centers for Disease Control and Prevention.^{374,375} Other case reports have occasionally linked other molds or mold by-products with lung injury (as opposed to self-limited ODTs, discussed previously).³⁷⁶

Lycoperdonosis is a potentially severe, acute pulmonary syndrome following intentional inhalation (sometimes as a natural medicinal treatment) of puffball mushroom (*Lycoperdon*) spores; in addition to human illness, fatal inhalation in pet dogs is a well-characterized veterinary syndrome.^{377–379} The pathophysiology of the syndrome is not understood, but its high attack rate with heavy exposure suggests a toxic rather than an allergic or infective mechanism.

Beginning in 2019, acute lung injury associated with “vaping” (use of electronic cigarettes or e-cigarettes) began to be widely observed.^{380,381} These devices work by heating liquids to produce an inhalable aerosol. Such aerosols can contain multiple intended and unintended component toxicants, including potential thermal breakdown materials. The topic of vaping, as well as classic cigarette smoking lung effects, is covered in [Chapter 65](#).

Additional information about toxicants and their effects can be accessed online from a variety of resources ([Table 103.3](#)).

Key Points

- Short-term inhalation exposures to toxicants have important effects on the lung as the target organ for damage.
- Acute lung toxicity results from a variety of exposures but nonetheless is manifest by a narrow repertoire of injury.
- Although modified by the solubility and other physical properties of the toxicant, injury largely depends on the intensity and duration of exposure.
- Extensive injury can lead to acute pulmonary edema and diffuse alveolar damage.
- Specific exposures of importance include chlorine, oxides of nitrogen, sulfur dioxide, acid aerosols, toxic metal fumes, and pyrolysis by-products.
- Aside from acute irritant or toxic lung insult leading to airway injury and diffuse alveolar damage, other patterns of acute responses include the inhalation fevers (which are self-limited and appear to be cytokine mediated) and certain target-specific effects, such as those elicited by cholinesterase inhibition.
- Exposure by *ingestion* of some substances (e.g., hydrocarbons and paraquat) can cause important acute pulmonary target organ toxicity.

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Reactive airways dysfunction syndrome and irritant-induced asthma

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INTRODUCTION

Reactive airways dysfunction syndrome (RADS) and irritant-induced asthma (IIA) are closely related forms of asthma that result from a single exposure to a high concentration of irritant agents or repeated exposure to moderate to low doses of irritant agents [\[1-9\]](#).

The diagnosis and management of RADS and IIA will be reviewed here. The diagnosis of asthma and the causes, evaluation, and management of occupational asthma are discussed separately. (See ["Asthma in adolescents and adults: Evaluation and diagnosis"](#) and ["Occupational asthma: Definitions, epidemiology, causes, and risk factors"](#) and ["Occupational asthma: Clinical features, evaluation, and diagnosis"](#) and ["Occupational asthma: Management, prognosis, and prevention"](#).)

DEFINITIONS

Irritant-induced asthma (IIA) is a general (umbrella) term to describe an asthma-like syndrome that results from a single or multiple high dose exposures to irritant products [\[3,10\]](#). The rapid onset of asthma within a few hours after a single exposure to very high levels of irritant substances (ie, acute-onset IIA or reactive airways dysfunction syndrome [RADS]) is the phenotype of IIA that has been the best characterized. Other clinical phenotypes such as "low-dose reactive airways dysfunction syndrome," "not-so-sudden IIA," or "IIA with latency" are mainly described in epidemiologic studies because the causal relationship with irritant exposures at the workplace and occurrence of respiratory symptoms is difficult to establish at the individual level [\[11-15\]](#). When IIA is caused by

workplace exposures, it is considered a type of occupational asthma, the non-immunologic type.

- **Acute onset IIA** – RADS, “acute onset IIA,” is described as the development of respiratory symptoms in the minutes or hours after a single accidental inhalation of a high concentration of irritant gas, aerosol, vapor, or smoke; these initial symptoms are followed by asthma-like symptoms and airway hyperresponsiveness that persist for a prolonged period ([table 1](#)) [1]. RADS can occur after exposure to a variety of chemicals generated as gas or aerosol, or exposure to high levels of particulates ([table 2](#)). Clinical and functional criteria for the diagnosis of RADS are listed in the table ([table 1](#)) [1]. IIA can be caused by multiple exposures to high doses of irritants which induce acute symptoms requiring acute medical care [16].
- **Subacute IIA** – The term “sub-acute IIA” has been proposed to describe instances of multiple high exposures to irritants where the onset of symptoms may be more insidious, as seen following the World Trade Center catastrophe [8,9], or less well-documented exposures in which the affected individuals are able to identify the timing, nature, and frequency of events [10,17].
- **Low-dose IIA** – IIA may also include a condition resulting from multiple exposures to low concentrations of an irritant that have led to bronchial mucosal injury and persistent asthma-like symptoms, although this is less well-established [11]. The term “low-dose IIA” (also called low-dose RADS) has been used to describe individuals in the latter group, but the pattern of repeated low-dose (as opposed to a single high-dose) exposure means that they do not formally fulfill the original criteria for RADS. In addition, when the intensity of the exposure is less, but is of greater duration (eg, >24 hours), symptoms may start after several hours or days, rather than within minutes of inhalation, thus further “widening the spectrum of IIA” [12]. However, “low-dose IIA” cannot currently be reliably diagnosed in an individual worker. The term Low Intensity Chronic Exposure Dysfunction Syndrome (LICEDS) has also been suggested to describe this form of IIA [17].

A position paper from the European Association of Allergy and Clinical Immunology has proposed definitions for different IIA phenotypes [3]:

- Definite IIA relates to acute-onset IIA manifested by rapid onset of asthma within 24 hours of a single very high-intensity exposure to an irritant compound (similar to the classic RADS phenotype).
- Probable IIA is characterized by the development of asthma following multiple symptomatic moderate-high level exposures to irritants.

- Possible IIA describes a delayed development of asthma following chronic and/or repeated exposure to low-moderate levels of irritant substances.

EPIDEMIOLOGY

Reactive airways dysfunction syndrome (RADS) may occur after inhalational accidents at home, in the workplace, or in the general environment. Irritant-induced asthma (IIA) due to multiple exposures is most commonly associated with inhaled irritants in the workplace. It is estimated that 60,000 inhalational accidents occur in the home and lead to medical consultation yearly in the United States [18]. Industrial accidents also have the potential to expose nonemployees to noxious inhalants; the release of isocyanates at Bhopal, for example, led to more than 2000 deaths due to pulmonary edema, and caused RADS in many others [19,20].

Estimating the incidence of RADS is difficult for several reasons. Precise, subject-specific information regarding the duration and magnitude of exposure at the time of an accident is rarely available. This is further complicated in IIA, where multiple exposures to irritant products are involved; the level of exposure to the inhaled irritant can vary between exposures and between exposed subjects; and several irritant agents can also be involved simultaneously [21,22]. The size of populations at risk after an incident can only be determined approximately in many cases.

The following observations, in which large numbers of patients were exposed to a chemical irritant, illustrate the variation in reported rates of development of RADS and IIA:

- After an accidental exposure to high concentrations of glacial acetic acid, the incidence of RADS among 51 hospital employees who were present during the 2.5 hours immediately following the accident was 16 percent [23].
- Among 289 workers exposed to chlorine gas in a pulp and paper mill, 71 (25 percent) developed respiratory symptoms shortly after the event [24]. Among 239 workers with repeated exposures to chlorine and other gases over a three-year period, significant respiratory symptoms were reported by 38 (16 percent) [22]. No association between exposure level and persistence of symptoms was documented. Subsequently, a longitudinal follow-up of the same workers over a three-year period showed: (1) an effect on airway function related to the estimated number of symptomatic exposures and incidents, mostly among smokers; (2) a detectable increase in airway responsiveness associated with gassing incidents [25].
- Professional cleaning is considered a high risk occupation for work-related asthma based on studies conducted in Europe and in the United States [26-28]. Among 123

cases of work-related IIA reported in a sentinel notification program in four states in the United States, cleaning agents were the most common reported implicated agent (15 percent) [29]. Some epidemiologic studies have supported the role of repeated and/or chronic exposure to lower levels of cleaning agents in the development of asthma in workers exposed to those agents [30].

Cleaning agents may also cause occupational asthma by a mechanism of sensitization. More frequent atopy and higher levels of total IgE are found in these workers [31]. In a group of 44 workers with symptoms on exposure to cleaning agents, 17 (39 percent) were found to have immunological occupational asthma [32]. Asthmatic symptoms are also associated to the domestic use of cleaning agents [33,34].

- Approximately 15 percent of all cases of occupational asthma accepted for compensation in Ontario, Canada, were of the RADS type [35]; a similar proportion (14 percent) was found in a sentinel notification program in four states in the United States [29].
- A number of studies have assessed the effects of exposure to the plume of particulate dust and smoke due to the fires and structural collapse of the World Trade Center towers on September 11, 2001 [8,9,36,37]. The rate of newly diagnosed asthma among workers and volunteers was almost 4 percent and correlated with an earlier time of arrival and greater duration of time at the site [36,38].
- Exposure to a low/moderate level of irritants has been shown to be associated with the diagnosis of asthma (OR 1.88, 95% CI 1.48-2.37) [39].

CAUSES AND RISK FACTORS

A number of agents have been implicated in the development of RADS and IIA, most commonly chlorine, isocyanates, oxides of nitrogen, acetic acid, and sulphur dioxide ([table 2](#)) [40,41]. As an example, one study identified 46 different agents as having caused occupational irritant-induced asthma, associated with apparently high concentration exposures without a latency period [42]. A separate study reported that paper, metal and chemical industries were responsible for the majority of their cases of IIA. Cases of acute IIA were related to accidents whereas subacute IIA occurred mainly among industrial operators performing usual work tasks with poor hygiene conditions [43].

Definitive risk factors for the development of RADS and IIA have not been confirmed, but probable risk factors likely include the chemical and physical nature and concentration of the irritant agent in addition to certain host factors such as atopy and cigarette smoking.

- **High concentration exposure** – Increased concentrations of offending agents are associated with higher risk, and vapors and wet aerosols generally appear to be more provocative of RADS than dry particulates [23,44]. Workers exposed to bleaching agents in paper mills (including chlorine) [45] and cleaning products [27,44] are particularly at risk. Excess rates of asthma have been documented in workers exposed to cleaning agents, and RADS/IIA may explain this phenomenon ([table 2](#)) [46]. The main risk factor for developing respiratory diseases identified among the World Trade Center (WTC) rescue workers was the presence on the site of the WTC during the first 48 hours and the duration of exposure during rescue [47].
- **Atopy** – While atopy has been described as a risk factor for the occurrence of the not-so-sudden-onset variant of IIA that develops days after an irritant exposure [12], there is no evidence that atopy is a risk factor for the development of RADS or other forms of IIA [23,24,48].
- **Airway hyperresponsiveness** – Previously documented airway hyperresponsiveness did not predispose to the development of RADS in firefighters at the World Trade Center [49]. It is likely that the pre-existing airway hyperresponsiveness was infrequent among these firefighters given that asthma is an exclusion criterion for recruitment. However, lifetime prevalence of asthma was increased in WTC responders by comparison with a large control population [50].
- **Smoking** – Smoking is more common among workers with RADS than in those with other types of occupational asthma and seems to increase the risk of functional decline in workers repeatedly exposed to puffs of chlorine [25,35]. However, some studies have suggested that the development of acute and sub-acute IIA was not associated with smoking [23,24].
- **Genetic factors** – Although some observations suggest a possible genetic predisposition to be more susceptible to the effects of irritants, as for sensitizing agents, this remains to be further examined [51].

PATHOLOGY AND MECHANISMS

Serial observations from two cases of reactive airways dysfunction syndrome (RADS) illustrate the histopathologic features of the disease ([table 3](#)) [52,53]. The initial change was rapid denudation of the mucosa with a fibrinohemorrhagic exudate in the submucosa. This was followed by subepithelial edema and signs of regeneration of the epithelial layer with proliferation of basal and parabasal cells. Desquamation, subepithelial fibrosis, thickening of the reticular basement membrane, and regeneration of basal cells are all more striking in RADS than in occupational asthma with a latency period ([table 4](#)). In addition,

bronchoalveolar lavage (BAL) reveals neutrophilia in the acute stage of RADS, whereas lymphocytes and eosinophils are more numerous in occupational asthma with a latency period. (See "[Occupational asthma: Pathogenesis](#)", [section on 'Pathology'](#).)

The acute changes of RADS have been reproduced by exposing rats to high concentrations of gaseous chlorine [54]. Histologic evaluation revealed epithelial flattening, necrosis, and evidence of epithelial regeneration. Bronchoalveolar lavage showed an increased number of neutrophils. Abnormalities in epithelial pathology and bronchial hyperresponsiveness were most prominent one to three days following injury. Epithelial abnormalities persisted in some animals for up to three months [54]. Similar findings have been described in a mouse model of RADS [55]. Chlorine can induce direct oxidative epithelium injury, but further damage may also occur with migration and activation of inflammatory cells such as neutrophils within the airway epithelium, with subsequent release of reactive oxygen species and proteolytic enzymes. In a mouse model, airway barrier impairment led to the development of airway hypersensitivity after low-dose chlorine exposure [56], suggesting that airway epithelial damage may be a risk factor for developing IIA after exposure to irritant agents.

The release of reactive oxygen species can contribute to airflow limitation and airway hyperreactivity [57]. In a separate study, an antioxidant preparation diminished many features of tissue damage following exposure to chlorine gas, including the increase in BAL neutrophils and macrophages [58].

The long term (approximately 10 years) pathological abnormalities of RADS have been described [59]. Bronchial biopsies obtained from 10 subjects with IIA at a mean of 10 years following an industrial accident showed neutrophilic and eosinophilic inflammation [59]. In addition, reticular basement membranes were thicker among patients with RADS than those with mild immunologic occupational asthma or healthy controls.

In one patient with IIA secondary to multiple exposures, an inflammatory infiltrate consisting of lymphocytes and polymorphonuclear cells was found on bronchial biopsy [16]. In the chronic stage of irritant-induced asthma, the infiltrate consisted of lymphocytes and eosinophils, with thickening of connective tissue and deposition of collagen fibers [16,60].

In a cross-sectional study of 999 adults, occupational exposure to irritants was associated with a specific respiratory endotype, suggesting that oxidative stress and neutrophilic inflammation were potentially associated biological mechanisms [61].

CLINICAL MANIFESTATIONS

- **History** – The clinical manifestations (eg, cough, dyspnea, wheeze, chest tightness) of RADS and IIA differ mainly in the rapidity of onset of symptoms.
 - The onset of symptoms in RADS is usually so abrupt that subjects are able to date their occurrence precisely, although a few patients report respiratory symptoms developing up to seven days after the exposure [17,62]. Patients with multiple exposures to high concentrations of products such as chlorine may be able to identify the timing, nature, and frequency of most events [10,17].
 - Patients with the not-so-sudden onset variant of IIA may not be aware of multiple low level irritant exposures and may report episodic symptoms that are not precisely linked to known exposures.

After an acute exposure to gas, smoke, fumes, or vapors with irritant properties, some subjects with no history of respiratory complaints report a burning sensation in the throat and nose referred to as respiratory upper airways distress syndrome (RUDS) [63], in addition to cough, dyspnea, wheeze, and chest pain [1,23,64]. These symptoms typically develop within 24 hours of the exposure and are severe enough that approximately 78 percent seek emergency room treatment [29]. In most series, cough is the predominant symptom in RADS and IIA [1,65,66]. (See '[Definitions](#)' above.)

Patients with IIA due to multiple low level exposures to irritant agents describe essentially the same symptoms as patients with RADS (eg, cough, dyspnea, chest tightness, and wheezing), although the time course of onset differs. Symptoms of nasal mucosal irritation, such as nasal congestion, sneezing, nasal pruritus and/or increased nasal secretions, may accompany the asthma-like symptoms and are often exacerbated by recurrent exposure in the workplace [67]. Occupational rhinitis is discussed in greater detail separately. (See "[Occupational rhinitis](#)".)

- **Physical examination** – For both RADS and IIA, physical examination findings are not well described, but have included conjunctivitis, pharyngeal erythema, tearing, tachypnea, and wheezing [24,68]. After an accidental chlorine exposure, 67 percent (42 of 63) had wheezing on initial presentation, and 84 percent had wheezing at some point in their hospitalization [64]. Exposure to ammonia may be associated with burns and blisters on exposed skin and damage to the surface structures of the eye. (See "[Topical chemical burns: Initial assessment and management](#)".)

EVALUATION

RADS and IIA should be suspected in patients with asthma-like symptoms following a well-defined exposure. An important component of the evaluation is to review the details of the

history, particularly when the patient is seen weeks or months after the initial exposure. Some relevant questions to be asked to all subjects when first assessed for possible asthma, and particularly for RADS or IIA, are listed in the table ([table 5](#)).

The evaluation of a patient with the acute onset of respiratory symptoms following an irritant exposure typically includes assessment of oxygenation by pulse oximetry or arterial blood gases and a chest radiograph to look for noncardiogenic pulmonary edema, pneumonia, or other causes of dyspnea. As soon as possible, spirometry should be performed to determine whether airflow limitation is present and reversible. (See ["Evaluation of the adult with dyspnea in the emergency department"](#).)

For patients with persistent symptoms due to RADS or IIA, the evaluation is the same for the two processes. In addition to spirometry, testing includes more complete pulmonary function testing with assessment of nonspecific hyperresponsiveness. An approach to the patient with dyspnea is provided separately. (See ["Approach to the patient with dyspnea"](#).)

Laboratory testing — Routine laboratory testing is usually not helpful in the diagnosis of irritant exposures. However, a complete blood count and differential are appropriate to help exclude other processes in the differential diagnosis of dyspnea such as anemia, eosinophilic pneumonia, and infection.

Skin and immunologic testing — For patients with chronic symptoms due to RADS or IIA, either allergy skin testing or immunoassay to a panel of common aeroallergens is appropriate to exclude allergic asthma due to common aeroallergens or a sensitizing process evocating immunologic occupational asthma. (See ["Overview of skin testing for allergic disease"](#) and ["Overview of in vitro allergy tests"](#).)

In vitro immunoassay for IgE antibodies to occupational sensitizers is available for a limited number of low molecular weight chemical-protein conjugates (eg, diisocyanates), but these are not standardized or commercially available. An acute increase in specific IgE antibodies to formaldehyde has been described in a case of RADS associated with high level exposure to formaldehyde, although the significance of this observation is not known [69].

Pulmonary function testing — One of the first steps in the evaluation of a patient with respiratory symptoms after an irritant inhalational exposure is pulmonary function testing to assess the presence, severity, and reversibility of airflow limitation. For patients without significant airflow obstruction, bronchoprovocation challenge can be used to document non-specific airways hyperresponsiveness. The roles of spirometry and bronchoprovocation challenge in the diagnosis of asthma are discussed separately. (See ["Pulmonary function testing in asthma"](#), [section on 'Tests for the diagnosis of asthma'](#) and ["Bronchoprovocation testing"](#).)

Spirometry — Baseline spirometry is obtained in all patients suspected of having RADS or IIA; bronchodilator reversibility is assessed if airflow limitation is present. In a series of 19 patients seen after chlorine exposure, 10 had airflow limitation when assessed soon after the exposure; many showed reversal of obstruction with time [70]. In a separate study of 10 subjects with RADS due to high level exposures to a variety of agents, four had airflow obstruction with a forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) ratio <70 percent [1]. (See "[Office spirometry](#)" and "[Pulmonary function testing in asthma](#)", [section on 'Tests for the diagnosis of asthma'](#).)

Following baseline spirometry, bronchodilator reversibility is assessed by inhalation of a short-acting beta agonist. In general, reversibility is defined as an increase in FEV₁ of 12 percent or more, accompanied by an absolute increase in FEV₁ of at least 200 mL in adults [71]. Airway obstruction is generally less responsive to a bronchodilator in RADS than in asthma, although some degree of reversibility may be present. A comparison of 30 subjects with immunologic occupational asthma and 15 subjects with RADS found a mean improvement in FEV₁ after bronchodilator of close to 20 percent in the subjects with immunologic occupational asthma, nearly double the response seen among those with RADS. However, significant heterogeneity was seen among the RADS group: 6 of the 15 subjects had a postbronchodilator improvement in FEV₁ of more than 15 percent [22]. (See "[Pulmonary function testing in asthma](#)", [section on 'Bronchodilator responses'](#).)

In a minority of patients, a restrictive defect is noted on pulmonary function testing, although an obstructive pattern is much more common [72]. (See "[Overview of pulmonary function testing in adults](#)", [section on 'Lung volumes'](#).)

Nonspecific bronchoprovocation challenge — If baseline spirometry shows absent or minimal airflow limitation and no significant bronchodilator reversibility, nonspecific (or nonallergic) bronchial challenge (eg, [methacholine](#)) is performed to assess for non-specific bronchial hyperresponsiveness. ([table 6](#) and [table 7](#)). The performance of bronchoprovocation challenge, contraindications to testing, and adjustments of medication prior to testing, are described separately. (See "[Bronchoprovocation testing](#)" and "[Bronchoprovocation testing](#)", [section on 'Pharmacologic challenge'](#).)

Among various case reports, a positive bronchoprovocation challenge was present at initial evaluation in virtually all patients who were able to perform the testing. (See "[Pulmonary function testing in asthma](#)", [section on 'Bronchodilator responses'](#).)

Specific bronchoprovocation challenge — Specific inhalation challenges are not performed to diagnose IIA with agents that are known to cause IIA [2]. The majority of these agents are not sensitizers and would not induce an acute asthmatic reaction when inhaled at low levels for a short period of time. (See "[Occupational asthma: Clinical features, evaluation, and diagnosis](#)", [section on 'Specific inhalation challenge'](#).)

However, rare individuals can experience a RADS after exposure to agents that have both irritant and sensitizing properties (eg, isocyanates) and subsequently develop occupational asthma. For example, a subject developed occupational asthma while exposed to lower levels of diisocyanates after an initial high exposure to this agent that induced RADS [73]. In this instance, performing specific inhalation was useful to confirm the diagnosis of occupational asthma. (See ["Occupational asthma: Definitions, epidemiology, causes, and risk factors", section on 'Low-molecular-weight'](#) and ["Occupational asthma: Clinical features, evaluation, and diagnosis", section on 'Specific inhalation challenge'.](#))

Imaging — A chest radiograph is typically obtained to exclude noncardiogenic pulmonary edema, alveolitis, or pneumonia in patients presenting after an acute irritant exposure or other causes of dyspnea in those presenting later in the course of RADS or after multiple lower dose irritant exposures. The chest radiograph in patients with RADS and IIA is typically normal or may show hyperinflation. (See ["Evaluation of the adult with dyspnea in the emergency department", section on 'Plain chest radiograph \(CXR\)'](#) and ["Approach to the patient with dyspnea", section on 'Chest computed tomography'.](#))

High resolution computed tomography (HRCT) is not required in the evaluation of RADS or IIA, but may be performed in atypical cases to exclude alternative diagnoses. HRCT scans, obtained in 29 symptomatic rescue and recovery workers at the World Trade Center site, showed evidence of air-trapping based on a mosaic pattern on the end-expiratory images in 25 of these workers [74].

DIAGNOSIS

The diagnosis of RADS and IIA is based upon a combination of exposure history ([table 5](#)), time course of symptom onset, and evidence of reversible airflow limitation and/or non-specific bronchial hyperresponsiveness.

The diagnosis of RADS is likely in individuals with:

- A history of acute exposure to an irritant agent or material preceding the onset of respiratory symptoms (see ["Clinical manifestations"](#) above)
- Acute onset of respiratory symptoms within 24 hours of the exposure, or within seven days at the latest (see ["Clinical manifestations"](#) above)
- Persistence of airway obstruction and/or hyperresponsiveness, generally for three months or more (see ["Pulmonary function testing"](#) above)

The diagnosis of subacute IIA, sometimes called “not-so-sudden RADS,” is often not as straightforward as the diagnosis of RADS due to the lack of a single episode of high level exposure. However, a history of single or multiple exposures to an irritating inhalational

agent ([table 5](#)), the presence of asthma-like symptoms, and the presence of reversible airway obstruction and/or hyperresponsiveness are necessary to the diagnosis. (See ['Pulmonary function testing'](#) above.)

The absence of specific testing that can establish a causal role of an irritant agent makes it difficult to establish the diagnosis of IIA with certainty. However, data from epidemiologic studies that have identified occupations with an increased risk of asthma, such as cleaners [\[46,75\]](#) and pulp mill workers [\[45\]](#), can be used to support a diagnosis of IIA in a patient with similar exposures [\[21\]](#) (see ['Epidemiology'](#) above). However, distinguishing IIA caused by repeated, moderate or low level exposures from coincidental non-work related asthma is very difficult and often impossible on a clinical basis.

DIFFERENTIAL DIAGNOSIS

Acute presentation — At the time of an acute presentation with possible RADS, the differential diagnosis includes the following:

- Underlying asthma that may have been exacerbated by an irritant exposure
- Acute respiratory infection
- Cardiogenic or noncardiogenic pulmonary edema
- Other causes of an acute onset of dyspnea

A careful history provides guidance regarding the severity of the exposure and thus the likelihood of RADS versus an exacerbation of underlying asthma. A conventional chest radiograph can help exclude pneumonia, pulmonary edema, and acute eosinophilic pneumonia. A complete blood count and differential provides supportive information for or against infectious or eosinophilic pneumonia. (See ["Asthma in adolescents and adults: Evaluation and diagnosis"](#), [section on 'Diagnosis'](#) and ["Acute bronchitis in adults"](#) and ["Clinical evaluation and diagnostic testing for community-acquired pneumonia in adults"](#) and ["Evaluation of the adult with dyspnea in the emergency department"](#).)

Persistent symptoms — For patients presenting with persistent symptoms, the differential diagnosis of RADS and IIA typically includes underlying asthma that may have been exacerbated by an irritant exposure, occupational asthma due to an immunologic reaction to an agent in the workplace, paradoxical motion of the vocal cord (also known as vocal cord dysfunction or irritable larynx syndrome), and nonasthmatic eosinophilic bronchitis as well as other causes mimicking asthma.

- **Pre-existing asthma** – A history of prior symptoms of cough or dyspnea, possibly exacerbated by respiratory infection or exposure to irritants, favors a diagnosis of pre-existing asthma.

- Occupational asthma** – A number of features are common to IIA and immunologic occupational asthma. Wheezing and airflow obstruction are common to both conditions. A differentiating feature is that immunologic occupational asthma is reproduced by inhalation challenge with low levels of the offending workplace agent, while RADS and IIA are not ([table 4](#)). Differentiation may also be based on the type of exposure. As an example, exposure to chlorine and cleaning agents is associated with IIA [\[28,76\]](#), while exposure to flour and latex is associated with occupational asthma. A few of these agents, however, have been associated with both syndromes (eg, diisocyanates, cleaning agents). (See ['Clinical manifestations'](#) above and ['Pulmonary function testing'](#) above and ["Occupational asthma: Clinical features, evaluation, and diagnosis"](#) and ["Occupational asthma: Definitions, epidemiology, causes, and risk factors", section on 'Causative agents'.](#))
- Paradoxical vocal fold motion** – Paradoxical vocal fold motion (PVFM) refers to abnormal closure of the vocal cords, usually on inspiration; it may mimic asthma or accompany asthma. A temporal association of onset of PVFM and irritant exposure has been described, adding to the importance of differentiating these entities [\[77\]](#). The diagnosis of PVFM is usually suggested by the presence of dysphonia and abnormal slowing of the inspiratory flow volume loop obtained during routine spirometry or nonspecific bronchoprovocation challenge. The diagnosis is confirmed by direct visualization of the vocal cords by laryngoscopy. (See ["Inducible laryngeal obstruction \(paradoxical vocal fold motion\)", section on 'Evaluation and diagnosis'](#) and ["Bronchoprovocation testing", section on 'Pharmacologic challenge'.](#))
- Nonasthmatic eosinophilic bronchitis** – Nonasthmatic eosinophilic bronchitis (NAEB) is characterized by a cough that is usually nonproductive, eosinophilia in induced sputum, and the absence of airflow limitation or bronchial hyperresponsiveness. NAEB has been described in workers exposed to a variety of occupational agents that are associated with IgE-mediated sensitization [\[2,78,79\]](#). The key differentiating feature is the negative non-specific bronchoprovocation challenge among patients with NAEB. While induced sputum shows eosinophilia in NAEB, induced sputum analysis has not been fully evaluated in RADS and IIA and is not widely available. (See ["Evaluation of subacute and chronic cough in adults", section on 'Nonasthmatic eosinophilic bronchitis'](#) and ['Nonspecific bronchoprovocation challenge'](#) above.)

TREATMENT

Acute management of RADS — The management of an acute presentation of reactive airways dysfunction syndrome (RADS) is essentially the same as the treatment of an acute asthma exacerbation [\[60\]](#). However, the optimal treatment of this condition has never been

assessed prospectively in a clinical trial. (See "[Acute exacerbations of asthma in adults: Emergency department and inpatient management](#)" and "[Acute exacerbations of asthma in adults: Home and office management](#)".)

- **Bronchodilators** – Bronchodilator therapy is administered based on the severity of symptoms and response to treatment, even though the response to inhaled bronchodilator may be blunted in RADS compared with asthma. If a short-acting beta agonist (SABA) does not provide adequate symptomatic relief, we typically add [ipratropium](#), although data in support of this are limited.
- **Systemic glucocorticoids** – Treatment of acute RADS includes prompt administration of systemic glucocorticoids (eg, [prednisone](#) 40 to 60 mg daily) for patients with moderate to severe symptoms and a forced expiratory volume in one second (FEV₁) less than 70 percent predicted. No formal trials have been performed on glucocorticoid therapy in RADS, so the use of systemic glucocorticoids for RADS is based upon clinical experience and their well-documented role in asthma [[52,53](#)]. Support for systemic glucocorticoid therapy comes from their use in an animal model of RADS. Parenteral glucocorticoids, given for one week immediately after exposure, significantly attenuated expected increases in lung resistance and bronchial hyperresponsiveness; bronchoalveolar lavage (BAL) and histologic parameters were likewise improved [[54](#)].

We typically continue oral [prednisone](#) for 10 to 15 days, which is longer than that used for typical exacerbations of asthma, as it is our clinical observation that patients improve slowly and do not tolerate tapering sooner. High-dose inhaled glucocorticoids (eg, [fluticasone](#) propionate 1000 mcg/day or the equivalent), with or without concomitant inhaled long-acting beta-2 agonist, are also started to help control asthma symptoms developing upon tapering of prednisone. Relatively high doses of inhaled glucocorticoids may be required for long-term treatment as pathological evidence shows the persistence of eosinophils [[59](#)].

- **Inhaled glucocorticoids** – For patients who have a documented irritant exposure but whose initial symptoms and airflow obstruction are less severe (eg, FEV₁ ≥70 percent predicted), we suggest initiation of inhaled glucocorticoids rather than systemic glucocorticoids or inhaled beta agonist therapy alone. Data in support of inhaled glucocorticoids are limited, but a case report of a subject with RADS reflects our experience. In the report, treatment with inhaled glucocorticoids normalized bronchial hyperresponsiveness, but hyperresponsiveness worsened when therapy was stopped [[53](#)].

The initial dose of inhaled glucocorticoids is based on the step-wise approach to asthma outlined in the Global Initiative for Asthma (GINA) [[71](#)]; in our experience the majority of patients require a high dose to control symptoms ([table 8](#)). (See "[An](#)

[overview of asthma management", section on 'Initiating therapy in previously untreated patients'.\)](#)

Once patients have demonstrated symptomatic improvement, inhaled glucocorticoids can be tapered as tolerated. Airflow limitation is assessed serially with spirometry as the inhaled glucocorticoids are tapered. If asthma has remained well-controlled for several weeks and the FEV₁ is stable, then the inhaled glucocorticoids are decreased by 25 to 50 percent increments. When the FEV₁ is greater than 70 percent of predicted, bronchial responsiveness to [methacholine](#) may be used to guide tapering inhaled glucocorticoids, although this approach is not well-validated. The weaning of inhaled glucocorticoids may take six weeks to six months, and many patients require more long-term therapy. (See ['Prognosis'](#) below.)

Management of chronic RADS or IIA — For patients with RADS or irritant-induced asthma (IIA) who require long-term pharmacologic treatment for asthma symptoms, the step-wise approach described in the Global Initiative for Asthma (GINA) guidelines is followed even though it has not been formally assessed in this setting [71]. Over time, if the patient's asthma remains well-controlled, therapy is tapered according to the same guidelines. The long-term treatment of RADS and IIA is the same, even though the specific timing and pattern of onset differ. (See ["An overview of asthma management", section on 'Adjusting controller medication'.](#))

Nonpharmacologic treatment of RADS and IIA has not been studied directly; however, based on clinical experience patients are advised to avoid exposure to other respiratory irritants, including cigarette smoke [80]. For those patients who have underlying atopy, avoidance of known allergens to which they are sensitive is also appropriate. (See ["Trigger control to enhance asthma management"](#) and ["Allergen avoidance in the treatment of asthma and allergic rhinitis"](#) and ["Overview of smoking cessation management in adults"](#).)

EXPOSURE AVOIDANCE AND RETURNING TO WORK

Unlike workers with immunologic occupational asthma, most workers with RADS and IIA can return to their working environment with proper asthma treatment as long as their asthma is well-controlled and safety measures are taken to avoid unintentional high-level exposures [2,3]. Ongoing monitoring of symptoms and respiratory physiology is, however, key to early identification of any deterioration.

PROGNOSIS

The long-term outcome of RADS and IIA is unclear as longitudinal, prospective data are limited. The available evidence suggests a range of responses from complete clearance of symptoms and signs to persistent respiratory disability [59,65,67,81-84]. As examples:

- Among 20 patients who had repeated exposures to chlorine gas during a three-month period, two-thirds still had an abnormal response to [methacholine](#) three years later, and 85 percent reported wheezing, shortness of breath, or cough [81]. In a separate series of 71 workers suspected to have RADS following exposures to chlorine, 90 percent had persistent respiratory symptoms 18 to 24 months after exposure and 57 percent had bronchial hyperresponsiveness [24].
- A population-based study of 145 subjects exposed to chlorine gas found no changes in pulmonary function testing over the six-year follow-up period; however, airway responsiveness was not assessed [83].
- In a 10-year follow-up of 197 veterans of the Iran-Iraq war with acute poisoning with sulfur mustard gas, asthma symptoms, reversible airflow obstruction, and excessive diurnal peak expiratory flow variability were present in 11 percent [84]. In addition, chronic bronchitis or bronchiectasis occurred in 68 percent of patients, presumably due to extensive bronchial necrosis following acute exposure.
- Among 35 workers with IIA, almost all continued to have symptoms consistent with asthma and one-third were still using inhaled glucocorticoids at follow-up eight or more years later [65]. Spirometry was persistently abnormal in 74 percent. Among 23 who had repeat measurements of [methacholine](#) responsiveness, nine (25 percent) were no longer hyperresponsive. Bronchial biopsies were performed in 10 subjects at a mean of 10.9 years following the initial exposure and eosinophilic inflammation similar to that found in subjects with mild to moderate asthma was noted, but with more pronounced basement membrane thickening [59].
- Among 13,954 Fire Department of New York City rescue workers present on the site of the World Trade Center in September 2001, 91.6 percent participated in a routine surveillance program. After a median of 6.1 years of follow-up, the significant decline in FEV₁ seen during the first year persisted without recovery [72,85]. Greater than normal lung functions declines were associated with initial bronchodilator response and weight gain in a five year follow-up by the World Trade Center Worker and Volunteer Monitoring Program [86].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See ["Society guideline links: Occupational asthma"](#).)

SUMMARY AND RECOMMENDATIONS

- Irritant-induced asthma (IIA) is a general term to describe an asthmatic syndrome that results from single or multiple exposures to irritant products ([table 2](#)) that induce bronchial hyperresponsiveness. When symptoms promptly follow a single high-dose exposure, the syndrome is called reactive airways dysfunction syndrome (RADS). (See ['Definitions'](#) above and ['Epidemiology'](#) above.)
- Acute symptoms associated with RADS include a rapid onset of a burning sensation in the throat and nose, chest pain, dyspnea, cough and wheeze. In IIA, the symptoms are similar, but the onset is less acute than with RADS. Questions that are helpful in the evaluation of RADS and IIA are listed in the table ([table 5](#)). (See ['Clinical manifestations'](#) above.)
- The diagnosis of RADS requires the combination of exposure to a high-dose of an inhalational irritant, onset of symptoms within hours (rarely days), and evidence of reversible airflow limitation (eg, spirometry with bronchodilator reversibility or positive non-specific bronchoprovocation challenge), although a restrictive defect can also be present. A chest radiograph is often obtained to exclude other causes of dyspnea. Criteria for the diagnosis of RADS are summarized in the table ([table 1](#)). (See ['Evaluation'](#) above and ['Diagnosis'](#) above.)
- The diagnosis of IIA is based upon a history of single or multiple exposures to an irritating inhalational agent, the presence of asthma-like symptoms, and the presence of reversible airway obstruction and/or hyperresponsiveness. (See ['Diagnosis'](#) above and ['Pulmonary function testing'](#) above.)
- For patients who present with the acute onset of RADS, we use the same treatment approach that is used for acute asthma exacerbations in other settings, including oral glucocorticoids and high dose inhaled glucocorticoids with or without concomitant long-acting inhaled beta-2 agonist. In our experience high dose inhaled glucocorticoids are often needed to control symptoms ([table 8](#)). Inhaled rather than oral glucocorticoids are appropriate initial therapy for patients who present with less severe symptoms. (See ['Treatment'](#) above and ["Acute exacerbations of asthma in adults: Emergency department and inpatient management"](#).)

- For patients with persistent symptoms due to RADS or IIA, we suggest following the step-wise approach used in asthma management ([Grade 2C](#)). In addition, patients are advised to avoid respiratory irritants, including cigarette smoke, and allergens to which they are sensitive. (See ['Management of chronic RADS or IIA'](#) above and ["An overview of asthma management", section on 'Initiating pharmacologic treatment'](#) and ["Trigger control to enhance asthma management"](#).)
- In general, workers with RADS or IIA are able to return to their working environment with appropriate asthma treatment and safety measures to prevent further high dose exposures. The worker should have ongoing monitoring to detect any deterioration in respiratory status. (See ['Exposure avoidance and returning to work'](#) above.)
- The majority of patients with RADS and IIA improve over time, although many continue to have some respiratory symptoms for at least a year and have physiologic abnormalities such as non-specific bronchial hyperresponsiveness for several years. (See ['Prognosis'](#) above.)

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GRAPHICS

Criteria for diagnosis of reactive airways dysfunction syndrome

A documented absence of previous respiratory complaints.
The onset of symptoms should occur after a single specific exposure.
The exposure should be to a gas, smoke, fume, or vapor with irritant qualities that was present in very high concentrations.
The onset of symptoms should occur within 24 hours of exposure and should persist for at least three months.
The symptoms should simulate asthma with cough, wheezing, and dyspnea.
Pulmonary function tests may or may not show airflow obstruction.
Methacholine challenge should be positive.
Other types of pulmonary diseases should be ruled out.

Adapted from Brooks, SM, Weiss, MA, Bernstein, IL, Chest 1985; 88:376.

Graphic 77064 Version 1.0

Agents responsible for reactive airways dysfunction syndrome

Agent	Type of investigation	Evidence	Reference
Acetic acid	Epidemiological	H, S, BHR	Am Rev Respir Dis 1991; 144:1058
	Case report	H, S, P	Br J Ind Med 1989; 46:67
Chloridic acid	Case report	H, S, BHR	Chest 1988; 94:476 Chest 1990; 98:928
Sulfuric acid	Case report	H, S, BHR	Chest 1988; 94:476
Various acids	Case report	H, S, BHR, P	Chest 1994; 105:1895
	Case report	H, S, BHR	Chest 1989; 96:297
Bleaching agent	Case report	H, S, BHR	Chest 1988; 94:476
Cleaning agents	Case report	H, S	Chest 1976; 69:372
Sealing agents	Case report	H, S, BHR	Chest 1985; 88:376
Ammonia	Case report	H, S	Mayo Clin Proc 1983; 58:389
	Case report	H, S, P	Thorax 1992; 47:755
Phtalic anhydride	Case report	H, S, BHR	Rev Pneumol Clin 1993; 49:247
Bromochlorodifluoromethane (Halon 1211)	Case report	H, S, BHR	Occup Env Med 2004; 61:712
Bromotrifluoromethane (Halon 1301)	Case report	H, S	Eur Respir J 1999; 13:1192
Chlorine	Epidemiological	H, S, BHR	Occup Env Med 1994; 51:225
	Clinical study	H, S, BHR, P	J Allergy Clin Immunol 1994; 93:12 Eur Respir J 1997; 10:241
Chlorofluorocarbons (CFC)	Clinical study	H, S, BHR, P	Scand J Work Environ Health 2003; 29:71
Chloropicrin	Experimental	P	Toxicol Appl Pharm 1984; 74:417
Metal coat remover	Case report	H, S, BHR	Chest 1985; 88:376
Diesel	Case report	H, S, BHR	J Occup Med 1993; 35:149

Diethylaminoethanol	Epidemiological	H, S	J Occup Med 1994; 36:623
Sulfur dioxide	Case report	H, S, BHR, P	Chest 1990; 98:928 Am Rev Respir Dis 1979; 119:555
	Case report	H, S, BHR	Chest 1989; 96:297
Epichlorohydrin	Experimental	P	Toxicol Appl Pharm 1984; 74:417
Fire/smoke	Case report	H, S, BHR	Chest 1988; 94:476
	Case report	H, S	J Occup Med 1991; 33:458
Formalin	Case report	H, S	Lancet 1975; 2:603
Formaldehyde	Case report	H, S, BHR	Allergy 2004; 59:115
Hydrazin	Case report	H, S, BHR	Chest 1985; 88:376
Iodine	Case report	H, S, BHR, P	Ind Health 2009; 47:681
Diisocyanates	Case report	H, S, BHR	Scand J Work Environ Health 1981; 7:310
	Case report	H, S, BHR, P	Allergy 1996; 51:262
	Experimental	S	Toxicol App Pharmacol 1987; 89:332
	Case report	H, S, BHR	Chest 1989; 96:297
Calcium oxide	Case report	H, S, BHR	Chest 1989; 96:297
Ethylene oxide	Case report	H, S, BHR, P	Br J Ind Med 1992; 49:523
Heated paints	Case report	H, S, BHR	Chest 1989; 96:297
Pulverized paints	Case report	H, S, BHR, P	Chest 1989; 96:297 Chest 1985; 88:376
Perchloroethylene	Case report	H, S, BHR	Chest 1988; 94:476
Vapors (chlorine, mustard, phosgene, etc)	Case report	H, P	Br Med J 1915; 165

H: history; S: spirometry; BHR: bronchial hyperresponsiveness; P: pathology.

Time course of histologic lesions of RADS at different intervals after exposure

Interval After Exposure			
Case 1			
60 hours	15 days	60 days	150 days
Superficial fibrinohemorrhagic layer replacing bronchial epithelium that has sloughed	Persistence of hemorrhage, bronchial epithelium sloughing; increased deposition of collagen	Regeneration of epithelial cells (basal); collagen deposition; spots of lymphocytes; few PMNs; increase in thickness of basement membrane	Complete regeneration of the epithelium layer; numerous basal cells indicating regeneration.
Case 2			
45 days		98 days	
Severe damage of the epithelial layer with few remaining basal cells; subepithelial edema with inflammatory cells underneath the basement membrane.		Incomplete regeneration of the epithelial layer with few ciliated cells; inflammatory cells persisting in epithelium and connective tissue.	

Graphic 78151 Version 1.0

Comparison of occupational asthma with a latency period and reactive airways dysfunction syndrome

	Occupational asthma with a latency period	Reactive airways dysfunction syndrome and irritant-induced asthma
Latency period	Present	Absent
Diagnosis	Various - eg, peak expiratory flow monitoring, specific inhalation challenges; IgE-mediated allergy if suspected agent is of a high-molecular-weight nature	History; pulmonary function testing
Pathology	Similar to asthma	Acute: epithelial shedding and hemorrhage
		Chronic: regeneration of epithelial cells; few lymphocytes and neutrophils; increased collagen deposition and thickness of basement membrane
Pulmonary function testing	Better reversibility to bronchodilator	Less reversibility to bronchodilator

Graphic 80475 Version 4.0

Relevant information to be obtained from subjects with possible reactive airways dysfunction syndrome or with asthma

Was the onset of symptoms related to one "memorable" event in which there was exposure to a gas, fume, or dust?
Were there repeated gas, fume, or dust exposures of lesser intensities that still forced the subject to leave the premises?
Is there any ongoing exposure?
What was the nature of the substance? Has it been previously described as causing RADS (eg, acetic acid, ammonia, chlorine, isocyanates, mustard gas, fire/smoke)? Absence on a list of agents causing RADS does not exclude the diagnosis.
Was the concentration of the offending agent likely to be above accepted levels?
Were other workers or persons in the vicinity also affected?
Were there ocular or nasal symptoms? How long after the exposure(s) did they develop?
Describe the timing sequence of onset and diminution of symptoms: eg, immediate cough, shortness of breath after 30 min, wheezing after 1 hour, etc.
Was there a visit to an emergency room or a physician's office?
Were lung function tests, blood gases, or chest radiography performed soon after the event?
Was treatment initiated? What medications were used? What were the dose and duration?
Were there subsequent assessments, including records of symptoms, chest auscultation (wheezing), spirometry, bronchial responsiveness, and allergy skin tests?

Graphic 68098 Version 3.0

Contraindications to bronchial challenge testing

Airflow limitation
FEV ₁ <60% predicted (adults or children) or <1.5 L (adults)
FEV ₁ <75% predicted (adults or children) for exercise or eucapnic voluntary hyperpnoea challenge
Spirometry quality
Inability to perform acceptable and repeatable spirometry maneuvers throughout the test procedure
Cardiovascular and other problems
Myocardial infarction or stroke in last three months
Uncontrolled hypertension
Known aortic aneurysm
Recent eye surgery or intracranial pressure elevation risk
General
Inability to perform any of the testing maneuvers, such as inhaling the challenge agent consistently or exercising on treadmill or bicycle during an exercise challenge

FEV₁: forced expiratory volume in one second.

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Graphic 82058 Version 5.0

Medications that may affect bronchoprovocation challenge test^[1-3]

Medication	Minimum time to omit medication before challenge tests
Inhaled bronchodilators	
Albuterol	8 hours
Levalbuterol	8 hours
Terbutaline	8 hours
Formoterol, salmeterol	36 hours
Ultra long-acting beta agonists (eg, indacaterol, olodaterol, vilanterol)	48 hours
Short-acting muscarinic antagonist (ipratropium)	12 hours
Long-acting muscarinic antagonists (aclidinium, glycopyrrolate, tiotropium)	72 hours
Oral theophylline	24 hours
Oral albuterol	12 to 24 hours
Inhaled glucocorticoid (budesonide, fluticasone propionate)*	6 hours
Inhaled glucocorticoid (long acting; fluticasone furoate, ciclesonide)	24 hours
Oral glucocorticoid*	2 to 3 weeks
Cromolyn sodium[¶]	4 hours
Antihistamines (cetirizine, fexofenadine, loratadine)	72 hours ^Δ
Leukotriene modifiers	
Montelukast [◇]	4 days
Zafirlukast	4 days

* The authors do not recommend routinely withholding inhaled or oral glucocorticoids, but their anti-inflammatory effect may decrease bronchial responsiveness. A negative test while the patient is using glucocorticoids implies that the patient's current symptoms are not due to asthma.

¶ Cromolyn has minimal effect on methacholine bronchoprovocation challenge, but should be withheld prior to allergen challenge.

Δ Antihistamines are discontinued because of their anticholinergic effect.

◇ A single dose of montelukast has minimal effect on methacholine challenge, but a withhold time of 4 to 8 weeks would be needed for full resolution of the anti-inflammatory effects.

References:

1. Weiler JM, Brannan JD, Randolph CC, et al. Exercise-induced bronchoconstriction update-2016. *J Allergy Clin Immunol* 2016; 138: 1292–1295.
 2. Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J* 2017; 49.
 3. Hallstrand TS, Leuppi JD, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. *Eur Respir J* 2018; 52:1801033.
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Graphic 62151 Version 10.0

Estimated comparative daily doses for inhaled glucocorticoids in adolescents ≥12 years and adults

Drug	Low dose (total daily dose)	Medium dose (total daily dose)	High dose (total daily dose)*
Beclomethasone HFA (Qvar RediHaler product available in United States) Administer as 2 divided doses	80 to 160 mcg	>160 to 320 mcg	>320 to 640 mcg
40 mcg per actuation	2 or 4 inhalations	¶	¶
80 mcg per actuation	2 inhalations	4 inhalations	6 or 8 inhalations
Beclomethasone HFA^Δ (Qvar product available in Canada, Europe, and elsewhere) Administer as 2 divided doses	100 to 200 mcg	>200 to 400 mcg	>400 to 800 mcg
50 mcg per actuation	2 to 4 inhalations	¶	¶
100 mcg per actuation	2 inhalations	4 inhalations	6 or 8 inhalations
Budesonide DPI (Pulmicort Flexhaler product available in United States) Administer as 2 divided doses	180 to 360 mcg	>360 to 720 mcg	>720 to 1440 mcg
90 mcg per actuation	2 or 4 inhalations	¶	¶
180 mcg per actuation	2 inhalations	4 inhalations	6 or 8 inhalations
Budesonide DPI^Δ (Pulmicort Turbuhaler or Turbohaler product available in Canada, Europe, and elsewhere) Administer low doses (ie, ≤400 mcg/day) once daily; administer higher doses (ie, >400 mcg/day) as 2 to 4 divided doses	200 to 400 mcg	>400 to 800 mcg	>800 to 2400 mcg
100 mcg per actuation	2 to 4 inhalations	¶	¶
200 mcg per actuation	1 to 2 inhalations	3 to 4 inhalations	¶
400 mcg per actuation	1 inhalation	2 inhalations	3 to 6 inhalations
Ciclesonide HFA (Alvesco product available in United States, Europe, and elsewhere)	160 mcg	320 mcg	640 mcg

United States: Administer as 2 divided doses Australia, Europe, and elsewhere: Administer lower doses (ie, 160 to 320 mcg/day) once daily; administer 640 mcg dose as 2 divided doses			
80 mcg per actuation	2 inhalations	4 inhalations	¶
160 mcg per actuation	◇	2 inhalations	4 inhalations
Ciclesonide HFA^Δ (Alvesco product available in Canada) Administer lower doses (eg, 100 to 400 mcg) once daily; administer 800 mcg dose as 2 divided doses	100 to 200 mcg	>200 to 400 mcg	>400 to 800 mcg
100 mcg per actuation	1 to 2 inhalations	3 to 4 inhalations	¶
200 mcg per actuation	1 inhalation	2 inhalations	3 to 4 inhalations
Fluticasone propionate HFA (Flovent HFA product available in United States) Administer as 2 divided doses	176 to 220 mcg	>220 to 440 mcg	>440 to 1760 mcg
44 mcg per actuation	4 inhalations	¶	¶
110 mcg per actuation	2 inhalations	4 inhalations	¶
220 mcg per actuation	◇	2 inhalations	4 to 8 inhalations
Fluticasone propionate HFA^Δ (Flovent HFA product available in Canada; Flixotide Evohaler product available in Europe and elsewhere) Administer as 2 divided doses	100 to 250 mcg	>250 to 500 mcg	>500 to 2000 mcg
50 mcg per actuation	2 to 4 inhalations	¶	¶
125 mcg per actuation	2 inhalations	4 inhalations	¶
250 mcg per actuation	◇	2 inhalations	4 to 8 inhalations
Fluticasone propionate DPI (Flovent Diskus product available in United States and Canada; Flixotide Accuhaler product available in Europe and elsewhere) Administer as 2 divided doses	100 to 250 mcg	>250 to 500 mcg	>500 to 2000 mcg
50 mcg per actuation	2 to 4 inhalations	¶	¶
100 mcg per actuation	2 inhalations	4 inhalations	¶

250 mcg per actuation	◇	2 inhalations	4 to 8 inhalations
500 mcg per actuation (strength not available in United States)	◇	◇	2 or 4 inhalations
Fluticasone propionate DPI (Armonair Digihaler product available in United States; Aermony Respiclick product available in Canada) Administer as 2 divided doses	110 mcg	226 mcg	464 mcg
55 mcg per actuation	2 inhalations	¶	¶
113 mcg per actuation	◇	2 inhalations	¶
232 mcg per actuation	◇	◇	2 inhalations
Fluticasone furoate DPI (Arnuity Ellipta product available in United States, Canada, Australia, and elsewhere, but not available in Europe or UK) Administer once daily NOTE: Inhaled fluticasone furoate has a greater anti-inflammatory potency per microgram than fluticasone propionate inhalers. Thus, fluticasone furoate is administered at a lower daily dose and used only once daily.	50 mcg (by use of pediatric DPI, which is off-label in adolescents and adults)	100 mcg	200 mcg
50 mcg per actuation	1 inhalation	¶	¶
100 mcg per actuation	◇	1 inhalation	2 inhalations
200 mcg per actuation	◇	◇	1 inhalation
Mometasone DPI (Asmanex Twisthaler product available in United States) May administer lower doses (ie, 220 to 440 mcg/day) once daily; administer 880 mcg dose as 2 divided doses	220 mcg	>220 to 440 mcg	>440 to 880 mcg
110 mcg per actuation	2 inhalations	¶	¶
220 mcg per actuation	1 inhalation	2 inhalations	4 inhalations
Mometasone HFA (Asmanex HFA product available in United States) Administer as 2 divided doses	200 mcg	>200 to 400 mcg	>400 to 800 mcg
100 mcg per actuation	2 inhalations	4 inhalations	¶

200 mcg per actuation	◇	2 inhalations	4 inhalations
Mometasone DPI^Δ (Asmanex Twisthaler product available in Canada, Europe, and elsewhere) May administer lower doses (ie, 200 to 400 mcg/day) once daily; administer 800 mcg dose as 2 divided doses	200 mcg	>200 to 400 mcg	>400 to 800 mcg
200 mcg per actuation	1 inhalation	2 inhalations	¶
400 mcg per actuation	◇	1 inhalation	2 inhalations

- **The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.** The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.
- Suggested total daily doses for low, medium, and high dose inhaled glucocorticoid regimens are based on daily doses recommended by Global Initiative for Asthma (GINA), National Asthma Education and Prevention Program (NAEPP), and/or product labeling^[1-5]. This is not a table of equivalence.
- Depending on the specific product, total daily doses are administered once or divided and given twice daily. Refer to local product information or a clinical drug reference (eg, Lexicomp).
- Some doses are outside the approved product information recommendations.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant metered dose inhaler.

* Evidence for additional improvement with dose increases >1000 mcg/day is limited.

¶ Select alternate preparation with higher mcg/actuation to improve convenience.

Δ Products shaded in light gray color are not available in the United States but are available widely elsewhere.

◇ Select preparation with fewer mcg/actuation.

Data from:

1. Global Initiative for Asthma (GINA); Global Strategy for Asthma Management and Prevention; 2021. Available at www.ginasthma.org.
2. National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma; 2007. NIH Publication 08-4051 available at <http://www.nhlbi.nih.gov/rproxy.tau.ac.il/health-pro/guidelines/current/asthma-guidelines/full-report> and pro.
3. US Food & Drug Administration (FDA) approved product information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov/dailymed/index.cfm.)
4. Health Canada-approved product monograph. Health Canada. (Available online at <https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>.)
5. European Medicines Agency (EMA) summary of product characteristics. European Medicines Agency. (Available online at www.ema.europa.eu/en/medicines.)

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